EFFECTS OF REPEATED ABOBOTULINUMTOXINA INJECTIONS IN UPPER LIMB SPASTICITY

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ABSTRACT: *Introduction:* The efficacy of single injections of abobotulinumtoxinA (Dysport) is established in adults with upper limb spasticity. In this study we assessed the effects of repeated injections of abobotulinumtoxinA over 1 year. *Methods:* Patients ($n = 258$, safety population) received 500 U, 1,000 U, or 1,500 U (1,500-U dose included 500-U shoulder injections) for up to 4 or 5 treatment cycles. Assessments included treatment-emergent adverse events (TEAEs), muscle tone, passive and active range of motion (X_{V1}, X_A), angle of catch (X_{V3}), Disability Assessment Scale (DAS) score, Modified Frenchay Scale (MFS) score, and Physician Global Assessment (PGA) score. *Results:* The incidence of TEAEs decreased across cycles. Muscle tone reduction and X_{V1} remained stable across cycles, whereas X_{V3} and X_A continued to improve at the finger, wrist, and elbow flexors. DAS and PGA improved across cycles. MFS improved best with 1,500 U. *Discussion:* A favorable safety profile and continuous improvements in active movements and perceived and active function were associated with repeated abobotulinumtoxinA injections in upper limb muscles.

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In hemiparesis after stroke or traumatic brain injury (TBI), passive and active antagonist muscle resistance may cause reduced active movement,

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impaired function, and abnormal limb postures.[1,2]

Botulinum toxin A (BoNT-A) is a first-line treatment for muscle overactivity in spastic paresis,[3–5] and coupling injections with neurorehabilitation may improve outcomes.[6–8] Although numerous studies have reported post-stroke or -TBI benefits of abobotulinumtoxinA (Dysport; Ipsen) on muscle tone[4,9–21] and passive function[4,9,14,17] for up to 24 weeks after a single injection, its effects on active function remained uncertain.[3,4,19,21,22] Few studies have addressed the safety and efficacy of repeated BoNT-A injections and none have shown effects on active movement.[19,20,23,24]

The present study is an open-label extension of a double-blind study that first demonstrated improvements in active range of motion after a single abobotulinumtoxinA injection.[25] This was observed alongside benefits for muscle tone, spasticity, and perceived function; however, no significant changes in active function were seen.[25] Herein we assessed 1-year safety and efficacy of abobotulinumtoxinA in adults with upper limb spasticity over repeated treatment cycles, using multiple outcomes, including active function, with active range of motion, spasticity, perceived function, and muscle tone.

METHODS

Study Population. This open-label extension included rollover patients from the double-blind trial (abobotulinumtoxinA and placebo groups)[25] and newly recruited patients receiving from 1 to 4 or 5 treatment cycles, respectively, ≥12 weeks apart over a fixed duration of 15 months per patient. The number of treatment cycles received depended on treatment interval duration, which varied according to each patient's individual needs. Patients' disposition data are shown in Figure 1.

Open-label cycle 1 includes newly recruited and rollover patients, representing the second abobotulinumtoxinA injection for double-blind study patients from the abobotulinumtoxinA group.

All double-blind study patients were eligible to be rollover patients providing they completed the double-blind study without major protocol deviations and/or ongoing adverse events (AEs) of unacceptable risk. Inclusion criteria for newly recruited patients were the same as for the double-blind study (refer to Supplementary Material available online).[25]

The primary target muscle group (PTMG; extrinsic finger, wrist, or elbow flexors) was selected by the investigators at baseline (rollover) or inclusion (newly recruited) as the muscle group with the highest Modified Ashworth Scale (MAS)[26] score. The PTMG remained constant throughout the study.

Study Objectives and Assessments. The primary objective was to assess safety of repeated abobotulinumtoxinA treatment cycles over 1 year in hemiparetic patients with upper limb spasticity post-stroke or -TBI. Treatment-emergent AEs (TEAEs) were elicited by direct, non-leading questioning or spontaneous reports from study consent to study end. Other safety parameters were vital signs (blood pressure, heart rate), laboratory data, electrocardiogram (ECG) analysis, and binding and neutralizing antibody analysis.

Secondary objectives were assessment of efficacy of repeated abobotulinumtoxinA treatment over 1 year on:

- Muscle tone (MAS) for finger, wrist, and elbow flexors, and shoulder extensors.
- Steps 2, 3, and 4 of the Five-Step Assessment [including the Tardieu Scale with passive range of motion (X_{V1}) and angle of catch (X_{V3}), as well as active range of motion (X_A); see below],[27] for finger, wrist, and elbow flexors; in shoulder extensors only X_{V1} and X_{V3} were assessed.
- Perceived function and pain [Disability Assessment Scale (DAS)].[28]
- Active upper limb function [Modified Frenchay Scale (MFS)][29,30] rated by assessors independent of the study.
- Physician Global Assessment (PGA) of treatment response, assessed using a 9-point scale from –4 (markedly worse) to 4 (markedly improved) and rated by an assessor other than the MAS assessor.
- Patient-reported ease of applying splint.[31]
- Quality of life (QoL), using the 36-item Short Form Health Survey (SF-36; perceived health score)[32] and Euro-QoL 5-Dimension Questionnaire (EQ-5D).[33]

