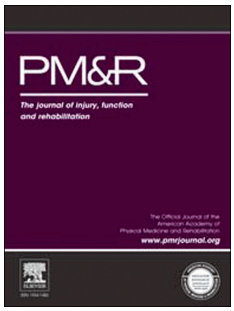
Accepted Manuscript



Dose-Dependent Effects of Abobotulinumtoxina (Dysport®) on Spasticity and Active Movements in Adults With Upper Limb Spasticity: Secondary Analysis of A Phase 3 Study

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PII: S1934-1482(17)30240-X

DOI: 10.1016/j.pmrj.2017.06.008

Reference: PMRJ 1921

To appear in: *PM&R*

Received Date: 1 March 2017

Revised Date: 23 May 2017

Accepted Date: 7 June 2017

Please cite this article as: O'Dell MW, Brashear A, Jech R, Lejeune T, Marque P, Bensmail D, Ayyoub Z, Simpson DM, Volteau M, Vilain C, Picaut P, Gracies JM, Dose-Dependent Effects of Abobotulinumtoxina (Dysport®) on Spasticity and Active Movements in Adults With Upper Limb Spasticity: Secondary Analysis of A Phase 3 Study, *PM&R* (2017), doi: 10.1016/j.pmrj.2017.06.008.

DOSE-DEPENDENT EFFECTS OF ABOBOTULINUMTOXINA (DYSPORT®) ON SPASTICITY AND ACTIVE MOVEMENTS IN ADULTS WITH UPPER LIMB SPASTICITY: SECONDARY ANALYSIS OF A PHASE 3 STUDY

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Conflicts of interest: AB reports grants payable to Wake Forest School of Medicine from Ipsen and personal consulting fees for protocol development from Ipsen during the conduct of this study. AB reports grants and personal fees for protocol development from Revance and Allergan, personal fees for protocol development from Concert and World Meds and grants from NINDS. AB is also a board member of the American Board of Psychiatry and Neurology. AB's conflict of interest is managed by Wake Forest School of Medicine. J-MG received payment per recruited patient by Ipsen during the conduct of this study. J-MG served as a consultant for and received research grant support from Allergan, Ipsen, and Merz. RJ has received grants from Ipsen during the conduct of this study. RJ has received grants from the Czech Science Foundation, Czech Ministry of Health, Czech Ministry of Education, and Charles University, Prague and honorarium from Ipsen for consultations and lectures. MOD reports grants from Ipsen during the conduct of this study and has served

on the Scientific Advisory Board for Ipsen, Allergan and Merz. TL reports grants from Ipsen during the conduct of this study. TL also reports grants from Ipsen and personal fees from Merz outside the submitted work. PM reports research support grants from Ipsen and Merz. PM served as a consultant for and participated in Scientific Advisory Boards for Allergan, Ipsen and Merz. PM has also participated in satellite symposia for Allergen, Ipsen and Merz and reports speaker fees from Almirall. DB reports grants, personal fees and non-financial support from Ipsen, during the conduct of the study. In addition, DB reports grants, personal fees and non-financial support from Allergan, Merz, Medtronic and Almirall outside the submitted work. ZA reports grants and personal fees from Ipsen during the conduct of this study. ZA also reports grants and personal fees from Allergan and Merz outside of the submitted work. DMS reports grants and personal fees from Ipsen, Allergan and Merz. MV, CV, and PP are employees of Ipsen.

Acknowledgements

Medical writing and submission support, under the direction of the authors, were provided by Jacqueline Harte and Germanicus Hansa-Wilkinson of Watermeadow Medical, an Ashfield Company, funded by Ipsen. Study sponsorship by Ipsen.

Dose-dependent effects of abobotulinumtoxinA (Dysport®) on spasticity and active movements in adults with upper limb spasticity: Secondary analysis of a Phase 3 study

Word Count: 3313/5000

Level of evidence: Level 1

Trial registration: ClinicalTrials.gov number NCT01313299

Keywords: AbobotulinumtoxinA; upper limb spasticity; stroke; traumatic brain injury; dosing***.***

Funding: This study was sponsored by Ipsen.

Abstract (299/300 words):

Background: AbobotulinumtoxinA has beneficial effects on spasticity and active movements in hemiparetic adults with upper limb spasticity (ULS). However, evidence-based information on optimal dosing for clinical use is limited.

Objective: To describe joint-specific dose effects of abobotulinumtoxinA in adults with ULS.

Design: Secondary analysis of a phase 3 study (NCT01313299).

Setting: Multi-center, international, double-blind, placebo-controlled clinical trial.

