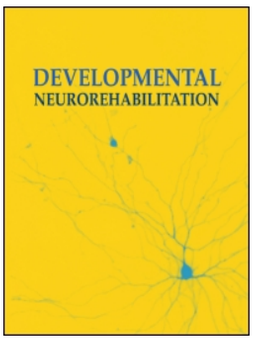
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Efficacy of Repeat AbobotulinumtoxinA (Dysport®) Injections in Improving Gait in Children with Spastic Cerebral Palsy

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ABSTRACT

Purpose: This secondary analysis of a randomized, double-blind study plus open-label extension (NCT01249417/NCT01251380) evaluated the efficacy of abobotulinumtoxinA versus placebo in improving gait pattern in children with dynamic equinus due to cerebral palsy (CP) as assessed by the observational gait scale (OGS).

Methods: Ambulatory children with CP (N = 241, aged 2–17) and dynamic equinus were randomized to treatment with abobotulinumtoxinA (10 or 15U/kg/leg) or placebo injected into the gastrocsoleus. All children received abobotulinumtoxinA in the open-label phase.

Results: In the double-blind phase, abobotulinumtoxinA significantly improved OGS total scores versus placebo at Week 4 (treatment effect vs. placebo: 10U/kg/leg: 1.5 [0.7, 2.3], $p = .0003$; 15U/kg/leg: 1.1 [0.3, 1.9], $p = .01$). In the open-label phase, treatment with abobotulinumtoxinA continued to improve the OGS score at the same magnitude as seen in the double-blind study.

Conclusion: Repeat treatment with abobotulinumtoxinA improved gait in children with dynamic equinus.

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KEYWORDS
Abobotulinumtoxina; botulinum toxin; cerebral palsy; dynamic equinus; gait

Introduction

Between 75 and 91% of patients with cerebral palsy (CP) have spasticity that interferes with motor function, thereby contributing to the significant restrictions in activity and participation frequently observed in these children.[1–3] A child with CP will often have both spasticity and weakness, which may affect different lower limb muscle groups causing torque imbalances around the joints.[4,5] These imbalances manifest as abnormal gait patterns and could lead to secondary musculoskeletal deformities that add to the patient's functional impairment. In children with gastrocnemius spasticity (affecting most children), overactivation of the gastrosoleous muscle complex often leads to an equinus gait pattern, which is characterized by an abnormal plantarflexion angle throughout the gait cycle. In ambulatory patients, the equinus foot position affects foot rockers from initial contact and disturbs progression over the supporting foot throughout the stance phase.[6,7] It also aggravates all prerequisites of normal gait and increases the risk of tripping and falling. Equinus in CP is initially dynamic, making it amenable to stretching and orthoses. However, its presence also interferes with the wearing of shoes and the use of orthoses, and may produce abnormal foot pressure distribution during the stance phase of gait, which can lead to foot pain and callus formation.[8]

Physiotherapy and orthotic interventions are considered central components in the multimodal management of lower limb-spasticity.[3] Within this context, use of botulinum toxin type-A (BoNT-A) is also considered an important treatment option to improve function and support motor development.[9] Several clinical guidelines now recommend that, when clinically indicated, BoNT-A should be offered as an effective and generally safe treatment for localized/segmental spasticity in children and adolescents with CP.[9–12] However, the vast majority of research has been directed toward the efficacy of BoNT-A in reducing spasticity and muscle tone,[13] with less focus on functional measures such as gait. This represents an important data gap because gait improvement is one of the most common goals of treatment for patients and their parents.[14] Whilst instrumented gait assessment that provides quantitative measures of three-dimensional gait kinematics and kinetics combined with EMG remains the gold standard for gait assessment, its use in routine clinical practice is limited by its high costs and need for specialized interpretation.[15] Simple and low-cost technology tools may offer clinicians a more accessible alternative for assessment.

The Observational Gait Scale (OGS) evolved from the Physician's Rating Scale (PRS) as a simple, but complete, tool to examine the spastic gait in 2-D. A key advantage of the OGS compared to the PRS is that it effectively measures the BoNT-A injection effect on equinus gait when looking at the sagittal

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plane of the foot.[16] The aim of this analysis of exploratory data from a Phase III pivotal study and its open-label extension was to determine the efficacy of abobotulinumtoxinA compared to placebo in improving gait pattern in children with dynamic equinus foot deformity due to CP, using the OGS.