In the Five-Step Assessment, steps 2, 3, and 4 evaluate angles of antagonist resistance. X_{V1} (angle of arrest upon slow and strong passive stretch) reflects passive extensibility of the muscle–tendon complex and spastic dystonia. X_{V1} is interpreted with respect to X_N (normal expected amplitude) using a coefficient of shortening, $C_{SH} = (X_N - X_{V1}) / X_N$ (finger, wrist, and elbow flexors, and shoulder extensors: $X_N = 300°$, 180°, 180°, and 180°, respectively). A higher coefficient of shortening indicates stiffer muscles.[29] X_{V3} (angle of catch upon fast stretch) reflects spasticity. X_A (maximal active range of motion against antagonist) reflects passive (stiffness) and active (spastic cocontraction) resistance to agonist effort.[27,29] Reliability of X_{V1}, X_{V3}, and X_A measurements has been demonstrated in children and adults.[34–36] Numerous studies support the value of X_{V1} and X_{V3} (Tardieu Scale) as compared with the MAS.[37,38]

Study Interventions. At cycle 1, all patients received 1,000 U abobotulinumtoxinA, except those who had TEAEs during the double-blind study who received 500 U abobotulinumtoxinA, based on the investigator's judgment. From cycle 2, patients received 500 U, 1,000 U, or 1,500 U injections at the investigator's discretion per cycle. For patients receiving 1,500 U abobotulinumtoxinA it was required that 500 U be injected into shoulder extensors (maximum 1,000 U across finger, wrist, and elbow flexors). Patients receiving <1,500 U total dose could receive shoulder muscle injections, providing PTMGs were injected with required doses. From cycle 3, patients could receive concomitant injections (500 U) into ≥1 calf muscle, providing the total dose was ≤1,500 U. To ensure optimal targeting of the injection, the protocol mandated that injections were administered using electrical stimulation (technique using an injection needle to deliver electrical pulses, which causes specific muscles to contract and thus ensures injection into the correct muscle).[39,40] At each visit from week 12 onward, patients were assessed to determine whether reinjection was required, based on the investigator's clinical judgment.
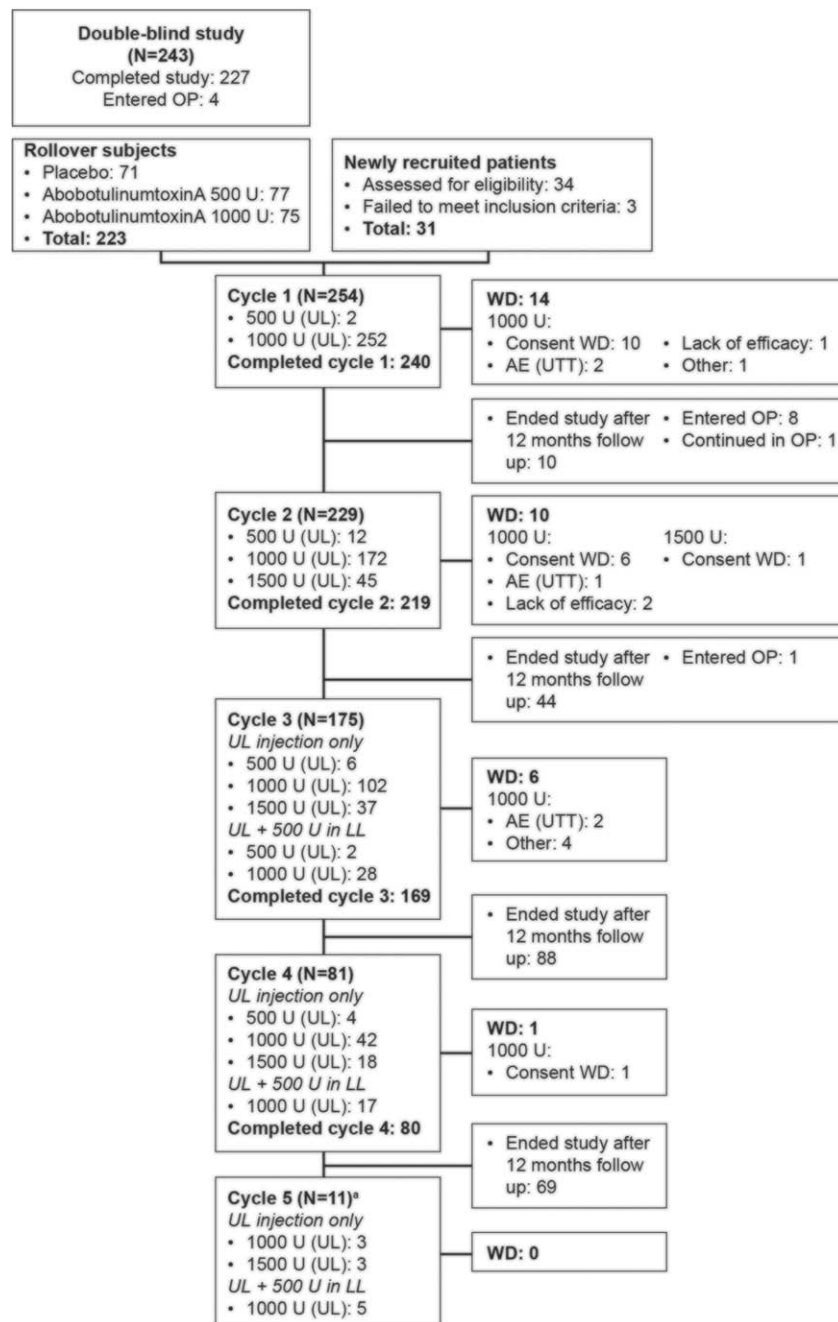
FIGURE 1. Disposition of patients. Differences in patient numbers between cycles due to patients entering the observational phase (OP) or ending the study after 12 months of follow-up. Patients in the OP were followed up every 4 weeks until they required reinjection or completed 12 months of follow-up. [a]Indicates newly recruited patients only. UL, upper limb; LL, lower limb; AE (UTT), adverse event (unrelated to treatment); WD, withdrawn.