Participants: 243 adults with ULS >6 months after stroke or traumatic brain injury, aged [mean (SD)] 52.8 (13.5) years and 64.3% male, randomized 1:1:1 to receive a single injection cycle of placebo or abobotulinumtoxinA 500 U or 1000 U (total dose).

Methods: The overall effect of injected doses were assessed in the primary analysis, showing improvement of angles of catch in finger, wrist and elbow flexors and of active range of motion against these muscle groups. This secondary analysis was performed at each of the possible doses received by finger, wrist and elbow flexors in order to establish possible dose effects.

Main Outcome Measures: Angle of arrest (X_{V1}) and angle of catch (X_{V3}) assessed using the Tardieu scale, and active range of motion (X_A).

Results: At each muscle group level (finger, wrist and elbow flexors) improvements in all outcome measures assessed (X_{V1}; X_{V3}; X_A) were observed. In each muscle group, increases in abobotulinumtoxinA dose were associated with greater

improvements in angle of catch (X_{V3}) and active range of motion (X_A), suggesting a dose-dependent effect.

Conclusions: Previous clinical trials have established the clinical efficacy of abobotulinumtoxinA by total dose only. The wide range of abobotulinumtoxinA doses per muscle groups used in this study allowed observation of dose-dependent improvements in spasticity and active movement. This information provides a basis for future abobotulinumtoxinA dosing recommendations for healthcare professionals based on treatment objectives and quantitative assessment of spasticity and active range of motion at individual joints.

Introduction:

Upper limb spasticity (ULS) is a common symptom following stroke and traumatic brain injury (TBI) associated with impaired self-care and additional burden of care [1,2,3,4,5]. Among several treatment strategies, guidelines recommend intramuscular botulinum toxin injections as a first-line treatment for adults with ULS [6,7,8,9,10,11].

Botulinum toxin type A (BoNT-A) injections may target upper extremity muscle groups from the shoulder, to decrease adductor and internal rotation tone, to the elbow, wrist, fingers and thumb, to decrease flexor tone [12,13]. Specific muscle selection is based on the pattern of muscle over-activity, functional deficits, and patient goals [6]. These goals include increased passive and active range of motion, improved function (feeding and dressing), easier care (palmar and axillary hygiene) and reduction of pain [13].

Evidence-based information on optimal dosing for clinical use is relatively sparse. Dosing is not interchangeable between different BoNT-A products, therefore improving our understanding of product-specific dosing will minimize confusion among injectors and improve the quality of patient care [13].

Among BoNT-A formulations, abobotulinumtoxinA (Dysport®) has been shown to decrease muscle tone (as measured by the Modified Ashworth Scale [MAS]) [13,14,15,16,17] and pain [18], and to facilitate goal attainment [19] in adults with ULS. A recent systematic review [13] of 12 randomized controlled trials (RCTs) in ULS concluded that abobotulinumtoxinA (total dose range, 500 U to 1500 U) was generally well-tolerated, with “strong evidence” to support reduced muscle tone.

This paper presents the results of a secondary analysis from a recently published large international clinical trial, demonstrating improved active range of motion following abobotulinumtoxinA treatment in adults with hemiparesis and ULS >6 months after stroke or TBI [20]. This phase 3, randomized, double-blind, placebo-controlled study demonstrated that a total dose of either 500 U or 1000 U abobotulinumtoxinA injected in the upper extremity also resulted in decreased muscle tone and improvements in global physician-assessed clinical benefit compared with placebo. Apart from a systematic measurement of active range of motion (X_A) against finger, wrist and elbow flexors, another unique aspect of the trial was the assessments of spasticity at the finger, wrist and elbow flexor groups using the Tardieu Scale (TS) [21,22]. The TS is a standardized evaluation assessing the angle of arrest at slow speed (ie, passive range of motion, X_{V1}) and the angle of catch at fast speed (X_{V3}). The trial demonstrated improvements for finger, wrist and elbow joints at week 4 in the angle of catch (X_{V3}) at both abobotulinumtoxinA doses, and in active range of motion (X_A) at 1000 U; for the 500 U dose, improvements in X_A were seen in the finger flexors. Both doses were associated with a favorable safety profile [20].

This analysis aims to provide a detailed description of improvements in spasticity and the active range of motion for individual muscle groups by dose, and to provide information on muscle-specific dosing, which can be used in future recommendations for injectors.