Methods

Reported here are pre-specified efficacy results from a prospective, international Phase III multicentre, double-blind study of abobotulinumtoxinA (Dysport®; Ipsen Biopharmaceuticals, Wrexham, UK) for dynamic equinus foot deformity (NCT01249417) and its open-label extension study (NCT01251380). The full methodologic and primary efficacy and safety details of both studies have been previously published.[17,18] The double-blind study was conducted in 23 outpatient centres across North and South America, Europe, and Asia; it started in July 2011 and completed in June 2014. The open-label study was conducted in 26 specialist outpatient centres; it started in October 2011 and completed in January 2014. Institutional review boards at the participating sites approved the protocol and the trial was executed in accordance with the Declaration of Helsinki and International Conference on Harmonization Good Clinical Practice Guidelines. Written informed consent was obtained for both the double-blind and open-label studies.

Patients

In brief, the double-blind phase of the study included children (aged 2–17 years) with equinus foot positioning during the stance phase of gait due to spastic CP. Eligible children were ambulatory (GMFCS Level I-III), and had a derived Modified Ashworth Scale (MAS) score ≥2 as well as a Tardieu Scale spasticity grade (Y) of 2–4 (2 = catch and release, 3 = fatigable clonus, 4 = non-fatigable clonus) and a spasticity angle [X] of ≥10° at the ankle joint of the most affected limb. Key exclusion criteria included: a non-ambulatory status, a fixed ankle plantarflexors myocontracture (defined by a passive range of motion angle by the Tardieu Scale [XV1] of ≤80° in ankle dorsiflexion), severe athetoid/dystonic movements in the targeted limbs(s), or a significant lower limb length difference (>2 cm). Patients were also excluded if they had previous surgery for lower limb spasticity, previous injections with alcohol and/or phenol or serial casting within the past 12 weeks, or BoNT treatment with the past 6 months.

All patients who completed at least 12 weeks of follow-up in the double-blind study without any major protocol deviations and/or any significant adverse events (AEs) were eligible to enter the open-label extension study.

Study Design

In the double-blind study, eligible patients were assessed at baseline and randomized (sponsors computer-generated scheme) in a ratio of 1:1:1 to a single treatment cycle of abobotulinumtoxinA 10 U/kg/leg (i.e. total dose for unilateral injection: 10 U/kg and total dose for bilateral injections: 20 U/kg), abobotulinumtoxinA 15 U/kg/leg (i.e. total doses of 15 U/kg or 30 U/kg, respectively), or placebo into the gastrocnemius-soleus complex (GSC). The open-label study consisted of a maximum of 4 treatment cycles of abobotulinumtoxinA at doses of 5 to 30 U/kg (total body weight), occurring at intervals of ≥12 weeks, depending upon overall individual duration of response to treatment.[18]

During Treatment Cycle 1 of the open label study, injections into the GSC were mandatory while injections in hamstrings were performed per Investigator judgement. From Treatment Cycle 2 onwards, the total dose could be tailored (increased or decreased) in 5 U/kg increments as clinically indicated and could include injections of other lower limb muscles (hamstrings, tibialis posterior, hip adductors or iliopsoas) or upper limb muscles. The total dose of abobotulinumtoxinA (irrespective of muscles injected) per cycle was no more than 30 U/kg or 1000 U, whichever was the lower value. If physical therapy or ankle-foot orthoses had been initiated prior to double-blind study, the therapy regimen was continued (at the same frequency and intensity) throughout both studies. If absolutely required during the open-label phase, new physical therapy, ankle-foot orthoses, and/or casting, were permitted only after the Week 12 study visit of the treatment cycle.

Observational Gait Scale

Patients were assessed for gait using the OGS at Weeks 4 and 12 of the double-blind phase and for open-label Cycles 1 to 3. The child was asked to repeatedly (6 times) ambulate back and forth over a 7-meter course in front of the video camera while demonstrating their most typical/natural gait pattern. The child's gait was video recorded in the frontal and sagittal plane. All sites received formal training in producing 2D motion analysis video recordings of adequate quality for evaluation.

