"AbobotulinumtoxinA (Dysport) in the treatment of adults with upper limb spasticity in a randomized, double-blind, placebo-controlled study"

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Abstract

Introduction and Objectives: Few extensive studies have assessed the effects of botulinum neurotoxin A in adults with upper limb spasticity (ULS) poststroke/ traumatic brain injury (TBI) on muscle tone, spasticity, active range of motion (AROM), and function. The aim of this study was to assess the efficacy and safety of abobotulinumtoxinA (Dysport) in hemiparetic adults with ULS poststroke/TBI. Methods: In this phase 3, prospective, double-blind, placebo-controlled study, 243 patients (34 sites, 9 countries) were randomly assigned (1:1:1) to Dysport 500 or 1000 U or placebo. The primary objective was assessment of upper limb muscle tone (Modified Ashworth Scale; MAS) in the primary targeted muscle group (PTMG; finger, wrist, or elbow flexors). Other measures included spasticity (Tardieu Scale), AROM, ease of applying splint (EOS), clinical benefit (Physician Global Assessment; PGA), and subjective function (Disability Assessment Scale; DAS). Results: Four weeks postinjection, a highe...

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AbobotulinumtoxinA (Dysport®) in the treatment of adults with upper limb spasticity in a randomized, double-blind placebo-controlled study

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INTRODUCTION AND OBJECTIVES

- Intramuscular injection of botulinum toxin A (BoNT-A) is recommended as a first-line treatment to reduce muscle tone (resistance to passive movement) in patients with focal spastic paresis.
- However, few extensive studies have assessed the effects of BoNT-A on muscle tone, active range of motion (AROM) and function in adults with upper limb spasticity (ULS) after stroke or traumatic brain injury (TBI).
- The aim of this study was to assess the efficacy and safety of abobotulinumtoxinA (Dysport®) in hemiparetic adults with ULS ≥6 months after stroke or TBI. Modifications in muscle tone and movement with abobotulinumtoxinA in the spastic upper limb are the focus of this poster.

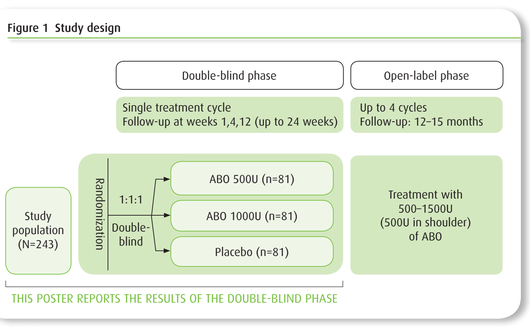
METHODS

- This was a Phase III, prospective, double-blind, placebo-controlled study of 243 patients (from 34 sites in 9 countries) randomized (1:1:1) to abobotulinumtoxinA 500 or 1000 units (U) or placebo (Figure 1).
- The primary endpoint was change in the Modified Ashworth Scale (MAS)[1] in the primary target muscle group (PTMG; finger, wrist or elbow flexors).
- Secondary endpoints included:
  - Physician Global Assessment (PGA; 9-point scale from -4 [markedly worse] to 4 [markedly improved]).
  - Disability Assessment Scale (DAS).[2,3]
  - Tardieu scale (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}]).
  - Active range of motion (AROM).
  - Ease of applying a splint (6-point scale from 0 [no splint needed] to 5 [splint needed but unable to apply]).
- Inclusion criteria were as follows:
  - Age 18–80 years.
  - One clinically defined stroke episode (WHO criteria) or one episode of brain trauma.
  - ≥6 months post-stroke or TBI.
  - MAS ≥2 in PTMG for toxin-naïve patients or MAS ≥3 in PTMG for toxin non-naïve patients.
  - DAS score ≥2 on principal target of treatment (PTT; limb position, dressing, hygiene or pain).
  - Spasticity angle ≥10° in PTMG.
  - Modified Frenchay Scale overall score 1-8.

RESULTS

- Baseline characteristics were well balanced across groups (Table 1). Extrinsic finger flexors were the most often targeted muscle group.

Figure 1 Study design



ABO: abobotulinumtoxinA

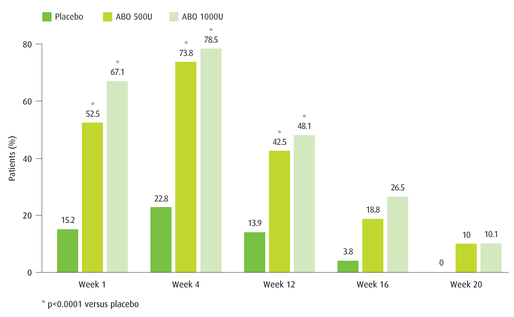
Table 1 Baseline patient and disease characteristics

