



Original Article

IncobotulinumtoxinA Efficacy/Safety in Upper-Limb Spasticity in Pediatric Cerebral Palsy: Randomized Controlled Trial



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ABSTRACT

Background: This randomized phase 3 study with double-blind main period (MP) and open-label extension (OLEX; NCT02002884) assessed incobotulinumtoxinA safety and efficacy for pediatric upper-limb spasticity treatment in ambulant/nonambulant (Gross Motor Function Classification System [GMFCS] I–V) patients, with the option of combined upper- and lower-limb treatment.

Methods: Patients were aged two to 17 years with unilateral or bilateral spastic cerebral palsy (CP) and Ashworth Scale (AS) score ≥ 2 in treatment-selected clinical patterns. In the MP, patients were randomized (2:1:1) to incobotulinumtoxinA 8, 6, or 2 U/kg body weight (maximum 200, 150, 50 U/upper limb), with optional lower-limb injections in one of five topographical distributions (total body dose ≤ 16 to 20 U/kg, maximum 400 to 500 U, depending on body weight and GMFCS level). In the OLEX, patients received three further treatment cycles, at the highest MP doses (8 U/kg/upper limb group). Outcomes included AS, Global Impression of Change Scale (GICS), and adverse events (AEs).

Results: AS scores improved from baseline to week 4 in all MP dose groups ($n = 350$); patients in the incobotulinumtoxinA 8 U/kg group had significantly greater spasticity improvements versus the 2 U/kg group (least-squares mean [standard error] for upper-limb main clinical target pattern -1.15 [0.06] versus -0.93 [0.08]; $P = 0.017$). Investigator's, child/adolescent's, and parent/caregiver's GICS scores showed improvements in all groups. Treatment benefits were sustained over further treatment cycles. AE incidence did not increase with dose or repeated treatment across GMFCS levels.

Conclusions: Data provide evidence for sustained efficacy and safety of multipattern incobotulinumtoxinA treatment in children and adolescents with upper-limb spasticity.

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Introduction

Spastic cerebral palsy (CP) is the most common pathophysiological motor type, affecting around 80% of patients with CP.^{1–3} Clinical manifestations are typical on a global level, but heterogeneous at the individual level, and can occur in upper and/or lower extremities depending on the time and locus of the lesion and reorganizational and developmental capacities.⁴ Effects are generally more pronounced in the lower limbs in children with bilateral involvement and in the upper limbs in children with unilateral involvement.^{2,4,5} However, almost 50% of all cases involve both the upper and lower limbs.⁶

Botulinum neurotoxin type A (BoNT-A) injections, in coordinated combination with other treatment options, can achieve functional benefits in children with CP,⁷ and their efficacy and safety have been demonstrated.^{8–13} At present, there are two BoNT-A formulations approved for the treatment of upper- and lower-limb spasticity due to CP in pediatric patients aged two years or older in the United States: abobotulinumtoxinA (Dysport, Ipsen Biopharm Ltd)¹⁴ and onabotulinumtoxinA (Botox, Allergan Inc)¹⁵; in most European countries, only treatment of pes equinus is approved, with¹⁶ or without¹⁷ upper-limb treatment. IncobotulinumtoxinA (Xeomin, Merz Pharmaceuticals) is a highly purified BoNT-A free from complexing proteins¹⁸ approved in the United States for the treatment of upper-limb spasticity in pediatric patients, excluding that caused by CP (due to marketing exclusivity granted to another manufacturer).¹⁹ Guidelines recommend BoNT-A treatment for focal upper- and lower-limb spasticity, and the diverse clinical presentation of spastic CP requires a multipattern treatment approach to simultaneously target several muscle groups.^{7,20} Moreover, with the wide-ranging disease severity and clinical course across Gross Motor Function Classification System (GMFCS) levels I–V,⁷ treatment recommendations should be available for patients with all disability levels allowing fair treatment access. The objective of the phase 3 study reported here was to investigate the efficacy and safety of incobotulinumtoxinA for upper-limb spasticity¹⁹ over four treatment cycles, with the option of combined upper- and lower-limb treatment, in children and adolescents with spasticity due to CP.

Materials and Methods

Study design and treatment

XARA (IncobotulinumtoxinA in Arm Treatment in Cerebral Palsy) was a prospective, double-blind, randomized, parallel-group, phase 3 trial conducted in 28 sites worldwide. The trial comprised a two-week screening period, a main period (MP) with a single double-blind treatment cycle of 14 (± 2) weeks, followed by three further 14 (± 2)-week treatment cycles as an open-label extension period (OLEX), giving an overall study duration of 50 to 66 weeks.

During the MP, patients were randomized 2:1:1 to receive fixed unilateral upper-limb incobotulinumtoxinA doses in three parallel dose groups: 8 U/kg, 6 U/kg, and 2 U/kg body weight (BW) per upper limb (maximum 200, 150, and 50 U, respectively). The 2 U/kg BW group served as a control. Patients could receive unilateral or bilateral upper-limb injections alone or with optional additional unilateral or bilateral lower-limb injections in one of five predefined multipattern topographical distributions (Fig 1), as clinically needed and allowed in a single treatment cycle. Lower-limb treatment was administered in the same dose groups as upper-limb treatment; maximum total body doses of 8 U/kg up to 20 U/kg (maximum 500 U) in children with GMFCS I to III, or 16 U/kg (maximum 400 U) in children with GMFCS IV to V, could be administered across the possible treatment combinations (Fig 1).

After completion of the MP, eligible patients continued treatment in the OLEX in the same treatment combination chosen at baseline, in a single treatment arm with doses equivalent to the highest MP dose group: 8 U/kg per upper limb (maximum 200 U) up to a total body dose of 20 U/kg (maximum 500 U, GMFCS I to III) or 16 U/kg (maximum 400 U, GMFCS IV to V). The main upper-limb clinical target pattern (or patterns of both sides with bilateral treatment) chosen at baseline was kept and treated with a fixed dose throughout the study. In patients receiving optional additional lower-limb injections, lower-limb patterns chosen at baseline could be changed in subsequent OLEX treatment cycles within predefined dose ranges.

At least one method among ultrasound, electrical stimulation, and/or electromyography was mandatory for localization of the target muscle and correct placement of the injection needle. Ultrasound, as the widely established option,^{21–24} was the preferred guidance technique. A data monitoring committee safeguarded patients by monitoring and assessing adverse events (AEs), AEs of special interest (AESIs) possibly indicating toxin spread, and serious AEs (SAEs) occurring after incobotulinumtoxinA treatment.

Stable centrally acting antispastic medication was allowed during the study as follows: drugs acting as central muscle relaxants (e.g., oral baclofen, tizanidine) and/or benzodiazepine medication (e.g., diazepam) and/or any other medication with antispastic effects (e.g., gabapentin, dronabinol) if administered at a stable dose within two weeks before the screening visit, during the screening period, and for the duration of the MP (doses could be changed during the OLEX). Peripherally acting muscle relaxants (e.g., dantrolene) or phenol or alcohol injections into any body region within six months before the study, during the screening period, and/or planned during the MP or OLEX were not allowed.

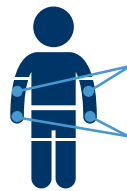
Patients

Eligible patients were children and adolescents aged two to 17 years with unilateral or bilateral CP, an Ashworth Scale (AS) score ≥ 2 in the main upper-limb clinical target patterns of flexed elbow and/or flexed wrist (at least unilaterally), and a clinical need, according to the investigator, for the treatment of upper-limb spasticity in one of five treatment combinations for upper- or combined upper- and lower-limb spasticity (AS score ≥ 2 for each targeted multipattern chosen for injection at baseline, Fig 1). Patients with the whole range of spasticity severity (GMFCS level I to V) were included in the study.

