Although onabotulinum toxin A (Botox®, Allergan) was initially approved for cervical dystonia, severe primary axillary hyperhidrosis, strabismus, and blephrospam, it was widely used outside its label indications, prior to FDA approval in 2002 (Botox Cosmetic®, Allergan) 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 or younger. Without any other neurotoxins available, Botox had the corner on the US market place for many years, during which time physicians gained great familiarity with it in a variety of settings.

In light of the US arrival of Dysport™, (abobotulinum toxin type A, Medicis), the second botulinum toxin product approved for cosmetic indications in the US, physicians now have more flexibility to address glabellar lines, as well as more possibilities for off-label uses of botulinum products. Clinicians should therefore be inclined to examine the findings from the clinical trials in order to gain a greater understanding of botulinum toxins. This article will provide a comprehensive overview of the Dysport pivotal trials, indications for usage, and critical prescribing information.

Analysis of Clinical Trials

Three clinical trials were crucial to FDA-approval of Dysport, (GL-1, GL-2, and GL-3). They studied the safety and efficacy of a single 50-unit dose of the BoNT-A, the long-term safety effects of retreatment, as well as the effect of variable dose (ranging from 50-80 units) injections on the appearance of glabellar lines.

GL-1. GL-1 was a multi-center, phase III, randomized, parallel-group, placebo-controlled, double-blind study that focused on the safety and efficacy of 50 units of Dysport. Its primary objective was to evaluate the efficacy of a single treatment of Dysport (50 units) compared with placebo in the treatment of mild to moderate glabellar lines. Secondary endpoints included Investigator’s and the Patient’s assessment 30 days post-treatment. It assessed the onset and duration of treatment and also evaluated the effect of age, gender, race, severity of glabellar lines at baseline and study center on product efficacy via subgroup analyses.

One hundred fifty-eight patients were randomized in a 2:1 ratio to receive Dysport (105) or placebo (53), respectively. Injections were given in 10-unit aliquots to five sites in the glabellar area. Importantly, only 143 subjects completed the study. Investigators and subject assessments were performed at every study visit (screening/day 0, 14, 30, 60, 90, 120, 150, and 180), and subjects completed a diary on days one through seven to determine onset of effect. Adverse effects and concomitant medications were reviewed and updated at every visit, and an additional safety assessment was performed via phone on day seven.

Patients used a four-point glabellar line severity score (GLSS) to evaluate their improvement (inde-
pendently of the investigator), with 0 representing no wrinkles, 1 representing mild, 2 representing moderate, and 3 representing severe wrinkles. Additionally, investigators performed a live assessment of the severity of the subjects’ glabellar lines at maximal frown and compared their appearance using the same four-point photographic scale. To maintain blinding, photographic assessment was the only method of evaluation at Day 14.

Responders were categorized as having a severity grade of 2 to 3 at baseline that improved to 0 to 1 at Day 30. The primary efficacy endpoint was the severity grade at day 30, but additional evaluations of improvement were taken at the other time points (day 14 to 180), as well. At day 30, the proportion of responders in the Dysport group compared to the placebo group was significantly higher (89 percent vs. 7.5 percent, p<0.001) for both investigator and subject assessments.

Gender, race, severity at baseline, and study site had no significant effect on the efficacy of Dysport. For those who had moderate to severe glabellar lines at rest, the proportion that responded to treatment was significantly higher than compared to placebo (64 percent vs. 11 percent at day 30, p<0.001), based on investigator assessment at rest. Although patients 50 years of age and older had less of a response than younger participants, their response was still greater when compared to placebo (53 percent vs. 0 percent, p=0.008).

The median time to onset was three days in the Dysport group as compared to 15 days in the placebo group. By day 14 the total response was 88 percent Dysport and 25 percent placebo (p<0.001).

The median duration of response in the Dysport group was 85 days, as measured by both investigator and subject assessments; 0 days for the placebo group. No subject in the placebo group had a response duration of greater than 15 days.

The number of treatment-emergent adverse events (TEAEs) was similar among the two groups (47 percent Dysport vs. 40 percent placebo). The most common were blepharospasm, eyelid ptosis, vomiting, injection site reaction and pain, nasopharyngitis, influenza, and headache, and all were mild to moderate in severity and considered unlikely or unrelated to treatment. The number of severe TEAEs was relatively low, but slightly higher in the Dysport group (nine percent vs. four percent).

