Subgroup analyses of adverse events by age, sex, race and prior BOTOX® treatment showed no statistically significant differences between the treatment groups.

**Reviewer's Comments and Conclusions on studies:** Clinical Trials ( were designed as identical Phase 3, multicenter, double blind, randomized, placebo-controlled, parallel group studies to evaluate the safety and efficacy of BOTOX®. There were no significant safety issues identified. Safety appeared to be consistent across both trials. There were no subjects who dropped out of the trials due to adverse events that appeared to be related to treatment. The most significant adverse event that was seen only in the treated group was ptosis. There was an inconsistency in the number of ptosis cases across study centers. This may have been related to investigator technique. One subject had unilateral ptosis for 52 days. Other adverse events that occurred slightly more often in the treated group of subjects compared to placebo were pain in the face and at the injection site, skin tightness, and muscle weakness.

There were no clinically significant differences in the laboratory findings or in the vital signs between groups. There was one subject in the BOTOX® treated group with abnormal laboratory studies possibly related to treatment. Baseline ALT and AST levels were elevated with an initially normal creatine phosphokinase level, which became elevated one month post treatment. The ALT and AST returned to normal but the CPK remained elevated. The patient admitted to using creatine as a supplement. Overall individual abnormalities in laboratory variables did not show any clinically meaningful differences between the treatment groups.

Subgroup analyses of adverse events by age, sex, race and prior BOTOX® treatment showed no statistically significant differences between the treatment groups. There were minimal protocol deviations, most due to other facial treatments being performed while subject was still in the trial.

BOTOX® appears to be efficacious, especially in those < 50 years of age. It appears to be least efficacious in those ≥ 65 years and those with severe glabellar lines. Efficacy appeared to be consistent across both trials.

## Open Label Study

Subjects who had completed Day 120 of either study and had glabellar lines of at least mild severity at maximum frown, plus fulfilled the other entry criteria were offered enrollment into study

This was a multicenter, open-label, non-comparative study where subjects received two additional treatments of BOTOX® at the same dose and procedure from the previous studies.

The object of this study was to evaluate the safety of BOTOX® for the treatment of glabellar lines.

The subjects were males and females age 18-75 years assigned to BOTOX® treatment, stratified by age group (≤50 years, ≥ 51 years).

*Inclusion Criteria:*

- Successful completion of study
- Male or female 18 to 75 years old at the time of enrollment in above studies
- Stable medical condition
- Willing and able to complete the entire course of the study and to comply with study instructions
- Written informed consent has been obtained.
- Glabellar lines of at least mild severity at maximum frown

*Exclusion Criteria:*

- Any medical condition that may put the subject at increased risk with exposure to BOTOX®, including diagnosed myasthenia gravis, Eaton-Lambert syndrome, amyotrophic lateral sclerosis, or any other disorder that might interfere with neuromuscular function
- Concurrent use of aminoglycoside antibiotics, curare-like agents, or other agents that might interfere with neuromuscular function
- Evidence of recent alcohol or drub abuse
- Psychiatric problems that, in the investigator's opinion, are severe enough to interfere with study results
- Infection or skin problem at the injection site
- Marked facial asymmetry, ptosis, excessive dermatochalasis, deep dermal scarring, thick sebaceous skin, or inability to substantially lessen glabellar lines even by physically spreading them apart
- History of facial nerve palsy
- Females who are pregnant, nursing, or planning a pregnancy during the study period or females of childbearing potential, not using a reliable means of contraception (females of childbearing potential must have a negative pregnancy test on Day 0 prior to injection)
- Any other planned facial cosmetic procedure during the study period
- Known allergy or sensitivity to the study medication or its components
- Concurrent participation in another clinical study or participation in the 30 days immediately prior to enrollment (exceptions for study

- Any condition or situation that in the investigator's opinion may put the subject at significant risk, may confound the study results, or may interfere significantly with the subject's participation in the study

**COMMENT:** *FDA Review Team requested verification that the occurrence of a serious or unexpected adverse event would satisfy the criteria for discontinuation of further treatments under this protocol and discontinuation of a subject's participation in this study but Allergan did not revise the protocol accordingly.*

The lots used in the studies were new bulk toxin [redacted]

Subjects continued to use the same subject number that was assigned to them in Study [redacted]

Day 0 was the same day at Day 120 (exit visit) of Study [redacted] and [redacted] At Day 0 and Day 120 of study [redacted] subjects received a single treatment of intramuscular injections of BOTOX® with a sterile 30-gauge 1" needle on a tuberculin 1cc syringe. A vial containing 100U of BOTOX® was diluted with 2.5ml of sterile 0.9% saline without preservative, for a dilution of 40 U/mL (4 U/0.1 mL). Injection volume was 0.1mL/injection site, for a dose/injection site of 4U. Patients were injected in 5 sites, 1 in the procerus and 2 in each corrugator supercilii, for a total dose of 20U.

First injection was at Day 0 with follow-up visits Days 30, 60, 90, and 120. Second injection was at Day 120 with follow-up visits at Days 150, 180, 210, and 240.

Use of concurrent medication, prescription or over-the-counter, was to be recorded on the subject's case report form along with the reason the medication was taken. Subjects would continue their standard facial skin care regimen throughout the duration of the study. Subjects would not take or receive aminoglycoside antibiotics, curare-like agents, or agents that interfere with neuromuscular transmission.

Urine pregnancy was gotten Day 0 and Day 120 prior to each injection. A complete blood count, blood chemistry, and serum antibody was also gotten Days 120 and 240 (or at the exit visit if it occurs prior to Day 240). (Day 0 values were taken from the exit visit data from Study [redacted] Vital signs were gotten at each visit. (Day 0 values were taken from the exit visit data from Study [redacted]

Clinic visits and investigator questioning occurred Days 0, 30, 60, 90, 120,150, 180, 210, 240. At each post-injection visit the investigator asked, "How have you been feeling since the last visit?" Directed questioning and examination was done as appropriate. Investigators documented adverse events on case report

forms- date of onset, resolution date, action taken, outcome, type, severity and relationship to study drug.

If female became pregnant, investigator would notify Allergan immediately, notify the subject's physician, follow the progress of the pregnancy to term and document the outcome.

Subjects were discontinued from the study early for adverse events, administrative reasons (e.g., lost to follow-up, withdrawal of consent), and failure to qualify at Day 120 for re-injection.

A serious adverse event was defined as any adverse event occurring at any dose that resulted in death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Others could be added based upon appropriate medical judgment.

The severity of an adverse event was graded as:

> Mild: Awareness of sign or symptom, but easily tolerated
>
> Moderate: Discomfort enough to cause interference with usual activity
>
> Severe: Incapacitating with inability to work or do usual activity
>
> Not applicable: In some cases, could be an "all or nothing" finding that could not be graded.

**COMMENT:** *As requested for the previous studies, FDA recommended that subjects be queried for specific adverse events that had been observed in previous off-label BOTOX® clinical trials. Allergan did not incorporate this recommendation into the protocol.*

Missing data would be replaced by the mean of all non-missing data for the efficacy variables investigator's rating of glabellar line severity at maximum frown and at rest, and subject's global assessment of change in appearance of glabellar lines. Missing values would be replaced in the intent-to-treat data set only. For safety and other variables, data were only analyzed without replacement of missing values.

