Time to retreatment after abobotulinumtoxinA (Dysport®) injections in children with dynamic equinus foot deformity

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Introduction

- Evidence-based clinical guidelines consistently recommend botulinum neurotoxin type A (BoNT-A) as an effective and generally safe and well tolerated treatment for localised/segmental spasticity in children and adolescents with cerebral palsy (CP).[1, 2] However, the effects of chemodenervation with BoNT-A are transient, and repeat injections are often necessary to achieve and maintain clinical benefit.
- The minimum interval between BoNT-A injections is currently mandated by regulatory authorities to be 12 weeks, which, for a child undergoing regular repeated BoNT-A treatment, could mean as many as 4 injection appointments per year.
- While there is little published data on the caregiver burden associated with attending frequent healthcare visits, the multimodal approach to managing CP often necessitates several appointments with various healthcare professionals per year. From the patient/caregiver perspective, the time required for a BoNT-A injection can be particularly substantial; for each injection visit, the child will likely miss a day from nursery/school, and the parental guardian must make the necessary arrangements (e.g. time off work, travel arrangements) to accompany their child. The emotional burden of undergoing an injection procedure, especially as this may require sedation, should also be considered. Thus, a longer injection interval is of interest to this patient population.
- From the economic perspective, longer time to retreatment is of interest as a way to reduce costs. Direct medical costs include the cost of toxin and associated clinic costs (e.g. staffing, use of injection guidance technique, day bed allocation), which can significantly increase with sedation/anaesthesia.[3]
- We have previously reported the primary efficacy results of a large, international, randomised, placebo-controlled Phase 3 study which demonstrated superiority of abobotulinumtoxinA versus placebo in improving hypertonia (MAS) and spasticity (Tardieu), Function (Physician Global Assessment) and attainment of treatment goals (Goal attainment scaling).[4, 5]
- This study permitted flexible injection intervals based on specific re-treatment criteria. The aim of this analysis was to describe the time to retreatment for patients having received active treatment in the double-blind phase of the study.

Methods

Study design[4]

- This was a Phase 3, international, multicentre, double-blind, prospective, randomised, placebo-controlled, single-dose study (NCT01249417; Figure 1).
- All patients who successfully completed the double-blind study and who continued to meet eligibility criteria (Table 1) could enter the open-label phase of the study (NCT01251380; Figure 1).
- During the double-blind study, patients received injections of placebo, 10 U/kg/leg abobotulinumtoxinA (i.e. 20 U/kg for bilateral injections) or 15 U/kg/leg abobotulinumtoxinA (i.e. 30 U/kg for bilateral injections) into the gastrocnemius and soleus muscles. The maximum total dose was 30 U/kg or 1000 U, whichever the lower value.
- Following treatment administration, patients attended follow-up visits at Week 4 and Week 12. Additional visits to evaluate eligibility criteria for retreatment were permitted at Week 16 (for patients who in the clinical judgment of the investigator did not require retreatment at Week 12), at Week 22 (patients who did not require retreatment at Week 16) and at Week 28 (patients who did not require retreatment at Week 22).
- If assessed as eligible for retreatment, patients were then included in the open-label study.
- Eligibility for retreatment was defined as follows:
  1. If the patient has not demonstrated a decrease from baseline of ≥1 grade in the MAS score in the gastrocnemius-soleus complex at the ankle joint and has no improvement on the PGA (i.e. score ≤ 0), and if based on the investigator's judgement there is no unacceptable safety risk

  OR

  2. If the patient has demonstrated a decrease from baseline of ≥1 grade in the MAS score in the gastrocnemius-soleus complex at the ankle joint and/or has demonstrated an improvement on the PGA (i.e. a score ≥ +1), the Investigator will decide based on the other efficacy and safety assessments whether the patient needs to be injected on the same day or whether the injection is postponed to the next scheduled visit (i.e. Week 16, 22, 28 or later).
- The minimum retreatment interval was 12 weeks.

Table 1. Key eligibility criteria[4]

- Ambulatory children (aged 2–17 years) with a diagnosis of spasticity due to CP and equinus foot positioning during the stance phase of the gait
- Gross Motor Function Classification System (GMFCS) Level of I-III
- Modified Ashworth Scale (MAS) ≥2 and a spasticity grade (Y) of 2-4 on the Tardieu scale (with a spasticity angle (X) of 10° or more) at the ankle joint
- No fixed ankle flexion myocontractures, previous surgery, or alcohol/phenol injections
- No serial casting in the past 12 weeks
- BoNT naïve or a minimum of 6 months' washout from the last BoNT injection for any condition

Table 2. Time to retreatment in the double-blind phase (by active treatment arm)

Eligible for retreatment at Visit, n (%) ITT	AboBoNT-A 10 U/kg/leg (n=79)	AboBoNT-A 15 U/kg/leg (n=79)
Total eligible for retreatment*	66 (83.5)	68 (86.1)
At week 12	12 (15.2)	5 (6.3)
At week 16	21 (26.6)	32 (40.5)
At week 22	16 (20.3)	20 (25.3)
At week 28	14 (17.7)	7 (8.9)
After week 28	3 (3.8)	4 (5.1)