Baseline characteristics	Placebo (n=79)	ABO 500U (n=80)	ABO 1000U (n=79)
Mean (SD) age, years	52.7 (13.9)	52.8 (12.9)	52.8 (13.7)
Male/female ratio, %	62/38	65/35	66/34
Stroke, %	88.6	90.0	92.4
TBI, %	11.4	10.0	7.6
Primary target muscle group (PTMG), %			
Extrinsic finger flexors	51.9	55.0	60.8
Elbow flexors	29.1	31.3	24.1
Wrist flexors	19.0	13.8	15.2

ABO: abobotulinumtoxinA. TBI: traumatic brain injury

- The mean reduction (improvement) in MAS score of the PTMG from baseline to week 4 was significantly greater with abobotulinumtoxinA 500U and 1000U versus placebo.
- One, four and twelve weeks after injection of abobotulinumtoxinA 500U and 1000U, a higher proportion of patients achieved a ≥1 grade improvement in MAS than with placebo (Figure 2).
- In the abobotulinumtoxinA groups, 35.0% (500U) and 36.7% (1000U) improved MAS by ≥2 grades, vs 3.8% in the placebo group after 4 weeks.

Figure 2 Responders to abobotulinumtoxinA or placebo according to a MAS ≥1 grade improvement



MAS: Modified Ashworth Scale. ABO: abobotulinumtoxinA

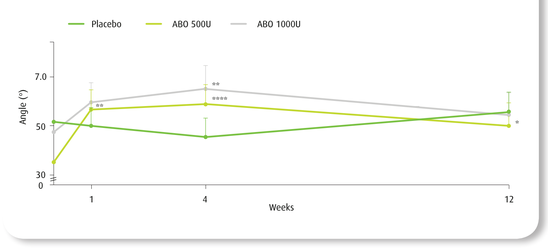
Table 2 Mean change from baseline to Week 4 in X_{V1}, X_{V3} and X for all muscle groups

		Finger flexors Mean (SEM)	Wrist flexors Mean (SEM)	Elbow flexors Mean (SEM)
Tardieu scale				
X_{V1} (°)	Placebo	1.9 (3.3)	4.4 (3.0)	-0.5 (1.5)
	500U	12.0 (3.5) p=NS	10.8 (2.1) p<0.05	2.1 (0.7) p=NS
	1000U	18.2 (4.1) p<0.01	12.2 (2.3) p<0.01	1.0 (1.0) p=NS
X_{V3} (°)	Placebo	9.8 (5.1)	2.5 (2.7)	4.5 (1.9)
	500U	39.3 (6.3) p<0.001	27.1 (4.0) p<0.001	19.6 (3.2) p<0.001
	1000U	47.7 (5.6) p<0.001	34.7 (3.6) p<0.001	25.7 (4.2) p<0.001
X (°)	Placebo	-7.9 (5.4)	1.9 (2.3)	-5.0 (2.2)
	500U	-27.3 (5.9) p<0.01	-16.4 (4.5) p<0.01	-17.5 (3.2) p<0.05
	1000U	-29.5 (5.9) p<0.01	-22.5 (3.9) p<0.001	-24.7 (4.2) p<0.001

X_{V1}: angle of arrest. X_{V3}: angle of catch. X: spasticity angle. SEM: standard error mean. p-values are versus placebo.

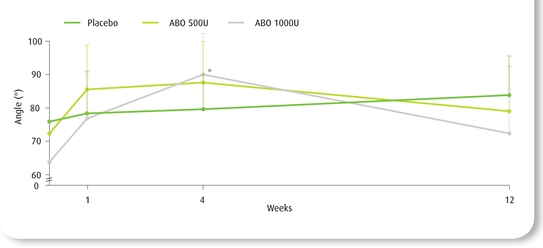
- Four weeks after injection of abobotulinumtoxinA 500U and 1000U, improvements were observed using the Tardieu scale in finger, wrist and elbow flexors in:
  - passive range of motion (angle of arrest X_{V1})
  - angle of catch (X_{V3})
  - spasticity angle (X) (Table 2).
- AROM was improved with abobotulinumtoxinA 1000U after 4 weeks in all muscle groups. AROM of the finger flexors was also improved with abobotulinumtoxinA 500U after 4 weeks (Figures 3-5).
- After 4 weeks, ease of applying splints did not change in the placebo group but was significantly improved in the abobotulinumtoxinA 500U and 1000U groups: -0.3 decrease (p=0.0159 and p=0.0189 versus placebo, respectively).