Two patients (both in Dysport group) experienced a total of six serious adverse events (SAEs), which included vomiting, malignant melanoma, squamous cell carcinoma of the skin, excision of a skin neoplasm, and parotidectomy. None of the SAEs were thought to be treatment-related. The majority of ocular adverse events occurred before day 30 (6.7 percent Dysport vs. 5.7 percent placebo), and were thought to be possibly or probably-related to treatment.

GL-2. The GL-2 was also a phase 3, randomized, double-blind, placebo-controlled study that assessed the efficacy and safety of Dysport but it focused on the re-treatment of glabellar lines following open-

<table>
<thead>
<tr>
<th>Table 1. Treatment-Emergent Adverse Events</th>
</tr>
</thead>
<tbody>
<tr>
<td>System Organ Class</td>
</tr>
<tr>
<td>Preferred Term</td>
</tr>
<tr>
<td>Number of patients with any treatment-emergent adverse event</td>
</tr>
<tr>
<td>Eye disorders</td>
</tr>
<tr>
<td>Blepharospasm</td>
</tr>
<tr>
<td>Eyelid ptosis</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
</tr>
<tr>
<td>Vomiting</td>
</tr>
<tr>
<td>General disorder and administration site conditions</td>
</tr>
<tr>
<td>Injection site reaction</td>
</tr>
<tr>
<td>Injection site pain</td>
</tr>
<tr>
<td>Infections and infestations</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
</tr>
<tr>
<td>Influenza</td>
</tr>
<tr>
<td>Nervous systems disorders</td>
</tr>
<tr>
<td>Headache</td>
</tr>
</tbody>
</table>

Source: Clinical Trial Y-97-52120-719 © 2009 Medicis Pharmaceuticals Corporation
Number and percent of patients experiencing treatment-emergent adverse events (Reported by at least 3% of patients)
label treatment. Its objectives were to evaluate the efficacy of a 50-unit dose of Dysport after repeat injections in the treatment of moderate to severe glabellar lines and assess the safety of repeat treatment with Dysport.

A total of 311 subjects received up to four repeat treatments of Dysport (50 units) over 23 months. There were two phases to this study: 1.) Open-label and 2.) Double-blind. In the Open-Label Phase, there were two treatment cycles (A1 and A2). After the initial screening, all 311 subjects were treated and followed monthly until day 120 (Cycle A1). The subjects were then assessed and reassigned to Group 1 (190) or 2 (94) based on the GLSS. Group 1 was then retreated with Dysport (Cycle A2), while Group 2 had no further treatment until Cycle B. The minimum interval between Cycle A2 and re-treatment with Dysport in Cycle B was 85 days.

In the Double-Blind Phase, there were also two treatment cycles (B and C). Two hundred fifty-five patients were randomized in Cycle B. Of those, 142 eligible patients were re-randomized 1:1 in Cycle C (71 Dysport, 71 placebo). (Fig. 3) If re-treatment was not required then the patient was not randomized into the treatment phase. The primary efficacy endpoints were assessed at Day 30 of Cycle C.

Investigator and patient assessments with the GLSS occurred at each visit:
  * Cycle B - Day 0, day 14, day 30, and then monthly until retreatment, study exit, or early discontinuation
  * Cycle C - Day 0, day 14, and day 30 after administration of treatment.

Patients also completed a diary card on days one through seven (similar to Brandt, et al.) of each treatment cycle to record the onset of treatment effect.

Inclusion Criteria described that patients be over the age of 18 with moderate to severe glabellar lines at the maximum frown. In addition,
patients must have the time and ability to complete the study and demonstrate an understanding of the study, as well as the contents of the informed consent. Female patients of childbearing potential must also test negative for pregnancy. Patients who have had previous treatment with any type of botulinum toxin to any area of the body, or had other soft tissue procedures, filler injections, laser skin resurfacing, or other forms of treatment to the glabellar area within the last 12 months were excluded from the study. (Source: Clinical Trial Y 97 5210 085 © 2009 Medicis Pharmaceutical Corporation)

Results indicated a significantly higher proportion of patients responded to Dysport than to placebo at Day 30 of Cycle C (p<0.001). Furthermore, a great number of responders did not show attenuation of effect after three or four re-treatments (Fig. 4). Dysport also appeared to be equally efficacious in patients of all skin types.