Visit windows:

| | |
|---|---|
| Day 30 | 1-45 |
| Day 60 | 46-75 |
| Day 90 | 76-105 |
| Day 120 | 106-to second injection |
| Day 150 | 1-45 |

| | |
|---|---|
| Day 180 | 46-75 |
| Day 210 | 76-105 |
| Day 240 | 106-last visit |

All sites used the same photonumeric guide used in Study [redacted]

The primary efficacy measurements were (1) the investigator's rating of glabellar line severity at maximum frown and (2) subject's global assessment of change in appearance of glabellar lines using a none, mild, moderate, severe grading scale Day 30, 60, 90, 120, 150, 180, 210, and 240 (or exit visit). For the global assessment of change in appearance of glabellar lines, the subject responded to the question, "How would you rate the change in the appearance of your glabellar lines compared with immediately before your most recent injection?" The rating of responses were:

| | |
|---|---|
| +4 | Complete improvement (about 100%) |
| +3 | Marked improvement (substantial improvement, about 75%) |
| +2 | Moderate improvement (definite improvement, about 50%) |
| +1 | Slight improvement (some improvement, about 25%0 |
| 0 | Unchanged |
| -1 | Slight worsening (about 25% worse) |
| -2 | Moderate worsening (about 50% worse) |
| -3 | Marked worsening (about 75%) |
| -4 | Very marked worsening (about 100% worse or greater) |

Secondary efficacy endpoint was the investigator's rating of glabellar line severity at rest Day 30, 60, 90, 120, 150, 180, 210, and 240 (or exit visit).

There were no power/sample size calculations since the number enrolled was dependent on the number of subjects available and willing to participate following completion of the [redacted] studies. Maximum number expected was 512 subjects.

Prior to study completion a detailed analysis plan was generated. No interim analysis was planned or performed. Data was to be summarized with descriptive statistics, frequency tables, and data listings. Continuous and categorical variables were to be summarized with descriptive statistics.

Intent-to-treat analyses were planned as the primary safety and efficacy analyses.

The primary analysis was the calculation of incidence of adverse events over the entire open label study period as well as over each injection cycle in the open label study. Two-sided 95% confidence intervals would also be calculated for the overall adverse event incidences. All remaining analyses would be secondary.

The null hypothesis in change from baseline analyses is that there was no change from baseline and the alternative was that there was a change from baseline. When p-values for change from baseline analyses were calculated they will be two-sided, and the results of each hypothesis test will be called "statistically significant" if $p \leq .05$. For selected variables, change form baseline analyses will include two-sided 95% confidence intervals. Two-sided 95% confidence intervals would be provided for responder incidences as described below.

Key efficacy variables were (1) glabellar line severity at rest and at maximum frown and (2) subject's global assessment of change in appearance of glabellar lines from the most recent injection. Efficacy variables were evaluated for change from baseline (baseline would be the timepoint of the most recent injection).

Responder analysis was done with investigator's scores (0 and 1 represent responder; 2 and 3 represent non-responder) and with subject's global assessment of change in appearance of glabellar lines (+2, +3, +4 represents responder and <+2 represents non-responder).

Paired t-tests were to be performed for change from baseline analyses. Confidence intervals were to be 95% two-sided intervals based on the t-distribution.

Worsening of the disease/condition being evaluated that occurred during the study was considered an adverse event. Lack of efficacy of the study treatment was not considered an adverse event. Baseline was Day 0 of preceding study. Two-sided 95% confidence intervals were to be calculated for adverse event incidences.

Secondary safety variables were hematology, electrolytes, blood chemistry, and vital signs. Allergan's modified COSTART nomenclature was to be used to code adverse events. For each adverse event reported, the number and percent of subjects was to be tabulated. Tables were to be generated by relationship to treatment as well as by body system. For laboratory values, blood pressure, and heart rate, the Wilcoxon signed-rank test was performed for within-group analyses.

Secondary analysis was to include the evaluation of change from baseline. P-values for change from baseline analyses was to be two-sided and the result of each hypothesis test was to be called "statistically significant" if its P-value was $\leq .05$.

Subgroup analysis would be performed by study center for the follow groups:

- Age ($\leq$50 years, $\geq$ 51)
- Race (white, non-white)
- Sex (male, female)

**COMMENT:** *FDA Review Team asked that additional subgroup analyses for safety and efficacy be included for : age ≥ 65 years and history of previous BOTOX® treatment for glabellar lines.*

The endpoint was to be that BOTOX® has an acceptable safety profile when used for the treatment of subjects with glabellar lines.

**Results:**
There were 27 US sites involved.
There were 514 subjects who were eligible to enroll.

A total of 373 subjects (72.6%) were enrolled in this open-label study. 318 (85.3%) of these subjects completed the study.

156 eligible subjects did not enroll, 124 previously treated with BOTOX® and 32 previously treated with placebo. Reasons given:

| | BOTOX® | Placebo |
|---|---|---|
| ➢ Subject did not want to participate (no reason) | 45 | 12 |
| ➢ No compensation offered | 7 | 1 |
| ➢ Too busy | 10 | 2 |
| ➢ Wanted to become pregnant | 2 | 0 |
| ➢ Planning elective surgery | 2 | 0 |
| ➢ Worried about side effects of treatment | 1 | 0 |
| ➢ Did not like effects of BOTOX® treatment | 1 | 0 |
| ➢ Center did not want to participate (1901, 3164, 3163) | 29 | 9 |
| ➢ Subject excluded due to thrombophlebitis | 1 | 0 |
| ➢ Subject excluded due to low platelet level | 1 | 0 |
| ➢ Subject excluded due to colon cancer | 1 | 0 |
| ➢ Subject excluded due to elevated CK level | 1 | 0 |
| ➢ Subject did not meet age criteria | 2 | 0 |
| ➢ Subject pregnant | 0 | 1 |
| ➢ Subject noncompliant with visit schedule | 1 | 0 |
| ➢ Prior medical condition unstable | 1 | 0 |
| ➢ Subject exited previous study too late | 17 | 4 |
| ➢ Subject moved from area | 1 | 3 |

55 discontinued, 30 after the first treatment, 25 after the second treatment

- ➢ 2 subjects discontinued due to adverse events
  Subject 2932-E57 was diagnosed with breast cancer
  Subject 2935-G15 had an unplanned pregnancy
- ➢ 25 subjects discontinued for personal reasons
- ➢ 21 subjects were lost to follow-up
- ➢ 7 subjects discontinued for other reasons
  4 subjects' glabellar lines had not returned to at least mild severity

1 subject moved
1 subject could not have blood drawn prior to the second treatment
1 subject had misunderstood scheduling visits

277 subjects had been treated with BOTOX® in the previous study
96 subjects had been treated with placebo in the previous study.

343 subjects received both BOTOX® injections. 30 subjects received only one BOTOX® injection.

There are a total of 258 subjects who received BOTOX® in the previous trial and both injections of BOTOX® during this trial (for a total treatment time of 12 months). Of these, 239 subjects completed the 120 days of follow-up after the final injection.

The age range was 22-76 years with the mean being 45.9 years.
69.4% (259/373) were ≤ 50 years and 30.6% (114/373) were ≥ 51 years of age.
6.2% (23/373) were ≥ 65 years old.
There were 315 females (85%) and 58 males (16%).
There were 317 Caucasians (85%).
There were 28 Hispanics (8%).
There were 13 African-Americans (4%).
There were 10 Asians (3%).
There were 5 other races (1%).