Figure 3 Active range of motion against finger flexors



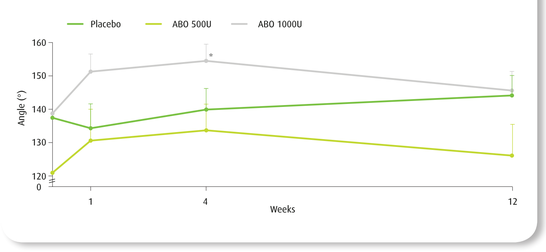
Change from baseline (ABO vs. placebo): *p<0.05; **p<0.01; ****p<0.0001
Active range of motion was measured in patients for which finger flexors were the PTMG

Figure 4 Active range of motion against wrist flexors



Change from baseline (ABO vs. placebo): *p<0.05
Active range of motion was measured in patients for which wrist flexors were the PTMG

Figure 5 Active range of motion against elbow flexors



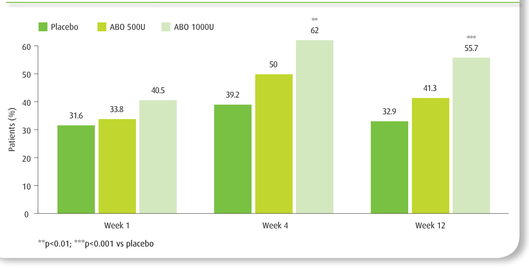
Change from baseline (ABO vs. placebo): *p<0.05
Active range of motion was measured in patients for which elbow flexors were the PTMG

- More patients had a PGA score ≥1 (at least 'slightly improved') at 4 weeks in the abobotulinumtoxinA 500U and 1000U groups (75.0% and 87.3%, respectively; p<0.001) compared with placebo (40.5%). Likewise, more patients had a PGA score ≥2 (at least 'improved') at 4 weeks in the abobotulinumtoxinA 500U and 1000U groups (45.0% and 57.0%, respectively; p<0.01) compared with placebo (25.3%).
- More patients in the 1000U group (62.0%) than in the placebo group (39.2%) improved on DAS as measured by ≥1 grade decrease from baseline to week 4 for the PTT (p<0.01; Figure 6).
- Limb position was the domain most frequently chosen as PTT and more patients receiving abobotulinumtoxinA 500U or 1000U achieved ≥1 grade decrease in that domain at week 4 than with placebo (placebo; 29.1%, 500U; 36.3%, p<0.05; 1000U; 50.6%, p<0.001).

Safety profile

- No adverse events were reported that were inconsistent with the known published safety profile of abobotulinumtoxinA (Table 3).
- No deaths or serious adverse events were assessed as being related to treatment.

Figure 6 DAS for the PTT (≥1 grade decrease)



**p<0.01; ***p<0.001 vs placebo

ABO: abobotulinumtoxinA. DAS: Disability Assessment Scale. PTT: Principal Target of Treatment

Table 3 Any adverse events after injection (>3% in any group)

Adverse event	Placebo (n=81)	ABO 500U (n=81)	ABO 1000U (n=81)
Nasopharyngitis	1 (1.2)	7 (8.6)	1 (1.2)
Muscle weakness in injected limb	2 (2.5)	2 (2.5)	4 (4.9)
Injection site pain	3 (3.7)	1 (1.2)	0 (0)
Increased blood triglycerides	0 (0)	3 (3.7)	1 (1.2)
Nausea	0 (0)	3 (3.7)	0 (0)

Data are presented as number of patients (percentage of patients); ABO: abobotulinumtoxinA

CONCLUSION

- This is the first international large study reporting a significant improvement of muscle tone (MAS) and clinical benefit (PGA; independent of MAS), together with a clinically meaningful improvement in active range of motion and an objective reduction in spasticity (Tardieu scale), associated with abobotulinumtoxinA (Dysport®; 500U and 1000U) in the hemiparetic upper limb.
- The efficacy of abobotulinumtoxinA was observed as early as 1 week after injection and continued for 12 weeks, and provided benefit for up to 20 weeks in some patients.
- The higher dose of 1000 U provided additional benefit on active range of motion and perceived function (DAS).
- Safety profile was consistent with the known profile of abobotulinumtoxinA in this disorder.
- This study undertook training of all raters using in-person and/or video training with real patients, which led to standardization of the use of the 2 main scales used: MAS and Tardieu and the measurement of the active range of motion. This process likely contributed to less variation between rating sessions.

DISCLOSURE

Dr Gracies served as a consultant and received research grant support from Allergan, Ipsen and Merz. Drs Lejeune, Denes and Vecchio have no conflicts of interest. Dr Timerbaeva has served as a consultant and received research grants from Allergan, Ipsen and Merz. Dr Brashear served as a consultant for Concert, Allergan and Ipsen, and receives salary support by NINDS; conflict of interest managed by Wake Forest School of Medicine. Dr O'Dell is an investigator on Ipsen and SPR clinical trials and a member of the Ottobock Advisory Board. Drs Marque and Boyer served as a consultant for Allergan, Ipsen and Merz; were involved with a training programme organised by Allergan, Ipsen and Merz and received research grant support from Ispen and Merz. Dr Vilain and Dr Picaut are employees of Ipsen Innovation, France.

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