Recommended injection volumes for individual muscle groups are summarized in Table S1 (refer to Supplementary Material online). The rationale for total injection volumes and dilutions used is also presented in the Supplementary Material.

No standardized physiotherapy regimen was associated with this protocol, but community physiotherapy initiated before study enrollment remained unchanged whenever possible until study end.

Statistical Analysis. No formal statistical comparisons were performed owing to the open-label study design. A descriptive analysis is presented for safety and efficacy parameters, and for comparisons of MAS in PTMG between toxin-naive and non–toxin-naive patients as well as between patients undergoing physiotherapy at baseline and those who were not. As patients could move between dose groups at each cycle, technical efficacy results for individual muscles (X_{V1}, X_{V3}, and X_A) were presented for all doses pooled; for comparison, a subanalysis of these parameters was performed for 27 patients who received a constant 1,000 U dose throughout the double-blind study to cycle 3. A *post-hoc* analysis assessed mean ($\pm$ standard deviation [SD]) coefficients of shortening at baseline.

An additional *post-hoc* analysis exploring linear relationships between composite X_A (sum of X_A against finger, wrist, and elbow flexors) and MFS was performed using Pearson correlation coefficients at baseline and week 4 of each cycle.

Standard Protocol Approval, Registration, and Patient Consent.
Our study was performed in compliance with the Declaration of Helsinki, good clinical practice guidelines, and local regulatory requirements, and with approval from all relevant institutional review boards and ethics committees. All patients signed site-specific, approved, written informed consent forms before study entry.

RESULTS

Baseline Characteristics and Exposure.
In total, 258 patients (227 rollover and 31 newly recruited patients; 4 rollover patients entered the observation phase before cycle 1 and were not injected in the open-label phase) were enrolled over 34 sites in Belgium, Czech Republic, France, Italy, Poland, Russia, Slovakia, and the USA. Age was 52.4 ± 13.9 years, 64.3% were male, and 45.0% were toxin-naive in the paretic limb. Hemiparesis was stroke-induced in 89.1% of patients and TBI-induced in 10.9%; time since event was 5.1 ± 4.2 years and 9.9 ± 8.0 years, respectively. The proportion of patients undergoing physiotherapy before the study was 48.4%; this proportion remained similar throughout the study.

Extrinsic finger flexors were selected as PTMG in 56.6% of patients, wrist flexors in 16.7%, and elbow flexors in 26.7%. Coefficients of shortening at baseline[29] were 34.5 ± 16.4% for extrinsic finger flexors ($n = 225$), 20.7 ± 16.2% for wrist flexors ($n = 186$), 3.9 ± 7.2% for elbow flexors ($n = 185$), and 25.4 ± 14.1% for shoulder extensors ($n = 31$).[29] Principal target of treatment for DAS was limb position in 44.6% of patients, dressing in 26.4%, hygiene in 22.1%, and pain in 6.6%.

Duration of repeated abobotulinumtoxinA treatment was 54.0 ± 9.9 weeks for rollover (including double-blind study) patients and 55.8 ± 11.9 weeks for newly recruited patients. Overall, 240 patients completed cycle 1, 219 completed cycle 2, 169 completed cycle 3, 80 completed cycle 4, and 11 completed cycle 5 (Fig. 1). Injection doses and prevalence by muscle group (PTMG and overall) are summarized in Table S2 (Supplementary Material). At cycle 1, 99.2% of patients received 1,000 U abobotulinumtoxinA in the upper limb. Across cycles, a trend toward using higher doses was observed: 1,500 U abobotulinumtoxinA was used in 19.7% of patients at cycle 2 and 43.2% by cycle 4 (Fig. 1). The proportion of patients injected in shoulder extensors (regardless of dose) progressed from 13.8% (cycle 1) to 40.7% (cycle 4). Affected lower limbs were injected in 17.1% and 21.0% of patients during cycles 3 and 4, respectively.

Safety Results.
Figure 1 shows most patients who left the study between cycles did so because they reached maximum treatment duration (15 months), due to injection intervals of >12 weeks, and not because of AEs. Under these circumstances, overall incidence of TEAEs decreased across subsequent treatment cycles for all doses combined, from 40.2% (cycle 1) to 13.6% (cycle 4). Similarly, TEAEs considered treatment-related decreased from 7.1% to 2.5% (Table 1). Most TEAEs were of mild to moderate intensity. The most frequently reported TEAEs were focal muscle weakness, falls, and pain in extremities. Over all open-label cycles, muscle weakness was reported in 11 (4.3%) and 3 (5.0%) patients after 1,000 U and 1,500 U injections, respectively. After injections of 500 U, 1,000 U, and 1,500 U, falls occurred in 2 (11.8%), 15 (5.9%), and 4 (6.7%) patients, respectively, and pain in extremities occurred in 1 (5.9%), 11 (4.3%), and 4 (6.7%) patients, respectively. In cycles 3 and 4 (when lower limb injections were permitted), occurrence rates of falls were 5.5% ($n = 2$ of 36) in patients receiving lower limb injections and 3.6% ($n = 5$ of 139) in patients receiving upper limb injections only. None of these falls at cycles 3 and 4 were considered treatment-related by the investigator and none led to fractures.