The onset of response was reported as early as 24 hours, with the median time to onset being three days for all treatment cycles. The median duration of effect was about 88 days after Cycle B. The Open-Label Cycles (Cyles A1 and A2) had similar durations of effect. There was no significant effect on repeat treatment from race, baseline severity, study site, or whether subjects began later cycles from either Cycle A1 or A2. In fact, all groups had significant treatment responses with Dysport, but the proportion of responders was higher in patients less than age 65 as compared with older patients.

Regarding safety, 67 percent of subjects experienced TEAEs, with the highest incidence in Cycle A1 (41 percent), compared to Cycle B (37 percent) and Cycle C (38 percent). In all treatment cycles, the majority of TEAEs were mild to moderate in severity. Twelve subjects had 15 SAEs, none of which were considered to be related to treatment. The highest number of TEAEs that were probably or possibly related to Dysport were nervous system disorders (43 events), general disorders and injection site reactions (42 events), and eye disorders (21 events). The frequency of these events was comparable between the two groups, except for ptosis (3.2 percent for Dysport vs. 0 percent for placebo). Ten patients reported 11 cases of eyelid ptosis. Incidence was as follows: 1.6 percent for Cycle A1, 1.7 percent for Cycle A2, 1.2 percent for Cycle B, and 0 for Cycle C.

Importantly, the GL-2 study showed that even after three to four treatments with Dysport, efficacy is still maintained without evidence of tachyphylaxis. Moreover, a significantly higher proportion of subjects in this group had a response at day 30 of Cycle C (p<0.001). These results were comparable in all cycles. Finally, retreatments were well-tolerated as compared to placebo.

GL-3. Study GL-3 (not yet published) was single dose, double-blind, multi-center, randomized, placebo-controlled and examined the effects of 50 units of Abobotulinum Toxin A Data

### Table 3. Dilution of Dysport compared to Botox

<table>
<thead>
<tr>
<th>Diluent Added (0.9% sodium chloride)</th>
<th>Resulting Dose (units/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 mL</td>
<td>10 units/0.08 mL</td>
</tr>
<tr>
<td>1.5 mL</td>
<td>10 units/0.05 mL</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Diluent Added (0.9% sodium chloride)</th>
<th>Resulting Dose (units/0.1 mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 mL</td>
<td>10.0 units</td>
</tr>
<tr>
<td>2.0 mL</td>
<td>5.0 units</td>
</tr>
<tr>
<td>2.5 mL</td>
<td>4.0 units</td>
</tr>
<tr>
<td>4.0 mL</td>
<td>2.5 units</td>
</tr>
<tr>
<td>8.0 mL</td>
<td>1.25 units</td>
</tr>
</tbody>
</table>

Source: Dysport PI 2009 and BOTOX PI 2009

### Figure 3. Response at maximal frown at day 30 of cycle C.

Source: Clinical Trial Y 97 5210 085 © 2009 Medicis Pharmaceutical Corporation
Dysport, administered in five aliquots of 10 units in 300 previously untreated patients.3 The mean age was 44 years and the majority of subjects were women (87 percent Total, Caucasian 75 percent, Hispanic 18 percent). The study lasted 150 days. During that period, investigators and subjects used the GLSS to assess their response to treatment on days 14, 30, 60, 90, 120, and 150. At Day 30, 60 percent (120/200) of the Dysport group were responders (2-grade improvement), as assessed by investigators and subjects (Table 2).

The outcomes and data from all of the three clinical studies supported FDA-approval of Dysport and influenced protocols for use and safety considerations that are now a part of the package insert.

Making Sense of the Data

Dysport inhibits the release of acetylcholine from peripheral cholinergic nerve endings, and through a series of steps, leading to the intracellular blockage of neurotransmitter release into the neuromuscular junction. This in turn causes chemical denervation of the treated muscle resulting in a localized decrease of muscle activity. The result is temporary, since transmission across the neuromuscular junction recovers (in about three months) and new nerve endings are formed. This novel formulation of BoNT-A differs from others in that its potency units are specific to the preparation and assay method. Therefore, the units of biologic activity can’t be compared to any other botulinum toxin products. Furthermore, with the current technology, it is not possible to detect Dysport in the peripheral blood following intramuscular injection at the recommended doses.

