Original Research—CME

Efficacy and Safety of AbobotulinumtoxinA (Dysport) for the Treatment of Hemiparesis in Adults With Upper Limb Spasticity Previously Treated With Botulinum Toxin: Subanalysis From a Phase 3 Randomized Controlled Trial

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Abstract

Objective: To assess the efficacy and safety of abobotulinumtoxinA in adults with upper limb spasticity previously treated with botulinum toxin A (BoNT-A).

Design: A post hoc analysis from a Phase 3, prospective, double-blind, randomized, placebo-controlled study (NCT01313299).

Setting: A total of 34 neurology or rehabilitation clinics in 9 countries.

Participants: Adults aged 18-80 years with hemiparesis, ≥6 months after stroke or traumatic brain injury. This analysis focused on a subgroup of subjects with previous onabotulinumtoxinA or incobotulinumtoxinA treatment (n = 105 of 243 in the total trial population) in the affected limb. The mean age was 52 years, and 62% were male.

Intervention: Study subjects were randomized 1:1:1 to receive a single injection session with abobotulinumtoxinA 500 or 1000 U or with placebo in the most hypertonic muscle group among the elbow, wrist, or finger flexors (primary target muscle group [PTMG]), and ≥2 additional muscle groups from the upper limb.

Main Outcome Measurements: Efficacy and safety measures were assessed, including muscle tone (Modified Ashworth Scale [MAS] in the PTMG), Physician Global Assessment (PGA), perceived function, spasticity, active movement, and treatment-emergent adverse events.

Results: At week 4, more subjects had ≥1 grade improvement in MAS for the PTMG with abobotulinumtoxinA versus placebo (abobotulinumtoxinA 500 U, 81.1%; abobotulinumtoxinA 1000 U, 75.0%; placebo, 25.0%). PGA scores ≥1 were achieved by 75.7% and 87.5% of abobotulinumtoxinA 500 and 1000 U subjects versus 41.7% with placebo. Perceived function (Disability Assessment Scale), spasticity angle (Tardieu Scale), and active movement were also improved with abobotulinumtoxinA. There were no treatment-related deaths or serious adverse events.

Conclusions: The efficacy and safety of abobotulinumtoxinA in subjects previously treated with BoNT-A were consistent with those in the total trial population. Hence, abobotulinumtoxinA is a treatment option in these patients, and no difference in initial dosing appears to be required compared to that in individuals not treated previously.

Level of Evidence: III

Introduction

Upper limb spasticity (ULS) is common after stroke or traumatic brain injury (TBI). The impact can be highly significant, including abnormal hand and arm positions, impaired self-care, and limited passive/active range of motion, as well as additional burden to the caregiver [1-5].

The effectiveness of treatment with intramuscularly injected botulinum toxin A (BoNT-A) in reducing muscle tone in patients with ULS is well established [5-8]. Several guidelines now recommend BoNT-A injections

as a first-line treatment option in these patients [6,7,9-11].

AbobotulinumtoxinA (Dysport; Ipsen Biopharm, Wrexham, UK) is a BoNT-A preparation approved in the United States and Europe for the treatment of ULS in adult patients [12,13]. A recent clinical trial examined the efficacy and safety of a single injection session of abobotulinumtoxinA (500 or 1000 U) in 243 adults with ULS who had hemiparesis at least 6 months after stroke or TBI [14]. The effects observed included improvements in muscle tone, perceived function, spasticity, and active range of motion. Furthermore, the treatment was well tolerated, and all treatment-related adverse events (AEs) were mild or moderate in severity.

Among the subjects enrolled in this study, 105 had previously undergone treatment in the upper limb with onabotulinumtoxinA or incobotulinumtoxinA. The aim of the present analysis was to assess the efficacy and safety of abobotulinumtoxinA in adults with ULS who had been previously treated with a BoNT-A, and to describe the doses of abobotulinumtoxinA administered to these subjects.

Methods

Study Design and Subjects

This was a post hoc analysis of data from a phase 3, prospective, double-blind, randomized, placebo-controlled study conducted in 34 neurology or rehabilitation clinics in 9 countries: Belgium, Czech Republic, France, Hungary, Italy, Poland, Russia, Slovakia, and the United States. The study is registered with ClinicalTrials.gov (NCT01313299).

The trial was performed between August 4, 2011, and September 4, 2013, in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and local regulatory requirements, and with the approval of relevant institutional review boards and ethics committees.

All subjects signed written informed consent forms before trial entry.

Full details of the study design have been reported previously [14]. A summary is given below.

