Phase 3 Trial to Evaluate AbobotulinumtoxinA (Dysport®) Injections in Children with Upper Limb Spasticity due to Cerebral Palsy: A Study Design

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Introduction

- Upper limb impairment occurs in 50% to 70% of individuals with cerebral palsy (CP), and is an important source of disability – particularly in children with hemiparesis.[1,2] Functional improvement of the upper limb can impact education, participation in activities of daily living and vocational activities.[3]
- Common upper limb impairments in CP include weakness, spasticity, spastic contracture, dystonia, sensory deficit and learned non-use.[3] The most common pattern of deformity consists of shoulder adduction and internal rotation, elbow flexion, forearm pronation, wrist and finger flexion, and thumb adduction and flexion.[3]
- Children with CP often experience difficulties in reaching, pointing, grasping, releasing and manipulating objects.[3,4]
- Although botulinum toxin-A (BoNT-A) has been used in the management of upper limb spasticity in CP for many years, most clinical trials have been small, without an adequate comparator and limited in duration.
- This pediatric study will prospectively assess the efficacy and safety of abobotulinumtoxinA (aboBoNT-A) at doses of 8 U/kg and 16 U/kg vs. aboBoNT-A 2 U/kg (control group) for the treatment of upper limb spasticity due to CP.

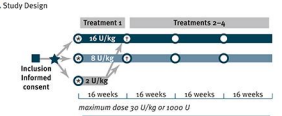
Objective

- The primary study objective is to assess the efficacy of two doses of aboBoNT-A (8 U/kg and 16 U/kg) compared to aboBoNT-A 2 U/kg used in the treatment of upper limb spasticity in children with CP following a single treatment.
- The secondary study objective is to assess the long term safety of multiple treatments of aboBoNT-A used in this study population.

Study Design

- Prospective, multicenter, double blind, randomized, controlled, multiple treatment (4 treatment cycles over 1 year) study.
- Patients will be randomized (1:1:1) to injections of aboBoNT-A 2 U/kg, aboBoNT-A 8 U/kg or aboBoNT-A 16 U/kg in cycle 1, using a prespecified injection protocol under electrical stimulation/ultrasound guidance.
- At study entry, a primary targeted muscle group (PTMG), either the elbow flexors or wrist flexors, will be selected by the investigator. The PTMG can be changed for subsequent treatments, from elbow to wrist flexors or wrist to elbow flexors, as long as re-treatment criteria are met.
- Control patients (aboBoNT-A 2U/kg in cycle 1) will be re-randomized to either aboBoNT-A 8 U/kg or aboBoNT-A 16 U/kg in subsequent cycles; the double-blind will be maintained. Eligibility to move to the next cycle will be assessed at Week 16 of each cycle.
- Patients will perform home exercises (under trained carer supervision) that are consistent with the chosen treatment goals throughout the study. Exercise instructions will be given at the baseline visit and the exercises will be adapted based on the subject's need through the study.

Figure 1. Study Design



For treatments 2-4, and according to patient response and last dose given, the investigator may request (i) a dose reduction of 50% for intolerability or (ii) a dose increase for additional efficacy (dose increases are not permitted for patients whose last dose was 16 U/kg). The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 U in the 16 U/kg group.

Patients

- Approximately 210 children with upper limb spasticity due to CP will be recruited by specialist centers.

Table 1. Patient characteristics and medication exposure

Key Inclusion Criteria	Key Exclusion Criteria
Diagnosis of CP[1]	Fixed contracture in the PTMG (Tardieu Scale X_{1+} 40°)
Aged 2-17 years	Severe choreo-athetoid/dystonic movements
Body weight ≥10kg	Previous or planned surgery of PTMG
Increased muscle tone/spasticity in at least one upper limb	Phenol/alcohol injections into PTMG within the past year
Modified Ashworth Scale (MAS) score ≥2 in the primary targeted muscle group (PTMG; elbow or wrist flexors)	Likelihood of requiring lower limb injection or injection into the non-study upper limb before Cycle 2
Gross Motor Function Classification System Level I-IV	Previous BoNT-A treatment <6 months in the study limb & <3 months in other body parts
Written informed consent from parent/ guardian, and child (as applicable)	Treatment with any drug that interferes either directly or indirectly with neuromuscular function (e.g. aminoglycoside antibiotic(s) or neuroblocking agent used during surgery within prior 30 days
	Treatment with baclofen within prior 30 days
	History of aspiration or conditions which put them at risk of aspiration, such as dysphagia