Reconstitution. Dysport is supplied in a single-use, sterile 300-unit vial for reconstitution with sterile normal saline (0.9% NaCl) without preservative. It can be reconstituted in two ways: with 2.5mL normal saline, to yield a solution of 10 units/0.08mL, or with 1.5mL normal saline, to yield a solution of 10 units per 0.05mL (Table 3). Both reconstituted and unopened Dysport vials should be kept refrigerated and protected from light.

A study assessing the efficacy and safety of a 50-unit dose of Dysport for glabellar lines was performed after reconstitution up to 15 days before injection. One hundred-five subjects (91 percent female) were randomized into three treatment groups with Dysport (500-unit vial diluted with 2.5mL of sterile normal saline, to a concentration of 200 units/mL:

1.) diluted 15 days prior to injection,
2.) diluted eight days prior to injection, and
3.) diluted no more than eight hours prior to injection.

Investigators and patients made motility assessments using a 4-point qualitative scale (1-unaltered, 2-slightly reduced, 3-moderately reduced, 4-very reduced) at baseline and days 28, 56, 84, and 112 after treatment. Blinded outcome evaluators who assessed a randomized series of subject photos used this same scale. Results indicated no statistical significance in motility of the treated area between the three study groups. In addition, bacteriological analysis of the reconstituted vials before and after the study showed no evidence of bacterial or microorganismal growth. It was therefore concluded that Dysport could safely and effectively be used up to 15 days after reconstitution. However, Medicis Aesthetics, Inc. still maintains that reconstituted vials of Dysport should be used within four hours to avoid any complications.3 Medicis also recommends a total dose of 50 units (divided into five 10-unit aliquots) of Dysport be administered to the affected muscles (procerus/corrugators). This value was determined after the completion of several randomized controlled trials.1,3,5-7

Dosing. In one trial, 373 subjects with moderate to severe vertical glabellar lines at frown were randomized to receive doses of 20, 50, or 75 units of Dysport (500 units reconstituted with 2.5mL of normal saline without preservative).3 The injection was performed across the procerus, corrugators supercilii, and orbicularis muscles (0.05mL/injection site). On days seven, 30, 60, 90, and 120 following treatment, investigators evaluated the effect of Dysport treatment on glabellar lines at rest and at maximal frown on a four point scale from zero (none) to three (severe). Patients were questioned at the same points in time: How would you rate the change in the
appearance of your glabellar lines compared with immediately before injection?

They responded using a nine-point scale, from -4 (very marked worsening) to +4 (completely improved), with zero representing no change at all. Importantly, all doses of Dysport resulted in a statistically significant improvement (investigators and subjects) in the appearance of glabellar lines as compared to the placebo. This response began at day seven and continued through day 90. Subjects who received doses of 50 and 75 units maintained a response through day 120 and had similar efficacies. It was concluded that 50 units was the minimal dose required to be safe and effective. The study also determined that repeat doses did not decrease the efficacy of Dysport.

Similar to the pivotal trial by Rubin, et al.; Moy, et al. completed a 13-month open label safety assessment of 1,200 patients treated with up to 5 injections with reconstituted Dysport (50 units). 10 units were injected into 5 sites in the glabellar region. Clinical evaluations using the GLSS occurred at days 14, 30, and then monthly until re-treatment, study completion, or early termination. Patients who still had moderate or severe glabellar lines at maximum frown (as determined by investigators and subjects independently) after treatment were given the opportunity to be re-treated at a minimum of 85 days. Importantly, 93 to 95 percent of patients in all cycles reported a response to treatment by day seven, with the median onset of three days for all cycles. Investigators found the response rate at day 30 to range between 80 percent and 91 percent during treatment cycles one through five. The mean duration of effect ranged from 89 to 90 days for the first three cycles. Moreover, it is unnecessary to retreat patients less than three months since their initial injection.

Regardless of the known advantages of the 50-unit dose of Dysport, dermatologists often modify the treatment dose of botulinum toxin A products based on the individual, and, more specifically, on the size of the target muscles. Accordingly, a randomized, multicenter, double-blind, placebo-controlled study compared a single treatment of variable doses of Dysport for moderate to severe glabellar lines, based on muscle mass. Researchers randomized 816 patients to receive Dysport (n=544) or placebo (n=272). The experimental group was further broken down based on gender and muscle mass. Women received doses of 50, 60, or 70 units, while men received doses of 60, 70, or 80 units. Blinded evaluator and patient self-assessments using the glabellar line severity score (GLSS) were performed on post-treatment days 14, 30, 60, 90, 120, and 150 to determine efficacy. Results showed that 87 percent (patient assessment) or 85 percent (blinded evaluator assessment) of Dysport-treated subjects reported an effect (GLSS 2-3 decreased to GLSS 0-1) after 30 days compared to five percent and three percent of placebo-treated subjects. Male subjects responded at a higher rate than in previous studies that used a 50-unit dose of Dysport. Adverse events were comparable not only between the experimental and control group, but also between patients treated with the highest doses and placebo.

