Efficacy and safety of abobotulinumtoxinA in pediatric lower limb spasticity: 2nd interim results from a phase IV, prospective, observational, multicenter study

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INTRODUCTION

- Spasticity is the velocity-dependent increase in muscle tone caused by central nervous system (CNS) lesions affecting descending neuroinhibitory pathways and a common part of the upper motor neuron syndrome.[1]
- Pediatric lower limb spasticity (PLLS) can result in various motor difficulties, including excess plantar flexion, hip adduction, and knee flexion.
- Therapeutic goals of treating PLLS, regardless of presentation and muscles affected, include interventions to reduce muscle spasms, improve mobility and coordination, minimize or delay development of contractures and limb deformity, and improve patient ease of care.[2]
- Many treatment options are either not approved or not suitable for pediatric patients.
- The available pharmacological treatments for spasticity are systemic oral medications, which do not target specific muscles and therefore may cause nonselective muscle weakness and have significant adverse effects on the CNS.[3]
- AbobotulinumtoxinA (aboBoNT-A) is approved for the treatment of PLLS and is recognized as an important treatment intervention to help alleviate symptoms, improve function, and delay or prevent the development of contractures.
- This phase IV, prospective, observational, multicenter study was designed to collect real-world data on the clinical use of aboBoNT-A in patients with PLLS.
- The first interim analysis included efficacy results from treatment cycle 1 in 144 children.

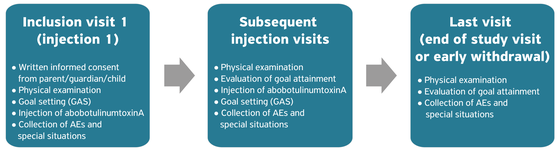
OBJECTIVE

- This 2nd interim analysis assessed the subject-centered, function-related goal attainment (GAS T-Score) after repeated aboBoNT-A injections for up to 5 treatment cycles. Long-term safety was also assessed for up to 18 months.

METHODS

- Eligible patients were recruited from the investigators' clinical practices and treatment decisions were made prior to, and independent from, study enrollment.
- At this 2nd interim analysis, 201 pediatric patients were enrolled, between 2 and 17 years old, with a primary diagnosis of PLLS who were or were not previously treated with aboBoNT-A or other botulinum toxins (BoNT).
- Patients participated for up to 30 months (with a maximum of 10 injection cycles, in intervals of ≥12 weeks).
  - AboBoNT-A injection doses, injection interval, number of injection points, and muscle injected were in accordance with the USPI and the physicians' clinical practices.
  - The dose of aboBoNT-A was not to exceed 15 Units (U)/kg for injections in one leg, or 30 U/kg for both legs, with a maximum dose of 1000 U, whichever was lower.
- The parent(s) or guardian(s) must have given written informed consent for their child to participate in the study, and written informed assent from the child was obtained, where applicable.
- Primary and secondary functional goals were identified by patient/parent/caregiver in consultation with investigators.
- These goals were assessed at the end of each injection cycle and redefined at each injection visit.
  - Goal assessment scale is defined as a 5-point Likert scale from -2 (much less than expected) to +2 (much more than expected), the GAS T-score is derived from these scores and quantifies the outcome in a single aggregated goal-attainment score.
  - If all goals are achieved as expected, the GAS T-score is 50.
  - If all goals are overachieved, the GAS T-score is >50.
- Adverse events were recorded.

Figure 1. Study flow chart



RESULTS

Table 1. Patient demographic & baseline characteristics

	Patients (N=201)	BoNT naïve (n=44)	BoNT non-naïve (n=157)	2 to 9 years old (n=139)	10 to 17 years old (n=62)
Age at time of enrollment (years) Mean (SD)	7.5 (4.2)	6.2 (4.3)	7.8 (4.1)	5.1 (2.2)	12.8 (2.1)
Gender n (%)					
Male	129 (64.2%)	30 (68.2%)	99 (63.1%)	94 (67.6%)	35 (56.5%)
Female	72 (35.8%)	14 (31.8%)	58 (36.9%)	45 (32.4%)	27 (43.5%)
Weight (kg), Mean (SD)	27.49 (16.41)	26.70 (19.33)	27.71 (15.55)	19.12 (6.92)	47.65 (15.10)
Race n (%)					
Asian	4 (2.0%)	0	4 (2.5%)	1 (0.7%)	3 (4.8%)
Black or African American	21 (10.4%)	5 (11.4%)	16 (10.2%)	16 (11.5%)	5 (8.1%)
White	164 (81.6%)	38 (86.4%)	126 (80.3%)	113 (81.3%)	51 (82.3%)
Other	8 (4.0%)	1 (2.3%)	7 (4.5%)	5 (3.6%)	3 (4.8%)
Multiple	4 (2.0%)	0	4 (2.5%)	4 (2.9%)	0