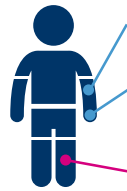
Key exclusion criteria included fixed contracture, predominant forms of muscle hypertonia other than spasticity (e.g., dystonia) in the target limbs, or pure dyskinetic CP or CP mixed with predominantly dyskinetic movements. Patients with severe neurological diagnoses and comorbidities outside the spectrum of CP, ongoing severe or unstable medical conditions (e.g., systemic infection, bleeding disorder, or pulmonary disease), and those who received BoNT treatment ≤ 14 weeks before screening, for any indication, were also excluded. Surgical interventions were considered an exclusion criterion if they affected the treated limbs (upper limbs only) and if they took place within 12 months before screening/baseline or were planned for the time of study participation.

Eligibility for reinjection was assessed at the final visit of the MP and at the end-of-cycle visits during the OLEX. Patients meeting the following criteria were eligible for reinjection in the OLEX: a clinical need for injection of the main upper-limb clinical target pattern chosen at baseline with a total incobotulinumtoxinA dose of 8 U/kg (maximum 200 U) per upper limb, a clinical need for lower-limb treatment at the dose used in the previous treatment cycle in patients receiving combined upper- and lower-limb

A Uni- or bilateral UL treatment only (GMFCS I–V)

	Clinical pattern	Dose per clinical pattern	Maximum dose per limb	Maximum body dose
	Main: Flexed elbow and/or flexed wrist	4 U/kg BW (≤ 100 U) 2 U/kg BW (≤ 50 U)	8 U/kg BW or 200 U per single UL	16 U/kg BW or 400 U
	Other: Clenched fist, thumb in palm, and/or pronated forearm	Remaining dose up to 8 U/kg BW or 200 U per UL		

B Unilateral UL and unilateral LL treatment (GMFCS I–V)

	Clinical pattern	Dose per clinical pattern	Maximum dose per limb	Maximum body dose
	Main: Flexed elbow and/or flexed wrist	4 U/kg BW (≤ 100 U) 2 U/kg BW (≤ 50 U)	8 U/kg BW or 200 U	16 U/kg BW or 400 U
	Other: Clenched fist, thumb in palm, and/or pronated forearm	Remaining dose up to 8 U/kg BW or 200 U per UL		
	Other: Pes equinus, flexed knee, adducted thigh, and extended great toe		8 U/kg BW or 200 U per single LL	

C Unilateral UL and bilateral LL treatment (GMFCS I–III)

	Clinical pattern	Dose per clinical pattern	Maximum dose per limb	Maximum body dose
	Main: Flexed elbow and/or flexed wrist	4 U/kg BW (≤ 100 U) 2 U/kg BW (≤ 50 U)	8 U/kg BW or 200 U	20 U/kg BW or 500 U
	Other: Clenched fist, thumb in palm, and/or pronated forearm	Remaining dose up to 8 U/kg BW or 200 U per UL		
	Other: Pes equinus, flexed knee, adducted thigh, and extended great toe		12 U/kg BW or 300 U for both LLs	

D Unilateral UL and bilateral LL treatment (GMFCS IV and V)

	Clinical pattern	Dose per clinical pattern	Maximum dose per limb	Maximum body dose
	Main: Flexed elbow and/or flexed wrist	4 U/kg BW (≤ 100 U) 2 U/kg BW (≤ 50 U)	8 U/kg BW or 200 U	16 U/kg BW or 400 U
	Other: Clenched fist, thumb in palm, and/or pronated forearm	Remaining dose up to 8 U/kg BW or 200 U per UL		
	Other: Pes equinus, flexed knee, adducted thigh, and extended great toe		8 U/kg BW or 200 U for both LLs	

E Bilateral UL and bilateral LL treatment (GMFCS I–III)

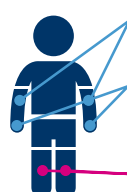
	Clinical pattern	Dose per clinical pattern	Maximum dose per limb	Maximum body dose
	Main: Flexed elbow and/or flexed wrist	4 U/kg BW (≤ 100 U) 2 U/kg BW (≤ 50 U)	8 U/kg BW or 200 U per single UL	20 U/kg BW or 500 U
	Other: Clenched fist, thumb in palm, and/or pronated forearm	Remaining dose up to 8 U/kg BW or 200 U per UL		
	Other: Pes equinus, flexed knee, adducted thigh, and extended great toe		4 U/kg BW or 100 U for both LLs	

FIGURE 1. XARA treatment combinations. The highest dose regimen (8 U/kg BW per upper limb, maximum 200 U in patients ≥ 25 kg BW) is presented for each of the treatment distributions. During the MP, doses in the 6 U/kg and 2 U/kg groups were 75% and 25%, respectively, of the doses presented. Treatment of M. biceps brachii was mandatory for the treatment of flexed elbow. M. brachialis or M. brachioradialis were injected if clinically appropriate at the investigator's discretion. BW, body weight; GMFCS, Gross Motor Function Classification System; LL, lower limb; M., musculus; MP, main period; U, unit; UL, upper limb.

treatment, and an AS score ≥ 2 in all treated clinical patterns. The investigator could decide on the need for reinjection in patients with an AS score of 1.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and was registered on clinical trials.gov (NCT02002884). Study protocols, informed consent

forms, and other appropriate study-related documents were reviewed and approved by the local independent ethics committees and institutional review boards. Written informed consent was obtained from all patients and/or their parents in accordance with regional laws or regulations (further details in [Supplemental Methods](#)).

Efficacy

The primary efficacy variable was change from baseline at MP week 4 in AS score for the main clinical target pattern chosen from flexed elbow or flexed wrist, assessed using the original AS²⁵ (five-point scale from 0, no increase in muscle tone, to 4, limb rigid in flexion/extension) by the same trained investigator at all study visits where possible. The coprimary efficacy variable was the investigator's Global Impression of Change Scale (GICS) score for the upper limb at MP week 4, assessed on a seven-point Likert scale from −3 (very much worse) to +3 (very much improved) based on the impression of change in spasticity compared with the condition before the last injection.

Secondary variables included change from baseline in AS score for treated upper-limb clinical patterns at week 4 and all other MP postbaseline visits, change from baseline in Questionnaire on Pain caused by Spasticity (QPS) scores,^{26,27} and child/adolescent's and parent/caregiver's upper-limb GICS scores at MP week 4. Other efficacy variables included change from baseline in Canadian Occupational Performance Measure (COPM) scores²⁸ (rating performance and satisfaction with performance for five important problems on 10-point scales); change in AS scores for each treated lower-limb clinical pattern; investigator's, child/adolescent's, and parent/caregiver's lower-limb GICS scores; and all OLEX efficacy variables.

Safety

AEs, AESIs possibly indicating toxin spread, SAEs, and treatment-related AEs were assessed overall and per treatment cycle. Clinical and laboratory parameters, investigator's global assessment of tolerability (four-point ordinal scale from 1, very good, to 4, poor), and suicidality (Columbia-Suicide Severity Rating Scale) were assessed.