All subjects were between 18 and 80 years of age and had hemiparesis for at least 6 months after a clinically defined stroke episode (World Health Organization criteria) or one episode of TBI, occurring ≥6 months before enrollment. Included subjects were also required to have the following: a Modified Ashworth Scale (MAS) [15] score ≥3 in the primary target muscle group (PTMG; the muscle group with the highest MAS score among the elbow, wrist, and finger flexors); a Disability Assessment Scale (DAS) [16,17] score ≥2 rated on a 4-point scale from 0 (no disability) to 3 (severe disability) in the domains of dressing, hygiene, limb position, or pain; a spasticity angle ≥10° in the PTMG [18,19]; and a mean Modified Frenchay Scale (MFS) score of 1-8 out of a total possible score of 10 [18].

Key exclusion criteria included major limitations in the passive range of motion in the paretic limb (maximum passive elbow extension <150° or maximum passive wrist finger extension <70°), physical therapy initiated <4 weeks before the expected enrollment, treatment with BoNT-A of any type in the previous 4 months, and previous surgery or administration of alcohol or phenol in the study limb. A full list of exclusion criteria has been published previously [14].

A total of 243 study subjects were enrolled and randomized 1:1:1 to receive a single injection session with abobotulinumtoxinA 500 U, abobotulinumtoxinA 1000 U, or placebo in selected overactive upper limb muscles (Figure 1). Computer-generated randomization lists were independently created, and treatment numbers were assigned via a 24-hour interactive voice response system from an external contract research organization (S-Clinica, Brussels, Belgium). A double-dummy technique was used to maintain the masking of patients and investigators.
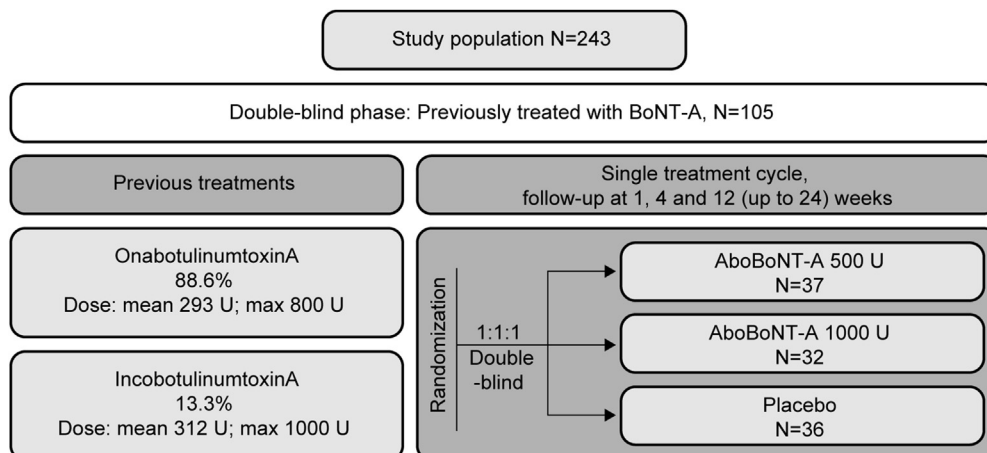

Figure 1. Patient population. AboBoNT-A = abobotulinumtoxinA; BoNT-A = botulinum toxin A.

Patients were stratified according to whether or not they had been previously treated with a BoNT-A. The present analysis comprises only the 105 subjects who had been previously treated in the affected limb with a BoNT-A other than abobotulinumtoxinA: 36 subjects from the placebo group, 37 from the abobotulinumtoxinA 500-U group, and 32 from the abobotulinumtoxinA 1000-U group (Figure 1).

Procedures

Study drugs (abobotulinumtoxinA or placebo) were reconstituted with saline solution to a volume of 5 mL. This volume was injected into the PTMG (selected from among the elbow, wrist, and finger flexors) and at least 2 other upper limb muscles (from among the elbow, wrist or finger flexors, or shoulder extensors) in a single injection session. Electrical stimulation was the only technique allowed for targeting the muscle [20].

Mandatory volumes for the PTMG were 2-3 mL for elbow flexors (2 mL for brachialis and an extra 1 mL for brachioradialis if injected), 2 mL for wrist flexors (1 mL for each of the flexor carpi radialis and flexor carpi ulnaris), and 2 mL for extrinsic finger flexors (1 mL each for flexor digitorum profundus and flexor digitorum superficialis). The remainder of the 5 mL was injected into other upper limb muscles, as selected by the investigator.

