<table>
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<th>Name of Company:</th>
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<tbody>
<tr>
<td>Allergan</td>
<td>BOTOX® Purified Neurotoxin Complex</td>
<td>Botulinum Toxin Type A</td>
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</tbody>
</table>

**Number and Title of Study:**
191622-066: A Multicenter, Double-Blind, Randomized, Placebo-Controlled, Parallel Study of the Safety and Efficacy of BOTOX (Botulinum Toxin Type A) Purified Neurotoxin Complex in Subjects with Postherpetic Neuralgia (PHN)

**Study Center(s):** 21 centers in the United States and 3 centers in Canada

**Publication (reference):** None at the time of the clinical study report

**Studied Period:**
- Study Initiation Date (First Patient Enrolled): 06 June 2004
- Study Completion Date (Last Patient Completed): 18 June 2005

**Phase of Development:** 2

**Objectives:**
To evaluate the safety and efficacy of BOTOX compared with placebo in the treatment of PHN.

**Methodology:**
- **Structure:** Multicenter, double-blind, placebo-controlled, parallel-group study
- **Randomization:** Randomized by stratum, based on PHN with or without trigeminal involvement, to receive BOTOX or placebo in a 1:1 ratio
- **Visit Schedule:** Day -30, day -7, day 0 (randomization and injection), and weeks 1 (telephone call only), 2, 4, 8, and 12 (exit)

**Number of Patients (Planned and Analyzed):**
Planned enrollment was 130 patients to have 115 completed patients. Actual enrollment was 117 patients (60 BOTOX, 57 placebo).

**Diagnosis and Main Criteria for Inclusion:**
- **Diagnosis:** PHN defined as pain present for > 3 months after healing of herpes zoster skin rash affecting the trigeminal, lower cervical, thoracic, lumbar, or sacral regions
- **Key Inclusion Criteria:** Patient required ≤ 6 U/kg (up to a maximum of 200 U) of BOTOX to treat areas of pain and allodynia; chronic pain medications (if any) at stable doses for ≥ 3 months; based on diary information collected during the baseline week (days -7 to 0), completed at least 4 diary entries and had average daily pain rating ≥ 4 on 11-point pain rating scale.
- **Key Exclusion Criteria:** Active herpes zoster, ophthalmic zoster, or Ramsay-Hunt syndrome; any medical condition that may have put the patient at increased risk with exposure to BOTOX or any other disorder that might have interfered with neuromuscular function; previous neurolytic or neurosurgical therapy for PHN; concurrent treatment with antiviral medications (for herpes zoster), acupuncture, steroids, opioids, tricyclic antidepressants, anticonvulsants (other than gabapentin), muscle relaxants, or topical analgesic agents; anticipated alteration of chronic stable (ie, at least 3 months) therapy with agents that could have had a substantial effect on pain (eg, gabapentin), or introduction of such agents during the study; anticipated need for transcutaneous electrical nerve stimulation (TENS) or acupuncture treatment during the study; previous exposure to or anticipated need for treatment with botulinum toxin of any serotype for any reason during the study (other than study treatment); requirement for > 200 U of study medication to treat all areas of PHN-related pain and allodynia.
Test Product, Dose and Mode of Administration:
BOTOX was reconstituted with 0.9% sterile nonpreserved saline and patients had 1 treatment session of 2 to 80 intradermal injections (5 U to 200 U) depending on the size of the areas of pain and allodynia. The total dose of BOTOX was not to exceed 6 U/kg (up to a maximum of 200 U).

Reference Therapy, Dose and Mode of Administration:
Placebo was reconstituted with 0.9% sterile nonpreserved saline and patients had 1 treatment session of 2 to 80 intradermal injections depending on the size of the areas of pain and allodynia.

Criteria for Evaluation:
Efficacy: The primary measure was pain score (11-point scale) recorded daily by the patient in a diary. Secondary measures included daily sleep interference score, Short Form McGill Pain Questionnaire (SF-MPQ), Short Form Brief Pain Inventory (SF-BPI), Medical Outcomes Study (MOS) Sleep Scale, Profile of Mood States (POMS) Brief Form, Postherpetic Pain and Neuralgia Treatment Satisfaction Questionnaire, Subject Global Impression of Change (SGIC), Clinical Global Impression of Change (CGIC), reduction in area of pain and allodynia, and reduction in maximum evoked pain score.

Safety: Safety measures were adverse events, physical examinations, and clinical laboratory evaluations, including pregnancy tests.

Statistical Methods:
The safety population included all patients who received study medication; the modified intent-to-treat (mITT) population included all randomized patients who received treatment and had any follow-up data.

