Efficacy and safety of incobotulinumtoxinA in the treatment of lower limb spasticity in Japanese patients

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Background

- The number of individuals experiencing stroke in Japan has increased rapidly over the past 20 years, along with the number of individuals >65 years of age in the population.[1] Around one-third of patients who have a stroke develop spasticity, often leading to pain, distress, and secondary complications.[2,3]
- Botulinum toxin type A (BoNT-A) treatment is recommended for the treatment of lower limb (LL) spasticity in adults.[3]
- IncobotulinumtoxinA (INCO; Xeomin®, Merz Pharmaceuticals GmbH) is a botulinum neurotoxin type A formulation (150 kD) free from complexing proteins.
- The efficacy and safety of incobotulinumtoxinA at total body doses of up to 800 units (U) has previously been demonstrated for the treatment of combined upper limb and LL spasticity in a phase III trial in predominantly non-Japanese patients.[4]
- With the currently approved BoNT-A preparation, Japanese patients can be injected for treatment of LL spasticity only at doses of up to 300 U.[5,6]

Objectives

- Lead-in tolerability period (LITP)
  - To investigate the safety and tolerability of a 400 U dose of INCO in the Japanese population.
- Main period (MP)
  - To confirm the efficacy and investigate the safety of INCO in Japanese patients with post-stroke LL spasticity.
- Open-label extension period (OLEX)
  - To investigate safety and further demonstrate the efficacy of repeated incobotulinumtoxinA injections in LITP and MP patients who had a clinical need for reinjection for a total treatment duration of up to 52 weeks.

Methods

Dose confirmation – LITP

LITP study design

- An open-label single injection cycle (400 U) and 12 weeks' observation in at least 10 patients was conducted as part of a phase III study (**Figure 1**).

LITP patients

- Eligibility criteria for the LITP included the following:
  - Male and female patients 20–<65 years of age
  - Unilateral LL post-stroke spasticity caused by a stroke at least 6 months prior to the screening visit
  - Bodyweight of at least 50 kg
  - The clinical need for a total dose of 400 U INCO in the affected LL
  - Modified Ashworth Scale (MAS) plantar flexor score of ⩾3 at screening and baseline injection visit
  - Patients with fixed contracture or other muscle hypertonia (e.g., rigidity) were not eligible.

LITP safety and tolerability assessment

- Tolerability was assessed on a 4-point Likert scale where 1 = "very good" and 4 = "poor".
- The safety assessment was primarily based on an analysis of adverse events (AEs). AEs were evaluated by the sponsor and an independent Data Monitoring Committee to determine whether 400 U was well tolerated. If a dose of 400 U was not well tolerated, patients would receive 300 U INCO or placebo in the MP.

Efficacy and safety in LL spasticity – MP

MP study design

- This was a phase III, prospective, double-blind, placebo-controlled, randomized, multi-center study.
- Provided that an acceptable safety profile was achieved during LITP, a minimum of 206 patients would be randomized to a single injection cycle of 400 U INCO or placebo over 12 weeks (**Figure 1**).

MP patients

- Eligibility criteria were the same as the LITP, except:
  - Patients 20–80 years of age could be enrolled
  - The requirement of a clinical need for a total dose of 400 U INCO only applied if 400 U was well tolerated in the LITP.

MP assessments

- The primary efficacy endpoint was the area under the curve (AUC) for the change from baseline (Day 1) in the MAS plantar flexors score to the end of the MP (Week 12).
  - The confirmatory analysis was performed by analysis of covariance (ANCOVA), with baseline MAS plantar flexors score as covariate and site, pre-treatment, and sex as factors.
- Secondary efficacy endpoints were change from baseline in MAS plantar flexors score to Weeks 4, 6, and 8 and response rates in MAS plantar flexors score at Weeks 4, 6, and 8 (responders = patients with a reduction of ⩾1 point from baseline).
- Safety assessment was primarily based on a descriptive analysis of AEs.

Efficacy and safety in LL spasticity – OLEX

OLEX study design

- Two-hundred-and-two patients were then enrolled in an OLEX of 3 injection cycles, 10–14 weeks in duration (cycle 3 was fixed at 12 weeks; **Figure 1**).

OLEX assessments

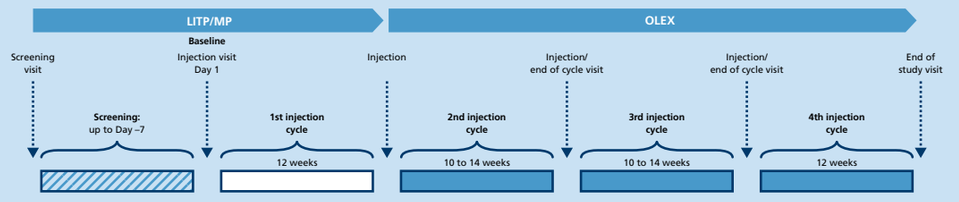
- Changes in MAS plantar flexor scores from baseline to Week 4 of each OLEX injection cycle were assessed and compared.
- Safety assessment was primarily based on a descriptive analysis of AEs.