BoNT antibody testing was conducted in patients ≥ 21 kg BW. Blood samples collected at screening and at the end-of-study visit were screened for BoNT antibodies using the fluorescence immunoassay for antibodies. Positive samples were validated using the functional mouse *ex vivo* hemidiaphragm assay (HDA).^{29,30}

Statistical analysis

The planned sample size was ≥ 344 patients randomized 2:1:1 to 8 U/kg, 6 U/kg, and 2 U/kg dose groups ($n \geq 172$, 86, and 86, respectively). For the primary and coprimary efficacy variables, this was estimated to yield 95.7% and 87.3% power to identify a statistically significant difference between the 8 and 2 U/kg and the 6 and 2 U/kg dose groups, respectively.

Efficacy was analyzed in the full analysis set, a subset of all patients in the safety evaluation set (SES) who had at least a baseline AS score in the clinical patterns flexed elbow or flexed wrist, or an investigator's upper-limb GICS score at week 4. Efficacy was analyzed for the three dose groups separately during the MP (cycle 1) and for pooled data from cycle 1 when analyzing changes during repeated treatment (cycles 2 to 4), where all patients received the highest incobotulinumtoxinA dose (8 U/kg). Safety variables were analyzed descriptively in the SES, which included all patients who received study medication at least once.

Primary and coprimary efficacy end points were analyzed using mixed model repeated measures (MMRM) or analysis of covariance, respectively, with a two-sided significance level of $\alpha = 0.05$. Comparison of least squares means was used for confirmatory analysis using a hierarchical testing approach to detect differences between the 8 and 2 U/kg dose groups for the primary, coprimary, and key secondary efficacy end points; then, if significant, the 6 and

2 U/kg dose groups were analyzed. Secondary and other end points were analyzed descriptively, and treatment differences were interpreted in an explorative manner. For patients with bilateral treatment, body sides were analyzed separately by the chosen primary and nonprimary body side where applicable. A nonparametric Wilcoxon rank sum test was performed as a sensitivity analysis for the change from baseline within the groups for AS and GICS.

Results

Patients

Among 372 patients screened, 351 were randomized to the three incobotulinumtoxinA dose groups (8 U/kg, $n = 176$; 6 U/kg, $n = 88$; 2 U/kg, $n = 87$). One patient in the 6 U/kg group was randomized but not treated, resulting in 350 patients in the SES. Discontinuation frequency was similar across all dose groups, and 331 of 351 patients (94.3%) completed the MP and entered the OLEX (Fig 2). In total, 281 patients (80.1%) completed the OLEX and received four treatment cycles.

Patients at baseline were predominantly male (62.9%), the mean (S.D.) age was 7.3 (4.4) years, and AS score was 2.6 (0.5). All GMFCS Expanded and Revised levels were represented in the total population. GMFCS levels II and III were most common (28.3% and 22.3%, respectively). Overall, baseline characteristics were generally similar across all dose groups (Table 1).

Most patients (83.4%) received upper-limb combined with lower-limb treatment; 16.6% received upper-limb treatment alone. The most common treatment combination was unilateral upper- and bilateral lower-limb treatment (combinations C and D), followed by unilateral upper- and unilateral lower-limb treatment (combination B) (Table 1). In total, 272 patients (77.7%) presented with concomitant diseases, the most common of which were epilepsy (20.6%), strabismus (20.0%), intellectual disability (16.6%), and developmental speech disorder including dysphagia (14.6%). Oral baclofen was the most frequently reported muscle relaxant concomitantly administered during the study to 10 patients during the MP and 8 during the OLEX. Surgical interventions were extremely rare during the study, with gastrostomy reported in two subjects.

Efficacy

Muscle tone and spasticity

Patients in all three incobotulinumtoxinA dose groups showed significant improvements in the AS score of the upper-limb main clinical target pattern (flexed elbow or flexed wrist) from baseline to week 4 ($P < 0.0001$, MMRM). In the primary analysis, significantly greater spasticity improvement in the 8 U/kg versus the 2 U/kg dose group was demonstrated ($P = 0.017$, MMRM; Table 2). A high proportion of patients in all three dose groups were classed as AS responders with at least 1-point improvement from baseline to week 4: 85.5%, 75.9%, and 70.6% of patients in the 8 U/kg, 6 U/kg, and 2 U/kg groups, respectively.

Investigator's upper-limb GICS scores also demonstrated spasticity improvements (between “+1, minimally improved” and “+2, much improved” overall) in all dose groups, with no significant difference between groups in the coprimary efficacy analysis ($P > 0.05$, analysis of covariance; Table 2).

Changes in AS score from study baseline to week 4 of the MP reflected an improvement in spasticity in all the three dose groups across all upper-limb clinical patterns treated, and the magnitude of improvement was generally similar across the three dose groups. The change in AS score for flexed elbow was significantly greater for