Three fatalities occurred due to serious AEs (SAEs), all following injections of 1,000 U; none were considered treatment-related by the investigator and all were considered most likely to be related to underlying clinical conditions. These were due to metastatic cancer, cardiopulmonary arrest, and myocardial infarction. In addition, 2 TEAE cases led to withdrawal, both after 1,000 U injections: 1 patient had emotional lability reported as an SAE, which was considered unrelated to treatment; and 1 patient had a pregnancy after initial open-label injection, after which she gave birth to a full-term, healthy neonate.

Although none of the AEs of special interest were assessed by investigators as causally related to abobotulinumtoxinA, the sponsor's evaluation identified 2 cases (constipation and diplopia) in which possible remote spread of toxin effect could not be ruled out. No cases of generalized muscular weakness, dysphagia, or dysphonia were seen as remote spread effects. In addition, no AE terms were assessed as suggestive of hypersensitivity-type reactions.

At baseline, 4 patients had neutralizing antibodies. Overall, 11 patients (4.3% of enrolled patients) converted for neutralizing antibodies during the study. Of these, 3 had transient

Events	Double-blind (N = 154)	Cycle 1 (N = 254)	Cycle 2 (N = 229)	Cycle 3 (N = 175)	Cycle 4 (N = 81)
Summary of TEAEs by treatment cycle					
aboBoNT-A 500 U (UL)	n = 78	n = 2	n = 12	n = 8	n = 4
TEAEs	32 (41.0) [89]	1 (50.0) [2]	3 (25.0) [10]	1 (12.5) [2]	0
Related TEAEs	6 (7.7) [11]	0	1 (8.3) [1]	0	0
AESI	4 (5.1) [7]	0	0	0	0
SAEs	3 (3.8) [3]	0	0	0	0
aboBoNT-A 1,000 U (UL)	n = 76	n = 252	n = 172	n = 130	n = 59
TEAEs	32 (42.1) [64]	101 (40.1) [192]	45 (26.2) [81]	31 (23.8) [83]	10 (16.9) [25]
Related TEAEs	7 (9.2) [10]	18 (17.1) [26]	4 (2.3) [5]	3 (2.3) [4]	2 (3.4) [3]
AESI	7 (9.2) [7]	14 (5.6) [15]	2 (1.2) [2]	2 (1.5) [3]	1 (1.7) [1]
SAEs	2 (2.6) [2]	10 (4.0) [12]	6 (3.5) [10]	5 (3.8) [10]	1 (1.7) [3]
aboBoNT-A 1,500 U (UL)	NA	NA	n = 45	n = 37	n = 18
TEAEs	—	—	14 (31.1) [29]	15 (40.5) [22]	1 (5.6) [1]
Related TEAEs	—	—	3 (6.7) [3]	2 (5.4) [2]	0
AESI	—	—	3 (6.7) [3]	1 (2.7) [1]	0
SAEs	—	—	0	1 (2.7) [1]	0
All doses (UL+LL)	n = 154	n = 254	n = 229	n = 175	n = 81
TEAEs	64 (41.6) [153]	102 (40.2) [194]	62 (27.1) [120]	47 (26.9) [107]	11 (13.6) [26]
Related TEAEs	13 (8.4) [21]	18 (7.1) [26]	8 (3.5) [9]	5 (2.9) [6]	2 (2.5) [3]
AESI	11 (7.1) [14]	14 (5.5) [15]	5 (2.2) [5]	3 (1.7) [4]	1 (1.2) [1]
SAEs	5 (3.2) [5]	10 (3.9) [12]	6 (2.6) [10]	6 (3.4) [11]	1 (1.2) [3]
Preferred term*					
All aboBoNT-A doses	n = 154	n = 254	n = 229	n = 175	n = 81
Fall	3 (1.9) [3]	9 (3.5) [9]	7 (3.1) [7]	6 (3.4) [7]	1 (1.2) [2]
Muscle weakness	6 (3.9) [6]	9 (3.5) [9]	2 (0.9) [2]	2 (1.1) [2]	1 (1.2) [1]
Pain in extremity	0	6 (2.4) [6]	6 (4.6) [8]	2 (1.1) [2]	2 (2.5) [2]
Nasopharyngitis	8 (5.2) [8]	4 (1.6) [5]	0	2 (1.1) [2]	0
Bronchitis	2 (1.3) [2]	0	1 (0.4) [1]	4 (2.3) [4]	0
Blood triglycerides increased	4 (2.6) [4]	0	1 (0.4) [1]	0	0

Data expressed as: **n** *(%) [number of events]. Results are from patients injected with active treatment only, and placebo group is not shown. Patients are grouped according to dose received in the UL, regardless of dose injected in the lower limb. aboBoNT-A, abobotulinumtoxinA; AESI, adverse event of special interest; LL, lower limb;* **N***, number of patients in group;* **n***, number of patients with data; NA, not applicable; SAE, serious adverse event; TEAE, treatment-emergent adverse event; UL, upper limb.*

**Preferred term for TEAEs displayed by ≥2% of patients at any cycle.*

seroconversion while continuously injected, returning to negative by study end, and 8 seroconverted for neutralizing antibodies up to study end. These 11 patients received various doses of abobotulinumtoxinA, in a proportion comparable to that of the whole study population. There was no suggestion of reduced abobotulinumtoxinA efficacy in patients with neutralizing antibodies at baseline or throughout the study.