All videos were analyzed by a central committee of independent clinical experts (physical therapists who were not otherwise involved in the studies) with experience of scoring the OGS. Each video was rated by 2 reviewers who assessed: knee position in midstance, initial foot contact, foot contact at midstance, timing of heel rise, position of hindfoot at midstance, base of support, gait assistive devices, and speed change. The change score was omitted as raters received the videos in a randomized (non-chronological) order with no reference to baseline.

Blinded analyses focused on change from baseline to Week 4 and Week 12 of the double-blind study versus placebo for the OGS Total score (maximum 'perfect' score of 20) in the most affected limb, and a responder analysis of the number of patients per group who had at least 1 grade improvement from baseline in item 2, which specifically assesses pattern of initial foot contact (toe = 0, forefoot = 1; foot flat = 2 and heel = 3) to evaluate the treatment objective of 'reducing toe walking'. In addition, post-hoc analyses evaluating the number of patients per group who had at least 1 grade improvement from baseline in item 3 (foot contact at midstance), item 4 (timing of heel rise), and a combined analysis of items 2, 3 and/or 4 were conducted. Double-blind analyses were performed on the intention-to-treat population (ITT) including all randomized patients who received at least 1 study treatment in the GSC and had recorded Modified Ashworth Scale (primary outcome measure) scores at baseline and

Week 4. Differences versus placebo at Week 4 and Week 12 were estimated using an analysis of covariance (ANCOVA) model with baseline OGS, BoNT status (BoNT naïve or previously treated at study entry), age and center included as covariates.

For the open-label study and post-hoc analyses, data were limited to descriptive analyses; no formal statistical significance testing was planned.

Results

Patient Disposition and Baseline Characteristics

Overall 253 patients were screened, 241 were randomized and 228 completed 12-weeks of treatment in the double-blind study phase (Supplementary figure e1). Of the 241 randomized patients, the ITT population included 235 patients (98%); of which 77 patients were randomized to placebo and 79 were randomized to each of the active treatment groups.[17] A total of 216 (90%) patients entered the open-label extension study at time points determined by their eligibility for retreatment during the double-blind phase.[17,18] Only 11 patients required four treatment cycles within the open-label study time frame, and therefore no analyses are presented for this final cycle.

Baseline characteristics for both study phases have been previously published[17,18] and are summarized in the Supplementary Table e1. At the start of the double-blind study, 60% of patients were male and 85% of patients were aged 2–9 years old (85%). Over half (56%) of patients were GMFCS level I, 33% were GMFCS level II and 11% were GMFCS level III. Half (50%) had unilateral and half (50%) had bilateral involvement. The majority (88.5%) of patients utilized concomitant orthosis and/or physiotherapy, prior to and during the study. There were no notable differences in patient demographics for those patients who continued into the open-label study. [18] Across the open-label treatment cycles, 17–24% of patients had injections (additional to GSC) into the hamstrings. During Treatment Cycles 2 and 3, 11–12% patients had injections into other lower limb muscles (including the tibialis posterior, hip adductors and iliopsoas) and 9–11% into upper limb muscles. Median [range] total doses in the open-label cycles were 10.0 U/kg [10–30 U/kg] in Cycle 1, 15.0 U/kg [8.5–30 U/kg] in Cycle 2, 15.0 U/kg [10–30 U/kg] in Cycle 3 and 19.1 U/kg [10–30 U/kg] in Cycle 4. Adverse events throughout both studies were mainly related to common childhood infections.[17,18] In the double-blind study phase, treatment-related local muscular weakness was reported by 3 patients (n = 1 placebo, n = 2 AboBoNT-A 10 U/kg).[17] In the open-label study phase, the only treatment-related AE reported by >2 patients was injection site pain (n = 10).