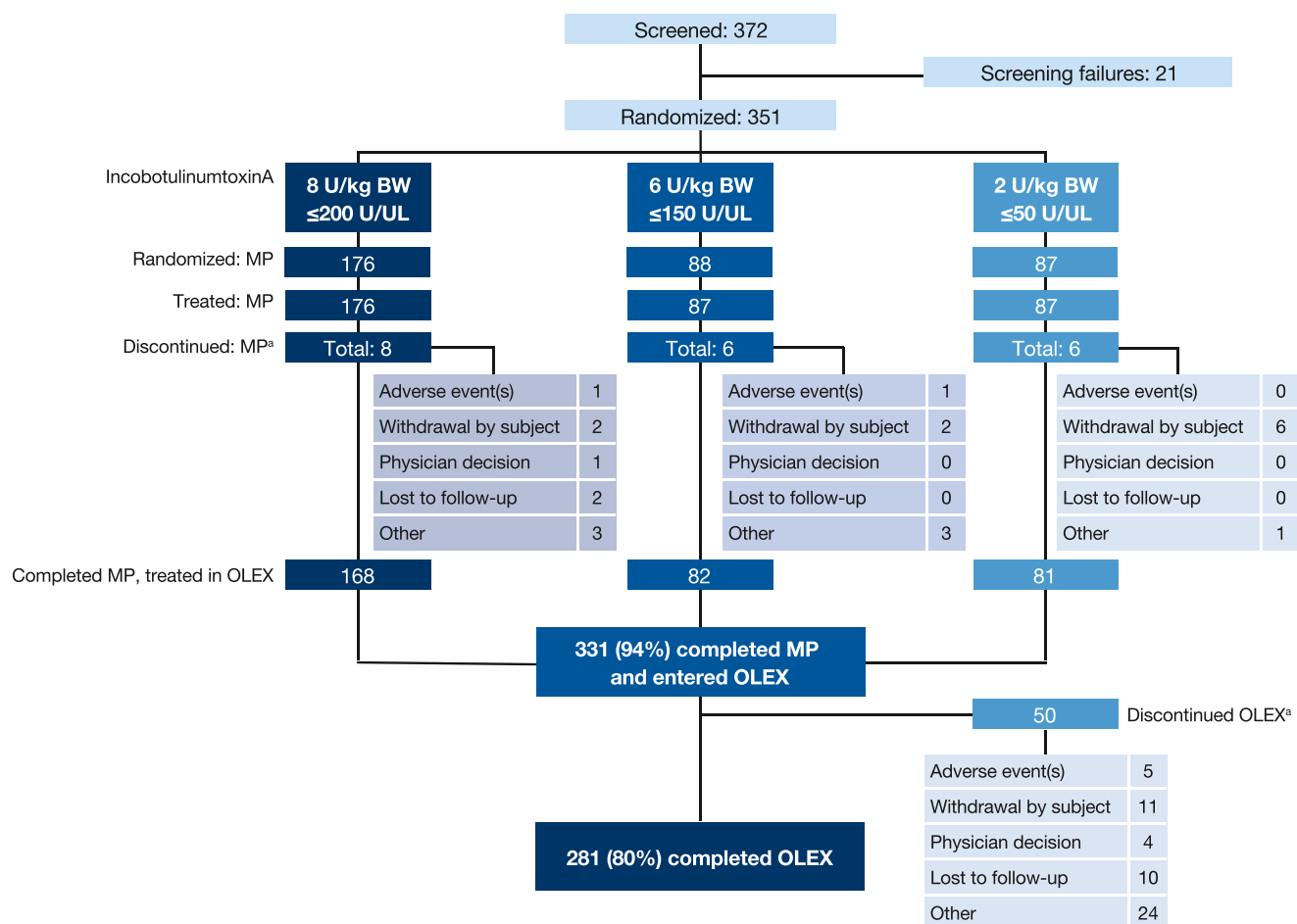


FIGURE 2. Study flow chart. ^aMultiple entries possible. "Other" was used as a reason for discontinuation when a patient had no need for re-treatment 16 weeks after the previous injection. MP, main period; OLEX, open-label extension; U, unit. The color version of this figure is available in the online edition.

the 8 U dose group versus the 2 U dose group ($P < 0.05$), as was the change in AS score for clenched fist ($P < 0.01$) (Supplemental Table 1). Pooled data also showed that spasticity improvements in AS scores were observed from study baseline to all post-treatment visits across all four treatment cycles in the MP and OLEX for all upper-limb clinical patterns treated (Fig 3A-E). Improvements were generally greatest at weeks 4 and 8 in all treatment cycles and were sustained with repeated treatment. Continuous improvements from cycle to cycle were observed for the main clinical target patterns of flexed elbow and flexed wrist. Statistical testing of change in AS scores from baseline to the end-of-study visit revealed significant improvements for all upper-limb clinical target patterns ($P < 0.001$, one-sample t test).

In patients who received additional unilateral or bilateral lower-limb incobotulinumtoxinA injections, changes in AS score from study baseline to week 4 of the MP again reflected an improvement in spasticity in all the three dose groups across the three clinical patterns treated, and the magnitude of improvement was generally similar for the three dose groups (Supplemental Table 1). Pooled data showed that AS scores for all treated lower-limb clinical patterns also improved from baseline to all post-treatment visits across all four treatment cycles (Fig 3F-H). Again, improvements were greatest at weeks 4 and 8 and were sustained and even increased with repeated treatment.

Child's/adolescent's and parent/caregiver's GICS scores for the upper limb and investigator's, child's/adolescent's, and parent/

caregiver's GICS scores for the lower limb confirmed improvements in spasticity in all three incobotulinumtoxinA dose groups at MP week 4 (Supplemental Figure S1).

Improvements were maintained at week 4 of each OLEX treatment cycle. Mean (S.D.) investigator's, child/adolescent's, and parent/caregiver's GICS scores at week 4 of OLEX cycle 3 were 2.0 (0.7), 2.1 (0.7), and 1.9 (0.7), respectively, for the upper limb and 1.8 (0.7), 2.0 (0.6), and 1.8 (0.8), respectively, for the lower limb.

Pain and functional performance

QPS scores reported by the child/adolescent and parent/caregiver for the upper and lower limb showed reductions from study baseline to the MP final visit, indicating less-severe and less-frequent experienced and observed spasticity-related pain in all three incobotulinumtoxinA dose groups. Sustained improvements were reported with repeated treatment of the highest dose (8 U/kg) during the OLEX. A detailed analysis on spasticity-related pain after incobotulinumtoxinA treatment will be discussed in a separate publication.

COPM scores improved from baseline to the final visit of the MP in all three incobotulinumtoxinA dose groups. In the 8 U/kg, 6 U/kg, and 2 U/kg groups, respectively, the LSM changes in COPM performance score were 0.84 (0.10), 0.57 (0.14), and 0.71 (0.13) and in COPM satisfaction score were 1.03 (0.10), 0.74 (0.15), and 0.95 (0.13).

TABLE 1.
Patient Demographics and Baseline Characteristics

Characteristic	IncobotulinumtoxinA			
	8 U/kg BW; Maximum 200 U/UL N = 176	6 U/kg BW; Maximum 150 U/UL N = 87	2 U/kg BW; Maximum 50 U/UL N = 87	TOTAL N = 350
Sex, n (%)				
Male	114 (64.8)	57 (65.5)	49 (56.3)	220 (62.9)
Female	62 (35.2)	30 (34.5)	38 (43.7)	130 (37.1)
Age, years; mean (S.D.)	7.3 (4.4)	7.5 (4.2)	7.2 (4.7)	7.3 (4.4)
Weight, kg; mean (S.D.)	24.3 (13.7)	26.6 (17.2)	24.8 (15.4)	25.0 (15.0)
Patients pretreated with BoNT, n (%)				
Pretreated with BoNT	75 (42.6)	35 (40.2)	42 (48.3)	152 (43.4)
Treatment naïve	101 (57.4)	52 (59.8)	45 (51.7)	198 (56.6)
GMFCS E&R, n (%) [*]				
Level I	23 (13.1)	28 (32.2)	14 (16.1)	65 (18.6)
Level II	54 (30.7)	26 (29.9)	19 (21.8)	99 (28.3)
Level III	44 (25.0)	17 (19.5)	17 (19.5)	78 (22.3)
Level IV	22 (12.5)	9 (10.3)	18 (20.7)	49 (14.0)
Level V	33 (18.8)	7 (8.0)	19 (21.8)	59 (16.9)
AS score; mean (S.D.) [n]	2.7 (0.56) [173]	2.7 (0.48) [87]	2.6 (0.52) [85]	2.6 (0.53) [345]
Treatment combination, n (%)				
A: unilateral/bilateral UL only	31 (17.6)	13 (14.9)	14 (16.1)	58 (16.6)
B: unilateral UL and unilateral LL	57 (32.4)	39 (44.8)	25 (28.7)	121 (34.6)
C: unilateral UL and bilateral LL (GMFCS E&R I–III)	31 (17.6)	14 (16.1)	15 (17.2)	60 (17.1)
D: unilateral UL and bilateral LL (GMFCS E&R IV–V)	39 (22.2)	13 (14.9)	28 (32.2)	80 (22.9)
E: bilateral UL and bilateral LL (GMFCS E&R I–III)	18 (10.2)	8 (9.2)	5 (5.7)	31 (8.9)
Limbs planned to be treated, n (%) [†]				
LL right	119 (67.6)	56 (64.4)	63 (72.4)	238 (68.0)
LL left	114 (64.8)	52 (59.8)	57 (65.5)	223 (63.7)
UL right	112 (63.6)	54 (62.1)	57 (65.5)	223 (63.7)
UL left	96 (54.5)	42 (48.3)	41 (47.1)	179 (51.1)

Abbreviations:

AS = Ashworth scale

BoNT = Botulinum neurotoxin

BW = Body weight

GMFCS E&R = Gross Motor Function Classification System Expanded and Revised

LL = Lower limb

U = Unit

UL = Upper limb

^{*} GMFCS E&R Level: I, walks without limitations; II, walks with limitations; III, walks using a handheld mobility device; IV, self-mobility with limitations, may use powered mobile; V, transported in a manual wheelchair.

[†] Multiple entries possible.

Improvements in COPM scores were also observed from study baseline to the end of all OLEX treatment cycles with 8 U/kg. Improvements were sustained to the end-of-study visit, with a mean (S.D.) change in COPM performance and satisfaction scores of 2.02 (1.44) and 2.41 (1.57), respectively.

