Treatment frequency for long-term efficacy of abobotulinumtoxinA injections: a phase 3 study in patients with lower limb spasticity following stroke or traumatic brain injury

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Presenting on behalf of the original authors

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Anne-Sophie Grandoulier	Employee of Atlanstat, subcontracted to Ipsen
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Introduction

Introduction & objective

- Resistance to movement in patients with limb spasticity is caused by neurogenic and biomechanical components.[1]
- Several randomised, double-blind studies have demonstrated abobotulinumtoxinA (aboBoNT-A; Dysport®), a botulinum neurotoxin (BoNT) type A, to be an effective treatment for patients with lower limb spasticity.[2]
- The long-term safety and efficacy of repeated aboBoNT-A injections in adult patients with LL spasticity has been established.[3]
  - Improvements in walking speed and community ambulation were demonstrated during a 12-month open label (OL) study, and no unexpected safety signals were reported.[3]

Objective

Describe the number of aboBoNT-A injections that patients with adult lower limb spasticity required over the 12-month open-label period

1. Royal College of Physicians. Spasticity in adults: management using botulinum toxin. National guidelines. 2018; 2. Dashtipour K. Medicine 2016; 3. Gracies JM. Neurology 2017.

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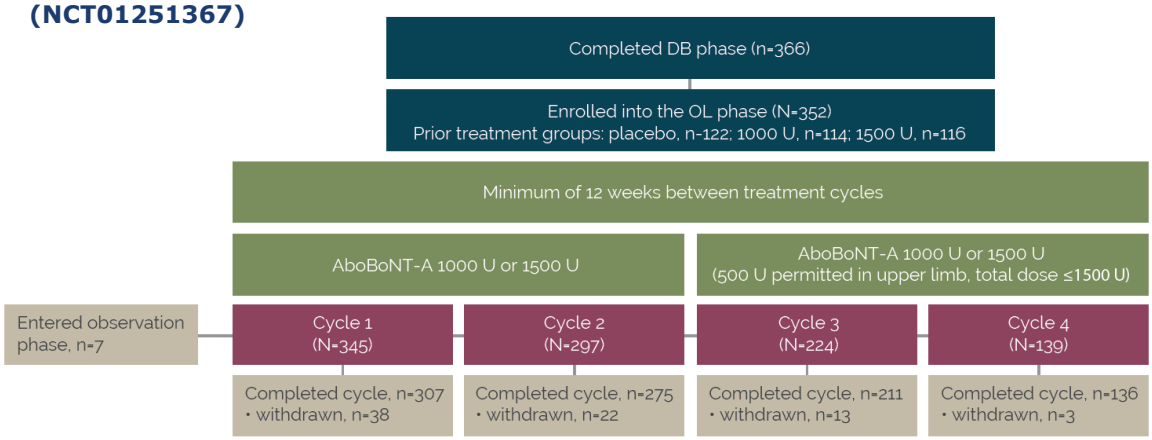
Methods

Adult lower limb open-label study design

- **12-month, phase 3, prospective, international, open-label extension study (NCT01251367)**



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Participants

Inclusion criteria	Exclusion criteria
Provision of written informed consent	Major limitation in passive range of motion in affected LL joint
Adult patients with spastic hemiparesis due to stroke or TBI	Previous surgery, or phenol and/or alcohol treatment for spasticity in the affected LL.
Patients who had participated in the DB study (NCT01249404) up to the Week 12, 16, 20 or 24 follow-up visit, without any major protocol deviations and/or any ongoing adverse events	Cognitive impairment
	Severe neurological impairment affecting gait
	Known disease of the neuromuscular junction

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Treatment

- AboBoNT-A 1000U or 1500U administered by intramuscular injection in the lower limb
- Patients could receive ≤4 additional treatment cycles during the open-label study
  - Excluding single treatment cycle in prior double-blind study
- The open-label study had a 12-month duration
  - Reinjection occurred ≥12-week intervals, at the discretion of the investigators, depending on each patients' efficacy and safety response
  - Patients' who did not require retreatment by Week 24 of each cycle entered an observational phase
- At open-label Cycle 1, patients received aboBoNT-A 1500U, or 1000U if they experienced an AE during DB study that would pose unacceptable risk were they to receive 1500U
- From Cycle 3, patients could additionally receive aboBoNT-A 500U in their upper limb, if required. Maximum total dose was 1500U
- Here we evaluate how many injection cycles patients required during the 12-month open-label study