The Day 0 mean baseline severity score of glabellar line severity at maximum frown based on the investigator's assessment was 2.2 and at Day 120 was 2.0. Baseline severity was mild for 17.7% (66/373) of subjects, moderate for 48.5% (181/373) of subjects, and severe for 33.8% (126/373) of subjects.

Protocol deviations
- Subject 2935-G15 became pregnant
- Subject 1938-X09 had a facial procedure (filler around eyes)
- Subject 1938-X01 had a facial procedure (dermalogen injections)
- Subject 2934-J61 had a facial procedure (eyeliner tattooed)
- Subject 3159-Y04 had blood drawn for lab analysis after BOTOX® injection
- Subject 3158-U02 refused second blood draw after vial broke
- Subject 3158-U06 refused Day 240 blood draw
- Subject 3161-161 was unable to have Day 240 blood draw
- Subject 3159-Y10 had Day 120 injection administered too late after mixed
- Subject 2936-F13 was treated from the same vial as subject 2936-F58
- At study center 2934, vials were refrigerated but the temperatures were not monitored.

*Efficacy:*

The proportion of subjects who responded in all 3 treatment cycles was >70% for all efficacy measurements at Day 30. There were more subjects at rest who maintained a treatment response in all 3-treatment cycles at Day 120 compared to the investigator's maximum frown assessment.

**Responder Rates of Glabellar Line Severity With Three Treatments**

| | **Investigator's Assessment at Maximum Frown % rated 0 or 1** | **Subject's Assessment % +2 or better** | **Investigator's Assessment at Rest % rated 0 or 1** |
|---|---|---|---|
| **DAY** | **BOTOX®** | **BOTOX®** | **BOTOX®** |
| 30 | 85.8%<br>320/373 | 92.5%<br>345/373 | 87.9%<br>131/149 |
| 60 | 70.8%<br>264/373 | 87.4%<br>326/373 | 82.6%<br>123/149 |
| 90 | 43.7%<br>163/373 | 68.1%<br>254/373 | 75.8%<br>113/149 |
| 120 | 22%<br>82/373 | 40.2%<br>150/373 | 69.1%<br>103/149 |
| 150 | 88.0%<br>302/343 | 91.8%<br>315/343 | 89.9%<br>125/139 |
| 180 | 77.8%<br>267/343 | 86.3%<br>296/343 | 88.5%<br>123/139 |
| 210 | 57.7%<br>198/343 | 74.9%<br>257/343 | 84.9%<br>118/139 |
| 240 | 27.4%<br>94/343 | 54.5%<br>187/343 | 77.0%<br>107/139 |

The results were equally robust regardless of the subjects' treatment assignments in the preceding studies and between the first and second treatment cycles of the study.

For the 258 subjects who received BOTOX® all three treatments, responder rates tended to increase across treatment cycles. The responder rate was significantly higher ($p \leq 0.028$) in the third cycle than in the first cycle at days 30, 60 and 90; in the second cycle than the first cycle at Day 30; and in the third cycle than in the second cycle at Days 60 and 90.

Of the 258 subjects who received 3 BOTOX® treatments, 22 (20.8%) did not respond in the first treatment cycle, 10 (9.4%) did not respond in the second treatment cycle, and 10 (9.4%) did not respond in the third treatment cycle.

**Responder Rates of Glabellar Line Severity With Three BOTOX Treatments**

| | Investigator's Assessment at Maximum Frown % rated 0 or 1 | Subject's Assessment % +2 or better | Investigator's Assessment at Rest % rated 0 or 1 |
|---|---|---|---|
| **DAY** | **BOTOX®** | **BOTOX®** | **BOTOX®** |
| | ***CYCLE 1*** | ***CYCLE 1*** | ***CYCLE 1*** |
| 30 | 79.8%<br>206/258 | 89.1%<br>230/258 | 74.5%<br>79/106 |
| 60 | 69.8%<br>180/258 | 81.0%<br>209/258 | 72.6%<br>77/106 |
| 90 | 46.5%<br>120/258 | 62.8%<br>162/258 | 73.6%<br>78/106 |
| 120 | 21.7%<br>56/258 | 38.4%<br>99/258 | 60.4%<br>64/106 |
| | ***CYCLE 2*** | ***CYCLE 2*** | ***CYCLE 2*** |
| 30 | 85.7%<br>221/258 | 91.9%<br>237/258 | 89.6%<br>95/106 |
| 60 | 73.6%<br>190/258 | 86.0%<br>222/258 | 82.1%<br>87/106 |
| 90 | 45.0%<br>116/258 | 67.1%<br>173/258 | 76.4%<br>81/106 |
| 120 | 22.1%<br>57/258 | 41.9%<br>108/258 | 68.9%<br>73/106 |
| | ***CYCLE 3*** | ***CYCLE 3*** | ***CYCLE 3*** |
| 30 | 89.1%<br>230/258 | 90.3%<br>233/258 | 90.6%<br>96/106 |
| 60 | 79.5%<br>205/258 | 85.3%<br>220/258 | 87.7%<br>93/106 |
| 90 | 60.1%<br>155/258 | 75.6%<br>195/258 | 85.8%<br>91/106 |
| 120 | 27.5%<br>71/258 | 54.7%<br>141/258 | 74.5%<br>79/106 |

In the subgroup analyses, the responder rates for the co-primary efficacy variables were slightly lower for subjects ≥65 years than for younger subjects. Four subjects were nonresponders across all cycles. All were in the ≥ 65 years of age group. Two had baseline scores of severe and two had baseline scores of moderate. None of these subjects had positive antibody assay results.

The responder rates for the co-primary efficacy variables were slightly lower for males than females. All of the subjects were female at centers 1978 (n=6), 2940 (n=9) and 3162 (n=5).

**Responder Rates of Glabellar Line Severity**
**BY SEX**

| | Investigator's Assessment At Maximum Frown % rated 0 or 1 FEMALE | | Investigator's Assessment At Maximum Frown % rated 0 or 1 MALE | |
|---|---|---|---|---|
| **DAY** | **BOTOX®** N = 315 | | **BOTOX®** N= 58 | |
| 30 | 89.2% (85.12, 92.31) | | 67.2% (53.54, 78.65) | |
| 120 | 23.8% (19.29, 28.98) | | 12.1% (5.39, 23.91) | |

**Responder Rates of Glabellar Line Severity**
**BY SEX**

| | Subject's Assessment % +2 or better FEMALE | | Subject's Assessment % +2 or better MALE | |
|---|---|---|---|---|
| **DAY** | **BOTOX®** N = 315 | | **BOTOX®** N= 58 | |
| 30 | 93.0% (89.47, 95.47) | | 89.7% (78.16, 95.72) | |
| 120 | 43.2% (37.66, 48.85) | | 24.1% (14.27, 37.46) | |

The responder rates for the co-primary efficacy variables were slightly lower for those subjects with baseline scores of severe glabellar facial lines compared to a moderate score.

