Dosing of abobotulinumtoxinA (Dysport®) injections for adults with lower limb spasticity

Salvatore Napoli,1,2,3,4 Peirrorg Bergkovic,2,5 Theodore Brown,3 Ziyad Ayoubi,6,7,8 Gustavo Suarez,9 Philippe Picault,9 Peter Hedera10

1Mazzucchelli Centre of New England, Framingham, MA, USA; 2Wayne State University, Detroit, Detroit, MI, USA; 3University of Southern California, Los Angeles, CA, USA; 4Kwangwoon-Health Multiple-Sclerosis Centre, Kirkland, WA, USA; 5Francisco Los Angeles Regional National Rehabilitation Center, Downey, CA, USA; 6UC Davis Geffen School of Medicine at UCI, Los Angeles, CA, USA; 7University of Health Sciences, Panama, Panama; 8CAS, Biopharmaceuticals, Basking Ridge, NJ, USA; 9Ipsen Pharma, La Jolla, France; 10Department of Neurology, Division of Movement Disorders, Vanderbilt University, Nashville, TN, USA

Presented at the Annual Meeting of the Consortium of Multiple Sclerosis Centers, 30 May – 2 June 2018, Nashville, TN, USA. This study was sponsored by Ipsen Pharma SAS

Inclusion criteria included:

- Adults (18–80 years) with spastic hemiparesis of the lower limb, at least 6 months post-stroke or -TBI.
- Time since traumatic brain injury, median (range) years: 6–60 (1–186)
- Ethniciy, n (%): Non-Hispanic 116 (90.6), Hispanic 11 (8.6), other 9 (7.0)
- BMI, mean (SD) kg/m²: 27.4 (5.6)
- Test of gait speed at baseline between 0.1 m/s and 0.8 m/s
- Flexor hallucis brevis
- Flexor digitorum brevis
- Flexor digitorum longus
- Gracilis
- Adductor magnus
- Soleus complex (GSC) with knee extended
- Gastrocnemius (GAS) with knee flexed
- Comfortable barefoot walking speed between 0.1 m/s and 0.8 m/s at baseline measured using a 15-m motorized treadmill walk test (MMT) with walking aids.
- Spasticity score on the Goniometer Scale of the lower extended.

Exclusion criteria included:

- Current or planned treatment with any drug that interferes directly or indirectly with ataxia or reduces spasticity.
- Pharmacological treatment with any drug that induces use of any other antispasticity drug or any other antispasticity drug or any other discontinuing drug or discontinuing drug.
- Patients who had used only 5 mg/5 mL intramuscular injection of at least 6 months post-stroke or -TBI.
- Patients who had only 1 clinically defined stroke episode or one-time trauma at least 6 months prior to study entry.
- Modified Ashworth Scale (MAS) score of 0–2 is assessed in all randomized patients at least one injection of study medication.

Methods

Study population

- Inclusion criteria related to:
  - Adults (≥18 years of age) with spastic hemiparesis of the lower limb, at least 6 months post-stroke or TBI.
  - Patients who had only 1 clinically defined stroke episode or one-time trauma at least 6 months prior to study entry.

Study design and treatment

- This was a phase 3, multicenter, prospective, double-blind, randomized, placebo-controlled, single-blind, randomized, patients were randomized into one of three treatment groups (aboBoNT-A 1000 U or 1500 U, or placebo) at a ratio of 1:1:1.
- Patients were in-grouped in a multisite, multicenter, blinded, randomized, placebo-controlled, single-blind, 132 (62.9) 30 (68.9) 40 (37.4)
- The safety population was defined as all randomized subjects who received at least one injection of study medication.

Results

Patient disposition and characteristics

- 40 (37.4) 30 (68.9) 40 (37.4)
- The incidence of muscular weakness was higher in the aboBoNT-A 1500 U group (6.3%) than in the aboBoNT-A 1000 U (2.4%) or placebo groups (3.1%).
- The most frequent adverse events were falls, pain in extremity, and muscular weakness (which was localized weakness in the injected muscles in the majority of patients in the aboBoNT-A 1500 U group received between 800 and 1500 U in any single muscle.
- The pooled change in the aboBoNT-A 1000 U group was 164–1600 U in patients in the aboBoNT-A 1052 (9) 1000–700 (50) 60–300 (44) 50–300 (38) 0–500 (128)
- The dose ranges injected per muscle are shown in Table 2. GSC (knee extended) vs. 67–200 vs. 100–300 U administered to the lateral gastrocnemius soleus complex (GSC) with knee extended, for test muscle rotation (n=130) in a randomized, blinded, controlled, single-blind, blinded, randomized, placebo-controlled, single-blind, 132 (62.9) 30 (68.9) 40 (37.4)
- The development of binding or neutralizing antibodies was not detected during the trial.
- Change from baseline in spasticity of the lower limb spasticity in hemiparetic adults (18–80 years) with spastic hemiparesis of the lower limb, at least 6 months post-stroke or -TBI.
- Patients were randomized into one of three treatment groups (aboBoNT-A 1000 U or 1500 U, or placebo) at a ratio of 1:1:1.