Safety

IncobotulinumtoxinA was generally well tolerated at all doses and across all treatment cycles, in patients representing the range of GMFCS levels. During the MP, AEs occurred in 76 of 350 patients (21.7%) overall. The incidence of AEs was the highest in the 8 and 2 U/kg dose groups and was not dose related (Table 3). Most AEs were of mild or moderate intensity across doses, and the most common were nasopharyngitis (4.0%) and bronchitis (2.3%). AEs in three patients in the 8 U/kg group, assessed as treatment-related, were pruritic rash and contusion, dermatitis, and pain in the extremity, all of which were mild and resolved.

No new or unexpected safety concerns were identified with any incobotulinumtoxinA dose. SAEs and AESIs occurred at low frequencies in all dose groups; all were assessed as unrelated to treatment and resolved by the end of the study. One patient in the 6

U/kg group discontinued due to severe brain edema, aspiration, and respiratory arrest, judged to be unrelated to study treatment by the investigator.

During the OLEX, AEs occurred in 114 of 331 (34.4%) patients overall, and the incidence did not increase with increasing treatment cycles (Table 3). Most AEs were mild or moderate in intensity, and the most common overall were nasopharyngitis (5.4%), upper respiratory tract infection (4.8%), pharyngitis (3.3%), bronchitis and pharyngotonsillitis (3.0% each), vomiting and pyrexia (2.4% each), and pain in extremity (2.1%). AEs assessed as treatment-related in five patients were AESIs of mild hypotonia and moderate eyelid ptosis in one patient each in OLEX cycle 1, an AESI of mild dysphagia and SAE of moderate influenza-like illness in one patient each in cycle 2, and mild pain in the extremity in one patient in cycle 3.

Overall, in the OLEX, 16 patients (4.8%) experienced SAEs (2.1%, 2.9%, and 1.0% of patients in OLEX cycles 1, 2, and 3, respectively; Table 3). Four patients discontinued due to SAEs of active epilepsy, generalized tonic-clonic seizures, and pneumonia (one patient) and angioedema, influenzalike illness, and spinal cord neoplasm (one patient each); all except influenzalike illness were assessed as unrelated to treatment. The incidence of AESIs was low during the OLEX and did not increase with additional treatment cycles

TABLE 2.

Change From Baseline in the AS Score of the Upper-Limb Main Clinical Pattern and the Investigator's GICS Score for the Upper Limb at Week 4 in the MP (Primary and Coprimary End Points)

	IncobotulinumtoxinA					
	8 U/kg, ≤200 U		6 U/kg, ≤150 U		2 U/kg, ≤50 U	
	LS Mean (SE)	P Value*	LS Mean (SE)	P Value*	LS Mean (SE)	P Value*
AS score	−1.15 (0.06) [†]	0.017	−1.02 (0.08) [†]	0.546	−0.93 (0.08) [†]	–
Investigator's GICS score	1.64 (0.06)	0.340	1.44 (0.09)	0.297	1.55 (0.08)	–

Abbreviations:

ANCOVA = Analysis of covariance

AS = Ashworth Scale

BW = Body weight

GICS = Global Impression of Change Scale

LSM = Least squares mean

MMRM = Mixed model repeated measures

MP = Main period

SE = Standard error

U = Unit

UL = Upper limb

GICS was assessed on a seven-point Likert scale from −3 (very much worse) to +3 (very much improved), based on the impression of change in spasticity compared with the condition before the last injection.

* Versus 2 U/kg BW (maximum 50 U/UL) dose group. Significance based on the comparison of LSMs using a four-step hierarchical testing procedure, analyzing the 8 U/kg BW (maximum 200 U/UL) versus the 2 U/kg BW (maximum 50 U/UL) dose groups, followed by the 6 U/kg BW (maximum 150 U/UL) versus the 2 U/kg BW (maximum 50 U/UL) dose groups, using MMRM (AS) or ANCOVA (investigator's GICS) models.

[†] $P < 0.0001$ for change in AS score versus baseline, MMRM.

(Table 3). Dysphagia, reported in two patients in OLEX cycle 2, was the only AESI reported in more than one patient overall. AESIs of moderate eyelid ptosis and aspiration pneumonia in one patient each in OLEX cycles 1 and 2, respectively, led to discontinuation. No fatal AEs occurred over four treatment cycles in this study.

The investigator's global assessment of tolerability was rated as “good” or “very good” for most patients at the final visit of the MP, and at the end of OLEX cycles 1 to 3 (91.1%, 91.5%, 92.5%, and 87.3%, respectively). There were no relevant changes in vital signs, laboratory parameters, height, BW, or body mass index throughout the study. Columbia-Suicide Severity Rating Scale (C-SSRS) results were negative throughout the study for all patients assessed (106, MP; 103, OLEX), with the exception of one patient with suicidal ideation or behavior (wish to be dead, end of OLEX cycle 2) who completed the study as planned.

Five pretreated patients (≥ 21 kg) tested positive for BoNT antibodies using the HDA assay: one patient at both screening and the end-of-study visit and two each at screening or at the end-of-study visit only (HDA results were missing at the other visits). All five patients had positive fluorescence immunoassay for antibodies (FIA-AB) results. There were no cases of secondary nonresponse due to neutralizing antibody formation based on the investigator's GICS rating of minimally, much, or very much improved function.

Discussion

The phase 3 XARA study investigated the efficacy and safety of incobotulinumtoxinA doses of 8, 6, or 2 U/kg for pediatric upper-limb spasticity. The study enrolled all GMFCS levels I to V and allowed for combined multipattern treatment of upper- and lower-limb spasticity in children and adolescents with CP, with a total body dose of up to 16 to 20 U/kg (maximum of 400 to 500U). Significant improvements in upper-limb spasticity for the primary clinical pattern, as measured by change from baseline in AS scores at week 4, were observed during the MP in all dose groups, with significantly greater reductions in muscle tone in the 8 U/kg group compared with the 2 U/kg group. Clinical meaningfulness of AS changes in the investigated dose groups was supported through AS responder analysis, showing an AS score change of ≥ 1 point in 70.6% to 85.5% of patients in the MP at week 4.

Demonstrated efficacy in muscle tone improvements for upper-limb spasticity with incobotulinumtoxinA¹⁹ are in alignment with results from other recent double-blind, randomized studies of abobotulinumtoxinA³¹ or onabotulinumtoxinA.³² Improvements in upper-limb spasticity, as measured by physician's global parameters, were noted with all abobotulinumtoxinA and onabotulinumtoxinA doses in these studies, with no significant difference versus low-dose (2 U/kg) abobotulinumtoxinA³¹ or placebo,^{15,32} respectively. Similarly, in the XARA study, statistically significant improvements in investigator's GICS scores from baseline were observed across all incobotulinumtoxinA dose groups, and both child/adolescent's and parent/caregiver's GICS scores at week 4 confirmed meaningful improvements in upper-limb spasticity after incobotulinumtoxinA treatment. Observed benefits in the treatment of upper-limb as well as lower-limb spasticity are further supported by AS, global, pain-related, and functional efficacy outcomes. Moreover, sustained and consistent spasticity improvements were observed in all outcomes over time with three further treatment cycles with the highest incobotulinumtoxinA dose in the OLEX.