**Responder Rates of Glabellar Line Severity**
**BY BASELINE SCORE**

| | Investigator's Assessment At Maximum Frown % rated 0 or 1 MODERATE | | Investigator's Assessment At Maximum Frown % rated 0 or 1 SEVERE | |
|---|---|---|---|---|
| **DAY** | **BOTOX®** N=150 | | **BOTOX®** N= 223 | |
| 30 | 95.3% (90.25, 97.94) | | 79.4% (73.34, 84.36) | |
| 120 | 12.1% (29.07, 44.96) | | 30.0% (8.27, 17.30) | |

The responder rates for the co-primary efficacy variables were generally similar for Caucasian and non-Caucasian subjects.

No formal drug-drug interactions were performed. Most subjects (85.5%, 319/373) used some other medication during the study. The most commonly used medications were anilides (12.3%, 46/373), selective serotonin reuptake inhibitors (12.1%, 45/373), multivitamins (11.5%, 43/373), fixed combinations of progestogens and estrogens (11.3%, 42/373) and propionic acid derivatives (11.0%, 41/373).

*Safety:*
No subject died during the study.

Two subjects discontinued the study due to adverse events, both considered unrelated to medication:

- Subject 2932-E57 was diagnosed with breast cancer approximately 175 days after the first open-label treatment.
- Subject 2935-G15 had an initial negative pregnancy test but had an unplanned pregnancy and discontinued from further study participation approximately 125 days after the first open-label treatment. It is reported that the subject delivered a healthy baby at term.

Six subjects experienced serious adverse events

- Subject 1938-X01 was a 42-year-old female who experienced nausea, vomiting, diarrhea hours after her treatment with BOTOX®. She was hospitalized for 3 days and was diagnosed with transient colitis.
- Subject 1996-R01 was a 30 year old male who underwent orthopedic surgery for a past bone fracture approximately 1 month after his BOTOX® treatment. He developed fat emboli, which led to a cardiac arrest with resuscitation. He later fell and sustained another fracture that required hospitalization.
- Subject 2932-E57 was a 66-year-old female who was discovered to have breast cancer approximately 5 months after BOTOX® treatment.
- Subject 2046-C15 was a 54-year-old female who underwent elective spinal fusion surgery for a previously diagnosed herniated disc approximately 6 months after BOTOX® treatment.
- Subject 3159-Y59 was a 50-year-old female who underwent elective bladder sling surgery for stress urinary incontinence approximately 6 weeks after BOTOX® treatment.
- Subject 2936-F11 was a 36-year-old female who developed a fever and enlarged right groin lymph node approximately 7 weeks after BOTOX® treatment. She underwent surgery and antibiotic treatment.

Adverse events were reported for 49.1% of subjects (183/373).

Adverse events reported in ≥ 3% of subjects:

| | CYCLE 1<br>N=373 | CYCLE 2<br>N=343 |
|---|---|---|
| Any event | 38.9% (145) | 35.3% (121) |
| Respiratory infection | 6.4% (24) | 6.1% (21) |
| Flu syndrome | 4.0% (15) | 2.9% (10) |
| Headache | 4.0% (15) | 2.6% (9) |

One headache was reported as severe

Also of note, blepharoptosis was reported for 2.1% (8/373) of subjects in the first treatment cycle and 1.2% (4/343) of subjects in the second treatment cycle.

There were 11 subjects, all female, with ptosis. 8 were Caucasian, 3 non-Caucasian. 5 were ≤ 50 years of age and 6 were ≥ 51 years of age. It was unilateral for 10 and bilateral for 1 subject (1996-R08). It was considered mild in most of the cases, with an average duration of 33 days and moderate for 3 cases with an average duration 25 days. Of the 11 cases, 7 had received BOTOX® in the previous trial. 1 had experienced ptosis in the preceding study (subject 3159-Y04, study — The 6 study sites involved were:

- 0093 22% (4/18)
- 1996 8% (1/12)
- 3157 14% (3/22)
- 3159 6% (1/17)
- 3161 8% (1/13)
- 3187 8% (1/13)

Any medical conditions that developed during the preceding studies and that were still ongoing at the time subjects enrolled into the open-label study were considered adverse events. The most common medical conditions were:

- Gynecologic disorders (56.2%, 177/315)
- Drug sensitivities (24.7%, 92/373)
- Musculoskeletal (24.1%, 90/373)
- Gastrointestinal (22.0%, 82/373)
- Dermatological conditions (20.1%, 75/373)

There were 62 adverse events in 46 subjects that were ongoing at study exit. None were considered treatment-related (anemia, ulcer, back pain, depression, arthritis, acne, vertigo, rib fractures, laceration, hiatal hernia, urethritis, macular degeneration, thyroid disease, colitis, hypertension, bone spur, dyspepsia, dry skin on hands, perforated colon, anxiety, hypercholesterolemia).

Adverse events were reported for a higher proportion of subjects ≥ 65 years of age (65.2%, 15/23) than for subjects ≤ 50 years of age and those ≥ 51 years of age.

Adverse events were reported for a higher proportion of females than males, 51.4% (162/315) compared with 36.2% (21/58). No male subject reported headache or blepharoptosis.

Adverse events were reported for a higher proportion of Caucasians (51.4%, 163/317) than non-Caucasians (36.2%, 21/58).

Adverse events were reported for a higher proportion of subjects with no prior history of BOTOX® treatment for facial lines (50.3%,162/322) than for subjects with a history of previous treatment (41.2%, 21/51).

There were a few clinically relevant changes from baseline for laboratory variables. For ALT, AST, bicarbonate, triglycerides, urea nitrogen, basophils, and neutrophils, a higher proportion of subjects shifted from normal to high after treatment than from normal to low. For alkaline phosphatase, calcium, total bilirubin, RBC, and MCV, a higher proportion of subjects shifted from normal to low after treatment than from normal to high. However, for glucose and lymphocytes, the shifts were similar. Blood samples were not taken under fasting conditions. Individual subjects with possible meaningful changes were:

- Subject 2137-D10 was a 42 year old female who had a baseline hemoglobin of 12.4 at the beginning of the preceding double-blind study, was treated with BOTOX®, had an exit hemoglobin of 13.4 and had an exit hemoglobin in this study of 10.9.
- Subject 3160-V57 was a 52-year-old female treated in the preceding double-blind study with BOTOX® and had a baseline ALT of 41, a Day 120 ALT of 29 and an exit ALT from this study of 167.
- Subject 3187-P07 was a 39-year-old female treated with placebo in the preceding trial with normal baseline ALT and AST values. Day 120 ALT was 55 and AST was 191.
- Subject 3157-608 was a 40-year-old female treated in the preceding study with BOTOX® with normal baseline ALT and AST that on Day 120 were 116 and 174.
- Subject 1938-X02 was a 50-year-old female treated with BOTOX® in the preceding trial with mildly elevated AST and alkaline phosphatase at baseline.
- Subject 1938-X07 was a 50-year-old male treated in the preceding study with BOTOX® who had a slightly elevated alkaline phosphatase at baseline.
- Subject 3159-Y03 was a 54-year-old male treated with placebo in the preceding trial that had worsening of his hypertriglyceridemia.
- Subject 1978-M58 was a 62-year-old female on a diuretic treated in the preceding trial with placebo that had an arrhythmia and hypokalemia approximately 90 days after BOTOX® treatment.
- Subject 2941-K10 was a 37-year-old female treated in the preceding trial with BOTOX® who was discovered to have low hemoglobin at baseline during this study with the repeat results being similar. She was lost to follow-up after Day 210 and no further labs were drawn.