Methods:

Trial design

The clinical trial (NCT01313299) was conducted between August 4, 2011 and September 4, 2013, and involved 34 sites across 9 countries (Belgium, Czech Republic, France, Hungary, Italy, Poland, Russian Federation, Slovakia, USA). The trial was a phase 3, prospective, randomized, placebo-controlled study involving one double-blinded treatment cycle with at least 12 weeks follow-up. Subjects were randomized to three treatment groups (1:1:1) receiving a total upper extremity dose of 500 U abobotulinumtoxinA, 1000 U abobotulinumtoxinA, or placebo, attributed in a blinded manner. A full description of the main study design and primary results has been published previously [20].

Inclusion / Exclusion Criteria

Pertinent inclusion criteria for the current analyses were persons aged between 18 and 80 years with residual hemiparesis >6 months after a clinically defined stroke or TBI. For each subject, the most hypertonic (greatest MAS score) muscle group was identified and designated the primary targeted muscle group (PTMG) from the following three:

- finger flexors (flexor digitorum profundus [FDP] and flexor digitorum superficialis [FDS])
- wrist flexors (flexor carpi ulnaris [FCU] and flexor carpi radialis [FCR])
- elbow flexors (brachialis with optional addition of brachioradialis).

Of note, a greater MAS threshold was required to designate the PTMG if the subject had received BoNT previously (MAS ≥3) as opposed those who were BoNT-naïve (MAS ≥2) in the affected limb. Additional criteria included a substantial subjective perception of disability (score ≥2 on the Disability Assessment Scale in the domain selected as the principal target of treatment), spasticity angle ≥10° on the TS for the

most spastic muscle group, and a mean Modified Frenchay Scale score of 1–8 (average of all items, range 0–10). Pertinent exclusion criteria included major limitations in the angle of arrest (X_{V1}); history of BoNT non-response; BoNT treatment within 4 months prior to enrolment or the need for lower extremity treatment during the study; previous treatment with surgery, alcohol or phenol in the affected limb; medical conditions increasing the risk of BoNT-A-related adverse events; and major neurological impairment (other than hemiparesis) influencing functional performance.

Study Treatment

Once identified, muscles of the PTMG received a fixed, pre-determined injection volume containing a lower or higher abobotulinumtoxinA dose or placebo, depending on the total dose attributed by the blinded randomization (Table 1). In addition to the PTMG, the investigators were required to inject at least two other upper limb muscles. The volume/dose for these additional muscles was not fixed, but rather selected by the investigator within a pre-specified recommended range (Table 1).

Initial data review revealed that, for a given muscle, investigators consistently chose to inject lower abobotulinumtoxinA volumes/doses into non-PTMGs compared with the required volume/dose for the PTMG at each of the three selected joints. This allowed the designation of four mean dose groups corresponding to the four following situations (lowest to highest dose): 500 U/non-PTMG, 500 U/PTMG, 1000 U/non-PTMG, and 1000 U/PTMG for muscles eligible to be PTMGs: finger, wrist and elbow flexors. For the other muscles two dose levels were identified corresponding to the two possible randomized total doses (Table 2).

Outcomes

For this analysis, outcomes considered were the angle of arrest (X_{V1}) and angle of catch (X_{V3}) assessed using the Tardieu scale, and the active range of motion (X_A) for finger, wrist and elbow flexors measured at week 4 post-injection.

Statistical Analyses

Descriptive statistics (mean, standard deviation [SD], range, percentages) were used to characterize demographics, abobotulinumtoxinA dosage and efficacy variables.

The mean change in angle of arrest (X_{V1}), angle of catch (X_{V3}), and active range of motion (X_A), measured in degrees, between baseline and the follow-up assessment at week 4 post-injection was calculated. Results were plotted by mean abobotulinumtoxinA dose injected in each treatment group as PTMG and non-PTMG (and placebo) and muscle group (finger, wrist or elbow flexors).

Results:

Sample Demographics

As described in the primary publication [20], 243 subjects were randomized, with 81 subjects in each treatment group (placebo, 500 U abobotulinumtoxinA, 1000 U abobotulinumtoxinA). Baseline characteristics were similar across all treatment groups, with a mean (SD) age of 52.8 (13.5) years and 64.3% male subjects. Etiology of spasticity was stroke in 90.3% of subjects, and 45.4% subjects were BoNT-naïve in the affected limb.

Finger Muscles: Dosage and Outcomes

Mean abobotulinumtoxinA doses by individual finger muscles are outlined in Table 2. Mean (SD) abobotulinumtoxinA doses, regardless of PTMG, were 93.5 (17.0) U and 195.5 (25.9) U for FDP, and 95.4 (14.3) U and 196.8 (28.4) U for the FDS in the 500 U and 1000 U groups, respectively. When these muscles were injected as non-PTMG, the doses were 8 to 35% lower than in the PTMG situation. Thumb muscles (injected in 12–40% of subjects, Table 2) were not eligible for PTMG designation and, therefore, the dosing entirely reflects the clinical choice of investigators within the limits outlined in Table 1.

