Efficacy and safety of incobotulinumtoxinA for upper- or combined upper- and lower-limb spasticity in children and adolescents with cerebral palsy: results of the phase 3 XARA study

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Background

- Spasticity is the most common movement disorder in patients with cerebral palsy (CP).[1,2]
- IncobotulinumtoxinA (Xeomin®, Merz Pharmaceuticals, GmbH) is a botulinum neurotoxin type A (150 kD) free from complexing proteins, approved in the USA for the treatment of upper-limb (UL) spasticity in pediatric patients 2–17 years of age except in those with CP.[3]

Objective

- To investigate the efficacy and safety of incobotulinumtoxinA for UL alone or combined UL and lower-limb (LL) spasticity in ambulant and non-ambulant children and adolescents with CP.

Methods

Patients

- Patients were 2–17 years of age with uni- or bilateral CP, an Ashworth Scale (AS) score ≥2 in main clinical target patterns for treatment (flexed elbow and/or flexed wrist), and a clinical need for UL treatment.

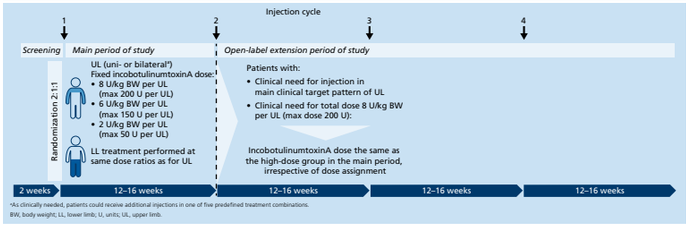
Study design

- XARA (incobotulinumto**X**in**A** in a**R**m treatment in cerebral p**A**lsy) was a multinational, multicenter, randomized phase 3 study with a double-blind main period and an open-label extension period (**Figure 1**; NCT02002884).
  - In the main period, patients received a single injection cycle (IC) and were randomized (2:1:1) to three incobotulinumtoxinA dose groups: 8, 6, 2 U/kg body weight (BW), maximum 200, 150, 50 U per UL.
  - In the open-label extension period, patients received up to three additional ICs; all patients received doses as per the 8U/kg BW group in the main period.
- Additional multipattern treatment was allowed with total body doses up to 16–20 U/kg BW (≤400–500 U) depending on Gross Motor Function Classification System (GMFCS) levels I–V (**Figure 2**).
- Uni/bilateral injections into at least one primary clinical target pattern were required with the option of an additional three possible pattrns. If clinically required, LL uni/bilateral injections could be added in four possible patterns (**Figure 2**).

Endpoints

- Primary efficacy variable: change from baseline in AS score at Week 4 of the main period for the main clinical target pattern.
  - Assessed on a 5-point scale from 0 (no increase in muscle tone) to 4 (limb rigid in flexion).
- Co-primary efficacy variable: Investigator's Global Impression of Change Scale (GICS) score for UL at Week 4 of the main period.
  - Assessed on a 7-point Likert scale from –3 (very much worse) to +3 (very much improved).
- Other important variables: change from baseline in AS score at all other post-baseline visits for all clinical patterns treated in the primary body side, through the main and open-label extension periods.
- Safety variables were assessed overall and per treatment cycle.
- The safety evaluation set (SES) comprised all patients who received ≥1 dose of study medication.
  - The full analysis set was a subset of the SES of the main period for whom the primary or co-primary efficacy variables were available.
- Statistical comparison of least squares mean change in AS scores from baseline to 4 weeks used a mixed model of repeated measures (MMRM); comparisons between dose groups used MMRM (AS) or analysis of covariance (investigator's GICS) models. Changes from baseline in the open-label extension period were assessed using a one-sample t-test.

Figure 1. XARA study design



*As clinically needed, patients could receive additional injections in one of five predefined treatment combinations.
BW, body weight; LL, lower limb; U, units; UL, upper limb.