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>aboBoNT-A 1000 U (N=125)</th>
<th>aboBoNT-A 1500 U (N=128)</th>
<th>Total (aboBoNT-A) (N=253)</th>
<th>Placebo (N=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (50 years)</td>
<td>52 (10)</td>
<td>54 (14)</td>
<td>53 (10)</td>
<td>54 (12)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>87 (69.6)</td>
<td>79 (61.7)</td>
<td>87 (69.6)</td>
<td>90 (70.3)</td>
</tr>
<tr>
<td>BMI, mean (SD) kg/m²</td>
<td>27.4 (5.6)</td>
<td>24.5 (5.3)</td>
<td>27.4 (5.6)</td>
<td>25.7 (5.4)</td>
</tr>
<tr>
<td>Cause of spasticity (%)</td>
<td>60 (48.4)</td>
<td>67 (52.4)</td>
<td>61 (48.4)</td>
<td>65 (61.3)</td>
</tr>
<tr>
<td>Grade</td>
<td>67–133</td>
<td>67–133</td>
<td>67–133</td>
<td>67–133</td>
</tr>
<tr>
<td>Time since stroke, median (years)</td>
<td>13 (1)</td>
<td>13 (1)</td>
<td>13 (1)</td>
<td>13 (1)</td>
</tr>
<tr>
<td>Time since traumatic brain injury, median (years)</td>
<td>10 (5)</td>
<td>5 (10)</td>
<td>10 (5)</td>
<td>10 (5)</td>
</tr>
<tr>
<td>Change in gait speed, median (years)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Change from baseline in GSC muscle tone (assessed by the MAS) at Week 4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Change from baseline in the MAS score</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Change from baseline in GSC muscle tone (assessed by the MAS) at Week 4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>
| Safety

- All patients received a single treatment cycle at Week 0.
- Change from baseline in spasticity of the lower limb spasticity in hemiparetic adults (18–80 years) with spastic hemiparesis of the lower limb, at least 6 months post-stroke or -TBI.
- The safety population was defined as all randomized subjects who received at least one injection of study medication.

Conclusions

- The incidence of muscular weakness was higher in the aboBoNT-A 1500 U group than in the aboBoNT-A 1000 U (2.4%) or placebo groups (3.1%).
- The safety population was defined as all randomized subjects who received at least one injection of study medication.

Table 2. Dose ranges injected per muscle for each aboBoNT-A treatment group

- The results of this phase 3 randomized study demonstrate the efficacy of aboBoNT-A (approved in the US for any ataxia in patients with lower limb spasticity).
- Safety was consistent with the known profile of aboBoNT-A.

Limitations

- No data on drug interactions with other antispasticity drugs or other discontinuing drug.
- The development of binding or neutralizing antibodies was not detected during the trial.
- The results of this phase 3 randomized study demonstrate the efficacy of aboBoNT-A (approved in the US for any ataxia in patients with lower limb spasticity).
- Safety was consistent with the known profile of aboBoNT-A.

References

- SN is a consultant for: Acorda Therapeutics; Biogen; Novartis; Pfizer; Questcor Pharmaceuticals; Sanofi Genzyme; Teva.  GS is an employee of Ipsen. PP has served research grants from Ipsen, Allergan, Merz and US WorldMeds. TB is the recipient of a research grant from Astellas, Merck and Biogen, and is a consultant for Ipsen, Biogen, Sanofi Genzyme and Teva.  and Ipsen.

Contact

- The safety population was defined as all randomized subjects who received at least one injection of study medication.

Dose ranges injected per muscle

- Spasticity is a common and frequently disabling symptom of multiple sclerosis, associated with functional impairment that can affect quality of life.
- Distal and proximal muscles (Table 2) for aboBoNT-A 1000 U (n=105), respectively.
- The most frequent adverse events were falls, pain in extremity, and muscular weakness (which was localized weakness in the injected muscles of patients in the aboBoNT-A 1500 U group).

Screening (N=456)

- Change from baseline in spasticity of the lower limb spasticity in hemiparetic adults (18–80 years) with spastic hemiparesis of the lower limb, at least 6 months post-stroke or -TBI.
- The safety population was defined as all randomized subjects who received at least one injection of study medication.

Figure 2. Change from baseline in Modified Ashworth Scale score.

Figure 3. Study design and patient disposition.