As shown in Figure 1A, placebo had little or no effect on the angle of arrest (X_{V1}), angle of catch (X_{V3}), and active range of motion (X_A). For abobotulinumtoxinA, a progressive improvement in the angle of arrest (X_{V1}) was observed from 103 U to 402 U, with a lesser improvement at 284 U. Angle of catch (X_{V3}) improved regularly with increasing mean abobotulinumtoxinA doses. A maximum effect was observed for active range of motion (X_A), at a mean dose of 200 U and slightly reduced improvements were observed at higher doses. Additional details of these changes are shown in Table 3.

Wrist Muscles: Dosage and Outcomes

Mean abobotulinumtoxinA doses for the wrist muscles are outlined in Table 2. Mean (SD) abobotulinumtoxinA doses, regardless of PTMG, were 92.2 (18.1) U and 178.1 (45.5) U for FCR and 89.9 (25.7) and 171.2 (45.2) U for FCU, for the 500 U and 1000 U groups, respectively. When these same muscles were injected as a non-PTMG, the doses were approximately 10 to 12% lower.

As with the finger flexors, placebo had little or no effect on the angle of arrest (X_{V1}),

angle of catch (X_{V3}), and active range of motion (X_A) in the wrist muscles (Figure 1B and Table 3). However, abobotulinumtoxinA was again associated with improvements in all three outcome measures. For the angle of arrest (X_{V1}), abobotulinumtoxinA was associated with improvements from 149 U to 288 U, though the higher dose of 392 U showed a reduced improvement. Angle of catch (X_{V3}) increased with mean abobotulinumtoxinA doses of 149 U through to 288U and stabilized at the highest dose of 392 U. For active range of motion (X_A), progressive improvements were observed across all doses, with less improvement at 288 U.

Elbow Muscles: Dosage and Outcomes

Mean abobotulinumtoxinA doses by individual elbow muscles are outlined in Table 2. Mean (SD) abobotulinumtoxinA doses, regardless of PTMG, were as follows: 148.5 (60.2) U and 321.4 (103.2) U for brachialis and 88.3 (28.5) U and 172.1 (44.8) U for brachioradialis in the 500 U and 1000 U abobotulinumtoxinA groups, respectively. When these same muscles were injected as a non-PTMG, the doses were approximately 35 to 40% lower for the brachialis and 25% lower for the brachioradialis (Table 2). Investigators often chose to inject the brachialis without injecting the brachioradialis. Similar to the thumb muscles, the biceps brachii and pronator teres were not eligible for PTMG designation; therefore, doses represent clinical acumen rather than required protocol dosing.

As with the other muscle groups, minimal changes in the elbow muscles were observed with placebo (Figure 1C). For abobotulinumtoxinA, there were very limited changes in the elbow angle of arrest (X_{V1}) for any of the doses. The angle of catch (X_{V3}) increased with mean abobotulinumtoxinA doses of 139 U through to 520 U, with a lessor change at 275 U, while active range of motion (X_A) showed regular

improvements across all doses. Details of all changes (X_{V1}, X_{V3} and X_A) are shown in Table 3.

Safety Evaluation

Safety assessments, including the recording of adverse events and vital signs, electrocardiogram and laboratory variables monitored throughout the study were reported previously [20]. Both 500 U and 1000 U total abobotulinumtoxinA doses in the upper limb showed favorable safety data and were consistent with previous literature on abobotulinumtoxinA and other BoNT-A. No dose-dependent effect on type or severity of adverse events was reported.

Discussion:

Using data from a recently published international, phase 3, double-blind, randomized clinical trial [20], these analyses outline the characteristics of abobotulinumtoxinA doses at individual upper extremity muscles associated with favorable clinical outcomes among 162 subjects with hemiparesis. All doses administered were within the approved dose limits for abobotulinumtoxinA [6]. Improvements in the angle of arrest (X_{V1}), angle of catch (X_{V3}), and active range of motion (X_A) were demonstrated in those subjects receiving abobotulinumtoxinA at specific upper extremity joints compared to subjects receiving placebo. Moreover, a higher abobotulinumtoxinA dose was generally associated with greater improvements in X_{V1}, X_{V3} and X_A.