Results of the XARA study contribute specifically to the evidence base for multipattern incobotulinumtoxinA treatment of upper- and combined upper- and lower-limb spasticity in pediatric patients for all GMFCS levels (I to V) across a broad age range (2 to 17 years old). The study design that included additional lower-limb treatment together with upper-limb treatment provides a complete multipattern view. Most patients in the study received combined multipattern treatment for unilateral or bilateral upper- and lower-limb spasticity, reflecting clinical treatment needs in pediatric patients.^{2,3,6} The observed distribution of ambulatory disabilities/independence in this study also resembles real-world clinical practice.^{6,7,20} Prior clinical research has frequently focused on BoNT treatment in patients with lower GMFCS levels, with most studies having investigated the safety and efficacy of BoNT largely in ambulant participants,^{8,9,33–35} or in children with GMFCS levels of I to IV.³¹ However, patients with GMFCS IV to V accounted for ~30% of the XARA study population, and the results showed notable efficacy and safety, with a reduced maximum total body dose for GMFCS IV to V, in line with best practice guidelines.^{7,36,37} The inclusion of all GMFCS levels and the most severe children in the CP

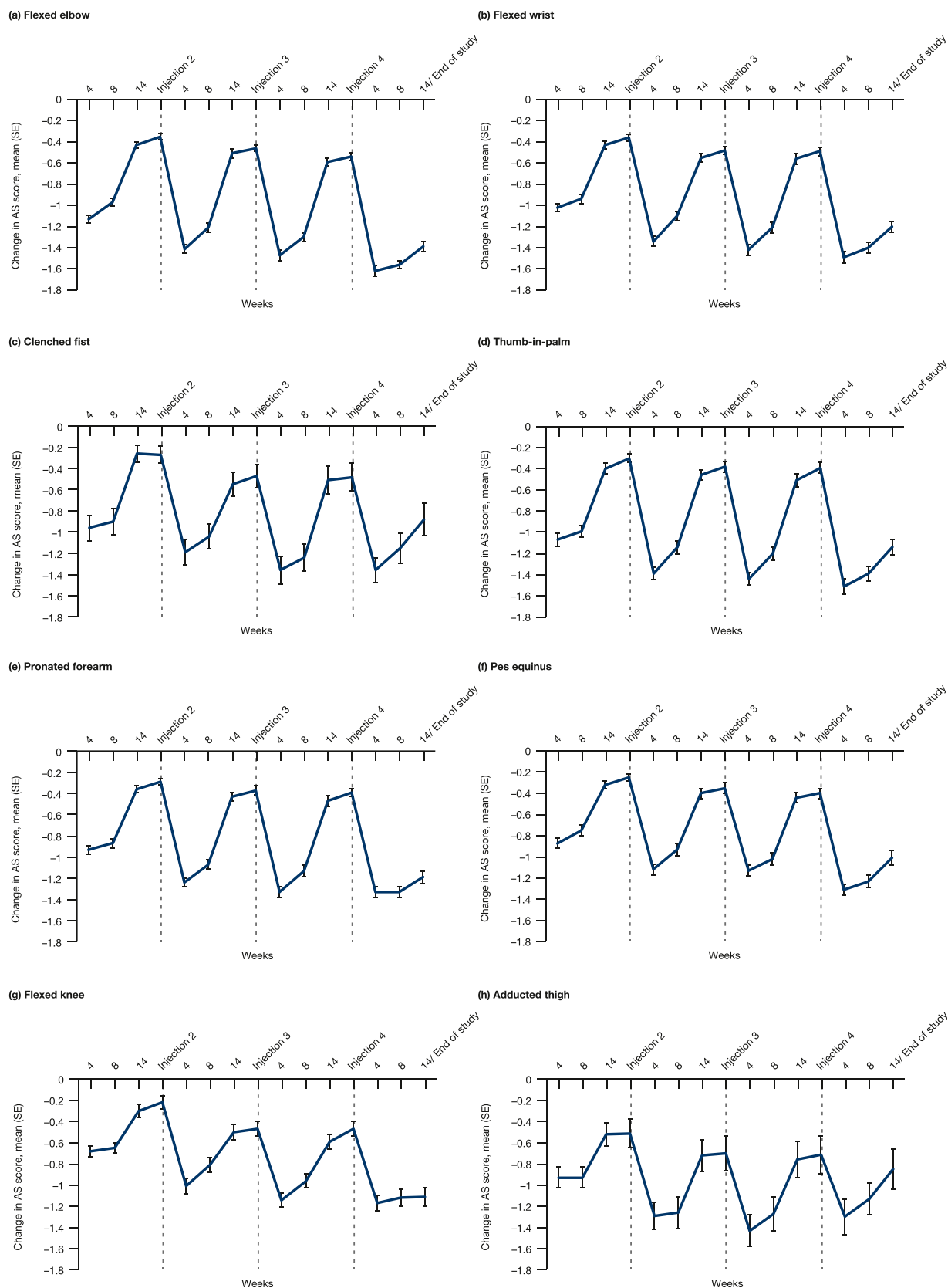


FIGURE 3. Change in AS scores from study baseline for all upper- and lower-limb clinical patterns treated in the primary body side across four treatment cycles in the MP^a and OLEX. (A) Flexed elbow, (B) flexed wrist, (C) clenched fist, (D) thumb-in-palm, (E) pronated forearm, (F) pes equinus, (G) flexed knee, and (H) adducted thigh. ^aData pooled from all three MP dose groups. AS, Ashworth Scale; MP, main period; OLEX, open label extension; SE, standard error. The color version of this figure is available in the online edition.

TABLE 3.
Summary of AEs During the MP and OLEX

Number of patients, n (%)	Main Period				Open-Label Extension			
	IncobotulinumtoxinA				IncobotulinumtoxinA 8 U/kg BW (Max 200 U/UL)			
	8 U/kg BW (Max 200 U/UL) N = 176	6 U/kg BW (Max 150 U/UL) N = 87	2 U/kg BW (Max 50 U/UL) N = 87	Overall N = 350	Cycle 1 N = 331	Cycle 2 N = 307	Cycle 3 N = 290	Overall N = 331
Any AE*	42 (23.9)	13 (14.9)	21 (24.1)	76 (21.7)	64 (19.3)	42 (13.7)	48 (16.6)	114 (34.4)
Mild	33 (18.8)	10 (11.5)	15 (17.2)	58 (16.6)	43 (13.0)	23 (7.5)	28 (9.7)	62 (18.7)
Moderate	7 (4.0)	2 (2.3)	6 (6.9)	15 (4.3)	18 (5.4)	15 (4.9)	19 (6.6)	44 (13.3)
Severe	2 (1.1)	1 (1.1)	0 (0.0)	3 (0.9)	3 (0.9)	4 (1.3)	1 (0.3)	8 (2.4)
Treatment-related†	3 (1.7)	0 (0.0)	0 (0.0)	3 (0.9)	2 (0.6)	2 (0.7)	1 (0.3)	5 (1.5)
AEs of special interest	1 (0.6)	1 (1.1)	1 (1.1)	3 (0.9)	2 (0.6)	3 (1.0)	1 (0.3)	5 (1.5)
Treatment-related‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (0.6)	1 (0.3)	0 (0.0)	3 (0.9)
Serious AEs	2 (1.1)	1 (1.1)	2 (2.3)	5 (1.4)	7 (2.1)	9 (2.9)	3 (1.0)	16 (4.8)
Treatment-related‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)	1 (0.3)
AEs leading to discontinuation†	1 (0.6)	1 (1.1)	0 (0.0)	2 (0.6)	3 (0.9)	2 (0.7)	0 (0.0)	5 (1.5)
Treatment-related‡	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.3)	0 (0.0)	2 (0.6)
Fatal AEs	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations:

AE = Adverse event

BW = Body weight

Max = Maximum

MP = Main period

OLEX = Open-label extension

U = Unit

UL = Upper limb

* Patients with more than one AE within a preferred term were counted once at the patient's highest intensity category.

