

**EFFECTS ON WALKING OF SIMULTANEOUS UPPER/LOWER LIMB ABOBOTULINUMTOXINA INJECTIONS IN PATIENTS WITH STROKE OR BRAIN INJURY WITH SPASTIC HEMIPARESIS\***

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**Objective:** To compare walking speed in patients with spastic hemiparesis who received abobotulinumtoxinA either in the lower limb or simultaneously in both the lower and upper limbs.

**Design:** Post hoc analysis from a phase 3 study of abobotulinumtoxinA (Dysport®, NCT01251367).

**Patients:** Adult patients with spastic hemiparesis causing gait dysfunction.

**Methods:** Comfortable barefoot walking speed over 10 m was evaluated in 127 patients receiving lower limb vs lower and upper limb injections over ≤4 treatment cycles; 1,000 U or 1,500 U in lower limb for cycle 1/2; optional upper limb injections from cycle 3 (500 U: upper limb, 1,000 U: lower limb).

**Results:** Mean (standard deviation; SD) lower limb cycle 3/4 doses were lower in the lower plus upper limb group vs lower limb only (1,000 U (SD 50), 1,000 U (SD 50) vs 1,380 U (SD 210), 1,360 U (SD 220). Baseline comfortable barefoot walking speed was similar between groups. Changes at cycle 3 week 4, in m/s, were: lower and upper limb: +0.063 (SD 0.131); lower limb only: +0.078 (SD 0.114), and cycle 4 week 4: lower and upper limb: +0.086 (SD 0.166); lower limb only: +0.086 (SD 0.123).

**Conclusion:** Simultaneous lower and upper limb abobotulinumtoxinA treatment does not hamper improvement in walking speed compared with lower limb treatment alone. Thus, physicians may split the 1,500 U abobotulinumtoxinA dose as needed to best treat patients with spastic paresis.

**Key words:** muscle spasticity; paresis; botulinum toxin, type A; walking speed, stroke, traumatic brain injury.

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Spastic hemiparesis can result from stroke and often involves both the lower (LL) and upper limb (UL)

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**LAY ABSTRACT**

Spastic hemiparesis is a condition in which the muscles on one side of the body become weak and stiff, often after a stroke. One treatment involves injecting botulinum toxin (e.g. abobotulinumtoxinA) into the affected muscles. Patients may find walking difficult, but repeated injections of abobotulinumtoxinA into the legs have been associated with improved walking speed. However, it is not known whether improvements in walking speed are maintained when the dose of abobotulinumtoxinA is split to treat other affected areas, such as the arms. This study shows that splitting the dose of abobotulinumtoxinA across the arms and legs does not hamper walking speed, compared with injecting into the legs only. This suggests that doctors can split the dose across the arms and legs as needed to best treat the symptoms of spastic hemiparesis.

(1). Up to 75% of stroke survivors depend on caregivers for activities of daily living, and impaired gait contributes to decreased independence (2). In a global survey of patients living with spasticity, 72% and 44% of respondents reported decreased quality of life and a loss of independence, respectively (2). Improvement in walking is a common goal for patients, with walking speed shown to be a predictor for reintegration into the community and increased probability of survival (3, 4).

Management of spastic paresis often requires treatment of both the LL and UL. However, limited data are available regarding their simultaneous treatment with botulinum neurotoxin type A (BoNT-A), which is known to improve symptoms in spastic paresis. BoNT-A treatment of the UL may impact on walking ability by improving trunk control and posture (5). In preliminary studies, improved gait and faster walking speed were observed in patients with hemiparesis following stroke and in children with cerebral palsy, following BoNT-A treatment of the affected UL (5–7).

AbobotulinumtoxinA (Dysport®, aboBoNT-A) has proven efficacious in the treatment of both LL and UL spasticity when injected separately (8, 9). Repeated aboBoNT-A injections into the LL or UL have been associated with improvement in both active movement and function, with increased walking speed observed following repeated LL injections (10, 11).

We report here the results of a *post hoc* analysis of data from a phase 3 study of aboBoNT-A (11). The objective of this analysis was to evaluate walking speed in patients with spastic hemiparesis who received aboBoNT-A, comparing outcomes in those patients treated solely in the LL with those receiving simultaneous treatment in both the LL and UL.