Mandatory assessment visits were made at weeks 1, 4, and 12.

Outcome Measures

Multiple efficacy endpoints are included within the present analysis. Muscle tone was assessed in the PTMG using the MAS, which measures resistance during passive soft-tissue stretching on a scale of 0 (no increase in muscle tone) to 4 (affected part rigid in flexion or extension). This endpoint was assessed as the proportion of responders (subjects with a ≥1 grade improvement) in each group. Treatment response was evaluated according to the Physician Global Assessment (PGA), a 9-point scale from −4 (markedly worse) to 4 (markedly improved), measured as the percentage of responders (subjects with a score ≥1) in each group. Perceived upper limb function was assessed by a DAS, recorded as the percentage of responders (subjects with a ≥1 grade improvement) in each group. The principal target of treatment was selected by the patient and physician from 1 of the 4 domains with a score ≥2 at baseline.

Spasticity was also evaluated, based on the Tardieu Scale, measuring angle of arrest at slow speed (X_{V1}), angle of catch at fast speed (X_{V3}) and spasticity angle (X; defined as $X_{V1}-X_{V3}$) in extrinsic finger, elbow, and wrist flexor muscles.

Other assessments included active range of motion (AROM) for joint extension, against extrinsic finger, elbow and wrist flexor muscles; active upper limb function assessed using the Modified Frenchay Scale (which assesses 10 activities of daily living on a scale of 0 [no movement] to 10 [normal movement]); and ease of applying a splint, if applicable, measured using a 6-point scale from 0 (no splint needed) to 5 (splint needed but unable to apply).

Safety assessments included AEs, classified as mild, moderate, severe, or serious.

Statistical Analysis

This was a post hoc analysis, and the study was not powered to detect statistical significance. Hence, only descriptive statistics (mean, standard error of the mean, standard deviation, and range) are provided. Missing data were not imputed.

Results

Baseline Characteristics

The baseline characteristics of subjects included in this analysis were well matched between groups (Table 1). The mean age was 52 years, and 62% of all subjects were male. The mean time since stroke or TBI was 5-10 years. In total, 93 subjects (88.6%) had received previous treatment with onabotulinumtoxinA (mean dose 293 U); 14 subjects (13.3%) had been previously treated with incobotulinumtoxinA (mean dose 312 U). The PTMG was the extrinsic finger flexors for 55 subjects (52.4%), the elbow flexors for 31 (29.5%), and wrist flexors for 19 (18.1%).

Doses Administered

The doses of abobotulinumtoxinA administered to each muscle are provided in Table 2. For the finger flexors, abobotulinumtoxinA was administered to the flexor digitorum profundus in 71.0% of subjects, either as PTMG or non-PTMG. Mean doses were 100.0 U (PTMG) and 62.5 U (non-PTMG) in the 500-U group, and 194.4 U (PTMG) and 181.3 U (non-PTMG) in the 1000-U group. AbobotulinumtoxinA was injected into the flexor digitorum superficialis in 84.1% of subjects, with mean doses of 100.0 U (PTMG) and 82.5 U (non-PTMG) in the 500-U group, and 200.0 U (PTMG) and 196.2 U (non-PTMG) in the 1000-U group.

For the wrist flexors, abobotulinumtoxinA was administered to the flexor carpi radialis in 84.1% of subjects. Mean doses were 100.0 U (PTMG) and 90.6 U (non-PTMG) in the 500-U group, and 191.7 U (PTMG) and 174.7 U (non-PTMG) in the 1000-U group. Furthermore, abobotulinumtoxinA was administered to the flexor carpi ulnaris in 68.1% of subjects, with the mean dose ranging from 94.1 to 191.7 U.