No clinically significant differences in clinical hematology or biochemistry parameters occurred at any dose or cycle from baseline to last visit. Mean changes in systolic and diastolic blood pressure and heart rate between baseline and week 4 were within clinically normal ranges and, despite slight increases in blood pressure and heart rate, these were not considered significant for any dose or cycle. ECG analysis showed no cardiac safety risk at any dose or cycle.

Efficacy Results. Muscle tone improvements (MAS) after initial injection into PTMGs in the double-blind study from baseline (3.9 ± 0.4) to week 4 (2.7 ± 1.1)[25] remained stable across cycles (cycle 4 week 4, 2.6 ± 1.1) (see Table S3 in Supplementary Material). Effects on muscle tone were similar between toxin-naive and non–toxin-naive patients, and between patients who underwent physiotherapy and those who did not.

X_{V1}, X_{V3}, and X_A improved at week 4 of each cycle in PTMGs and shoulder extensors (Fig. 2). In PTMGs, X_{V1} remained relatively stable across cycles, whereas X_{V3} and X_A continued to improve (Fig. 2). For extrinsic finger flexors, X_{V1} was maintained across cycles (between 207.6 ± 47.6° at cycle 4 and 217.2 ± 40.7° at cycle 2; baseline 193.1 ± 49.6°), whereas X_{V3} and X_A continued to improve up to 162.2 ± 50.1° (baseline 98.6 ± 53.2°) and 91.4 ± 56.2° (baseline 41.9 ± 48.9°), respectively (Fig. 2A). Comparable results were observed for wrist and elbow flexors (Fig. 2B and C, respectively). In elbow flexors, X_A was noted to consistently reach higher values than X_{V3} (Fig. 2C). In shoulder extensors, improvements in X_{V1} and X_{V3} were observed over cycles with increases in mean change from baseline, from +3.2 ± 8.0° (double-blind) to +10.8 ± 26.1°
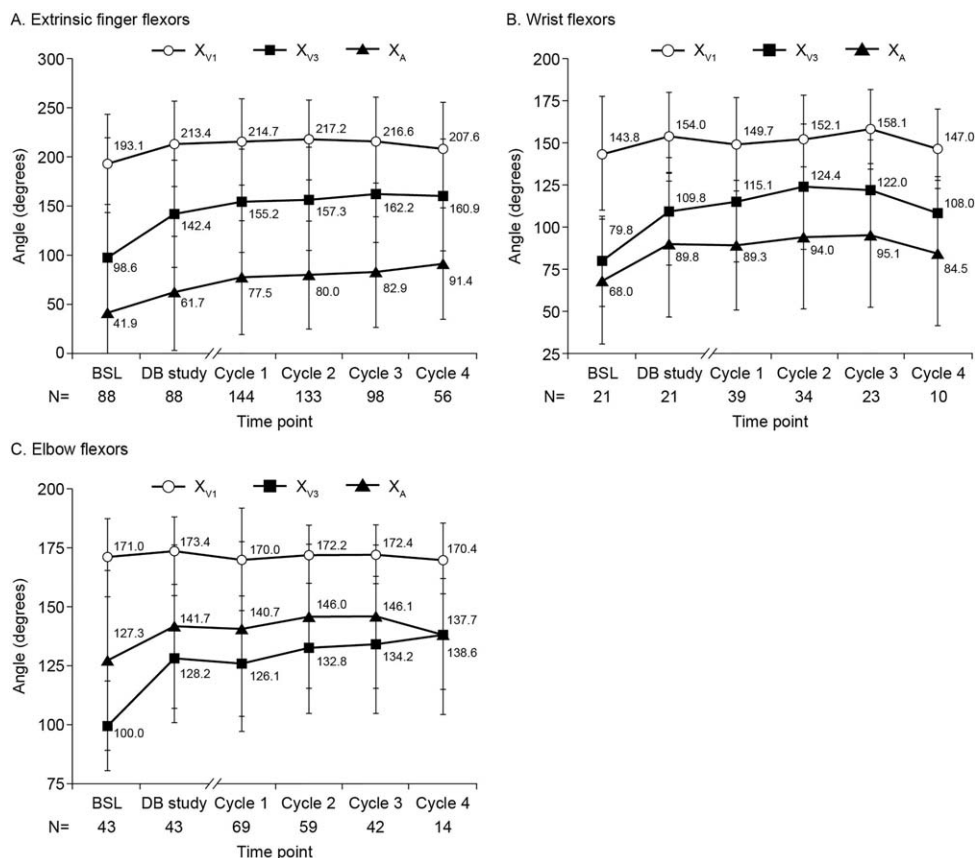
FIGURE 2. Passive range of motion (X_{V1}), angle of catch (X_{V3}), and active range of motion (X_A) at baseline and week 4 of each cycle in each primary target muscle group for all patients and all doses pooled. Values are presented as mean (standard deviation). BSL, baseline of double-blind study; DB, double-blind.