## METHODS

### Study design and treatment

The phase 3, open-label (OL) extension study of aboBoNT-A (NCT01251367) followed a double-blind (DB) study (NCT01249404), as described previously (11). Briefly, the DB phase was a multicentre, prospective, randomized, placebo-controlled study in adults with chronic hemiparesis who received a single injection of 1,000 U or 1,500 U aboBoNT-A or placebo into both soleus and gastrocnemius muscles and  $\geq 1$  other (investigator-selected) LL muscle(s).

The OL extension was based on multiple injections of 1,000 U or 1,500 U aboBoNT-A for  $\leq 4$  treatment cycles (TCs), undertaken at 52 centres across 11 countries. At TC1 of the OL phase, patients received aboBoNT-A 1,500 U in the LL, except those who experienced treatment-emergent adverse events (AEs) during the DB phase that the investigator considered to pose an unacceptable risk, who instead received 1,000 U. At TC2, 1,000 U or 1,500 U could be administered in the LL (according to the investigator's clinical judgement). At TC3 and TC4, either 1,000 U or 1,500 U was administered into the LL; patients with co-existing disabling muscle overactivity in the UL could receive simultaneous injections of up to 500 U in the affected UL (as per investigator's clinical judgement), with the total aboBoNT-A dose not exceeding 1,500 U. The minimum time between TCs was 12 weeks.

This study was conducted in accordance with the Declaration of Helsinki, International Conference on Harmonisation Good Clinical Practice Guidelines, and local regulatory requirements, with approval from relevant independent ethics committee/institutional review boards. Written informed consent was obtained from patients prior to study entry.

This *post hoc* analysis evaluates the subgroups of patients who were injected with aboBoNT-A at both TC3 and TC4 of the OL phase and received either simultaneous injections of aboBoNT-A in the LL and UL, or injections in the LL only (Fig. 1).

### Patients

Inclusion criteria for the overall study population are described elsewhere (11) and included the following requirements to enter the DB trial: adults (18–80 years) with spastic hemiparesis causing gait dysfunction; comfortable barefoot walking speed (CBWS) 0.1–0.8 m/s without walking aids or orthotics; at least 6 months after a stroke (ischaemic or haemorrhagic) or traumatic brain injury (TBI). To continue into the OL phase, patients had to have completed follow-up visits in the DB trial without any major protocol deviations and/or ongoing adverse events. Key exclusion criteria were: major limitation in passive range of motion at hip, knee or ankle; known sensitivity to any form of botulinum neurotoxin (BoNT) or aboBoNT-A excipients;

pregnancy; severe cognitive impairment that interfered with consent provision.

### Outcome measures

Duration of the walk in a 10-m walk test (10MWT) was recorded using a stopwatch. Walking speed outcomes, assessed as change in unassisted CBWS between baseline and week 4 of each TC, were compared between patients who received simultaneous injections in the LL+UL during TC3 and TC4 and patients who received LL injections only throughout the study (Fig. 1).

### Statistical analysis

Due to the *post hoc* nature of these analyses, descriptive statistics only were performed. No hypothesis testing or *p*-values are presented.

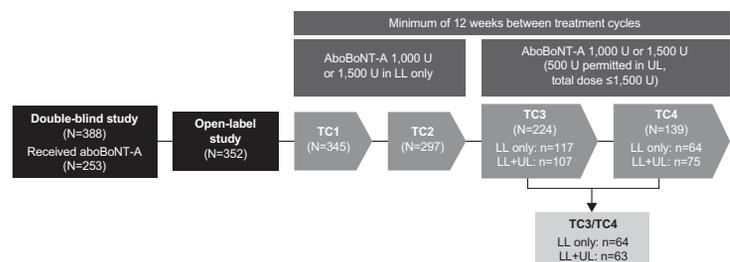
## RESULTS

### Patient disposition and baseline characteristics

A total of 352 patients entered the OL study; 127 were injected at both TC3 and TC4 and were thus included in these analyses ( $n=63$  received co-injection in LL+UL;  $n=64$  received injection in LL only, Fig. 1).