A major strength of this study was that outcomes were collected by clinicians with extensive initial and follow-up training, who were competency tested and blinded to randomization assignment [20]. The favorable outcomes and trends observed over a

wide range of abobotulinumtoxinA doses (two-fold with regard to total abobotulinumtoxinA dose, and 2.5- to four-fold from lowest to highest dose), with few adverse events, suggest robust clinical decision-making in selecting abobotulinumtoxinA doses for a given muscle [20].

Comparing these findings with those of previous studies is challenging as a result of the wide variety of methodologies used: blinded RCTs [13,16,17] versus open-label trials [23]; BoNT injection at varying time points post-neurological injury [17]; the absence of investigator training [19,24] versus extensive training [20]; and a wide array of muscle-injection schemes and outcome measures [3,8,13,25,26]. Yet, the overall dosing characteristics within the setting of this highly regimented, international clinical trial (see Table 2), are generally in line with previous research studies. In a recent systematic review, Dashtipour *et al*. [13] reported a wide range of abobotulinumtoxinA dosing, with total doses ranging from 500 to 1500 U in upper extremity muscles in the 12 studies identified. Understandably, larger dose variations were observed in larger muscles (biceps brachii: 100–600 U compared to FCR: 50–225 U) [13]. Two previous studies have reported abobotulinumtoxinA dosing in non-research settings. In a survey of 275 European injectors, Hubble *et al.* [27] found ULS doses ranging from 508 to 773 U abobotulinumtoxinA, giving a maximum upper extremity dose slightly lower than the one presented here. Nonetheless, the individual muscle doses of the present article are similar to those reported across five countries [27], except for FDS at 218 U (range 100–1000) in the United Kingdom, which was somewhat higher than the highest mean dose of 196.8 U in the present study. Turner-Stokes *et al.* [24] identified the same trend of larger dose variations in larger muscles among injectors in a real-life setting (biceps brachii: 50–750 U vs. FCR: 20–350 U). No mean upper limb abobotulinumtoxinA dose was

reported [24]. None of these studies provided joint specific outcomes associated with abobotulinumtoxinA dose. Despite our standardized protocol [20], our data likely reflects real-world injections in that numerous different muscle and dose injection combinations were used, as in past studies [8,13,14,17,19].

Two aspects of the clinical trial reported here allowed for a unique consideration of abobotulinumtoxinA dose-response by joint. Firstly, the inclusion of X_{V1}, X_{V3} and X_A as outcome measures provides unique, joint-specific data, including active (X_A) and passive (X_{V1}) range of motion and angle of catch (X_{V3}). X_{V1}, X_{V3} and X_A measures appear to be less subject to placebo effects than MAS [20]. The TS (including X_{V1} and X_{V3} reported here) has not yet been widely used as an outcome assessment for spasticity. Turner-Stokes *et al.* [24] reported that <20% of 456 adults were assessed using the TS in their world-wide, observational study. Among those subjects with TS data, about 90% improved after BoNT treatment and the scale had some correlation with goal attainment scaling results ($r=0.43$, $p<0.001$) [24]. Secondly, in this study, a given muscle fell under two scenarios for finger, wrist and elbow flexors in the abobotulinumtoxinA dose groups – a mandatory, predetermined dose for PTMGs and a flexible dosing option within a predetermined range for non-PTMGs. This allowed for the evaluation of four dosing groups by total upper extremity dose (500 U or 1000 U) and PTMG or non-PTMG. Investigators administered lower abobotulinumtoxinA doses to non-PTMG muscles, which is not unexpected given that the most hypertonic muscles were part of the PTMG. This may also reflect a relative uniformity in assessment and decision-making among injectors from 34 sites around the world. In addition, injectors could not exceed the total volume/dose, thus once the PTMG was injected the available volume/dose was reduced. Injectors may

also be conservative and inclined to select a lower, rather than higher, dose when presented with a potential range of options, at least for the first injection.

In this study, an abobotulinumtoxinA dose-dependent effect was most evident for the angle of catch (X_{V3}), a direct measure of velocity-dependent stretch responses. The dose–response trend for the active range of motion (X_A) was also generally consistent, especially for the wrist and elbow flexors. By contrast, for finger flexors there was a reduced improvement in the active range of motion (X_A) at the higher doses, which might have been due to concomitant higher dose injections into wrist flexors, which would have reduced the tenodesis effect and therefore hampered improvement in finger extension. It is important to note that the trends in active range of motion (X_A) reflect a net gain in active range compared with placebo for every dose at every joint. Moreover, the improved active range of motion alongside a reduction in muscle tone and spasticity improvement is an important observation, as this indicates the patient can improve movement in their joints without over-weakening the muscles.