(cycle 4) for X_{V1}, and $+11.4 \pm 18.3°$ (double-blind) to $+18.0 \pm 19.6°$ (cycle 4) for X_{V3} (see Table S3 in Supplementary Material). Results for X_{V1}, X_{V3}, and X_A in 27 patients injected with a constant 1,000-U dose throughout double-blind to cycle 3 were comparable.

For perceived function (DAS), percentage of responders (≥ 1 grade reduction from baseline) at week 4 progressively increased in all 4 domains from double-blind to cycle 4 (Fig. 3). Increases for all doses combined were observed from 45.4% to 53.1% for limb position, 32.9% to 53.1% for dressing, 34.9% to 46.9% for hygiene, and 28.3% to 48.1% for pain. Figure 3 suggests more marked effects at cycles 3 and 4 with 1,500 U of abobotulinumtoxinA compared with 1,000 U for limb position (70.3% vs. 56.9% and 61.1% vs. 49.2%, respectively) and dressing (59.5 vs. 42.3% and 61.1 vs. 47.5%, respectively). Results for patients injected with 500 U are not presented, as very few patients received this dose.

For active function, mean change from baseline in global MFS score across cycles peaked at $+0.43 \pm 0.82$ (cycle 2) after 1,000 U injections and $+0.76 \pm 0.67$ (cycle 2) after 1,500 U injections (Fig. 4, see also Table S3 in Supplementary Material). There

was high correlation between composite X_A and MFS at each of these study visits (Table 2).

PGA scores (1.5 at double-blind week 4) were 1.7, 1.9, 1.9, and 2.0 for all doses at cycle 1 to cycle 4, respectively. Mean scores for ease of applying a splint (improved during the double-blind study) remained stable across open-label cycles at week 4. Slightly positive changes in SF-36 or EQ-5D scores were observed from baseline to final visit: SF-36 physical component, $+1.07 \pm 6.76$; SF-36 mental component, $+0.96 \pm 11.1$; and visual analog scale of EQ-5D, $+2.8 \pm 19.0$.

Across open-label cycles, a large proportion of patients did not require reinjection at week 12 (all doses combined). For patients who received a second treatment cycle in the open-label phase, 35% were reinjected at week 16 or later (20% at week 16, 7.0% at week 20, 8% at week 24 or later). For those who received a third treatment cycle in the OL phase, 24% were reinjected at week 16 or later (19% were retreated at week 16, 3% at week 20, 2% at week 24 or later).

DISCUSSION

This open-label extension to a double-blind study in 223 rollover and 31 newly recruited
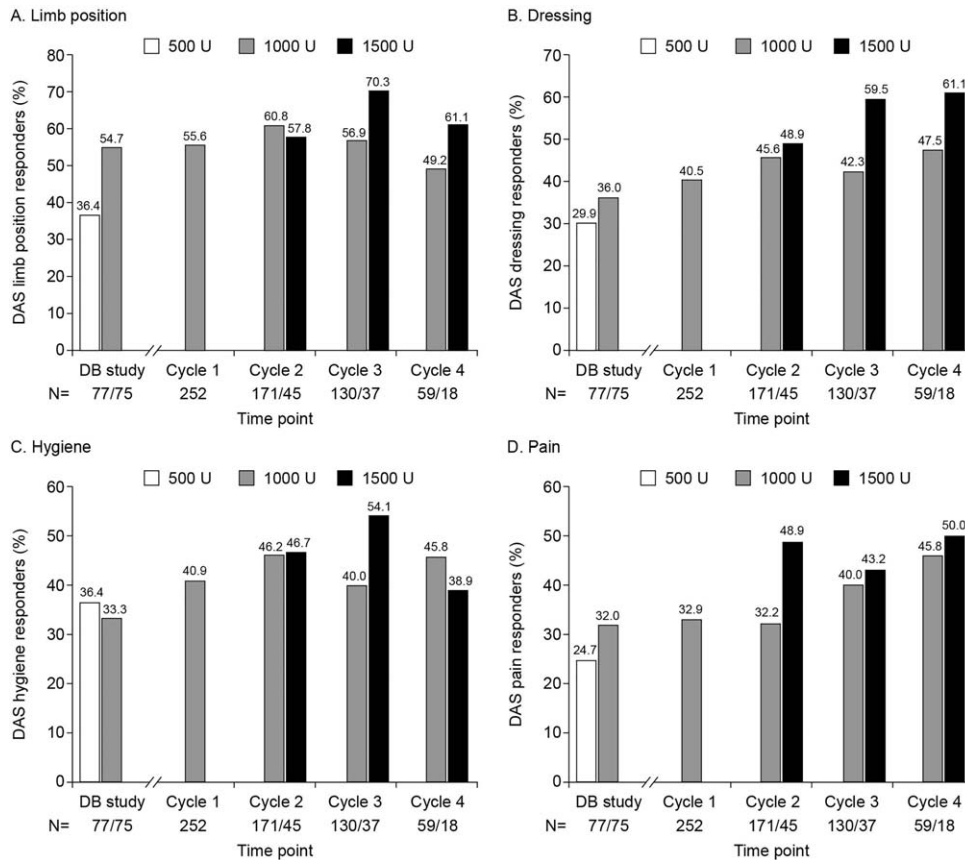
FIGURE 3. Disability Assessment Scale responders for each domain by abobotulinumtoxinA dose at week 4 of each cycle. Data for 500 U are not presented for cycles 1–4 due to small patient numbers, which provide little statistical value. N values are presented in order of doses shown (500 U, 1,000 U, 1,500 U). DAS, Disability Assessment Scale; DB, double-blind.
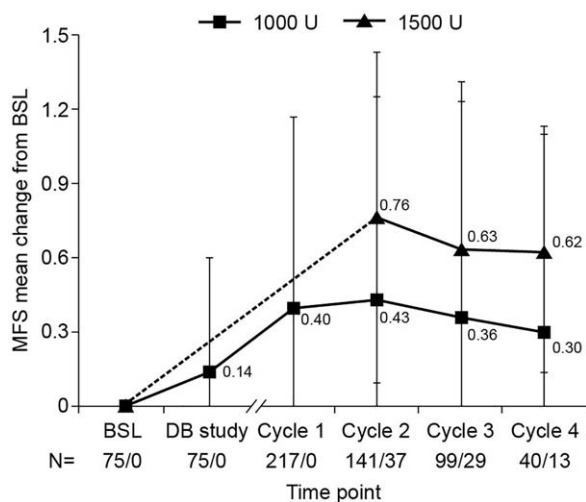
FIGURE 4. Mean change in Modified Frenchay Scale overall score by abobotulinumtoxinA dose at week 4 of each cycle. Values are presented as mean (standard deviation). Data for 500 U are not presented due to small patient numbers, which provide little statistical value. N values are presented as those for 1,000 U and 1,500 U. The dotted line indicates change from baseline to cycle 2 for 1,500 U, as patients could not receive this dose in the DB study and at cycle 1. BSL, baseline of DB study; DB, double-blind; MFS, Modified Frenchay Scale.