All statistical testing was 2-sided and performed without adjustment for testing multiple measures. Statistical significance was to be declared if p < 0.10 for treatment comparisons for the final analysis, tests of treatment-by-center interaction, tests of treatment-by-area treated (with or without trigeminal involvement), and tests of treatment-by-baseline interaction, and if p < 0.01 for tests of normality and homogeneity of variance.

The incidence of all adverse events and treatment-related adverse events were compared between the treatment groups using Fisher's exact test.

Summary – Conclusions:
A total of 117 patients were randomized (safety population) and 116 were treated (mITT population, 60 BOTOX, 56 placebo); 102 patients completed the study (54 BOTOX, 48 placebo). There were no statistically significant differences between the treatment groups in demographic or baseline characteristics. In the mITT population, age ranged from 23 to 87 years, with a mean of 69.2 years. The proportion of males was 53.4%, 91.4% of patients were Caucasian, and 81.0% had no trigeminal involvement.
Summary – Conclusions (continued):

Efficacy:
In the mITT population, both the BOTOX and placebo groups showed the same improvement from baseline in average daily pain score at week 4, the primary efficacy endpoint.

<table>
<thead>
<tr>
<th>Modified Intent-to-Treat Population</th>
<th>BOTOX (N = 60)</th>
<th>Placebo (N = 56)</th>
<th>Difference (90% CI)</th>
<th>P-valuea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline, n</td>
<td>57</td>
<td>56</td>
<td>-0.2</td>
<td>0.434</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>6.1 (1.48)</td>
<td>6.4 (1.59)</td>
<td>(-0.71, 0.25)</td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>6.0 (3.5 to 10.0)</td>
<td>6.1 (2.6 to 9.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 4 change, n</td>
<td>54</td>
<td>56</td>
<td>0</td>
<td>0.917</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>-1.2 (1.91)</td>
<td>-1.2 (1.64)</td>
<td>(-0.6, 0.53)</td>
<td></td>
</tr>
<tr>
<td>Median (Range)</td>
<td>-0.9 (-5.9 to 2.8)</td>
<td>-1.1 (-5.1 to 1.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a P-value for baseline is from 2-way analysis of variance (ANOVA) with treatment and disease characteristics in the model. P-value for the follow-up visit is from analysis of covariance with treatment and disease characteristics in the model, and baseline value as covariate.
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**Summary – Conclusions (continued):**

**Efficacy (continued):**

In the mITT population, there were no statistically significant differences between treatment groups in average daily pain scores at weeks 2, 8, and 12; maximum evoked pain score, surface area of pain, surface area of allodynia, SF-MPQ scores, POMS scores, SGIC, and CGIC. On the SF-BPI, the BOTOX group had a significantly lower proportion of patients with pain other than everyday kinds of pain at week 12 compared with the placebo group (43.4% vs. 66.7%, p = 0.018), and showed significantly greater improvement on the pain interference score at week 2 (-1.0 vs. -0.4, p = 0.060). On the MOS Sleep Scale, the BOTOX group showed significantly greater improvement than the placebo group in snoring at week 8 (-1.0 vs. -2.0, p = 0.018) and significantly less improvement in sleep shortness of breath or headache at week 8 (3.9 vs. -3.5, p = 0.056). On the Postherpetic Pain and Neuralgia Treatment Satisfaction Questionnaire, a significantly lower proportion of patients in the BOTOX group compared with the placebo group had at least a 1-point improvement from baseline in their assessment of whether the benefits of the current medication outweighed the side effects, willingness to continue using the current medication in the future, and whether the current medication worked better than other medications used. The mean dose per area of pain was similar in both the BOTOX and placebo groups (1.3 ± 0.85 U/cm² and 1.1 ± 0.21 U/cm² respectively).

**Safety:**

Adverse events were reported for a significantly higher proportion of patients in the BOTOX group than in the placebo group, 56.7% (34/60) compared with 40.4% (23/57). Treatment-related adverse events were reported for 11.7% (7/60) of patients in the BOTOX group and 8.8% (5/57) of patients in the placebo group; the between-group difference was not significant (p = 0.763). The most frequently reported adverse events in the BOTOX group were muscular weakness (4 patients), back pain, headache, upper respiratory tract infection, and urinary tract infection (3 patients each). The most frequently reported adverse events in the placebo group were diarrhea, abdominal pain, chest discomfort, injection site hemorrhage, back pain, muscle spasms, headache, rash, and pruritus (2 patients each).

One patient had a serious adverse event (urinary tract infection in the BOTOX group), which was considered not related to treatment by the investigator. One patient died prior to randomization and therefore received no study medication.

**Conclusion:**

The present study does not support that BOTOX is beneficial in the treatment of PHN. Both the Botox and placebo treatment groups showed a similar improvement from baseline on the primary and secondary outcome measures. Botox was well tolerated in this study.