- This 2nd interim analysis included N=201 patients, of which 78.1% (n=157) had received prior BoNT treatment.
- At time of enrollment, 69.2% were aged 2-9 years.
- The average times until the 1st and 2nd re-treatments (i.e., study infusions #2 and #3) in the total population were 24.79 (SD 12.38) weeks (n=193) and 21.59 (SD 7.49) weeks (n=143), respectively.

Figure 2. Mean baseline GAS T-scores

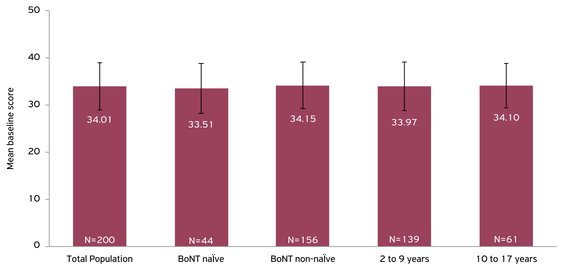
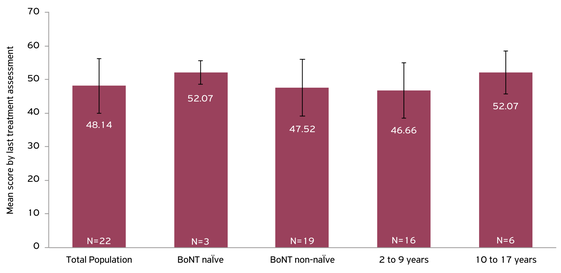


Figure 3. Mean GAS T-scores by last treatment assessment



- The cumulative GAS T-score for the total population (N=200) was 51.60 (SD 9.69).
- Although the number of patients completing the 5 treatment cycles by the time of this 2nd interim analysis was very small (N=22), the mean GAS T-score for the total population was 48.14 (SD 8.08).
- In patients aged 2-9 years (n=16), GAS T-score was 46.66 (SD 8.31) versus 52.07 (SD 6.41) in patients aged 10-17 years (n=6).

Table 2. Summary of safety and tolerability

	Patients (N=243)
Patients with any TEAE	26 (10.7%)
Severe	1 (0.4%)
Moderate	9 (3.7%)
Mild	20 (8.2%)
Treatment-related	3 (1.2%)
Not related	24 (9.9%)
Serious adverse events	3 (1.2%)
TEAE leading to study drug withdrawal	0
TEAE leading to death	0

TEAE, treatment-emergent adverse event.

- In the safety population (N=243), 44 treatment-emergent adverse events (TEAEs) were reported in 26 patients (10.7%); most events were mild to moderate, with 1 reported as severe.
  - Most TEAEs reported were due to otitis media, pharyngitis streptococcal, upper respiratory tract infection, and falls (2 each).
  - Pain in extremity, limb discomfort, muscle swelling, and myalgia reported in 3 patients were deemed treatment related.
- No reported TEAEs led to study drug withdrawal or death.
- Safety data only reflects data collected at the time of this 2nd interim analysis.

CONCLUSIONS

- Goal attainment outcomes were better than expected (T-score slightly larger than 50) for the overall PLLS population.
- AboBoNT-A was well tolerated, with a low incidence of TEAEs.
- These results further support aboBoNT-A as an effective treatment option with a positive risk-benefit profile for pediatric patients two years of age or older with lower limb spasticity.

References

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2. NICE Clinical Guideline 145. 2012;1-54.
3. Delgado MR., et al. *Neurology.* 2010;74(4):336-43.

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