Table 1
Baseline characteristics of study participants

Parameter	Placebo (n = 36)	AboBoNT-A 500 U (n = 37)	AboBoNT-A 1000 U (n = 32)
Age, y, mean (SD)	49.6 (22-69)	53.8 (22-75)	50.9 (23-76)
Gender ratio, male/female, %	58.3/41.7	59.5/40.5	68.8/31.3
Affected arm, n (%)			
Left	17 (47.2)	17 (45.9)	22 (68.8)
Right	19 (52.8)	20 (54.1)	10 (31.3)
Cause of spasticity, n (%)			
Stroke	29 (80.6)	32 (86.5)	30 (93.8)
TBI	7 (19.4)	5 (13.5)	2 (6.3)
Time since event, y, mean (SD, range)			
Stroke	6.0 (4.8, 1.7-20.9)	7.6 (4.5, 1.0-16.8)	4.6 (2.6, 0.7-11.3)
TBI	4.6 (2.6, 0.8-7.4)	9.7 (5.8, 4.9-18.3)	8.7 (2.8, 6.8-10.7)
Previous BoNT-A treatment, n (%)*			
OnabotulinumtoxinA	32 (88.9)	35 (94.6)	26 (81.3)
IncobotulinumtoxinA	6 (16.7)	4 (10.8)	4 (12.5)
Other[†]	3 (8.3)	1 (2.7)	4 (12.5)
Dose of previous treatment, U, mean (range)			
OnabotulinumtoxinA	287.3 (50-600)	291.7 (50-650)	302.8 (70-800)
IncobotulinumtoxinA	291.3 (170-425)	425.0 (200-1000)	180.0 (100-200)
Other[†]	966.7 (200-2500)	—	4500.0 (4500-4500)
Primary target muscle group, n (%)			
Elbow flexors	11 (30.6)	12 (32.4)	8 (25.0)
Extrinsic finger flexors	18 (50.0)	19 (51.4)	18 (56.3)
Wrist flexors	7 (19.4)	6 (16.2)	6 (18.8)
Principal target of treatment, n (%)			
Dressing	10 (27.8)	7 (18.9)	7 (21.9)
Hygiene	5 (13.9)	12 (32.4)	5 (15.6)
Limb position	16 (44.4)	17 (45.9)	18 (56.3)
Pain	5 (13.9)	1 (2.7)	2 (6.3)

AboBoNT-A = abobotulinumtoxinA; BoNT-A = botulinum toxin A; SD = standard deviation; TBI = traumatic brain injury; y = years.

 * Some subjects had previously received more than one other BoNT-A.

[†] Included Lantox, Myobloc, and treatments for which the drug name was unknown.

For the elbow flexors, abobotulinumtoxinA was administered into the brachialis in 63.8% of subjects, with mean dose ranging from 124.0 to 400.0 U, and into the brachioradialis in 34.8% of subjects, with mean dose ranging from 81.3 to 200.0 U. The biceps brachii could not be selected as a PTMG, but abobotulinumtoxinA was administered into this muscle in 31.9% of subjects, with a mean dose of 103.3 U in the 500-U group and 228.6 U in the 1000-U group.

Finally, although the shoulder muscles could not be selected as a PTMG, the protocol allowed abobotulinumtoxinA administration in these muscles, and 10.1% of subjects were injected in shoulder muscles (Table 2).

Disposition of Subjects

All randomized subjects included in this analysis had efficacy data available at week 4, the main time point of the study. At week 12, data were not available for 5 subjects: 3 who withdrew between weeks 4 and 12 (2 in the placebo group [1 for an adverse event and 1 for a protocol deviation] and 1 in the abobotulinumtoxinA 500 U group [for an adverse event]) and 2 subjects who had missing data at week 12 (both in the abobotulinumtoxinA 500 U group).

Efficacy

With regard to muscle tone, there were more responders (subjects with ≥1 grade improvement in MAS score for the PTMG) in the 2 abobotulinumtoxinA groups compared with placebo at weeks 1, 4, and 12 (Figure 2). The number of responders peaked at week 4: 81.1 and 75.0% in the abobotulinumtoxinA 500-U and 1000-U groups versus 25.0% in the placebo group.

Physician-perceived clinical improvement rates were also higher with abobotulinumtoxinA. At week 4, PGA score ≥1 had been achieved by 75.7% and 87.5% of subjects treated with abobotulinumtoxinA 500 and 1000 U, respectively, compared with 41.7% of the placebo group (Figure 3). At 12 weeks, differences in clinical improvement rates were still evident between groups (45.9%, 53.1%, and 33.3% of abobotulinumtoxinA 500-U, 1000-U, and placebo subjects, respectively).

Perceived function was assessed by a DAS at weeks 4 and 12. At week 4, the proportion of subjects with a ≥1 grade decrease from baseline in DAS score for the principal target of treatment was greater with abobotulinumtoxinA 500 or 1000 U (62.2% and 53.1%, respectively) compared with placebo (44.4%) (Figure 4). Differences in response rates between groups were still present at week 12 (45.9%, 56.3%, and 38.9% of

Table 2
Prevalence and doses of abobotulinumtoxinA administered to each muscle group