Double-blind Study versus Placebo

Mean (SD) baseline OGS Total scores in the most affected limb were reflective of children with dynamic equinus foot deformity[16]: 9.8 (3.6) in the placebo group, 10.0 (3.8) in the abobotulinumtoxinA 10 U/kg/leg group, and 9.1 (3.7) in the abobotulinumtoxinA 15 U/kg/leg group. In the double-blind phase, treatment with abobotulinumtoxinA significantly improved OGS total scores in the most affected leg versus placebo at Week 4 (mean [95% CI] treatment effect vs. placebo: 10 U/kg/leg: 1.5 [0.7, 2.3] (p = .0003); 15 U/kg/leg: 1.1 [0.3, 1.9] (p = .01)) and a significant effect versus placebo was maintained until Week 12 in the 10 U/kg/leg (0.9 [0.0, 1.7] (p = .04)), but not 15 U/kg/leg, group (Figure 1a).

The proportion of OGS item 2 (initial foot contact) responders was statistically significantly higher in the abobotulinumtoxinA 10 U/kg/leg group and abobotulinumtoxinA 15 U/kg/leg group compared to placebo at Week 4 (odds ratio = 9.8 [3.5, 27.8] and 7.8 [2.8, 22.0] respectively) and at Week 12 (odds ratio = 5.2 [1.6, 16.8] and 7.5 [2.4, 23.5] respectively). The proportion of responders was highest at Week 4, with the significant effect maintained at Week 12. (Figure 1b).

Post-hoc analyses at double-blind Week 4 found that numerically more patients in the abobotulinumtoxinA 10 U/kg/leg and 15 U/kg/leg groups showed at least one grade improvement in OGS item 4 (timing of heel rise) than in the placebo groups (35.9% and 36.2% vs. 10.6%, respectively). For OGS item 3 (foot contact at midstance) more patients in the 10 U/kg/leg group were classified as responders than in the 15 U/kg/leg and placebo groups (24.1%, 9.5% and 5.3%, respectively). When taken overall (i.e. improvement on OGS items 2, 3 and/or 4), the percentage of responders both at Week 4 and 12 was higher in abobotulinumtoxinA 10 U/kg/leg and 15 U/kg/leg groups versus placebo (Week 4: 46.5% and 42.9% vs.12.3%, Week 12: 31.7% and 34.4% vs. 13.6%, respectively) (Table 1)

Open-label Extension Study

In the open-label phase, treatment with abobotulinumtoxinA (all doses combined) continued to improve the OGS Total score at the same magnitude as seen in the double-blind study (Figure 2).

In Treatment Cycle 1 of the open-label study, when all patients received abobotulinumtoxinA 10 U/kg/leg, the proportion of responders compared to double-blind baseline at Week 4 was 29.5% (51/173) this increased to 36.0% (50/139) at Week 4 of Treatment Cycle 2 when patients could receive tailored dosing and a third of patients (33.3%, 23/69) were classified as responders at Week 4 of Treatment Cycle 3.

Discussion

It has previously been reported that, in children with CP, single and repeated injections of abobotulinumtoxinA significantly are generally well-tolerated and improve muscle hypertonia and spasticity, attainment of treatment goals[14] and the overall global clinical impression.[17,18] The results of these analyses provide further evidence for the efficacy of abobotulinumtoxinA and demonstrate that abobotulinumtoxinA treatment provides functional improvements in gait that are sustained over repeated treatment cycles.

Treatment with abobotulinumtoxinA improved overall OGS scores as well as individual items of the OGS scale. In the absence of an agreed minimally clinically relevant difference for total scores, we prespecified the OGS item 2 (initial foot contact) as the item most clinically relevant to ambulatory children with dynamic equinus foot deformity. Significantly more children in the abobotulinumtoxinA treatment groups showed at least one