The wide range of abobotulinumtoxinA doses per muscle group used in the present study allowed for flexibility of the doses injected according to the investigators assessment of individual patient impairment and treatment objectives. Quantitative measurements of spasticity (X_{V1} and X_{V3} using the Tardieu Scale) and active range of motion (X_A), in conjunction with treatment objectives, are clinically important to assess and follow the patient evolution throughout treatment, and should therefore be used to guide dosing at individual joints. In particular, while the objective of injecting abobotulinumtoxinA is to improve spasticity, it should not negatively impact

the active range of motion, which may be seen when exceeding the recommended range of doses.

There are a limited number of published studies with multiple abobotulinumtoxinA dosing groups to which these results might be compared. Smith *et al.* [28] reported a small RCT (N = 21) with abobotulinumtoxinA doses of 500 U, 1000 U, 1500 U (individual muscle dosing was not standardized). A dose–response relationship was reported for spasticity at the elbow (dose range 322–980 U) and wrist (dose range 127–280 U), and for range of motion at the elbow, up to 1000 U. No relationship was noted at the fingers (dose range 113–238 U).

Limitations of the study

There are limitations to the present analysis that should be noted. On average, the subjects involved had suffered initial neurological injury 5 to 10 years prior to this study, suggesting a highly motivated and engaged group of individuals at high risk of severe muscle shortening; however, this may not reflect general clinical practice. It is important to note that while the total dose administered to the upper limb was determined by randomization, the PTMG was not, and for each muscle group there were some muscles not injected at all. The four dose groups likely differed in characteristics other than the mean abobotulinumtoxinA dose (eg, baseline spasticity, voluntary movement, contracture, naïve or previous exposure, etc.) and this may have contributed to some of the variability in angle of arrest (X_{V1}), angle of catch (X_{V3}), and active range of motion (X_A) parameters among doses. These groups also had variable subject numbers reflecting the higher proportion of subjects where finger flexors were designated the PTMG over wrist or elbow flexors. It should be kept in mind that the relationship between BoNT dose at a given muscle and

outcomes at a given joint are complicated. The biomechanical and neurophysiological interaction among other treated or untreated muscles is complex and may impact findings at the joint. For example, the tethering effect of the finger flexors as they cross the wrist [29].

Conclusion

This analysis presents novel data relating abobotulinumtoxinA dosing at specific muscles to outcomes at specific joints in the upper extremity. Previous clinical trials have established the clinical efficacy of abobotulinumtoxinA by total dose, but did not fully characterize the effective mean doses of abobotulinumtoxinA by muscle. All abobotulinumtoxinA doses yielded important improvements in both spasticity and in subjects' active range of motion. The dose–response is generally consistent, with positive clinical outcomes at specific upper extremity muscle groups over a wide range of doses. This information thus provides a basis for future dosing recommendations for abobotulinumtoxinA for injectors based on treatment objectives and quantitative assessment of spasticity and active range of motion at the individual joints.

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Tables and figures

Table 1: Injection volumes and dose ranges recommended for upper limb muscles

All muscles injected	Volume (mL)*		Dose range	
	Non-PTMG	PTMG	aboBoNT-A 500 U	aboBoNT-A 1000 U
Finger and thumb muscles		**2**		
Flexor digitorum profundus†	0–1	1‡	0–100	0–200
Flexor digitorum superficialis†	0–1	1‡	0–100	0–200
Flexor pollicis longus	0–1	–	0–100	0–200
Adductor pollicis	0–0.25	–	0–25	0–50
Wrist muscles		**2**		
Flexor carpi ulnaris†	0–1	1‡	0–100	0–200
Flexor carpi radialis†	0–1	1‡	0–100	0–200
Elbow muscles		**2–3**		
Brachialis†	0–2	2‡	0–200	0–400
Brachioradialis†	0–1	1§	0–100	0–200
Biceps brachii	0–2	–	0–200	0–400
Pronator teres	0–1	–	0–100	0–200
Shoulder muscles		–		
Triceps brachii (long head)	0–1.5	–	0–150	0–300
Pectoralis major	0–1.5	–	0–150	0–300
Subscapularis	0–1.5	–	0–150	0–300
Latissimus dorsi	0–1.5	–	0–50	0–300

aboBoNT-A = abobotulinumtoxinA; PTMG = primary target muscle group.

*The total volume was fixed at 5 mL for all upper extremity muscles injected; †muscles included in the PTMG; ‡ mandatory injection volume if designated a PTMG; §optional injection volume, if elbow muscles were selected as PTMG.