Muscle Group	AboBoNT-A 500 U (n = 37) n Mean Dose (SD, Range)	AboBoNT-A 1000 U (n=32) n Mean Dose (SD, Range)	Prevalence of Administration (Either AboBoNT-A Dose; n = 69), n (%)
Finger muscles			
Flexor digitorum profundus			49 (71.0)
PTMG	19 100.0 (0, 100-100)	18 194.4 (23.6, 100-200)	37 (53.6)
Non-PTMG	4 62.5 (25.0, 50-100)	8 181.3 (37.2, 100-200)	12 (17.4)
Flexor digitorum superficialis			58 (84.1)
PTMG	19 100.0 (0, 100-100)	18 200.0 (0, 200-200)	37 (53.6)
Non-PTMG	8 82.5 (24.3, 50-100)	13 196.2 (43.1, 100-300)	21 (30.4)
Flexor pollicis longus	10 72.5 (27.5, 25-100)	13 150 (45.6, 100-200)	23 (33.3)
Adductor pollicis	3 25.0 (0, 25-25)	6 50.0 (0, 50-50)	9 (13.0)
Wrist muscles			
Flexor carpi radialis			55 (79.7)
PTMG	6 100.0 (0, 100-100)	6 191.7 (20.4, 150-200)	12 (17.4)
Non-PTMG	24 90.6 (19.2, 50-100)	19 174.7 (54.9, 100-300)	43 (62.3)
Flexor carpi ulnaris			47 (68.1)
PTMG	6 100.0 (0, 100-100)	6 191.7 (20.4, 150-200)	12 (17.4)
Non-PTMG	16 94.1 (30.5, 50-180)	19 156.8 (52.2, 80-200)	35 (50.7)
Elbow muscles			
Brachioradialis			24 (34.8)
PTMG	8 100.0 (0, 100-100)	4 200.0 (0, 200-200)	12 (17.4)
Non-PTMG	8 81.3 (25.9, 50-100)	4 105.0 (42.0, 50-150)	12 (17.4)
Brachialis			44 (63.8)
PTMG	12 187.5 (43.3, 50-200)	8 400.0 (0, 400-400)	20 (29.0)
Non-PTMG	15 124.0 (52.9, 50-200)	9 211.1 (78.8, 100-400)	24 (34.8)
Biceps brachii	15 103.3 (29.7, 50-200)	7 228.6 (75.6, 200-400)	22 (31.9)
Pronator teres	6 66.7 (25.8, 50-100)	9 136.7 (51.0, 80-200)	15 (21.7)
Shoulder muscles			
Triceps brachii (long head)	0	0	0
Pectoralis major	2 100.0 (0, 100-100)	2 250.0 (70.7, 200-300)	4 (5.8)
Subscapularis	1 100.0 (—, 100-100)	0	1 (1.4)
Latissimus dorsi	1 100.0 (—, 100-100)	1 100.0 (—, 100-100)	2 (2.9)

AboBoNT-A = abobotulinumtoxinA; PTMG = primary target muscle group; SD = standard deviation.

abobotulinumtoxinA 500-U, 1000-U, and placebo subjects, respectively).

Spasticity was evaluated at weeks 1, 4, and 12. The angle of catch (X_{V3}) in the finger, elbow, and wrist flexors improved from baseline to week 4 by a mean of 46.3°, 18.0°, and 27.5°, respectively, across abobotulinumtoxinA-treated subjects (Table 3), whereas the mean improvements in placebo-treated subjects were 10.7°, 4.6°, and −1.5°, respectively. Furthermore, the overall spasticity angle (X) in the finger, elbow and wrist flexors improved from baseline to week 4 by a mean of −31.3°, −15.9°, and, −14.6°, respectively, in abobotulinumtoxinA-treated subjects, compared with −11.0°, −4.7°, and 3.3° in the placebo group.
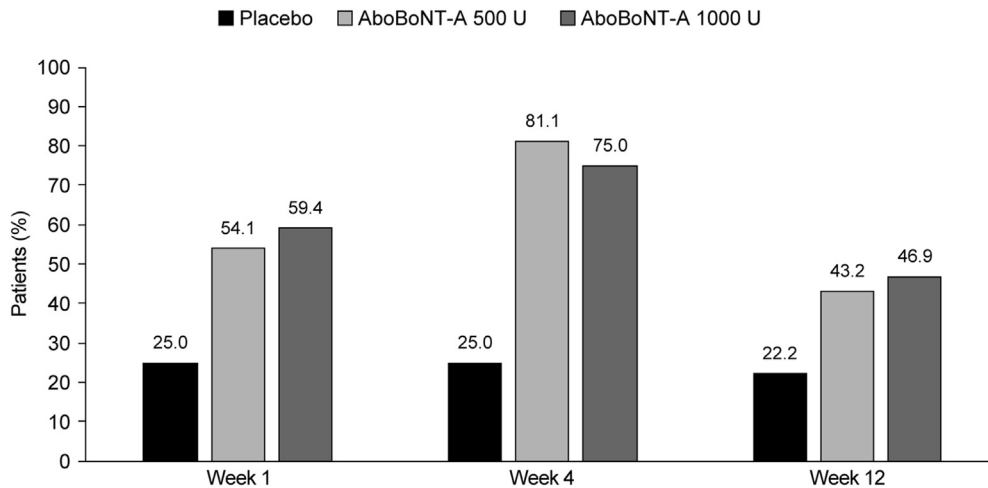
Figure 2. Responders to abobotulinumtoxinA according to MAS score improvement for the PTMG. Responders were defined as those subjects with a ≥1 grade improvement on the MAS for the PTMG. AboBoNT-A = abobotulinumtoxinA; MAS = Modified Ashworth Scale; PTMG = primary target muscle group.