Safety. The most common adverse effects, which are similar among other placebo-controlled clinical trials, were nasopharyngitis, sinusitis, headache, nausea, pain or reaction at the injection site, upper respiratory infection, and eyelid edema and ptosis. In the study by Monheit, et al., the most common adverse effects were mild headache and nasopharyngitis, which occurred at similar frequencies among the three study groups. Of the 373 participants, three reported mild ptosis (receiving doses of 50 units (n=1) and 75 units (n=2)), but further analysis suggests that two cases were not true ptosis. Brandt, et al. determined that the rate of adverse events for Dysport patients was not different than for placebo. Moreover, most events were mild to moderate and were considered unrelated or unlikely to be related to the study medication (Dysport 50 units injected in aliquots of 10 units to the glabellar region). In Moy’s study (n=1,200), 72 percent of treatments associated adverse events were unlikely or not related to treatment. Of the probably/possibly-related adverse events (36 percent), 18 percent were related to the injection site, 12 percent were headache, and four percent were ptosis. The latter occurred in less than two percent of patients in any of the treatment.
cycles. In a retreatment study, at the end of 23 months, more than three percent of patients reported the following adverse events regardless of relationship to treatment: Headache: 17 percent; Nasopharyngitis: 10 percent; Eye disorders: seven percent; Sinusitis: four percent; Injection site pain: four percent; Bruising: three percent. According to the overall safety database for the treatment of glabellar lines, 57 percent (1,425/2,491) of Dysport patients reported adverse events after up to 12 treatments. The incidence of eyelid ptosis did not increase in the long-term safety studies with multiple retreatments, and most resolved over several weeks.

Although most adverse events are mild to moderate in effect, as with any anticholinergic drug, systemic anticholinergic effects may be potentiated. In a clinical study testing for antibodies in 1,554 subjects who received up to nine treatment cycles with Dysport, two subjects tested positive at baseline for antibodies and three more tested positive after receiving treatment. However, no neutralizing antibodies were found. Nevertheless, patients with a hypersensitivity to any botulinum toxin products, cow’s milk protein allergy, or those with an infection at the proposed injection site should not receive treatment with Dysport.

Additionally, caution should be exercised when administering Dysport to patients with surgical changes to facial anatomy, atrophy of target muscles, marked facial asymmetry, ptosis, or deep dermal scarring. Retreatment should not occur more frequently than every three months. This recommendation is based on the results of the fixed- and variable-dose studies. The former studies (50-unit single dose or repeated doses) showed a median duration of response of 85 days, while the latter (doses ranged from 50-80 units) had a median duration of response of 109 days. These studies also supported the claim that retreatment at shorter than three-month intervals was unnecessary.

Discussion

This comprehensive review of the pivotal data focused exclusively on the labeled glabellar indication for cosmetic use. But, as with Botox, Dysport will likely be used in other areas for cosmetic treatments.

It’s worth noting that comparison of Botox Cosmetic to Dysport based on the summarization of data in the package insert does not constitute a valid approach to either agent. Classes of drugs and biologics can have common themes, but no two studies are identical. The most common mistake is to line up tables and data from one PI to another and draw conclusions that may change your prescribing or treatment habits without understanding where data came from. Each company that submits a new drug, biologic, or investigational drug application, negotiates their study design, primary and secondary outcome measurement tools, and categorization of adverse events. Therefore, a side-by-side package insert comparison of Botox Cosmetic to Dysport would be erroneous, as the study design, endpoints and measurement tools are not identical. To level the scientific playing field a comprehensive review of the studies performed on both toxins would be needed.

Dr. Desai has no relevant disclosures.

M.S. Hanna is on the speaker bureau for Astellas and is a consultant and on the speaker bureau for Johnson & Johnson.

Dr. Bhatia is consultant and clinical trainer for Johnson & Johnson, Medicis, and Bioform.