Baseline characteristics of patients from a pilot study to assess the effect of early use of abobotulinumtoxin-A (Dysport®) in spasticity progression post stroke

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Introduction

- Prevalence and severity of spasticity continue to increase during the first year post stroke, with up to 40% of stroke survivors developing post-stroke spasticity.[1–3]
- Reducing the burden of post-stroke spasticity is important for both the patient and caregivers.[1]
- Botulinum toxin A (BoNT-A) is an effective focal intervention for reducing upper limb spasticity (ULS).[4]
- In most studies to date, BoNT-A injection has been performed more than 6 months after stroke.[4,5]
- However, patients at highest risk for permanent and severe spasticity, may profit from much earlier treatment.[6,7]
- Muscle tone changes in the affected limb may already be apparent within 2 weeks post stroke; however, studies on the time frame for presentation of post-stroke spasticity symptoms are scarce.[2,8–9]

Objective

- The ONTIME pilot study aims to evaluate whether early treatment delays development of disabling (symptomatic) spasticity as a result of post-stroke spasticity.

Methods

Study design

- The ONTIME study (NCT02321436) was a 28-week, phase IV, randomised (2:1; abobotulinumtoxinA [Dysport®, aboBoNT-A] 500 U:placebo), double-blind, placebo-controlled, exploratory trial to assess the impact of aboBoNT-A injections administered within 2 to 12 weeks post stroke in four countries (Malaysia, Thailand, Singapore and the Philippines; Figure 1).

Figure 1. Study design.

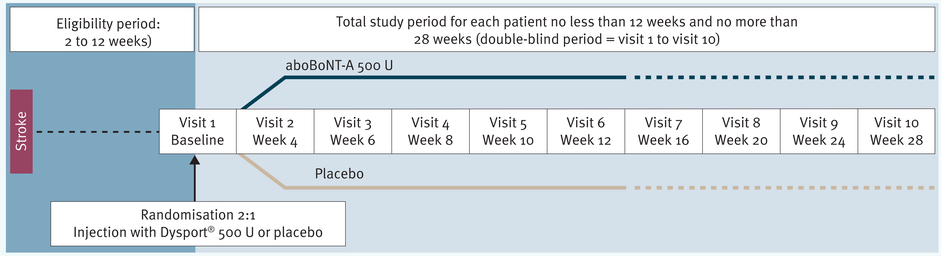

Table 1. Symptomatic spasticity criteria

Functional domain and measure used	Assessment scale	
Pain Numeric Pain Rating Scale (NPRS)[10]	0 – No pain 1–3 – Mild pain 4–6 – Moderate pain 7–10 – Severe pain (disabling and impacts upon movement)	NPRS ≥4 indicates appearance or reappearance of active symptoms of spasticity
Passive function Likert scale	"In general, how much does spasticity have an impact on the following activities of daily living and/or your rehabilitation programme?" 0 – No impact 1 – Mild impact 2 – Moderate impact 3 – Severe impact	A score ≥1 indicates appearance or reappearance of passive symptoms of spasticity
Active function Likert scale	"In general, how much does spasticity have an impact on the following activities of daily living and/or your rehabilitation program: reaching, grasping, releasing, gripping, holding, bimanual function, manipulating objects, dexterity, fine motor skills, lifting and carrying?" 0 – No impact 1 – Mild impact 2 – Moderate impact 3 – Severe impact	A score ≥1 indicates appearance or reappearance of active symptoms of spasticity
Involuntary movements Likert scale	0 – No involuntary movements 0 – Presence of involuntary movements that have a mild impact on posture and ambulation 0 – Presence of involuntary movements that have a moderate impact on posture and ambulation 0 – Presence of involuntary movements that have a severe impact on posture and ambulation	A score ≥1 indicates appearance or reappearance of involuntary movements

NPRS, Numeric pain rating scale

Inclusion criteria

- National legal adult age and ≤80 years.
- Experienced first ever stroke 2 to 12 weeks prior to baseline.
- Computerised tomography/magnetic resonance imaging scan confirmed ischaemic/haemorrhagic stroke.
- Spasticity, either symptomatic or increased muscle tone (Modified Ashworth Scale [MAS] ≥2).
- MAS score of ≥2 in at least one of four muscle groups (elbow flexors or pronators, wrist flexors or finger flexors).

Outcome measures

- Primary endpoint was the time between the first study injection and the visit at which composite reinjection criteria were met.
- A novel composite index, developed specifically for this study, was used to determine reinjection and defined:
  - MAS score increased to ≥2 in the primary targeted muscle group after first injection.
  - Appearance or reappearance of one of the following signs of symptomatic spasticity: pain, involuntary movements, impaired active or passive function (Table 1).
- Assessment of the impact on patients' global functioning.
- Safety endpoints included the incidence of treatment-emergent adverse events and changes in the patients' physical condition and vital signs, including blood pressure, heart rate, body temperature.