hemiparetic adults with upper limb spasticity showed that repeated abobotulinumtoxinA injections (500 U, 1,000 U, and 1,500 U), administered using electrical stimulation, were well tolerated over 1 year. Injections were associated with further improvements in active range of motion and active function, despite stabilization of tone and passive range of motion.

Safety of Repeated AbobotulinumtoxinA Injections over 1 Year. For patients remaining in the study there were decreasing reports of TEAEs across cycles. As many patients completed 15 months of follow-up before study end (Fig. 1), it cannot be concluded definitively that the incidence of TEAEs decreased across repeated injection cycles. These reports of decreasing TEAEs are still remarkable as patients present at later cycles received more injection cycles and tended to be injected with higher doses, yet reported fewer TEAEs. Possible explanations for increasingly higher injection doses across cycles, despite gradual spasticity reduction (Fig. 2), include patients developing a tolerance to side effects as well as the option to use the 1,500 U total dose to include shoulder muscles

Table 2. Correlation between Modified Frenchay Scale and composite active range of motion (X_A) at week 4 of each cycle (absolute values).

Visit	Placebo	aboBoNT-A 1,000 U	aboBoNT-A 1,500 U
Baseline (*n*)	37	43	—
Correlation coefficient	0.6600	0.6486	—
P-value	<0.0001	<0.0001	—
Double-blind (*n*)	36	43	—
Correlation coefficient	0.6077	0.5632	—
P-value	<0.0001	<0.0001	—
Cycle 1 (*n*)	—	119	—
Correlation coefficient	—	0.4987	—
P-value	—	<0.0001	—
Cycle 2 (*n*)	—	83	23
Correlation coefficient	—	0.5156	0.3905
P-value	—	<0.0001	0.0654
Cycle 3 (*n*)	—	49	19
Correlation coefficient	—	0.5407	0.5368
P-value	—	<0.0001	0.0178
Cycle 4 (*n*)	—	16	10
Correlation coefficient	—	0.3082	0.6654
P-value	—	0.2456	0.0358

Composite X_A equals the sum of X_A for extrinsic finger, wrist, and elbow flexors. Coefficients presented are Pearson correlations. Data for 500 U are not presented due to small patient numbers, providing little statistical value. aboBoNT-A, abobotulinumtoxinA; X_A, active range of motion.

and then lower limb injections after cycles 2 and 3, respectively. Thus, no cumulative detrimental effect on safety was suggested over several injections cycles.

A slightly higher percentage of falls (none considered treatment-related) was observed in patients receiving lower limb injections compared with those receiving upper limb injections only at cycles 3 and 4. This observation is difficult to interpret as the expected risk of falls would be higher in patients with higher levels of lower limb overactivity, which may have led the investigator to include the lower limb into the injection plan.

Slight increases in blood pressure and heart rate were not associated with clinical cardiac events or cardiac safety risk and were most likely related to underlying clinical conditions of the patient. Finally, the way TEAEs were elicited (non-leading questioning and spontaneous reports) may be open to risks of underreporting, as many leading questioning result in overreporting. Yet, TEAE elicitation methods remained consistent across treatment cycles, where reduced incidence of TEAEs was observed.