Results

Safety and tolerability – LITP

- A total of 11 patients were enrolled in the LITP (**Table 1**).
- AEs were observed in 72.7% of patients in the LITP, all of which were mild or moderate in severity.
- No AEs considered related to the treatment were reported.
- Tolerability was "very good" or "good" in 100.0% of patients in the LITP, so the dose of 400 U was deemed safe for MP enrolment.

Figure 1. Study design



LITP, lead-in tolerability period; MP, main period; OLEX, Open-label extension period.

Efficacy and safety in LL spasticity – MP

MP patients

- Across 48 sites, 208 patients were enrolled in the MP, of which 14 discontinued.
- Around three quarters of patients were male, and the mean weight was 66.8 kg (**Table 1**).

Table 1. Patient demographics and clinical characteristics

	LITP (N=11)	MP (N=208)
Sex, n (%)		
Male	8 (72.7)	158 (76.0)
Female	3 (27.3)	50 (24.0)
Age (years), mean (SD	48.7 (8.5)	59.2 (11.1)
Height (cm), mean (SD)	167.2 (10.3)	164.7 (8.5)
Weight (kg), mean (SD)	69.8 (10.5)	66.8 (10.8)
Time since the last stroke leading to spasticity (months), mean (SD)	49.9 (20.1)	82.9 (67.2)

LITP, lead-in tolerability period; MP, main period; N, number of patients in each period; SD, standard deviation.

MP efficacy

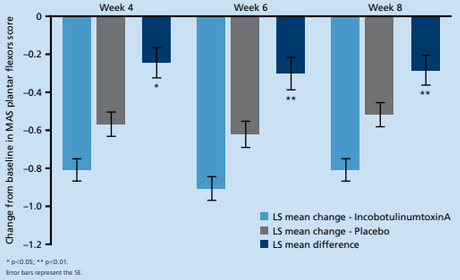
- The AUC for the change in the MAS plantar flexors score from baseline to Week 12 was statistically significantly greater in the INCO group versus placebo (–7.7 ± 7.0 and –4.8 ± 5.8, respectively; **Table 2**) regardless of sex, site, or pre-treatment.
- Change from baseline in MAS plantar flexors score indicated improvement of LL spasticity at Weeks 4, 6, and 8, with the largest effect at Week 6 (**Figure 2**). Improvements with INCO were statistically significantly greater than placebo at Weeks 4, 6, and 8.

Table 2. Summary statistics and ANCOVA of AUC for the change from baseline in MAS plantar flexors score to the end of MP (BOCF, FAS)

	INCO (N=104)	Placebo (N=104)
Mean ± SD	–7.74 ± 7.01	–4.76 ± 5.84
LS mean ± SE	–8.40 ± 0.661	–5.81 ± 0.713
LS mean difference (INCO – placebo) ± SE	–2.59 ± 0.892	
95% CI	–4.35; –0.83	
p-value	0.0041	

AUC, area under the curve; BOCF, baseline observation carried forward; 95% CI, 95% confidence interval; FAS, full analysis set; INCO, incobotulinumtoxinA; LS, least squares; MAS, modified Ashworth scale; MP, main period; SD, standard deviation; SE, standard error.

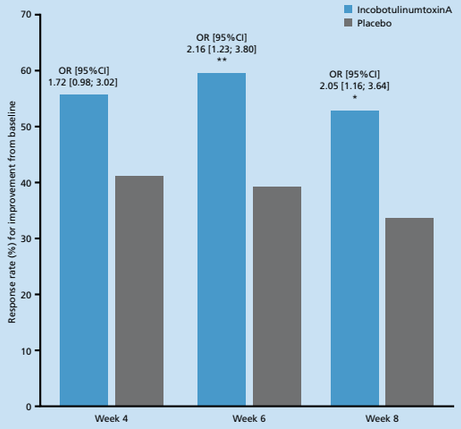
Figure 2. ANCOVA of change in MAS plantar flexors score from baseline to Weeks 4, 6 and 8 in MP (BOCF, FAS)



* p<0.05; ** p<0.01.
Error bars represent the SE.
ANCOVA, analysis of covariance; BOCF, baseline observation carried forward; FAS, full analysis set; MAS, modified Ashworth scale, SE, standard error.