† Designation of "treatment-related" was made by the investigator.

‡ AEs leading to discontinuation in the MP were bronchitis (n = 1 patient, 8 U/kg group) and brain edema, aspiration, and respiratory arrest (n = 1, 6 U/kg group). AEs leading to discontinuation in the OLEX were eyelid ptosis, spinal cord neoplasm, and angioedema (n = 1 patient each in cycle 1), epilepsy, generalized tonic-clonic seizure, and pneumonia aspiration (n = 1 patient in cycle 2), and influenza-like illness (n = 1 patient in cycle 2).

spectrum, only excluding those with other unstable medical conditions or recent surgery, demonstrates that incobotulinumtoxinA treatment can be beneficial to these patients and may provide treatment options for severely affected children with rehabilitation needs.

Combined with the high retention rate over four treatment cycles, enabling robust data for assessment, results provide evidence for sustained efficacy and safety of incobotulinumtoxinA for multipattern spasticity treatment in this patient population. Injections were administered via the mandatory use of guidance techniques for treatment accuracy, even in small muscles. Results show spasticity improvements with incobotulinumtoxinA, with evidence of additional improvements with higher doses and sustained or even increasing treatment effects resulting in cumulative improvements with repeated injections.

IncobotulinumtoxinA treatment also resulted in improvements in spasticity-related pain, as measured by the QPS, and in functional performance. Pain is often associated with spasticity in CP,^{27,38,39} and this symptomatic benefit of incobotulinumtoxinA treatment will be explored further. Functional improvements, as measured by COPM performance and satisfaction scores, were observed throughout the current study and were maintained until the end-of-study visit. Of note, coordinated rehabilitation therapy, including occupational and physiotherapy, was kept constant for every patient to isolate the treatment effect on goal-directed physical function. The varied physical manifestations of CP can impact physical function and activities of daily living, including self-care.⁴⁰ In a rehabilitation setting, it is important to identify functional goals established by caregivers and rehabilitation therapists that are consistent with the abilities of each patient.⁴¹ If patients attain treatment goals and sustain these achievements over time, the improvements will be reinforced. The COPM provides a dynamic and interactive tool to assist in setting,

implementing, and measuring performance goals based on individual patient need.²⁸

A favorable safety and tolerability profile was observed with incobotulinumtoxinA up to 8 U/kg per upper limb (total body dose ≤16 to 20 U/kg BW, maximum 400 to 500 U) in the MP and over three additional treatment cycles in the OLEX, with a total study duration of over one year (up to 66 weeks). Low discontinuation rates and low overall SAE and AESI incidence support the favorable tolerability profile. All three formulations of BoNT-A are well tolerated in pediatric patients. Local AEs at the injection site are common but mild, and systemic events are rare, although there is a greater risk of serious AEs in nonambulant children.⁴² As expected for a pediatric population,^{43,44} and as reported with other BoNT-A formulations,^{31,32} nasopharyngitis and other upper respiratory tract illnesses were among the most common AEs reported during this study and no new safety signals were observed. During the MP, most AEs occurred in the 8 U/kg and 2 U/kg groups with no increased frequency with additional treatment cycles in the OLEX, indicating that AE incidence may not be related to dose or repeated treatment. This is consistent with the results of previous analyses over up to six treatment cycles in a similar patient population.^{12,13} Of note, there were no cases of secondary nonresponse due to neutralizing antibody formation, and all patients who tested positive for neutralizing antibodies had been pretreated with BoNT-A. This lack of neutralizing antibodies, along with the good long-term safety profile, could be important for the treatment of chronic conditions such as spastic CP in a pediatric patient population. IncobotulinumtoxinA may be associated with lower immunogenicity than other BoNT-A formulations due to the lack of nontoxic accessory proteins in its formulation.⁴⁵

The lack of a placebo group in the XARA study is a limitation that could have influenced postinjection assessments, as investigators and participants/parents were aware that all participants received

incobotulinumtoxinA. However, it could be considered unethical to give placebo to a child with clinical need for upper limb spasticity treatment. Furthermore, the randomized, multiple-arm study design is a recognized study design that, like a placebo-controlled trial, provides class I evidence. The recent double-blind, randomized study of abobotulinumtoxinA also used a low dose of abobotulinumtoxinA as an active control group.³¹ In addition, results of the pivotal placebo-controlled onabotulinumtoxinA study showed that low doses of onabotulinumtoxinA (3 U/kg) provided a significantly greater reduction in muscle tone than placebo.³² Assuming a 1:1 dose conversion between onabotulinumtoxinA and incobotulinumtoxinA,⁴⁶ results of the XARA study suggest that the observed improvements in muscle tone from baseline in the low-dose incobotulinumtoxinA arm (2 U/kg) do represent a true drug effect.

Findings from the XARA study established the efficacy and safety of incobotulinumtoxinA for the multipattern treatment of upper-limb spasticity in children and adolescents with CP and provide further evidence for its sustained efficacy and safety in multipattern treatment, reflecting the real-world clinical needs of children with CP.