Limitations of the Efficacy Study. Patient numbers per dose varied at each cycle, as patients moved between doses. All doses are thus presented together for changes in X_{V1}, X_{V3}, and X_A; however, results for 27 patients receiving a constant dose (1,000 U) throughout double-blind study to cycle 3 proved comparable with the whole group for these parameters. Not all patients required reinjection at week 12 of each cycle; thus, time intervals between injections varied. This is to be considered for Figure 2, in which the slight downward trend

for X_{V3} and X_A by cycle 4 for wrist and elbow flexors corresponded to the limited number of patients injected at cycle 4. At cycle 4, the 10 patients injected into wrist flexors as PTMG (Fig. 2B) and 14 patients injected into elbow flexors as PTMG (Fig. 2C) are those patients injected most often, and therefore likely to have been more severe or less responsive to treatment compared with other patients. X_A was measured in PTMGs only, thus active shoulder flexion was not measured; this may have given specific insight into potential benefit of injections targeting shoulder extensors. Finally, goal attainment measurements could have added patient-centered reporting of outcomes, in addition to assessment of perceived function (DAS), as patient goals may vary across cycles.[9,17] In the present study, PTMGs remained constant throughout cycles, which may constitute a relative weakness of the study in terms of adjusting objectives and reaching maximal efficacy with each injection.[9,17]

Cumulative Effect of Repeated AbobotulinumtoxinA Injections on Active Movements. Although the improvements in muscle tone and X_{V1} observed after initial injection[25] were maintained across cycles, progressive improvements in X_{V3} (reflecting muscle activation upon fast stretch at rest) and X_A (reflecting muscle activation upon spastic cocontraction during voluntary command) continued for all PTMGs across injection cycles. For example, active finger extension more than doubled by cycle 4 from double-blind baseline (increase of about 50°), potentially allowing for sufficient active hand opening for some grasping tasks, as suggested by

the positive MFS results. Similar to cumulative spasticity reduction (X_{V3}), a large amount of descending motor unit recruitment in spastic cocontraction[41] remaining despite a first injection may be further diminished through additional injection cycles.

Interestingly, elbow flexors were the sole PTMG where X_A consistently surpassed X_{V3}. This may relate to particularly low coefficients of shortening in elbow flexors (3.9%), which are likely related to fewer shortening positions being imposed on this muscle group compared with other upper limb muscles (finger flexors, wrist flexors, and shoulder extensors) during acute and subacute stroke care.[29] A low coefficient of shortening may allow for reduced tension during elbow extension, generating less afferent volley and therefore less spastic cocontraction in elbow flexors.[41] In addition, the method of measuring active elbow extension (downward movement not requiring shoulder flexor recruitment)[25] may have placed elbow flexors at an additional advantage in terms of cocontraction.[42]

Improvement of Perceived and Active Function across Cycles. Progressive increases in perceived function (DAS responders) occurred across cycles, particularly for dressing, a domain mostly involving active upper limb movements.

Active function improvement on MFS across cycles was at least double that of the double-blind study (+0.14),[25] reaching a level considered clinically meaningful (>0.5 increase in mean change from baseline).[30] Although improvements in perceived function (DAS responders) have been demonstrated,[10] prior studies have not provided evidence supporting the benefit of BoNT-A injections in active function.[10,21]

For perceived and active function, responder rates were higher after 1,500 U injections compared with 1,000-U injections, which may suggest the importance of injecting the shoulder muscles. Indeed, shoulder extensor injections may have improved active shoulder flexion (not assessed here), a joint movement required in most daily activities,[43] as tested in the DAS and MFS. However, the present data could not demonstrate that higher responder rates were not simply due to higher doses injected, regardless of shoulder targeting. Patients injected with 1,500 U had notably lower baseline MFS scores (3.17 ± 0.96 vs. 3.94 ± 1.50; see Table S3 in Supplementary Material), which may explain why they received the highest dose and shoulder injections. Interestingly, MFS improvement patterns paralleled those of X_A, and strong correlations were demonstrated between active function and composite active motion at each visit. Yet, these functional improvements were

paralleled by positive but small changes in SF-36 and EQ-5D scores,[44,45] which could suggest functional upper limb changes of a greater magnitude may be needed for a meaningful impact on quality of life or perceived health scores. Overall, the results of the present study seem more positive than those obtained by Shaw et al. or Lagalla et al.,[19,20] which may be due to a number of factors, including the electrical stimulation localization method systematically used to target muscles in our study, overall doses injected, and the outcome measures used. MFS (using visual analog rating for each task instead of an ordinal scale) and X_A measurements used here may be more sensitive to change than the Action Research Arm Test,[19] or Frenchay Arm Test.[20]

In this study we obtained favorable safety data in hemiparetic adults with upper limb spasticity after repeated abobotulinumtoxinA injections over 1 year. Across cycles, efficacy on muscle tone and passive range of motion (X_{V1}) was maintained in the elbow, wrist, and extrinsic finger flexors, whereas angle of catch (X_{V3}) and active range of motion (X_A) continued to progress. Shoulder extensors also showed improvements in X_{V1} and X_{V3}. Perceived function (DAS) improved over repeated cycles. Higher efficacy was suggested when injecting 1,500 U vs. 1,000 U abobotulinumtoxinA for perceived and active function, possibly indicating the importance of shoulder muscle injections. In addition, the retreatment intervals of >12 weeks observed in many patients could potentially reduce the burden associated with frequency of injections for patients and their caregivers/families. This also highlights the need for a tailored approach in the treatment of patients with upper limb spasticity. As these results were obtained without a systematic standardized rehabilitation protocol, it may be worth exploring if repeated BoNT injections in combination with an aggressive, individually tailored rehabilitation program would yield greater improvements over time in hemiparetic patients.

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