- Subject 0093-B03 was a 42-year-old female treated in the preceding trial with placebo and was noted on exit labs during this study to have a low hemoglobin and low alkaline phosphatase.
- Subject 3187-P12 was a 44-year-old male treated in the preceding trial with placebo and discovered prior to his second BOTOX® dose to have a slightly elevated ALT and AST, which remained high at Day 240 exit.
- Subject 3155-208 was a 24-year-old male treated in the preceding trial with placebo and was found at baseline during this study to have elevated triglycerides and slightly elevated AST and ALT. Repeat labs were unremarkable.

The baseline mean heart rate was 71.9 beats per minute. The mean baseline systolic pressure was 117.4 and the diastolic pressure was 74.1. There were no clinically relevant changes from baseline for heart rate or blood pressure.

241 subjects had evaluable antibody analysis results for treatment cycle 1.

- 216 subjects (89.6%) were negative at both the pretreatment and the posttreatment timepoints for treatment cycle 1.

- 21 subjects (8.7%) were inconclusive at either the pretreatment or the posttreatment timepoint for treatment cycle 1.
  - 9 subjects had been treated with BOTOX® and were negative at baseline but inconclusive at Day 120. All responded to BOTOX® except subject 2934-J11.
  - 12 subjects were inconclusive at baseline. 6 had been treated with BOTOX® and 6 with placebo. All responded to BOTOX® in treatment cycle 1 except subjects 3161-109, 2172-862, and 2172-861.

- 4 subjects (1.7%) were positive at either pretreatment or posttreatment timepoints for treatment cycle 1.
  - 2 subjects were positive at baseline and negative at Day 120. One had been treated with BOTOX® and one with placebo. Both responded to BOTOX® in treatment cycle 1.
  - 2 subjects were negative at baseline and positive at Day 120. One had been treated with BOTOX® and one with placebo. Both responded to BOTOX® in treatment cycle 1.

184 subjects had evaluable antibody analysis results for treatment cycle 2.

- 166 subjects (90.2%) were negative at both pretreatment and posttreatment timepoints for treatment cycle 2.

- 17 subjects (9.2%) were inconclusive at either timepoint.
  - 8 subjects were negative at Day 120 and inconclusive at Day 240. 6 had been treated with BOTOX® and 2 with placebo. All responded to BOTOX® in treatment cycle 2 except subject 3187-P59.
  - 8 subjects were inconclusive at Day 120 and negative at Day 240. All had been treated with BOTOX®. All responded to BOTOX® in treatment cycle 2 except subject 2934-J11.
  - 1 subject was positive at Day 120 and inconclusive at Day 240 and had been treated with placebo. This subject responded to BOTOX® in treatment cycle 2.

- 2 subjects (1.1%) were positive at the pretreatment timepoint
  - 1 was positive at Day 120 and negative at Day 240 and was treated with BOTOX®. This subject responded to BOTOX® in treatment cycle 2.
  - 1 subject was positive at Day 120 and inconclusive at Day 240 and had been treated with placebo. This subject responded to BOTOX® in treatment cycle 2.

A total of 159 subjects received all three BOTOX® treatments and had analyzable antibody samples at Day 0 of the double-blind studies and day 240 of the open-label studies. None of these subjects had positive antibodies after three consecutive BOTOX® treatments.

**Reviewer's Comments and Conclusions on study:** This was a multicenter, open-label, non-comparative study where subjects received two additional treatments of BOTOX® at the same dose and procedure from the previous studies. The object of this study was to evaluate the safety of BOTOX® for the treatment of glabellar lines for a period of not less than 12 months. There were no significant safety issues identified in this study. There were no subjects who dropped out of the trial because of adverse events that appeared to be related to BOTOX®. There were no serious adverse events that appeared to be related to BOTOX® other than possibly one subject with a severe headache that resolved. There were abnormal laboratory values in some subjects, but most were not clinically significant. In the subjects whose laboratory work was clinically significant, an underlying pathology was discovered. There were no subjects who had positive antibody titers at the end of the three injection cycles, although a few had previous positive results.

Adverse events tended to decrease with each cycle of injections. This may have been due to the increasing experience of the investigators.

Efficacy was also monitored in this trial, although this was not part of the primary analyses. The number enrolled was dependent on the number of subjects available and willing to participate following completion of the [redacted] studies. Therefore, selection bias may have been a factor in the efficacy results. 156 eligible subjects did not enroll, 124 previously treated with BOTOX® and 32 previously treated with placebo. Efficacy appeared to be statistically significant and sustained throughout all three injection cycles. The proportion of subjects who responded in all 3 treatment cycles was >70% for all efficacy measurements at Day 30. Four subjects were nonresponders across all cycles. All were in the ≥ 65 years of age group. Two had baseline scores of severe and two had baseline scores of moderate. None of these subjects had positive antibody assay results.

**Overview of Efficacy-Across All Three Trials:**
A total of 501 subjects from all three trials received one treatment cycle of BOTOX®. A total of 362 subjects received two treatment cycles of BOTOX®. A total of 258 subjects received three treatment cycles of BOTOX®. For the subjects who received 3 BOTOX® treatments, the responder rates for all three efficacy variables increased over repeated treatment cycles.

For the pooled double-blind and open-label study data, the same analysis was applied to the responder scores for both co-primary efficacy variables. Analyses included number and percent of responders calculated by visit, over all visits within each treatment cycle, and over all treatment cycles. The statistical hypotheses were for comparisons between treatment cycles (120 days): cycle 1 vs. 2, cycle 1 vs. 3, and cycle 2 vs. 3. Paired test procedures were applied to test the hypothesis of no difference between the cycles compared with the alternative hypothesis that there was a difference. All tests were 2-sided and the result was considered statistically significant if $p \leq 0.05$.

Missing values were replaced at every visit for each treatment cycle in which the subject participated.

BOTOX® appears to have a longer duration of effect on appearance at rest than on appearance at maximum frown.

**Responder Rates of Glabellar Line Severity-Pooled from 010 and 023**

| | Investigator's Assessment at Maximum Frown % rated 0 or 1 | | Subject's Assessment % +2 or better | | Investigator's Assessment at Rest % rated 0 or 1 | |
|---|---|---|---|---|---|---|
| DAY | BOTOX® | Placebo | BOTOX® | Placebo | BOTOX® | Placebo |
| 7 | 73.8% | 6.1% | 82.5% | 9.1% | 68.3% | 24.5% |

| | | | | | | |
|---|---|---|---|---|---|---|
| | 299/405 | 8/132 | 334/405 | 12/132 | 110/161 | 12/49 |
| 120 | 25.3%<br>102/403 | 1.6%<br>2/128 | 39.0%<br>157/403 | 0.8%<br>1/128 | 59.0%<br>95/161 | 34.7%<br>17/49 |

Subgroup analyses for all three studies shows that the magnitude of the effect of BOTOX® for glabellar lines tended to be greater for younger (≤ 50 years) than for older subjects (≥ 50 years and ≥ 65 years), for females than for males, and for subjects with a moderate baseline score than for those with a severe baseline score. There were fifteen nonresponders across all treatment cycles by investigator's evaluation and there were 3 subjects judged as nonresponders across all treatment cycles by subject's evaluation. The majority of subjects who were nonresponders were in the ≥ 65 years age group and all but one had a rating of severe at baseline. None of these subjects had positive antibody assay results.