Baseline demographic characteristics were similar between the LL+UL and LL only treatment groups, including cause of spasticity (stroke or traumatic brain injury (TBI)), time since causal event, and whether naïve to any form of BoNT administered to the affected LL (Table I).

Injection doses are shown in Table II. Mean (standard deviation; SD) doses in LL at TC3 and TC4 were lower in patients injected in LL+UL vs LL only (1,006.7 U (SD 57.2), 1,001.1 U (SD 58.3) vs 1,381.8 U (SD 215.4), 1,367.2 U (SD 222.6)). Mean doses in the UL at TC3 and TC4 were 486.9 U (SD 56.1) and 491.0 U (SD 44.5), respectively. Overall LL dose ranges received at TC3 and TC4, respectively, were 937.5–1,500 U and 1,000–1,500 U in LL only and 1,300–1,500 U and 1,000–1,500 U in LL+UL. The most frequently injected UL muscles in TC3 and TC4, respectively, were the flexor digitorum superficialis



**Fig. 1.** Design of the *post hoc* analysis. Patient numbers decreased across cycles due to injection intervals of >12 weeks, with a maximum treatment duration of 1 year per patient. AboBoNT-A: abobotulinumtoxinA; LL: lower limb; TC: treatment cycle; U: units; UL: upper limb.

**Table I.** Baseline demographics and characteristics of patients included in the *post hoc* analysis

Characteristics	Patients injected at both TC3 and TC4	
	Injected in LL+UL (n=63)	Injected in LL only (n=64)
Age, years, mean (SD)	54.4 (10.6)	50.6 (14.1)
Sex, male, n (%)	48 (76.2)	45 (70.3)
Affected leg, left, n (%)	32 (50.8)	37 (57.8)
Cause, n (%)		
Stroke	58 (92.1)	52 (81.3)
Traumatic brain injury	5 (7.9)	12 (18.8)
Time since event, years, mean (SD)		
Stroke	4.64 (4.7)	4.73 (5.7)
Traumatic brain injury	9.67 (4.3)	9.62 (14.7)
Treatment naive <sup>a</sup> , n (%)	47 (74.6)	46 (71.9)

<sup>a</sup>Naïve to treatment with any form of botulinum neurotoxin administered to the affected LL.

LL: lower limb; SD: standard deviation; TC: treatment cycle; UL: upper limb.

(61.9% vs 63.5%), the flexor digitorum profundus (52.4% vs 44.4%), and the flexor carpi radialis (42.9% vs 41.3%).

### Efficacy

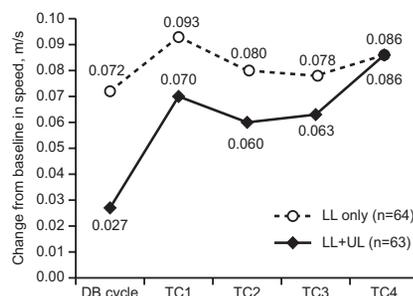
At baseline, unassisted CBWS (mean) was similar between patients injected in the LL+UL (0.419 m/s (SD 0.195), n=63) and LL only (0.420 m/s (SD 0.199), n=64). In the subgroup of patients who received LL injections only at TC3 and TC4, a consistently greater change from baseline in CBWS was observed at week 4 of the DB study through to OL TC2 (mean change, m/s, DB to TC2: 0.072 (SD 0.084) to 0.080 (SD 0.132)), compared with patients who received co-injection into the UL at TC3 and TC4 (DB to TC2: 0.027 (SD 0.095) to 0.060 (SD 0.135); Fig. 2).