Table 2: Mean doses of abobotulinumtoxinA administered to each upper limb muscle

Muscle group	aboBoNT-A 500 U (N = 81) N Mean dose (SD) [range]	aboBoNT-A 1000 U (N = 81) N Mean dose (SD) [range]	aboBoNT-A all doses (N = 162) Prevalence, N (%)
Finger and thumb muscles			
Flexor digitorum profundus	54 93.5 (17.0) [50–100]	65 195.5 (25.9) [100–300]	119 (73.5)
PTMG	44 100.0 (0) [100–100]	49 200 (20.4) [100–300]	
Non -PTMG	10 65.0 (24.1) [50–100]	16 181.9 (35.4) [100–200]	
Flexor digitorum superficialis	63 95.4 (14.3) [50–100]	73 196.8 (28.4) [100–300]	136 (84.0)
PTMG	44 100.0 (0) [100–100]	49 202.0 (14.3) [200–300]	
Non -PTMG	19	24	

	84.7 (23.2) [50–100]	186.3 (43.9) [100–300]	
Flexor pollicis longus	24 64.4 (25.6) [20–100]	32 139.7 (46.1) [50–200]	56 (34.6)
Adductor pollicis	10 30.0 (10.5) [25–50]	14 50.7 (14.9) [40–100]	24 (14.8)
Wrist muscles			
Flexor carpi radialis	57 92.2 (18.1) [25–100]	57 178.1 (45.5)[80–300]	114 (70.4)
PTMG	11 100 (0) [100–100]	12 195.8 (14.4) [150–200]	
Non -PTMG	46 90.3 (19.8) [25–100]	45 173.3 (49.7) [80–300]	
Flexor carpi ulnaris	47 89.9 (25.7) [25–180]	49 171.2 (45.2) [80–200]	96 (59.3)
PTMG	11 100 (0) [100–100]	12 195.8 (14.4) [150–200]	
Non -PTMG	36 86.8 (28.7) [25–180]	37 163.2 (48.9) [80–200]	
Elbow muscles			

Brachioradialis	42 88.3 (28.5) [50–200]	28 172.1 (44.8) [50–200]	70 (43.2)
PTMG	20 100 (0) [100–100]	12 200 (0) [200–200]	
Non -PTMG	22 77.7 (36.6) [50–200]	16 151.3 (50.2) [50–200]	
Brachialis	60 148.5 (60.2) [50–200]	43 321.4 (103.2) [100–400]	103 (63.6)
PTMG	26 194.2 (29.4) [50–200]	20 400 (0) [400–400]	
Non -PTMG	34 113.5 (54.1) [50–200]	23 253.0 (99.2) [100–400]	
Biceps brachii	28 106.4 (35.6) [50–200]	19 207.4 (62.6) [100–400]	47 (29.0)
Pronator teres	14 81.8 (42.4) [45–200]	30 157.3 (51.9) [80–200]	44 (27.2)
Shoulder muscles			
Triceps brachii (long head)	2 100.0 (0.0) [100–100]	1 200.0 (N/A) [200–200]	3 (1.9)

Pectoralis major	4 100.0 (0.0) [100–100]	6 200.0 (63.2) [100–300]	10 (6.2)
Subscapularis	2 100.0 (0.0) [100–100]	0 N/A	2 (1.2)
Latissimus dorsi	3 100.0 (0.0) [100–100]	4 175.0 (50.0) [100–200]	7 (4.3)

AboBoNT-A = abobotulinumtoxinA; N/A = not applicable; PTMG = primary target muscle group; SD = standard deviation.

Table 3. Change from baseline to week 4 of passive range of motion (X_{V1}), angle of catch at fast speed (X_{V3}), and active range of motion (X_A) against extrinsic finger flexors, wrist flexors and elbow flexors, as PTMG, non-PTMG and irrespective of PTMG.

Variable	Change from baseline at week 4								
	Non-PTMG			PTMG			Overall (irrespective of PTMG)		
	Mean dose	n	Mean change (SD)	Mean dose	n	Mean change (SD)	Mean dose	n	Mean change (SD)
Extrinsic finger flexors									
X_{V1} (°)									
Placebo	–	30	2.3 (31.0)	–	41	1.6 (25.6)	–	70	1.9 (28.0)
AbobotulinumtoxinA 500 U	103 U	22	4.8 (23.6)	200 U	44	15.7 (30.5)	167 U	66	12.0 (28.7)
AbobotulinumtoxinA 1000 U	284 U	25	7.0 (23.2)	402 U	48	24.0 (38.6)	361 U	73	18.2 (34.9)
X_{V3} (°)									
Placebo	–	30	11.7 (53.7)	–	41	8.0 (32.9)	–	70	9.8 (42.8)
AbobotulinumtoxinA 500 U	103 U	22	33.2 (54.3)	200 U	44	42.4 (50.1)	167 U	66	39.3 (51.3)
AbobotulinumtoxinA 1000 U	284 U	25	47.2 (39.3)	402 U	48	48.0 (51.8)	361 U	73	47.7 (47.7)
X_A (°)*									