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Supplementary data

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References

- Agarwal A, Verma I. Cerebral palsy in children: an overview. *J Clin Orthop Trauma*. 2012;3:77–81.
- Howard J, Soo B, Graham HK, et al. Cerebral palsy in Victoria: motor types, topography and gross motor function. *J Paediatr Child Health*. 2005;41:479–483.
- Minocha P, Sitaraman S, Sachdeva P. Clinical spectrum, comorbidities, and risk factor profile of cerebral palsy children: a prospective study. *J Pediatr Neurosci*. 2017;12:15–18.
- Bar-On L, Molenaers G, Aertbelien E, et al. Spasticity and its contribution to hypertonia in cerebral palsy. *Biomed Res Int*. 2015;2015:317047.
- Sakzewski L, Ziviani J, Boyd R. Systematic review and meta-analysis of therapeutic management of upper-limb dysfunction in children with congenital hemiplegia. *Pediatrics*. 2009;123:e1111–e1122.
- Yeargin-Allsopp M, Van Naarden Braun K, Doernberg NS, Benedict RE, Kirby RS, Durkin MS. Prevalence of cerebral palsy in 8-year-old children in three areas of the United States in 2002: a multisite collaboration. *Pediatrics*. 2008;121:547–554.
- Heinen F, Desloovere K, Schroeder AS, et al. The updated European Consensus 2009 on the use of botulinum toxin for children with cerebral palsy. *Eur J Paediatr Neurol*. 2010;14:45–66.
- Delgado MR, Bonikowski M, Carranza J, et al. Safety and efficacy of repeat open-label abobotulinumtoxinA treatment in pediatric cerebral palsy. *J Child Neurol*. 2017;32:1058–1064.
- Delgado MR, Tilton A, Russman B, et al. AbobotulinumtoxinA for equinus foot deformity in cerebral palsy: a randomized controlled trial. *Pediatrics*. 2016;137(2):e20152830.
- Tilton A, Russman B, Aydin R, et al. AbobotulinumtoxinA (Dysport®) improves function according to goal attainment in children with dynamic equinus due to cerebral palsy. *J Child Neurol*. 2017;32:482–487.
- Papavasiliou AS, Nikaina I, Foska K, Bouras P, Mitsou G, Filiopoulos C. Safety of botulinum toxin A in children and adolescents with cerebral palsy in a pragmatic setting. *Toxins (Basel)*. 2013;5:524–536.
- Heinen F, Kaňovský P, Schroeder AS, et al. Efficacy and safety of incobotulinumtoxinA for lower-limb spasticity in children and adolescents with cerebral palsy. *Toxicon*. 2018;156:S44.
- Kaňovský P, Heinen F, Schroeder S, et al. Long-term safety and efficacy of incobotulinumtoxinA for lower- of combined upper- and lower-limb spasticity in children and adolescents with cerebral palsy. *Toxicon*. 2018;156:S56.
- Ipsen Biopharm Ltd. Highlights of Prescribing Information – Dysport®; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125274Orig1s1181bl.pdf. Accessed November 24, 2020.
- Allergan Inc. Highlights of Prescribing Information – Botox®; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/103000s53171bl.pdf. Accessed October 12, 2020.
- Ipsen Biopharm Ltd. Dysport® 500 U Summary of Product Characteristics; 2020. Available at: <https://www.medicines.org.uk/emc/medicine/32114>. Accessed March 19, 2020.
- Allergan Ltd. Botox® 100 U Summary of Product Characteristics; 2020. Available at: <https://www.medicines.org.uk/EMC/medicine/112/SPC/>. Accessed March 19, 2020.
- Frevet J. Xeomin is free from complexing proteins. *Toxicon*. 2009;54:697–701.
- Merz Pharmaceuticals LLC. Highlights of Prescribing Information – Xeomin®; 2020. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/125360s0781bl.pdf. Accessed October 12, 2020.
- Unlu E, Cevikol A, Bal B, Gonen E, Celik O, Kose G. Multilevel botulinum toxin type A as a treatment for spasticity in children with cerebral palsy: a retrospective study. *Clinics (Sao Paulo)*. 2010;65:613–619.
- Berweck S, Schroeder AS, Fietzek UM, Heinen F. Sonography-guided injection of botulinum toxin in children with cerebral palsy. *Lancet*. 2004;363:249–250.
- Berweck S, Feldkamp A, Francke A, Nehles J, Schwerin A, Heinen F. Sonography-guided injection of botulinum toxin A in children with cerebral palsy. *Neuropediatrics*. 2002;33:221–223.
- Schroeder AS, Berweck S, Lee SH, Heinen F. Botulinum toxin treatment of children with cerebral palsy – a short review of different injection techniques. *Neurotox Res*. 2006;9:189–196.
- Fietzek UM, Schroeder AS, Wissel J, Heinen F, Berweck S. Split-screen video demonstration of sonography-guided muscle identification and injection of botulinum toxin. *Mov Disord*. 2010;25:2225–2228.
- Ashworth B. Preliminary trial of carisoprodol in multiple sclerosis. *Practitioner*. 1964;192:540–542.
- Geister TL, Bushnell DM, Yang J, et al. Initial psychometric validation of the questionnaire on pain caused by spasticity (QPS). *Health Qual Life Outcomes*. 2017;15:229.
- Geister TL, Quintanar-Solares M, Martin M, Aufhammer S, Asmus F. Qualitative development of the 'Questionnaire on Pain caused by Spasticity (QPS),' a pediatric patient-reported outcome for spasticity-related pain in cerebral palsy. *Qual Life Res*. 2014;23:887–896.
- Law M, Baptiste S, McColl M, Opzoomer A, Polatajko H, Pollock N. The Canadian occupational performance measure: an outcome measure for occupational therapy. *Can J Occup Ther*. 1990;57:82–87.
- Rasetti-Escargueil C, Lui Y, Rigsby P, Jones RGA, Sesardic D. Phrenic nerve-hemidiaphragm as a highly sensitive replacement assay for determination of functional botulinum toxin antibodies. *Toxicon*. 2011;57:1008–1016.
- Sesardic D, Jones RGA, Leung T, Alsop T, Tierney R. Detection of antibodies against botulinum toxins. *Mov Disord*. 2004;19:S85–S91.
- Delgado MR, Tilton A, Carranza-Del Rio J, et al. Efficacy and safety of abobotulinumtoxinA for upper limb spasticity in children with cerebral palsy: a randomized repeat-treatment study. *Dev Med Child Neurol*. 2021;63:592–600.
- Allergan Inc. Botox® Treatment in Pediatric Upper Limb Spasticity; 2018. Available at: <https://clinicaltrials.gov/ct2/show/study/NCT01603602>. Accessed October 14, 2020.
- Baker R, Jasinski M, Maciag-Tymiecka I, et al. Botulinum toxin treatment of spasticity in diplegic cerebral palsy: a randomized, double-blind, placebo-controlled, dose-ranging study. *Dev Med Child Neurol*. 2002;44:666–675.
- Chang HJ, Hong BY, Lee SJ, Lee S, Park JH, Kwon JY. Efficacy and safety of letibotulinum toxin A for the treatment of dynamic equinus foot deformity in children with cerebral palsy: a randomized controlled trial. *Toxins (Basel)*. 2017;9:252.
- Kim K, Shin HI, Kwon BS, Kim SJ, Jung IY, Bang MS. Neuronox versus Botox for spastic equinus gait in children with cerebral palsy: a randomized, double-blinded, controlled multicentre clinical trial. *Dev Med Child Neurol*. 2011;53:239–244.
- Strobl W, Theologis T, Brunner R, et al. Best clinical practice in botulinum toxin treatment for children with cerebral palsy. *Toxins (Basel)*. 2015;7:1629–1648.
- Love SC, Novak I, Kentish M, et al. Botulinum toxin assessment, intervention and after-care for lower limb spasticity in children with cerebral palsy: international consensus statement. *Eur J Neurol*. 2010;17:9–37.
- Poirot I, Laudy V, Rabilloud M, et al. Prevalence of pain in 240 non-ambulatory children with severe cerebral palsy. *Ann Phys Rehabil Med*. 2017;60:371–375.

39. Penner M, Xie WY, Binopal N, Switzer L, Fehlings D. Characteristics of pain in children and youth with cerebral palsy. *Pediatrics*. 2013;132:e407–e413.
40. Öhrvall AM, Eliasson AC, Löwing K, Ödman P, Krumlinde-Sundholm L. Self-care and mobility skills in children with cerebral palsy, related to their manual ability and gross motor function classifications. *Dev Med Child Neurol*. 2010;52:1048–1055.
41. Brandão MB, Oliveira RHS, Mancini MC. Functional priorities reported by parents of children with cerebral palsy: contribution to the pediatric rehabilitation process. *Braz J Phys Ther*. 2014;18:563–571.
42. Multani I, Manji J, Hastings-Ison T, et al. Botulinum toxin in the management of children with cerebral palsy. *Paediatr Drugs*. 2019;21:261–281.
43. Long JC, Williams HM, Jani S, et al. Assessing the appropriateness of the management of upper respiratory tract infection in Australian children: a population-based sample survey. *BMJ Open*. 2019;9(5):e026915.
44. Cardozo DM, Nascimento-Carvalho CM, Andrade ALSS, Souza FR, Silva NMS. The burden of acute nasopharyngitis among adolescents. *Arch Dis Child*. 2006;91:1045.
45. Bellows S, Jankovic J. Immunogenicity associated with botulinum toxin treatment. *Toxins (Basel)*. 2019;11:491.
46. Scaglione F. Conversion ratio between Botox®, Dysport®, and Xeomin® in clinical practice. *Toxins (Basel)*. 2016;8:65.