**Overview of Safety-Across All Three Trials**
A total of 501 subjects from all three trials received one treatment cycle of BOTOX®. A total of 362 subjects received two treatment cycles of BOTOX®. A total of 258 subjects received three treatment cycles of BOTOX®.

Adverse events of any causality were reported for 57.9% of BOTOX® treated subjects. The most frequently reported adverse events of any causality were headache (13.8%), respiratory infection (10.4%), flu syndrome (6.4%), blepharoptosis (4.6%), and nausea (4.0%).

No subject died during any of the three studies.

There were 19 serious adverse events noted in 12 subjects. All were considered to be unrelated to study medication.

| STUDY/ SUBJECT NUMBER | TREATMENT | SERIOUS AE | SEVERITY | RELATED |
|---|---|---|---|---|
| [ ] | BOTOX® | ovarian disorder | severe | unrelated |
| | BOTOX® | thrombophlebitis | severe | unrelated |
| | BOTOX® | colon cancer | severe | unrelated |
| | Placebo | perforated intestine | severe | unrelated |
| | BOTOX® | herniated disc | severe | unrelated |
| | BOTOX® | dyspnea/anxiety | moderate | unrelated |
| | BOTOX® | colitis/N/V/D | severe | unrelated |
| | BOTOX® | bone fracture | severe | unrelated |
| | BOTOX® | herniated disc | severe | unrelated |
| | BOTOX® | carcinoma breast | severe | unrelated |
| | BOTOX® | lymphadenopathy | severe | unrelated |
| [ ] | BOTOX® | urinary | severe | unrelated |

| | | | | |
|---|---|---|---|---|
| | | incontinence | | |

There were two severe events considered possibly related to BOTOX® treatment: elevated creatinine phosphokinase (1) and headache (1).

No subject in the double-blind studies discontinued due to an adverse event. Two subjects in the open-label study discontinued due to an adverse event. Both were considered unrelated to study medication.

- Breast cancer
- Pregnancy

There were 4 adverse events categorized as severe and reported for more than one subject: flu syndrome (2), back pain (2), migraine (2), and bone disorder (2).

**NUMBER OF SUBJECTS FROM ALL THREE TRIALS WHO RECEIVED BOTOX AND HAD TREATMENT RELATED ADVERSE EVENT (>1% OF TOTAL) n=501**

| | |
|---|---|
| Overall | 23.2% (116) |
| Headache | 8.6% (43) |
| Edema injection site | 2.2% (11) |
| Pain injection site | 1.8% (9) |
| Pain face | 1.8% (9) |
| Nausea | 1.2% (6) |
| Ecchymosis | 1.4% (7) |
| Erythema | 1.4% (7) |
| Blepharoptosis | 4.6% (23) |

The most frequently reported adverse events that were treatment related were headache and blepharoptosis.

The incidence of headache decreased from 11.8% of subjects in the first treatment cycle to 2.8% of subjects in the second cycle and 3.5% of subjects in the third cycle. All headaches were reported to be mild to moderate in severity except for one reported as severe.

Blepharoptosis decreased from 3.0% in the first cycle to 2.2% in the second cycle and 0.8% in the third cycle. Twenty-three subjects experienced ptosis. All subjects with ptosis were female and had received BOTOX®. 19 had no history of prior BOTOX® treatment and 4 had had prior treatment. Ptosis was unilateral for 20 subjects and bilateral for 3 subjects. 12/340 (3.5%) of cases were ≤ 50 years of age, 11/161 (6.8%) of cases were ≥51 years of age and 3/31 (9.7%) of cases were ≥65 years of age. Most cases of ptosis were considered mild, with an average duration of 27 days. 7 cases were considered moderate, with an average of 29 days. No cases were considered severe. The majority of reports (65%, 15/23) occurred after the first cycle.

There were 8 study sites that reported ptosis:

| | |
|---|---|
| 0093 | 6 cases |
| 2137 | 3 cases |
| 2940 | 3 cases |
| 3157 | 3 cases |
| 3161 | 2 cases |
| 3187 | 2 cases |
| 1996 | 1 case |
| 2934 | 1 case |
| 2941 | 1 case |
| 3158 | 1 case |

Ptosis is thought to result from the diffusion of BOTOX® through the orbital septum to the upper eyelid levator muscle and may be technique related.

Nausea decreased from 2.8% in the first cycle to 1.4% in the second cycle to 0.8% in the third cycle. Respiratory infection and flu remained relatively constant.

Subgroup analyses showed a lower incidence of adverse events among males (48.3%, 43/89) than females (60.0%, 247/412). Headache was reported by 4.5% (4/89) of males and 15.8% (65/412) of females. Blepharoptosis was reported in no males and 5.6% (23/412) of females.

Subgroup analyses showed a lower incidence of adverse events among non-Caucasian subjects (51.2%, 42/82) than Caucasian subjects (59.2%, 248/419). Headache was reported in 10 (12.2%) of non-Caucasians and 59 (14.1%) of Caucasians. Blepharoptosis was reported in 5 (6.1%) of non-Caucasians and 18 (4.3%) of Caucasians.

Subgroup analyses showed a lower incidence of adverse events among subjects with a history of BOTOX® treatment for facial lines (43.7%, 31/71) than subjects who had no history of BOTOX® treatment for facial lines (60.2%, 259/430). Headache was reported for 6 subjects (8.5%) with prior treatment and 63 subjects (14.7%) with no prior treatment. Blepharoptosis was reported for 3 subjects (4.2%) with prior treatment and 20 subjects (4.7%) with no prior treatment.

Adverse events were reported for 59.1% (201/340) of subjects ≤ 50 years, 55.3% (89/161) of subjects ≥ 50 years, and 61.3% (19/31) subjects ≥ 65 years of age. Headache was reported for 14.7% (50/340) of subjects ≤ 50 years, 11.8% (19/161) of subjects ≥ 50 years, and 9.7% (3/31) subjects ≥ 65 years of age. Blepharoptosis was reported for 3.5% (12/340) of subjects ≤ 50 years, 6.8% (11/161) of subjects ≥ 50 years, and 6.5% (2/31) subjects ≥ 65 years of age.

There were statistically significant changes for many laboratory variables in all three studies. However, the changes were small and not clinically significant. There were 10 individual narratives for laboratory values, 1 subject in study 010, 1 subject in study [redacted] and 8 subjects in study [redacted]

- Subject 3159-Y13 in study [redacted] had an abnormally high WBC value on Day 0, received BOTOX® treatment, and was discovered to have chronic myelogenous leukemia.
- Subject1938-X02 in study [redacted] had an increased alkaline phosphatase and AST phosphatase but repeat values were normal.
- Subject 1938-X07 in study [redacted] had an increased alkaline phosphatase but repeat values were normal.

There did not appear to be any increased incidence of adverse events with prolonged use of BOTOX®.

There is the potential for allergic reactions to this product as it is a protein. However, none occurred during these studies.

*Antibody Assay*
159 subjects had three BOTOX® treatments and had analyzable antibody samples at Day 0 of the initial double-blind trial and Day 240 of the open-label study.