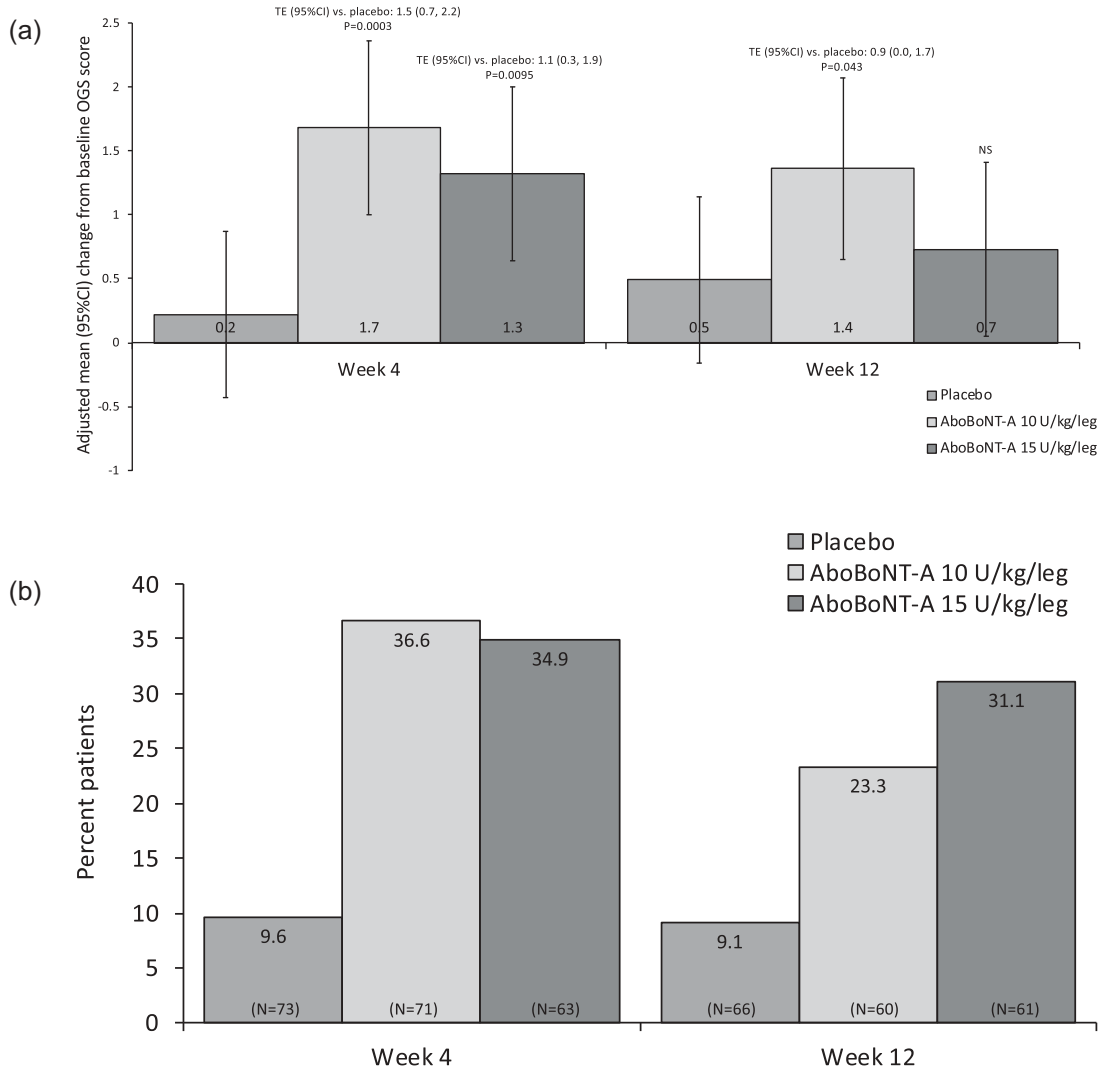


Figure 1. Observational Gait Scale scores during the double-blind study (a) Change from baseline to Weeks 4 and 12 in OGS total scores (b) Percentage of OGS item 2 (Initial Foot Contact) responders achieving ≥1 grade improvement at Weeks 4 and 12.

Legend: AboBoNT-A = abobotulinumtoxinA, CI = confidence interval, OGS = observational gait scale, pbo = placebo, NS = not significant versus placebo, TE = treatment effect.

Table 1. *Post hoc* analysis of OGS, including foot contact at midstance and timing of heel raise.