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RESULTS

Patient demographics and disease characteristics

Parameter	Patients from the DB study			All (N=352)
	Placebo (N=122)	AboBoNT-A 1000 U (N=114)	AboBoNT-A 1500 U (N=116)	
Age, mean (SD)	51.5 (13.2)	54.4 (12.6)	53.7 (12.1)	53.2 (12.7)
Sex, n (%)				
Male	85 (69.7)	82 (71.9)	72 (62.1)	239 (67.9)
Female	37 (30.3)	32 (28.1)	44 (37.9)	113 (32.1)
Mean weight, kg (SD)	79.6 (18.1)[a]	80.1 (16.8)	79.9 (14.7)	79.9 (16.5)[b]
Affected leg, n (%)				
Left	71 (58.2)	61 (53.5)	62 (53.4)	194 (55.1)
Right	51 (41.8)	53 (46.5)	54 (46.6)	158 (44.9)
Cause of spasticity, n (%)				
Stroke	101 (82.8)	103 (90.4)	105 (90.5)	309 (87.8)
TBI	21 (17.2)	11 (9.6)	11 (9.5)	43 (12.2)
Mean time since event, years (SD)				
Stroke	4.2 (3.7)	4.9 (5.3)	4.5 (5.3)	4.5 (4.8)
TBI	11.0 (13.2)	5.9 (5.5)	8.9 (5.4)	9.2 (10.1)

AboBoNT-A, abobotulinumtoxinA; DB, double-blind; n, number of patients; SD, standard deviation; TBI, traumatic brain injury. [a]n=121; [b]n=351

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Results

- 352 patients entered the open-label study, 12 entered an observational phase and 7 did not require further treatment. Thus, 345 patients were evaluated in this analysis
- Of the 345 patients, 269 completed the OL study. The remaining 76 patients withdrew:
  - withdrawal of consent (n=36), AEs (n=19), lost to follow-up (n=5) lack of efficacy (n=2), protocol deviation (n=1), other (n=13)

Treatment cycle and cumulative injections	Entered treatment cycle, n	Withdrawn from treatment cycle, n	Completed treatment cycle, n	Did not require re-injection in a subsequent cycle, n (cumulative %)
Cycle 1 (=1 injection)	345	38	307	10 (2.9)
Cycle 2 (=2 injection)	297	22	275	51 (17.7)
Cycle 3 (=3 injection)	224	13	211	72 (38.6)
Cycle 4 (=4 injection)	139	3	136	136*

*End of study, patients were not reinjected

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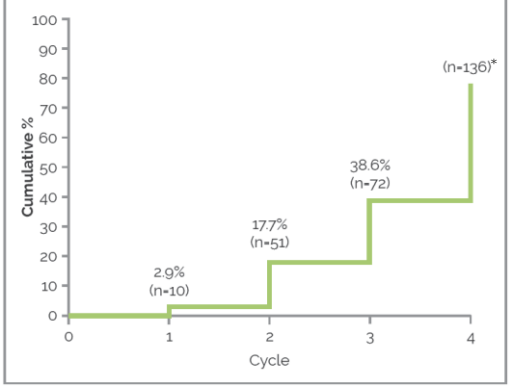
Re-injection frequency

- In total, 133 patients, who had completed ≥12 months of follow-up, completed the study before receiving all 4 treatment cycles:
  - 10 patients at the end of Cycle 1
  - 51 patients at the end of Cycle 2
  - 72 patients at the end of Cycle 3
- Over the course of the 12-month study:
  - 38.6% (n=133) of patients required 3 or fewer aboBoNT-A injections
  - 17.7% required 2 or fewer injections
  - 2.9% required 1 aboBoNT-A injection

Cumulative percentage of patients not requiring re-injection in a subsequent cycle



*End of study, patients were not reinjected

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Conclusions

- During the 12-months of this study, almost 40% of patients required 3 or fewer injections of aboBoNT-A.
- Current guidelines recommend aboBoNT-A injections are administered ≥12 weeks apart, suggesting approximately 4 injections per year are needed.[1,2]
- Decreased injection frequency, in LL spasticity, may be the result of a longer duration of response of aboBoNT-A used at the approved doses. This may help reduce the burden associated with BoNT treatment for patients and their caregivers/families.

This current study demonstrates that a proportion of patients with lower limb spasticity who received repeated aboBoNT-A injections over 12 months, on average, required less frequent injections

1. Sheean G. Eur J Neurol 2010; 2. Current approved Australian Dysport Product Information

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