- None of these subjects were antibody positive after three treatments.
- 7 subjects who were negative at baseline had inconclusive samples after three treatments.
- 8 subjects had inconclusive samples at baseline and negative samples after three treatments.
- 3 subjects had positive samples at baseline and negative samples after three treatments.

No special studies or analyses were performed to evaluate drug-drug interactions with BOTOX®. Multiple medications were used during the clinical trials, most commonly anilides, selective serotonin reuptake inhibitors, multivitamins, fixed combinations of progestogens and estrogens, and propionic acid derivatives.

There were no instances of overdose in the three clinical trials. However, Allergan has received reports of mistaken injections by physicians in clinical practice using BOTOX® for cosmetic treatment. If an overdose were to occur that could produce a life-threatening emergency, there is a botulism antitoxin, which is available from the Centers for Disease Control. However, if the adverse event is already established, the antitoxin cannot reverse the effect. It also must be given within 21 hours of the BOTOX® injection and cannot be given to subjects allergic to horse serum. According to Allergan, the antitoxin has only been administered once since the marketing of BOTOX®.

**Overview of All Efficacy Data:**

It is important for the health care provider to thoroughly evaluate a patient who may desire BOTOX® for cosmetic use and to assess the type of facial skin changes that are present. Patients should be assessed both at rest and at maximum frown. There should be the ability to substantially lessen glabellar lines by physically spreading them apart. The most successful cases for BOTOX® treatment of glabellar lines include subjects who frown inappropriately or have hyperactive muscles that control the frown. When used alone, BOTOX® does not have a significant affect on wrinkles caused by aging and sun damage. Therefore, it is best for those patients who are 50 years of age or younger.

Although the total patient numbers are small (32/537 subjects), in these three studies as well as published literature reports, the data is even less compelling for subjects age 65 years of age and older. The %response rate in the BOTOX® group is numerically higher than that in the placebo group in one study ——— 56% vs. 0%), but is lower in the other (023, 29% vs. 40%). Combining the data together from these identical trials shows that, for the investigator's assessment endpoint at day 30, 9/23 (39%) of subjects were responders in the BOTOX® group, compared to 2/9 (22%) in the placebo group. Although the %response rate is numerically higher in the BOTOX® group, this difference is neither statistically different (p=0.228) nor exceeds the pre-specified 30-percentage-point difference required by the definition of clinically significant.

For the subject's assessment endpoint, there are numerical differences between the two groups in favor of BOTOX® in both studies. The analysis based on the combined data set did reveal that the difference between the two groups in the subject's assessment endpoint is both statistically and clinically significant ($p \leq 0.036$) except at day 120.

Thus, it seems that the efficacy evidence for those who are 65 years old or older may not be strong enough to draw any firm conclusions.

Although the number of male subjects is relatively small, there are statistically significant differences in both investigator's and subject's assessment endpoints between genders in subjects who received BOTOX®. For the responder rate investigator's endpoint in protocol — it was 87% for females and 67% for males (p= 0.0129). For the responder rate subject's endpoint in protocol ——it was 93% for females and 73% for males (p=0.0033). For the responder rate investigator's endpoint in protocol —, it was 83% for females and 54% for males (p= 0.0003). For the responder rate subject's endpoint in protocol — it was 93% for females and 71% for males (p=0.0003).

Thus, although the %response rate is numerically higher in the male BOTOX® group compared to the male placebo group and exceeds the pre-specified 30-percentage-point difference required by the definition of clinically significant, further studies may be warranted to ascertain the etiology of the efficacy gender difference and the possible need for adjustment in treatment.

**Overview of All Safety Data:**
There has been extensive use of BOTOX® for the treatment of strabismus and blepharospasm as well as cervical dystonia. Although rare, there have been reports of death, sometimes associated with dysphagia, pneumonia, or other significant debility, after treatment with botulinum toxin. Patients with smaller neck muscle mass and patients who require bilateral injections into the sternocleidomastoid muscle have been reported to be at greater risk for dysphagia when being treated for cervical dystonia. Patients who receive injections into the levator scapulae may have an increased risk of upper respiratory infection and dysphagia.

Patients with blepharospasm can develop reduced blinking from BOTOX® injection of the orbicularis muscle that can lead to corneal exposure, persistent epithelial defect, and corneal ulceration. Postmarketing safety reports since 1988 have shown ptosis occurring in approximately 16% of patients. During the administration of BOTOX® for the treatment of strabismus, there have been reports of retrobulbar hemorrhages sufficient to compromise retinal circulation from needle penetration into the orbit. There has been one reported occurrence of transient diplopia with cosmetic use of BOTOX®.

Patients with neuromuscular disorders may be at increased risk of clinically significant systemic effects from typical doses of BOTOX®. The effects of BOTOX® therapy may be increased with the use of aminoglycoside antibiotics or with other drugs that interfere with neuromuscular transmission.

The use of BOTOX® for glabellar facial lines appears to be well tolerated with minimal adverse events recorded. It is important for the health care provider to thoroughly understand the anatomy of the facial muscles and other underlying structures. Blepharoptosis should be minimized by proper injections at the correct locations and depth. The relatively high incidence of headache in both active and placebo subjects may also be related to technique; therefore, it is important that the periosteum be avoided when injecting.

In the open-label safety study adverse events were reported for a higher proportion of subjects ≥ 65 years of age (65.2%, 15/23) than for subjects ≤ 50 years of age and those ≥ 51 years of age. Age: P=0.133 for >=65 (15/23) vs. <65 (168/340). Although one can argue that subjects of increasing age tend to have more health problems in general, the risk versus benefit assessment in this age group must be more carefully evaluated.

Adverse events were reported for a higher proportion of females than males, 51.4% (162/315) compared with 36.2% (21/58). No male subject reported headache or blepharoptosis. Gender: p=0.0448 for female (162/315) vs. male (21/58).

Adverse events were reported for a higher proportion of Caucasians (51.4%, 163/317) than non-Caucasians (36.2%, 21/58). Race: p=0.0417 for Caucasians (163/317) vs. others (20/56).

Although the differences in gender and race are statistically significant at the conventional level of 0.05, it should be pointed out that they are no longer significant if adjusting for the overall type I error rate for multiple comparisons. Thus, no firm conclusions can be made.

*Post-marketing Experience:*
BOTOX® was first marketed in 1990. Allergan reports that there have been 1233 adverse events in 567 patients reported as of August 2000. The most commonly reported local adverse events in subjects treated for cosmetic indications (not necessarily just glabellar lines) were:

- Blepharoptosis 168 subjects
- Injection site pain or burning 130 subjects
- Injection site edema 38 subjects
- Eyelid edema 36 subjects
- Muscular weakness 24 subjects
- Facial paralysis 21 subjects
- Facial edema 20 subjects
- Visual disturbance 20 subjects

Other adverse events of interest:

- Erythema 14 subjects
- Pruritus 12 subjects
- Diplopia 11 subjects
- Rash 11 subjects
- Twitching 7 subjects
- Urticaria 7 subjects

The most commonly reported systemic adverse events were:

- Headache 78 subjects
- Dizziness 27 subjects

There have been seven reports of serious adverse events:

- Decreased hearing
- Anaphylactic reaction
- Myasthenia, urinary incontinence, generalized weakness, arthralgias
- Ear noises, tongue edema, slurred speech, dysphagia, localized numbness
- Migraine, blurry vision, central retinal vein occlusion
- Eyelid edema, rhinitis, pruritus, worsening visual acuity, glaucoma
- Vertigo, dizziness, nystagmus, localized numbness, headache

There has been one published report of diplopia that lasted three weeks in the literature as of December 2000. The subjects in the trial received injections to

other facial muscles in the forehead and orbital area in addition to the procerus and corrugator muscles.