Percent responders achieving at least one grade improvement	AboBoNT-A 10 U/kg	AboBoNT-A 15 U/kg	Placebo
Item 3 (foot contact at midstance)			
Week 4	7/29 (24.14)	2/21 (9.52)	1/19 (5.26)
Week 12	4/26 (15.38)	1/21 (4.76)	1/20 (5.00)
Item 4 (timing of heel raise)			
Week 4	23/64 (35.94)	21/58 (36.21)	7/66 (10.61)
Week 12	13/54 (24.07)	16/57 (28.07)	8/63 (12.70)
Items 2, 3 or 4			
Week 4	33/71 (46.48)	27/63 (42.86)	9/73 (12.33)
Week 12	19/60 (31.67)	21/61 (34.43)	9/66 (13.63)

grade improvement on this individual item. In clinical practice, a one-grade improvement could mean, for example, that a child who previously walked on tip-toes now walks on their forefoot or a child who previously walked on their forefoot now walks with a flat foot. However, the results of the post-hoc analyses show that children with this pattern of spasticity may also benefit from injections into the gastrosoleus in terms of improving foot contact at midstance and timing of heel rise. When response at Week 4 was analyzed by an improvement in any of these clinically relevant gait parameters, 43–47% of children treated with abobotulinumtoxinA showed improvement versus 12% of children in the placebo group. Foot deformities result in an abnormal distribution of load on the plantar surface of the foot. The present analyses focus on the individual OGS components of gait most closely related with overactivity of the gastrocnemius-soleus muscle complex. In the open-label phase, few children required proximal injections. Previous studies have shown that BoNT-A injections into the calf muscles results in significant increases in dorsiflexion at initial contact, as well as from midstance through the rest of the gait cycle.[19] These data provide robust evidence for the clinical relevance of these changes.

The OGS has been shown to be valid and reliable,[15,16] with acceptable inter-rater and intra-rater reliability for initial foot contact,[20] despite this it has not been widely used in interventional trials.[15] To the best of our knowledge, this is the largest pediatric CP study to include the OGS as an outcome measure,

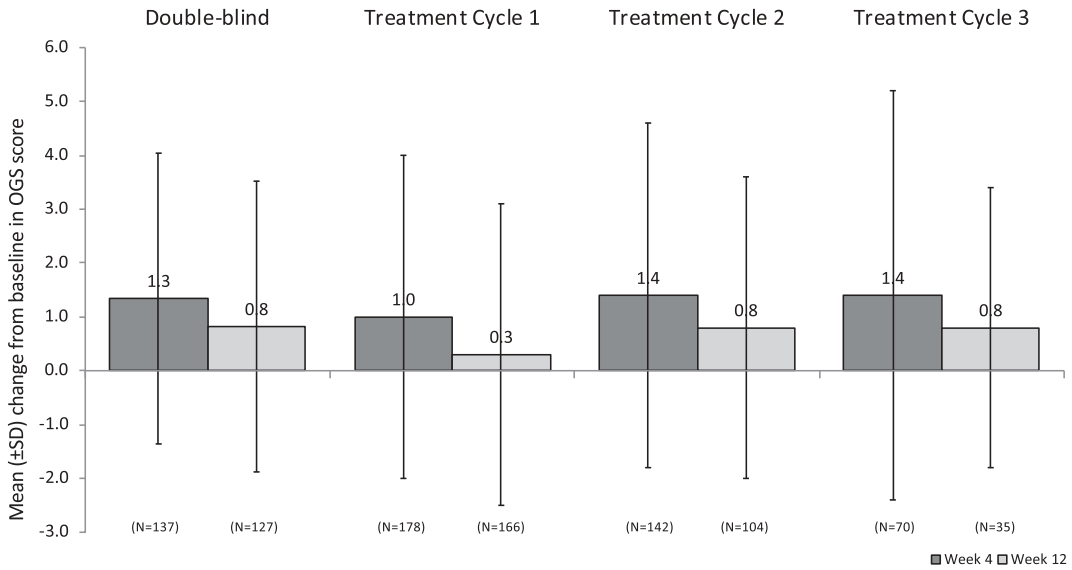


Figure 2. Mean (SD) change from double-blind baseline to Weeks 4 and 12 in OGS total scores during the double-blind and open-label studies (all doses combined). Legend: AboBoNT-A = abobotulinumtoxinA, OGS = observational g