- Response rates in MAS plantar flexors score were consistently higher in the INCO group versus placebo at Weeks 4, 6, and 8 (**Figure 3**), with the difference being statistically significant at Weeks 6 and 8. Patients in the INCO group had odds of being a responder that were at least 1.5-fold as high versus placebo.

Figure 3. Response rates (%) for at least 1-point improvement from baseline in MAS plantar flexors score at Weeks 4, 6, and 8 in MP (worst-case approach, FAS)



* p<0.05; ** p<0.01.
Comparisons between treatment groups were performed using a logistic regression model where response to treatment was the dependent variable, baseline plantar flexors MAS was a covariate, and site (pooled), treatment and sex were factors.
95% CI, 95% confidence interval; FAS, full analysis set; MAS, modified Ashworth scale; OR, odds ratio.

MP safety

- Tolerability was "very good" or "good" in 93.3% and 90.4% of patients receiving INCO and placebo, respectively.
- AEs were observed in 48.1% and 49.0% of patients receiving INCO and placebo, respectively (**Table 3**).
  - AEs considered related to the treatment were reported in six patients (5.8%) and five (4.8%) patients receiving INCO and placebo, respectively.
  - One serious AE considered related to treatment (severe cellulitis, resolved) was reported in a patient receiving INCO. The remaining AEs considered related to treatment were non-serious and mild or moderate in severity.

Efficacy and safety in LL spasticity – OLEX

OLEX efficacy

- The mean (standard deviation) changes in MAS plantar flexor scores from study baseline to Week 4 of each OLEX injection cycle were –1.05 (0.75), –1.16 (0.77) and –1.18 (0.73), respectively, for OLEX cycle 1, 2 and 3, showing improvement across repeated injection cycles.

OLEX safety

- AEs were observed in 131/202 patients (64.9%) across the three OLEX cycles (**Table 3**). The number of patients with AEs reduced slightly with each cycle (81 patients [40.1%] in cycle 1, 66 patients [34.7%] in cycle 2 and 63 [34.2%] in cycle 3).
  - AEs considered related to treatment were reported in 14/202 patients (6.9%).
  - No serious AEs considered related to treatment were reported. All AEs considered related to treatment were mild or moderate in severity.
  - No patient reported generalized weakness during the study.
- No deaths were reported in this study.

Table 3. AEs considered related to treatment reported in MP and OLEX by PT (SES)

	MP		OLEX (3 injection cycles)
	IncobotulinumtoxinA (N=104)	Placebo (N=104)	Total (N=202)
Patients with at least one AE, n (%)	50 (48.1)	51 (49.0)	131 (64.9)
Patients with at least one AE considered related to treatment, n (%)	6 (5.8)	5 (4.8)	14 (6.9)
AEs considered related to treatment			
Muscular weakness	2 (1.9)	2 (1.9)	3 (1.5)
Myalgia	0	3 (2.9)	1 (0.5)
Fall	0	1 (1.0)	2 (1.0)
Constipation	1 (1.0)	0	2 (1.0)
Limb discomfort	0	0	2 (1.0)
Blood creatine phosphokinase increased	0	0	2 (1.0)
Pain in extremity	0	1 (1.0)	1 (0.5)
Ligament sprain	0	0	1 (0.5)
Arthralgia	0	0	1 (0.5)
Malaise	1 (1.0)	0	0
Cellulitis	1 (1.0)	0	0
Post micturition dribble	1 (1.0)	0	0
Incontinence	0	1 (1.0)	0
Neurogenic bladder	0	1 (1.0)	0
Contusion	0	1 (1.0)	0
Dizziness	0	1 (1.0)	0
Pollakiuria	0	0	1 (0.5)
Urinary retention	0	0	1 (0.5)
Hemorrhage subcutaneous	0	0	1 (0.5)
Hyperkeratosis	0	0	1 (0.5)
Paralysis	0	0	1 (0.5)

AEs considered related to treatment ranked by overall incidence across all injection cycles in the MP and OLEX.
AE, adverse event; MP, main period; OLEX, open-label extension period; PT, preferred term; SES, safety evaluation set.

Conclusions

- This study confirmed the efficacy and demonstrated a favorable safety and tolerability profile of INCO at a dose of 400 U in a Japanese population with LL spasticity.
- These results were further supported by continued efficacy and safety profiles following repeated treatment in the OLEX.
- Efficacy, safety, and tolerability were generally similar to those observed in studies enrolling predominantly non-Japanese patients,[4] further supporting the results of the current study, which suggests that 400 U INCO is suitable for the treatment of LL spasticity in Japanese patients.

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