The FDA Adverse Event Reporting System has cosmetic use of BOTOX® accounting for 106 of 251 (42%) adverse reports for BOTOX® between 11/1997 and 1/2001. The cosmetic use of BOTOX® does involve more reports of certain adverse events, compared to other therapeutic uses. These events are ptosis (28% vs. 10%), headache (16% vs. 3%), injection site reactions (15% vs. 3%), ecchymosis (7% vs. 1%), and facial edema (5% vs. 2%).

**Human Reproduction Data**

The final study reports for the completed reproductive toxicity studies using BOTOX manufactured from bulk neurotoxin batch [redacted] (report numbers [redacted]) were submitted October 2000. The Review Team reviewed these studies with consult from Dr. Marion Gruber. The study reports, completed in 1998, were actually conducted at the request of and under a protocol design directed by the Japanese Ministry of Health. Allergan gave no rationale for this request by the Japanese Ministry of Health, (i.e., whether it was based on specific concerns regarding the product's safety for a particular indication).

The studies involved 2 animal species (rat/rabbit), daily dosing and evaluation of typical developmental toxicity endpoints. However, it was not specified if the dosage selected was based on a specific clinical dose and if the clinical dose schedule differed significantly from the one used in the developmental study.

In rabbits, there was significant maternal toxicity of the test article when administered at doses of ≥ 0.25 units/kg/day. Fetal body weights were significantly reduced in the 0.5 units/kg/day dosage group litters. This dose also caused delays in fetal ossification, a significant increased number of litters and fetuses with non-ossified pubic bones and decreases in the average number of ossification sites of the hyoid, caudal vertebrae, metacarpals and metatarsals. At doses of 0.5 units/kg/day two does were found dead, three aborted and one delivered. These events were related to test article administration.

In rats, body weight gains were significantly reduced in animals receiving 0.5, 1, 4 and 8 units/kg/days. There was a significant reduction in mean fetal body weights of the group receiving 4 and 8 units/kg/day. The 4 and 8 units/kg/day dosages of the test article caused delays in fetal ossification.

The maternal NOAEL in rabbits was determined to be 0.125 units/kg/day and less than 0.5 units/kg/day in rats.

The studies conducted and endpoints evaluated (exception corpora lutea counts) did not specifically address potential effects on fertility in females or males.

Internal discussions have involved determining if the sponsor should repeat additional reproductive toxicity studies to evaluate if the maternal/fetal toxicity observed in the studies performed was due to the dose rather than to the dosing schedule applied

Allergan was informed that the above preclinical study reports did not allow an estimation of risk of botulinum toxin type A to reproduction when administered to humans for any specific indication. The Review Team referred Allergan to the ICH guideline entitled "Detection of toxicity to reproduction for medicinal products" (S5A) emphasizing that any preclinical testing strategy should be determined by the anticipated drug use (Section 1.1). Thus, in order to assess the potential risk of botulinum toxin type A to reproduction, it was critical for the design of the preclinical study (with regard to dose, route and frequency of administration) to be based on the intended human use.

The Review Team further stated that any requirement for preclinical safety evaluation(s) set forth by FDA for any biological product takes into consideration the potential risk versus benefit of the product in the specific target population. Consequently, any requests to perform a preclinical developmental toxicity study to support the safety of a product would depend on the clinical indication and the target population.

The Review Team recommended that additional animal studies be performed, using both rat and rabbit species, including injection via the IV as well as the IM route. The doses administered should appropriately bracket the range of potential clinical dose levels (based on body weight estimates). The dosing schedule should mimic the intended clinical schedule. Ideally, several groups of pregnant animals should be dosed only at defined intervals during gestation that represent crucial points of organogenesis, in an attempt to determine whether botulinum toxin type A is a selective developmental toxicant. The clinical indication that the developmental toxicity study is intended to support should be specified.

Allergan has since developed protocols that CBER determined to be appropriate and reasonable and the studies are currently in progress. The final study reports will be submitted to CBER at a later date.

**Conclusions:** The use of injectable BOTOX® for the temporary improvement of hyperfunctional glabellar facial lines has the advantage of being a nonsurgical, reversible procedure. Sufficient data has been submitted to support the safety and effectiveness of BOTOX® for the temporary improvement of the appearance of moderate to severe glabellar lines when subjects are adequately pre-evaluated and the product is used as directed.

**Recommendations:**

**Approvals (reviewer comments before Amendment A):** Sufficient data has been submitted to support the safety and effectiveness of BOTOX® for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age. The submitted studies are deemed inadequate to proceed with marketing approval for subjects > 65 years of age.

There are deficiencies in Allergan's proposed labeling for this indication. If these deficiencies are addressed and Allergan fulfills the commitment to complete reproductive toxicity testing studies and submit the corresponding study report to CBER within an agreed upon time, then I recommend approval of this Supplement to the License Application, for Botulinum Toxin Type A to include the indication of "for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult subjects ≤ 65 years".

**Phase 4 Studies:** There are no required studies concurrent with this approval.

**Labeling:**

The Review team has also determined that there are deficiencies in Allergan's proposed labeling for this indication. The proposed labeling submitted on January 16, 2001 is deficient with regards to the sections entitled Clinical Studies, Indications and Usage, Contraindications, Warnings, Precautions, Adverse Reactions, Overdosage, and Dosage and Administration. Please refer to the attached document for specific comments and revisions to be made to the proposed labeling.

**Amendment A revisions:** As stated earlier, on November 23, 2001, Allergan submitted an amendment to this supplement in response to the Agency's letter of November 15, 2001 which contained specific comments and revisions to be made to the proposed labeling. Amendment A contained a revision of the

original supplement submission to Section 8.9 "Integrated Summary of Safety Information" (ISS). In preparing their response to the Agency's requests, Allergan discovered that the incidence tables of the Adverse Events were inaccurate. These tables included events of placebo-treated patients from the two Phase III double-blind studies and excluded some BOTOX® treated patients from the open-label extension study from the analyses for the first treatment cycle of BOTOX®. None of the clinical study reports regarding effectiveness data were impacted.

The updated data has been incorporated into this review. The changes to Allergan's data concerning the Integrated Summary of Safety Information do not impact on the final recommendations and conclusions of this reviewer. Sufficient data has been submitted to support the safety and effectiveness of BOTOX® for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult patients ≤ 65 years of age.

After review of Amendment A submitted November 23, 2001, further revisions to the label need to be addressed. Comments are incorporated into Attachment 2.

If these labeling deficiencies are addressed and Allergan fulfills the commitment to complete reproductive toxicity testing studies and submit the corresponding study report to CBER within an agreed upon time, then I recommend approval of this Supplement to the License Application for Botulinum Toxin Type A to include the indication of "for the temporary improvement in the appearance of moderate to severe glabellar lines associated with corrugator and/or procerus muscle activity in adult subjects ≤ 65 years".