Baseline characteristics

- A cohort of 42 patients (28 aboBoNT-A 500 U, 14 placebo) from Malaysia, the Philippines, Singapore and Thailand were included.
- Mean [SD] age was 59.8 [12.3] years and 78.6% of patients were male (Table 2).
- Symptomatic spasticity was present in 32 patients (76.2%; Table 2).

Table 2. Baseline characteristics and demographics.

Characteristic	aboBoNT-A n=28	Placebo n=14	All subjects N=42
Age, years (SD)	61.5 (13.3)	56.5 (9.7)	59.8 (12.3)
Male, %	82.1	71.4	78.6
Country, n (%)			
Malaysia	3 (10.7)	1 (7.1)	4 (9.5)
Philippines	11 (39.3)	4 (28.6)	15 (35.7)
Singapore	9 (32.1)	5 (35.7)	14 (33.3)
Thailand	5 (17.9)	4 (28.6)	9 (21.4)
Spasticity at baseline (%)			
Symptomatic*	78.6	71.4	76.2
Asymptomatic†	21.4	28.6	23.8

*Status of subject is symptomatic if at least one of the following items was met: passive/active or involuntary movements (Likert score >0) and NPRS score ≥4. †Status of subject is asymptomatic if score is equal to 0 for passive/active functions and involuntary movements, NPRS score <4. aboBoNT-A, abobotulinumtoxinA; SD, standard deviation

Table 3. Disease history

	aboBoNT-A n=28	Placebo n=14	All subjects N=42
Type of stroke, n (%)			
Ischaemic	20 (71.4)	10 (71.4)	30 (71.4)
Haemorrhagic	8 (28.6)	4 (28.6)	12 (28.6)
Mean time since stroke diagnosis (weeks)	6.18	6.52	6.29
Arm affected			
Left, n (%)	16 (57.1)	8 (57.1)	24 (57.1)
Right, n (%)	12 (42.9)	6 (42.9)	18 (42.9)
Both, n (%)	0	0	0

aboBoNT-A, abobotulinumtoxinA

- Mean [SD] time since stroke was 6.29 [2.73] weeks and the most common type of stroke was ischaemic (71.4%) (Table 3).
- Elbow flexors were selected as the primary target muscle group in 73.8% of cases, followed by wrist flexors (14.3%) and finger flexors (2.4%; Table 4).
- At baseline, a Likert scale score of 2 (moderate impact) for passive and active function was more common in aboBoNT-A patients compared with placebo (passive function 39.3 vs. 7.1%, active function 35.7 vs. 21.4%, respectively; Table 4).
- A Likert scale of 3 (severe impact) was recorded more often in the placebo group than the aboBoNT-A group for passive function (14.3 vs. 10.7%), active function (21.4 vs. 14.3%) and involuntary movements (7.1 vs 3.6%), respectively.
- Mean NPRS rating was 3.1 in both groups (Table 4).

Table 4. Presence of symptomatic spasticity at baseline

	aboBoNT-A n=28	Placebo n=14	All subjects N=42
Primary targeted muscle group (%)			
Elbow flexors	71.4	78.6	73.8
Elbow pronators	14.3	0	9.5
Wrist flexors	14.3	14.3	14.3
Finger flexors	0	7.1	2.4
Modified Ashworth Scale score	2.11	2.14	2.12
Likert scale score			
Passive function, n (%)			
0 – No impact	8 (28.6)	7 (50.0)	15 (35.7)
1 – Mild impact	6 (21.4)	4 (28.6)	10 (23.8)
2 – Moderate impact	11 (39.3)	1 (7.1)	12 (28.6)
3 – Severe impact	3 (10.7)	2 (14.3)	5 (11.9)
Active function, n (%)			
0 – No impact	11 (39.3)	7 (50.0)	18 (42.9)
1 – Mild impact	3 (10.7)	1 (7.1)	4 (9.5)
2 – Moderate impact	10 (35.7)	3 (21.4)	13 (31.0)
3 – Severe impact	4 (14.3)	3 (21.4)	7 (16.7)
Involuntary movements, n (%)			
0 – No impact	15 (53.6)	7 (50.0)	22 (52.4)
1 – Mild impact	6 (21.4)	3 (21.4)	9 (21.4)
2 – Moderate impact	6 (21.4)	3 (21.4)	9 (21.4)
3 – Severe impact	1 (3.6)	1 (7.1)	2 (4.8)
NPRS score, n (SD)	3.1 (3.2)	3.1 (2.7)	3.1 (3.0)

aboBoNT-A, abobotulinumtoxinA; MAS, Modified Ashworth scale; NPRS, Numeric Pain Rating Scale; SD, standard deviation

Conclusions

- Symptomatic spasticity was present in 76.2 % of cases at 2 to 12 weeks after stroke.
- This indicates that current standard clinical practice to start spasticity treatment with botulinum toxin type A ≥3 months post stroke may not be optimal and there is rationale for earlier treatment.
- The ONTIME pilot study will investigate the impact of early post stroke treatment with abobotulinumtoxinA.
- Results from this study will provide insight into the optimal delivery of post stroke patient management.

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Disclosures

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