Figure 2. Treatment combinations used in XARA

	Clinical pattern	Dose per clinical pattern	Maximum dose per limb	Maximum body dose
a) Uni- or bilateral UL treatment only (GMFCS I–V)				
	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)				
	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)				
	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)				
	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)				
	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	

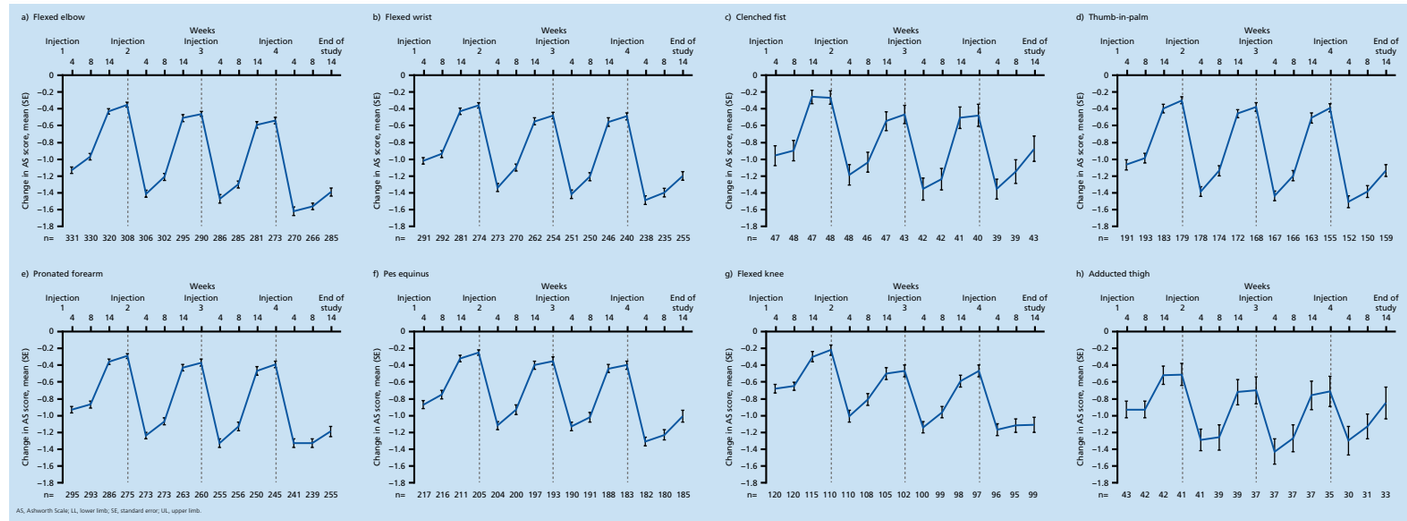
The highest dose regimen (8 U/kg BW per UL, maximum 200 U in patients >25 kg BW) is presented for each of the treatment distributions. During the MP, doses in the 6 U/kg and 2 U/kg groups were 75% and 25%, respectively, of the doses presented. Treatment of M. biceps brachii was mandatory for the treatment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

Table 1. Demographics and baseline characteristics of patients entering the main period of XARA

Characteristic	Main period, by incobotulinumtoxinA dose (SES)			
	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	Total N=350
Male sex, n (%)	114 (64.8)	57 (65.5)	49 (56.3)	220 (62.9)
Age, years; mean (SD)	7.3 (4.4)	7.5 (4.2)	7.2 (4.7)	7.3 (4.4)
Weight, kg; mean (SD)	24.3 (13.7)	26.6 (17.2)	24.8 (15.4)	25.0 (15.0)
GMFCS IV–V	55 (31.3)	16 (18.4)	37 (42.5)	108 (30.9)
AS score,[a] points; mean (SD) [N1]	2.7 (0.6) [173]	2.7 (0.5) [87]	2.6 (0.5) [85]	2.6 (0.5) [345]
Pre-treated with BoNT-A, n (%)	75 (42.6)	35 (40.2)	42 (48.3)	152 (43.4)
Planned treatment combination, n (%)				
a) Uni-/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)

[a]AS score in UL primary clinical target pattern, primary body side, observed cases.
AS, Ashworth Scale; GMFCS-E&R, Gross Motor Function Classification System expanded and revised edition; LL, lower limb; N1, total patients assessed for a given characteristic, where different from the total population; SD, standard deviation; SES, safety evaluation set; UL, upper limb.

Figure 3. Change in AS score from baseline for all UL and LL clinical patterns treated in the primary body side throughout the main period (injection cycle 1; all doses) and open-label extension period (injection cycles 2–4)



AS, Ashworth Scale; LL, lower limb; SE, standard error; UL, upper limb.

Results

Patients

- Overall, 350 patients were treated (**Table 1**); 281 patients (80.3%) completed all four ICs.