*13 patients in the 10 U/kg group and 11 patients in the 15 U/kg group moved to the open-label phase without needing reinjection or were withdrawn before completing the double-blind study

Table 3: Treatment related adverse events in double-blind phase (occurring ≥ 2 patients)

Preferred term, n (%)	AboBoNT-A 10 U/kg/leg (N=80)	AboBoNT-A 15 U/kg/leg (N=80)	Combined doses (N=160)
Any treatment related AE	6 (7.5)	5 (6.3)	11 (6.9)
Muscular weakness	2 (2.5)	0	2 (1.3)
Injection site pain	1 (1.3)	1 (1.3)	2 (1.3)
Pyrexia	1 (1.3)	0	1 (0.6)

Results

Time to retreatment

- Overall, 158 patients received abobotulinumtoxinA (10U/Kg/leg or 15U/kg/leg) in the double-blind study and 134 entered the open-label phase. Table 2 provides a breakdown of the double-blind visits at which patients in each active treatment group met retreatment criteria.
- The majority (74%) of abobotulinumtoxinA treated patients did not require retreatment for ≥16 weeks; of these, 17.7% did not meet eligibility criteria until week 28 or later (Figure 4).
- Figure 3 shows the proportion of MAS responders in each active treatment group at each visit during the double-blind phase.
- This reduction in muscle tone was reflected in the Physicians Global Assessment (PGA) of treatment response at every visit (Figure 3).

Safety

- The incidence of treatment-related TEAEs was low; the only treatment-related TEAE reported by more than 2% of abobotulinumtoxinA-treated subjects were local muscular weakness and injection site pain (Table 3).

Conclusions

- In this study, 74% of patients had a time to retreatment much longer than the 'standard' 12 weeks, following abobotulinumtoxinA injection
  - 18% patients did not require reinjection for at least 28 weeks after abobotulinumtoxinA injection
  - These data highlight the need to determine the time to retreatment on an individual basis
- At the 2 dose levels the retreatment interval was comparable and exceeded the standard 12 weeks
- In children with CP receiving regular BoNT-A treatments, extending the interval from 12 weeks to 16 weeks would mean one less injection per year.

Figure 1. Study design

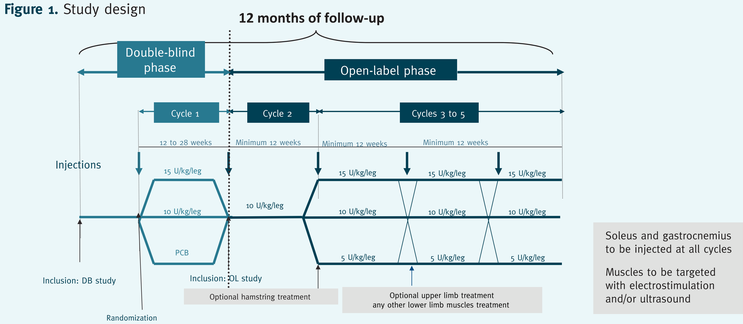
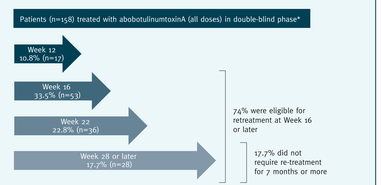
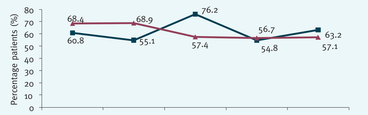


Figure 2. Time to retreatment in the double-blind phase (all abobotulinumtoxinA patients)



*By% of abobotulinumtoxinA patients met re-treatment eligibility criteria (MAS response return to ≤1 grade vs. baseline, return of PGA score to ≤0, or other criteria & in the absence of safety risks).

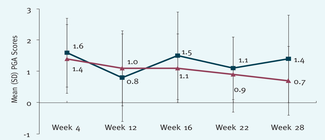
Figure 3. Percent of abobotulinumtoxinA treated patients achieving ≥1 grade reduction of MAS from baseline at each visit



Number of patients:

AboBoNT-A 10 U/kg/leg	79	69	42	31	19
AboBoNT-A 15 U/kg/leg	79	74	47	30	14

Figure 4. Mean (SD) PGA scores for abobotulinumtoxinA treated patients at each visit



Number of patients:

AboBoNT-A 10 U/kg/leg	79	69	41	32	19
AboBoNT-A 15 U/kg/leg	79	74	47	30	14

Acknowledgements

This study was funded by Ipsen Pharma. The authors would like to thank all investigators and patients involved in the studies and Anita Chadha-Patel (ACP Clinical Communications Ltd) for writing assistance (funded by Ipsen).

Disclosures

All authors (external from Ipsen) have been investigators in Ipsen-sponsored clinical trials (including the present study) and they or their institutions have received payment for participation. No author has received financial remuneration for the preparation of this abstract or poster.

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Presented at TOXINS 2017: Basic Science and Clinical Aspects of Botulinum and Other Neurotoxins, 18-21 January, 2017, Madrid, Spain.

This study was sponsored by Ipsen.