Placebo	–	28	3.0 (32.4)	–	41	-6.2 (33.8)	–	69	-2.4 (33.3)
AbobotulinumtoxinA 500 U	103 U	18	12.2 (46.8)	200 U	44	23.9 (27.6)	167 U	62	20.5 (34.3)
AbobotulinumtoxinA 1000 U	284 U	26	19.8 (42.3)	402 U	48	17.6 (30.9)	361 U	74	18.4 (35.0)
Wrist flexors									
X_{V1} (°)									
Placebo	–	41	3.2 (25.0)	–	15	7.5 (12.7)	–	55	4.4 (22.5)
AbobotulinumtoxinA 500 U	149 U	48	10.1 (15.1)	200 U	11	13.6 (19.2)	158 U	59	10.8 (15.8)
AbobotulinumtoxinA 1000 U	288 U	43	14.3 (17.7)	392 U	12	5.0 (12.6)	309 U	55	12.2 (17.1)
X_{V3} (°)									
Placebo	–	41	2.6 (20.8)	–	15	2.1 (16.7)	–	55	2.5 (19.8)
AbobotulinumtoxinA 500 U	149 U	48	26.0 (28.9)	200 U	11	31.8 (37.6)	158 U	59	27.1 (30.4)
AbobotulinumtoxinA 1000 U	288 U	43	35.0 (28.0)	392 U	12	33.7 (23.7)	309 U	55	34.7 (26.9)
X_A (°)*									
Placebo	–	36	-0.9 (23.1)	–	15	3.5 (29.1)	–	51	0.4 (24.8)
AbobotulinumtoxinA 500 U	149 U	43	6.3 (20.2)	200 U	11	15.7 (19.8)	158 U	54	8.2 (20.3)
AbobotulinumtoxinA 1000 U	288 U	42	9.6 (23.3)	392 U	12	26.4 (26.7)	309 U	54	13.4 (24.8)
Elbow flexors									

X_{V1} (°)									
Placebo	–	32	-2.2 (13.9)	–	23	2.0 (4.3)	–	55	-0.5 (11.1)
AbobotulinumtoxinA 500 U	139 U	40	1.2 (4.8)	271 U	25	3.5 (6.3)	191 U	65	2.1 (5.5)
AbobotulinumtoxinA 1000 U	275 U	29	1.1 (6.8)	520 U	19	0.7 (7.1)	373 U	48	1.0 (6.9)
X_{V3} (°)									
Placebo	–	32	3.4 (14.8)	–	23	6.1 (13.9)	–	55	4.5 (14.3)
AbobotulinumtoxinA 500 U	139 U	40	14.3 (23.6)	271 U	25	28.0 (26.7)	191 U	65	19.6 (25.5)
AbobotulinumtoxinA 1000 U	275 U	29	19.5 (28.8)	520 U	19	35.1 (27.6)	373 U	48	25.7 (29.2)
X_A (°)*									
Placebo	–	24	7.3 (24.1)	–	23	2.7 (14.9)	–	47	5.0 (20.0)
AbobotulinumtoxinA 500 U	139 U	30	4.5 (21.2)	271 U	25	12.6 (21.8)	191 U	55	8.1 (21.7)
AbobotulinumtoxinA 1000 U	275 U	21	13.4 (20.1)	520 U	19	15.8 (22.4)	373 U	40	14.6 (21.0)

*Number of subjects in the non-PTMG group for X_A are lower as this parameter was only compulsory in PTMGs. PTMG = primary targeted muscle group; SD = standard deviation; X_A = active range of motion; X_{V1} = passive range of motion; X_{V3} = angle of catch at fast speed.

Figure 1. Change from baseline of Tardieu Scale parameters and of active range of motion week 4 post-injection in A. extrinsic finger flexors; B. wrist flexors and C. elbow flexors

Dose groups were as follows (lowest to highest dose): 500 U/non-PTMG, 500 U/PTMG, 1000 U/non-PTMG and 1000 U/PTMG. Standard deviations and mean change from baseline values are detailed in Table 3.

PTMG = primary targeted muscle group; X_A = active range of motion; X_{V1} = passive range of motion; X_{V3} = angle of catch at fast speed.