Active movement was also assessed at the same time points as spasticity. For the finger, elbow, and wrist flexors, AROM increased from baseline to week 4 by a mean of 19.0°, 11.9°, and 14.6°, respectively, in subjects treated with abobotulinumtoxinA, compared with −1.3°, 4.2°, and 0° in the placebo group.

The evolution of both the spasticity and AROM data between weeks 1 and 12 are presented in Supplementary Table 1.

A small increase in MFS score from baseline was observed at week 4 in each of the 3 groups, with a numerically greater increase in the abobotulinumtoxinA 500-U dose group: 0.29 (standard deviation [SD] = 0.43) versus 0.15 (SD = 0.43) and 0.10 (SD = 0.36) with placebo and abobotulinumtoxinA 1000 U, respectively.

Finally, ease of applying a splint at week 4 was improved in the abobotulinumtoxinA 500-U and 1000-U groups, whereas there was no marked change in the placebo group (change from baseline: −0.4, −0.4, and 0.1, respectively).

Safety

Treatment-emergent AEs were experienced by 48.6%, 40.6%, and 22.2% of subjects in the abobotulinumtoxinA 500-U and 1000-U and placebo groups, respectively (Table 4). The most common treatment-emergent AE among abobotulinumtoxinA-treated subjects was nasopharyngitis (n = 5; 7.2%). No deaths or serious AEs were assessed by the investigator as related to treatment.

Discussion

This analysis of data from a phase 3 clinical study assessed the effect of abobotulinumtoxinA on various efficacy and safety parameters in hemiparetic adults who had previously undergone BoNT-A treatment

for ULS. Improvements were observed in muscle tone, spasticity angle, active movement, perceived function, and overall clinical improvement after treatment with abobotulinumtoxinA 500 or 1000 U. Importantly, all of these patients were treated at least 4 months after their last injection with either onabotulinumtoxinA or incobotulinumtoxinA. Hence, the results demonstrate that individuals treated with abobotulinumtoxinA ≥4 months after prior treatment with another BoNT-A experience a similar benefit and side effect profile.

The magnitude of the improvements observed in the present analysis was similar to that observed for the total population of the trial, which included both subjects who had been previously treated with a BoNT-A and those who had not [14]. For example, the number of responders with regard to MAS score at 4 weeks was 81.1% and 75.0% in the abobotulinumtoxinA 500-U and 1000-U groups in the present analysis, compared to
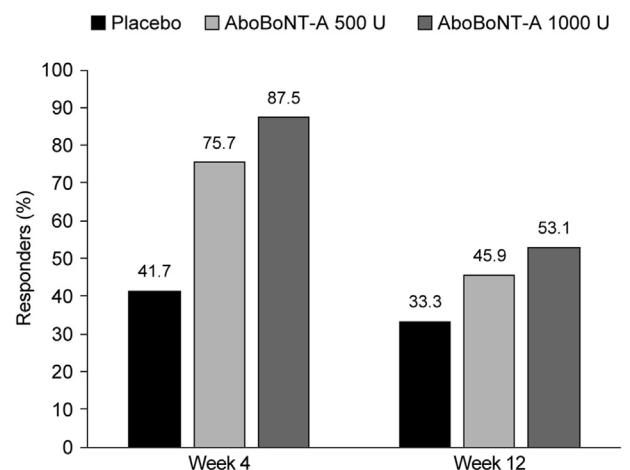
Figure 3. Clinical improvement with abobotulinumtoxinA according to PGA score ≥1. AboBoNT-A = abobotulinumtoxinA; PGA = Physician Global Assessment.
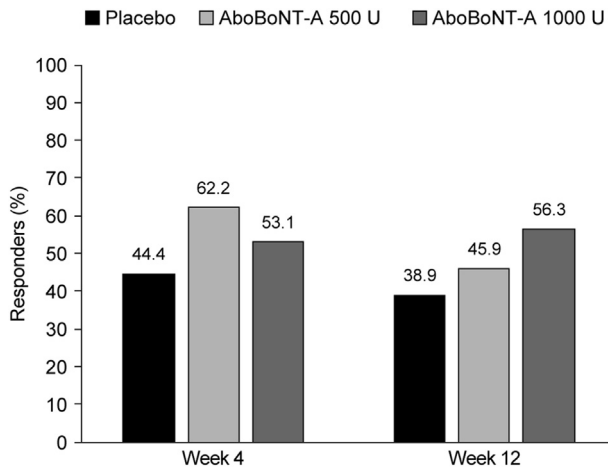
Figure 4. Subjects with ≥1 grade decrease in DAS score for the principal target of treatment. AboBoNT-A = abobotulinumtoxinA; DAS = Disability Assessment Scale.