Table 2. aboBoNT-A doses per muscle

Muscles	Injection Volume (mL)[a]	Number of Injection Sites	Dose per Muscle U/kg/Maximum U		
			Low 2 U/kg	Medium 8 U/kg[b]	High 16 U/kg[b]
Elbow flexors					
Brachialis[c]	0.6	2	0.75 U/kg/30 U	3 U/kg/120 U	6 U/kg/240 U
Brachioradialis[c]	0.3	1	0.375 U/kg/15 U	1.5 U/kg/60 U	3 U/kg/120 U
Wrist flexors					
Flexor carpi radialis[d]	0.4	1–2	0.5 U/kg/20 U	2 U/kg /80 U	4 U/kg/160 U
Flexor carpi ulnaris[d]	0.3	1	0.375 U/kg/15 U	1.5 U/kg/60 U	3 U/kg/120 U
Other Muscles					
Biceps (optional muscle)	0.6	2	0.75 U/kg/30 U	3 U/kg/120 U	6 U/kg/240 U
Pronator teres	0.2	1	0.25 U/kg/10U	1 U/kg/40 U	2 U/kg/80 U
Pronator quadratus	0.1	1	0.125 U/kg/10 U	0.5 U/kg/20 U	1 U/kg/40 U
Flexor digitorum profundus	0.2	1	0.25 U/kg/10 U	1 U/kg/40 U	2 U/kg/80 U
Flexor digitorum superficialis	0.3	2–4	0.375 U/kg/15 U	1.5 U/kg/60 U	3 U/kg/120 U
Flexor pollicis longus	0.2	1	0.25 U/kg/10 U	1 U/kg/40 U	2 U/kg/80 U
Flexor pollicis brevis/ opponens pollicis	0.1	1	0.125 U/kg/5 U	0.5 U/kg/20 U	1 U/kg/40 U
Adductor pollicis	0.1	1	0.12 U/kg/5/5 U	0.5 U/kg/20 U	1 U/kg/40 U
Pectoralis major	0.5	1–2	0.625 U/kg/25U	2.5 U/kg/100 U	5 U/kg/200 U
Pectoralis minor	0.5	1–2	0.625 U/kg/25 U	2.5 U/kg/100	5 U/kg/200 U
Total dose for the study limb	**1.6**		**2 U/kg/80 U**	**8 U/kg/320 U**	**16 U/kg/640 U**

[a]For Treatments 2, 3 and 4, investigators can reduce the individual muscle dose by reducing the injection volume of each muscle. Therefore, this is the maximum volume that they can inject into each individual muscle. The total injection volume of 1.6 mL will be the same for all treatments.
[b]The total dose for the study limb must not exceed 320 U in the 8 U/kg group and 640 in the 16 U/kg group.
[c]If elbow flexors are chosen as the primary targeted muscle group, both brachialis and brachioradialis have to be injected at the dose and volume specified.
[d]If wrist flexors are chosen as the primary targeted muscle group, both flexor carpi radialis and flexor carpi ulnaris have to be injected at the dose and volume specified.

Assessments

- Trained assessors will perform multi-dimensional efficacy assessments

Primary endpoint is change from baseline to Week 6 of cycle 1 in muscle tone, as assessed by Modified Ashworth Scale (MAS) in the PTMG

Secondary measures

- Physicians Global Assessment
- Goal Attainment Scaling
- Tardieu Scale
- Assisting Hand Assessment (patients with hemiparesis)
- Faces Pain Scale
- Pediatric Quality of Life

- An "independent" assessor will perform the MAS, Tardieu and passive range of motion assessments and will be different from the evaluator performing the Physician Global Assessment (PGA).
- Safety will be reviewed by an independent Data Safety Monitoring Board

Results

- The study is ongoing and first results are expected in 2017.
- Instrumentation of the MAS and Tardieu Scale has been standardized to limit inter and intra rater variability. Investigators have been trained on the positioning of the patient for assessments and to ensure the velocity of stretch movements are consistent. Each assessor has been trained using real cases and competency has been certified. Regular trainings are also ongoing.

Conclusions

- This will be one of the largest studies to simultaneously evaluate the effects of aboBoNT-A on muscle tone, spasticity and function in pediatric upper limb spasticity due to CP.

Disclosures

MRD, AT, JC, MB and ND are Investigators in Ipsen-sponsored clinical trials and they or their institutions have received payment for participation. In addition, AT and JC report personal fees from Ipsen for consultancy, MB reports personal fees from Ipsen, Allergan and Merz for consultancy and ND reports research support from Ipsen, Allergan and Merz. FC and PP are employed by Ipsen.
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References

1. Sarnes CA, Forrest de Moura RC, Lazzari RD, Dument AJ, Braun LA, Oliveiro CS. Upper limb function evaluation scales for individuals with cerebral palsy: a systematic review. J Phys Ther Sci 2015;27(5):1617-1620.
2. Colver A, Fairhurst C, Pharoah PO. Cerebral palsy. Lancet 2014;383(9924):1240-1249.
3. Boyd RN, Morris ME, Graham HK. Management of upper limb dysfunction in children with cerebral palsy: a systematic review. Eur J Neurol 2001;8 Suppl 5:150-166.
4. Corry IS, Cosgrove AP, Walsh EG, McClean D, Graham HK. Botulinum toxin A in the hemiplegic upper limb: a double-blind trial. Dev Med Child Neurol 1997;39(3):185-193.
5. Rosenbaum P, Paneth N, Leviton A, et al. A report: the definition and classification of cerebral palsy April 2006. Dev Med Child Neurol Suppl 2007;109:8-14.

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