Efficacy

- Mean AS scores significantly improved from baseline at Week 4 in all dose groups (**Table 2**).
  - Improvements in AS scores were significantly greater with incobotulinumtoxinA 8 U/kg BW per UL than 2 U/kg BW per UL; primary efficacy endpoint (**Table 2**).
- Investigator's GICS scores showed improvements across all three dose groups, with no significant difference between dose groups (**Table 2**).
- Mean AS scores improved from baseline at each post-treatment visit, and from each injection visit to the respective post-injection visits, across the main and open-label extension periods, in all UL clinical patterns treated (**Figure 3a–e**; $p<0.001$ from baseline to end of study; one-sample t-test).
  - Findings were similar for LL clinical patterns (**Figure 3f–h**).
  - Improvements in AS scores were sustained throughout the study, with continuous improvements observed from IC to IC for the main clinical target patterns of flexed elbow and/or flexed wrist (**Figure 3**).

Safety

- The incidence of treatment-related adverse events (AEs) was very low, and all were mild to moderate in intensity (**Table 3**).
  - The treatment-related AEs were pruritic rash and contusion, dermatitis, pain in extremity, hypotonia, eyelid ptosis, influenza-like illness, and dysphagia; all occurred in only 1 patient each, except pain in extremity (n=2 patients across all ICs).
- AEs were not dose-related and did not increase with treatment cycles (**Table 3**).

Table 2. Change from baseline in AS score of the UL main clinical target pattern (primary endpoint), and investigator's GICS score for the UL (co-primary endpoint), at Week 4 of the main period

	IncobotulinumtoxinA		
	8 U/kg, ◀200 U	6 U/kg, ◀150 U	2 U/kg, ◀50 U
	LS mean (SE)	LS mean (SE)	LS mean (SE)
AS score	–1.15 (0.06)***	–1.02 (0.08)***	–0.93 (0.08)***
Investigator's GICS score	1.64 (0.06)	1.44 (0.09)	1.55 (0.08)
Comparison versus 2 U/kg (maximum 50 U/UL) dose group[a]			
AS score	p=0.017	p=0.546	–
Investigator's GICS score	p=0.340	p=0.297	–

[a]Significance based on the comparison of LS means using a 4-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.
ANCOVA, analysis of covariance; AS, Ashworth Scale; BW, body weight; GICS, Global Impression of Change Scale; LS, least squares; MMRM, mixed model repeated measures; SE, standard error; UL, upper limb.

Table 3. Summary of treatment-emergent AEs reported during the main and open-label extension periods of XARA

Patients, n (%)	Main period, by incobotulinumtoxinA dose group				Open-label extension period			
	8 U/kg BW N=176	6 U/kg BW N=87	2 U/kg BW N=87	Overall[a] N=350	Cycle 1 N=331	Cycle 2 N=307	Cycle 3 N=290	Overall[a] 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)
Severe AE	2 (1.1)	1 (1.1)	0	3 (0.9)	3 (0.9)	4 (1.3)	1 (0.3)	8 (2.4)
AEs leading to discontinuation	1 (0.6)	1 (1.1)	0	2 (0.6)	3 (0.9)	2 (0.7)	0	5 (1.5)
Treatment-related AEs[b]	3 (1.7)	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)
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)
Fatal AEs	0	0	0	0	0	0	0	0

[a]Patients with >1 AE within a preferred term were counted once at the patient's highest intensity category.
[b]Treatment-related AEs in the main period: pruritic rash and contusion (n=1), dermatitis (n=1) and pain in extremity (n=1). All were in the 8 U/kg BW group, and all were mild in intensity. Treatment-related AEs in the open-label extension period: hypotonia (n=1, Cycle 1), eyelid ptosis (n=1, Cycle 1), influenza-like illness (n=1; Cycle 2), dysphagia (n=1, Cycle 2), pain in extremity (n=1, Cycle 3); all treatment-related AEs except the eyelid ptosis either recovered or resolved.
AE, adverse event; BW, body weight.

Conclusions

- Patients in all three dose groups experienced clinically relevant improvements in their spasticity, with significantly superior AS scores in the 8 U/kg BW versus 2 U/kg BW group for UL treatment.
- The study confirmed a favorable safety profile of incobotulinumtoxinA over four ICs, with no new or unexpected safety concerns identified.
- These findings established the efficacy and safety of incobotulinumtoxinA for treatment of UL spasticity in children and adolescents with CP, and provide further evidence for its efficacy in multipattern treatment, reflecting the real-world clinical needs of children with CP.

References

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Disclosures

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