73.8% and 78.5%, respectively, in the total study population. Similarly, the number of responders with regard to the DAS at 4 weeks was 62.2% and 53.1%, respectively, in the present analysis, compared to 50.0% and 62.0% in the total trial population.

As expected after a single injection, there were no significant differences with abobotulinumtoxinA versus placebo using the MFS in this population. There was a similar finding in the total trial population [14].

The safety profile of abobotulinumtoxinA in this analysis was consistent with the total trial population

and with its known profile across multiple studies conducted in patients with spasticity [14,21].

Hence, overall, the efficacy and safety of abobotulinumtoxinA in patients previously treated with BoNT-A were similar to those in the total trial population.

In the total trial population, there was some evidence that the 1000-U dose might provide additional clinical benefit compared with the 500-U dose [14]. There was no clear indication of such an effect in the current analysis, however, which may be explained by the fact that the study was not powered to detect such differences.

Study Strengths and Limitations

The key strength of the present analysis is that the data were derived from a Phase 3, prospective, randomized, placebo-controlled study. In addition, the degree of confidence that the efficacy of abobotulinumtoxinA is indeed as high in previously BoNT-A-treated patients as in the total trial population is increased by the wide range of efficacy endpoints assessed (and the similarity of the data in the 2 populations).

A key limitation is the lack of detailed efficacy and safety data relating to previous injection(s) with incobotulinumtoxinA or onabotulinumtoxinA, which makes direct comparison between different types of BoNT-A impossible. In addition, the study was not powered for this analysis, and hence only descriptive statistics could be reported. Also, because the study was not powered

Table 3
Change from baseline to week 4 in spasticity and active range of motion

Parameter		Finger Flexors, Mean (SEM)	Elbow Flexors, Mean (SEM)	Wrist Flexors, Mean (SEM)
Spasticity (Tardieu Scale)				
X_{V1} (°)	Placebo	−0.3 (4.8)	−0.1 (0.9)	1.8 (4.5)
	AboBoNT-A			
	500 U	10.2 (5.6)	2.9 (0.9)	13.6 (3.2)
	1000 U	19.7 (7.0)	0.8 (1.4)	12.0 (3.5)
	Either dose	15.0 (4.5)	2.1 (0.8)	12.9 (2.3)
X_{V3} (°)	Placebo	10.7 (7.4)	4.6 (2.7)	−1.5 (4.3)
	AboBoNT-A			
	500 U	46.0 (8.8)	19.2 (4.6)	25.5 (5.8)
	1000 U	46.6 (7.3)	15.9 (3.9)	30.0 (4.6)
	Either dose	46.3 (5.6)	18.0 (3.2)	27.5 (3.8)
X (°)	Placebo	−11.0 (8.4)	−4.7 (2.7)	3.3 (3.4)
	AboBoNT-A			
	500 U	−35.9 (7.4)	−16.4 (4.6)	−11.9 (6.6)
	1000 U	−26.9 (8.1)	−15.1 (3.9)	−18.0 (5.0)
	Either dose	−31.3 (5.5)	−15.9 (3.2)	−14.6 (4.4)
Active range of motion				
AROM (°)	Placebo	−1.3 (6.5)	4.2 (2.7)	0.0 (4.9)
	AboBoNT-A			
	500 U	25.2 (5.5)	6.8 (3.8)	16.6 (5.5)
	1000 U	12.8 (5.9)	18.1 (4.7)	12.4 (4.2)
	Either dose	19.0 (4.1)	11.9 (3.0)	14.6 (3.5)

AboBoNT-A = abobotulinumtoxinA; AROM = active range of motion; SEM = standard error of the mean; X = spasticity angle $(X_{V1}-X_{V3})$; X_{V1} = angle of arrest at slow speed; X_{V3} = angle of catch at fast speed.