At the first TC to include UL injections (TC3), both subgroups had continued improvements from baseline at week 4 (mean change: LL+UL: 0.063 (SD 0.131);

**Table II.** Doses (units) of aboBoNT-A administered

Statistic	Patients injected at both TC3 and TC4	
	Injected in LL+UL (n=63) Mean (SD) [range]	Injected in LL only (n=64) Mean (SD) [range]
TC3		
Overall dose <sup>a</sup>	1,493.7 (35.3) [1,300.0–1,500.0]	1,381.8 (215.4) [937.5–1,500.0]
LL dose	1,006.7 (57.2) [800.0–1,300.0]	1,381.8 (215.4) [937.5–1,500.0]
UL dose	486.9 (56.1) [200.0–600.0]	NA
TC4		
Overall dose <sup>a</sup>	1,492.1 (63.0) [1,000.0–1,500.0]	1,367.2 (222.6) [1,000.0–1,500.0]
LL dose	1,001.1 (58.3) [666.7–1,300.0]	1,367.2 (222.6) [1,000.0–1,500.0]
UL dose	491.0 (44.5) [200.0–500.0]	NA

<sup>a</sup>Overall dose is the treatment dose received in LL and/or UL. AboBoNT-A: abobotulinumtoxinA; LL: lower limb; NA: not applicable; SD: standard deviation; TC: treatment cycle; UL: upper limb.

**Fig. 2.** Mean change in comfortable barefoot walking speed (CBWS) at week 4 of each treatment cycle (TC) for patients who received lower limb (LL)+ upper limb (UL) injections or LL only injections at both TC3 and TC4 (doses combined). CBWS was assessed using the 10-m walk test (10MWT). DB: double-blind.

LL only: 0.078 (SD 0.114)). Further improvements were observed at week 4 of TC4 in both subgroups (LL+UL: 0.086 (SD 0.166); LL only: 0.086 (SD 0.123)). These values equate to improvements of 20.8% and 19.8% from baseline in unassisted CBWS in the LL+UL and LL group, respectively.

## DISCUSSION

In patients with spastic hemiparesis treated with aboBoNT-A, walking speed improved from the first injection and continued with repeated treatment throughout the OL phase. For patients requiring simultaneous treatment of muscle overactivity in the LL and UL, the total aboBoNT-A dose of 1,500 U split between LL and UL provided similar improvements in walking speed to those observed in patients injected in the LL only.

Retrospectively, the observed mean change in CBWS during the DB phase was markedly different between groups, with patients in the LL+UL group displaying less improvement than the group who did not require UL injections and received LL injections only (Fig. 2). In patients requiring concomitant UL injection, muscle overactivity in the UL may have had an impact on gait (5); thus in the LL+UL group, LL injections alone may not have been sufficient to overcome this overactivity. This may have explained the smaller improvements in CBWS compared with the LL only group prior to TC3. When UL injection became available, further improvements in CBWS were observed in this group, eventually reaching the same level as the LL only group by TC4.

Treatment of muscle overactivity in the UL with BoNT-A to improve gait has been associated with walking speed improvement in previous, smaller studies in patients with hemiparesis due to upper motor neurone syndrome or following a stroke (5, 12). However, these studies focused on specific UL muscles that were expected to improve walking speed by improving

UL symmetry of movement in gait and speed, whereas this study included all UL muscles. This may explain why patients with simultaneous injections showed less improvement than those injected only in the LL, and could suggest that specific UL muscles need to be targeted to improve walking speed and gait. This analysis provides initial data on split dosing of aboBoNT-A when injecting LL and UL simultaneously, and on the muscles injected, for an efficacious response. Importantly, data show that a 1,500 U dose of aboBoNT-A can be either injected entirely into the LL, or split between the UL and LL, as needed by the physician to enable best treatment of each patients' unique presentation of spastic paresis and treatment goals.

The post hoc exploratory nature of this analysis limits the extrapolation of these data, as the OL extension phase of the study was not powered for the statistical comparison of walking speed in patients who received aboBoNT-A either in the LL or both the LL and UL simultaneously (11). In addition, this study enrolled patients who were physically able to walk 10 m unaided; therefore, the results may not be generalizable to patients who walk permanently with orthotics or aids. Despite this, the results presented here provide an additional insight into the treatment of spastic hemiparesis. Further efficacy data is currently being prospectively collected from a larger patient group of adults with hemiparesis after stroke or TBI, following a 1,500 U dose of aboBoNT-A split between LL and UL, in the global ENGAGE study (NCT02969356).

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have no interests to disclose. PP is an employee of Ipsen. RR is an employee of Ividata subcontracted to Ipsen at the time of manuscript development. JMG has served as a consultant for and received research grant support from Allergan, Ipsen and Merz.

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