and to follow its use over the course of 1 year of repeat BoNT-A injections on a background of standard of care treatments. However, a number of earlier studies have used the PRS as an outcome measure. A meta-analysis of four smaller-scale randomized controlled trials (combining to a total of 183 patients) using the PRS also found statistically significant gait improvement in children treated with BoNT-A for spastic equinus foot versus placebo (Peto odds ratio 3.49, 95% CI 2.20–7.22).[21] In an prospective, open-label study Koman and colleagues also found that 55% (n = 63/115) of children with repeat BoNT-A injections had an improvement on the PRS, and that these improvements were maintained in 44% (n = 20/45) at the 2 year follow up.[22] Both gait pattern and hindfoot position during foot strike, were significantly improved with BoNT-A treatment in patients followed for 2 years.[22]

Strengths of this study include the large number of patients assessed and the long duration of follow-up. Most of the chosen goals in this study (chosen by parents in agreement with the investigators) centred on improving walking patterns, and thus the present results confirm the benefits of abobotulinumtoxinA in supporting the achievement of better gait, which is of prime importance to patients and their families. [14,17] Of note, we have also observed significant improvements versus placebo from baseline to Week 12 in the fatigue item of the Pediatric Quality of Life Inventory for both doses of abobotulinumtoxinA (10 U/kg/leg: p = .030 and 15 U/kg/leg: p = .037, the overall score was not significantly improved in either group).[23] Other studies of BoNT-A in children with CP have reported that treatment, not only reduces spasticity and improved ankle range of motion and walking pattern, but also reduces energy consumption.[24] One can hypothesize that improvements in gait may lead to reductions in the efforts made by the children to walk or run, and the feelings of tiredness, which is a common complaint in children with CP, often affecting their daily life.[25]

As with other outcome measures used in this trial,[17] the use of the OGS in the protocol involved considerable efforts toward standardization to ensure that all centers could provide reliable videos in this patient population that could be used for video analysis. The main purpose of the OGS is to rate gait parameters from video recordings using low-cost technology that can be easily implemented in routine practice. For the purposes of the study, independent reviewers provided feedback on the quality of video-recordings, and all investigators received certified training. From the practical perspective, once in place, the set up was easy to put to repeat use. The independent rating of gait prevented any investigator bias in the evaluation of OGS scores and added another dimension of consistency to OGS assessments. Nevertheless, an important limitation of the study included the difficulty of ensuring that young children were indeed walking in accordance with their typical pattern. In their original report, Boyd et al., suggested that the OGS may be particularly useful when children are too small or are insufficiently cooperative for instrumented gait analysis,[16] however it does still require a certain level of cooperation from the patient.

Very importantly, these findings continue to contradict an often-cited evidence base in which BoNT-A treatment has failed to show significant efficacy in terms of functionality.[26,27] A key barrier to showing functional efficacy in previous trials has been the use of inappropriate outcome measures or treatment objectives coupled with inadequate training and standardization. The findings from this large double-blind study and its long-term follow up now provide clear evidence that the injection of abobotulinumtoxinA in the relevant lower limb muscles, not only reduces muscle tone and spasticity, but also provides clear functional benefits in terms gait as assessed by the OGS. The OGS was chosen as an outcome in this study because it was specifically designed to be sensitive to detect changes following administration of BoNT-A and the individual OGS items

objectively assess the aspects of gait that are clinically relevant following injections into the gastrocnemius-soleus muscle complex in children with dynamic equinus foot deformity. As such, we not only recommend the OGS for routine use, but also endorse its use in future clinical trials.

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Data availability statement

Where patient data can be anonymised, Ipsen will share all individual participant data that underlie the results reported in this article with qualified researchers who provide a valid research question. Study documents, such as the study protocol and clinical study report, are not always available. Proposals should be submitted to DataSharing@Ipsen.com and will be assessed by a scientific review board. Data are available beginning 6 months and ending 5 years after publication; after this time, only raw data may be available.

Disclosure statement

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

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