Table 4
Adverse events (AEs) after injection

Treatment-Emergent AEs, n (%)	Placebo (n = 36)	AboBoNT-A 500 U (n = 37)	AboBoNT-A 1000 U (n = 32)
Any treatment-emergent AEs	8 (22.2)	18 (48.6)	13 (40.6)
Infections			
Nasopharyngitis	1 (2.8)	4 (10.8)	1 (3.1)
Sinusitis	0 (0)	1 (2.7)	1 (3.1)
Bronchitis	0 (0)	1 (2.7)	1 (3.1)
Urinary tract infection	0 (0)	1 (2.7)	1 (3.1)
Investigations			
Increased γ-glutamyl transferase	0 (0)	1 (2.7)	0 (0)
Increased triglycerides	0 (0)	2 (5.4)	0 (0)
Increased blood glucose	0 (0)	2 (5.4)	0 (0)
Musculoskeletal and connective tissue disorders			
Muscular weakness	2 (5.6)	1 (2.7)	1 (3.1)
Back pain	0 (0)	0 (0)	2 (6.3)
Arthralgia	1 (2.8)	0 (0)	0 (0)
Musculoskeletal pain	1 (2.8)	1 (2.7)	1 (3.1)
Nervous system disorders			
Headache	0 (0)	1 (2.7)	1 (3.1)
General disorders and injection site conditions			
Injection site erythema	0 (0)	0 (0)	2 (6.3)
Injection site bruising	1 (2.8)	0 (0)	1 (3.1)
Asthenia	0 (0)	1 (2.7)	0 (0)
Injection site pain	2 (5.6)	1 (2.7)	0 (0)
Respiratory, thoracic, and mediastinal disorders			
Cough	0 (0)	0 (0)	1 (3.1)
Epistaxis	0 (0)	1 (2.7)	0 (0)
Gastrointestinal disorders			
Diarrhea	0 (0)	0 (0)	1 (3.1)
Skin and subcutaneous tissue disorders			
Pruritus	1 (2.8)	0 (0)	1 (3.1)
Serious AEs*	1 (2.8)	2 (5.4)	1 (3.1)
Behçet syndrome	0 (0)	1 (2.7)	0 (0)
Cardiovascular disorder	0 (0)	1 (2.7)	0 (0)
Deep vein thrombosis	1 (2.8)	0 (0)	0 (0)
Muscular weakness	1 (2.8)	0 (0)	0 (0)
Sepsis	0 (0)	1 (2.7)	0 (0)
Syncope	0 (0)	0 (0)	1 (3.1)

AboBoNT-A = abobotulinumtoxinA.
 * If a participant experienced more than one event, that individual was counted only once.

for subanalysis of subjects who were previously treated and untreated with a BoNT-A, a comparison was made only against the total trial population and not against previously untreated subjects.

Conclusions

AbobotulinumtoxinA 500 U and 1000 U were each associated with improvements in muscle tone, perceived function, spasticity angle, and active movement in subjects with hemiparesis and ULS who had been previously treated with a BoNT-A. Efficacy and safety in this subgroup of subjects were comparable with those in the total trial population, at similar doses of abobotulinumtoxinA.

Based on these results, abobotulinumtoxinA appears to be a treatment option in hemiparetic patients previously treated with onabotulinumtoxinA or incobotulinumtoxinA for ULS. The data do not suggest that any

difference in initial dosing with abobotulinumtoxinA is required when initiating treatment in patients who have been previously treated with BoNT-A versus previously untreated patients.

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Supplementary Data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.pmrj.2017.06.007.

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CME Question

Based on the results of this study, patients receiving abobotulinumtoxinA (Dysport) who previously received botulinum toxin A (BoNT-A) treatment for upper limb spasticity demonstrated:

a. Improved scores on muscle tone and function compared to patients receiving placebo.
b. Clear dose dependent responses for 1000 U versus 500 U abobotulinumtoxin A injections.
c. Better relief of spasticity in wrist than finger flexors.
d. A concerning trend of increased adverse events compared to all participants in the Phase 3 trial.

Answer online at me.aapmr.org