

# RANDOMIZED, PLACEBO-CONTROLLED TRIAL OF INCOBOTULINUMTOXINA FOR UPPER-LIMB POST-STROKE SPASTICITY

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**ABSTRACT:** *Introduction:* Efficacy and safety of incobotulinumtoxinA in post-stroke upper-limb spasticity were studied. *Methods:* Subjects randomized 2:1 to incobotulinumtoxinA (fixed dose 400 U) or placebo, with fixed doses for the primary target clinical pattern (PTCP; flexed elbow, 200 U; flexed wrist, 150 U; clenched fist, 100 U). Doses for non-primary patterns were flexible within predefined ranges. *Results:* At week 4, incobotulinumtoxinA led to larger improvements in PTCP Ashworth scale (AS) scores than placebo [least-squares mean change  $\pm$  standard error:  $-0.9 \pm 0.06$  ( $n = 171$ ) vs.  $-0.5 \pm 0.08$  ( $n = 88$ );  $P < 0.001$ ], and more subjects were PTCP AS responders ( $\geq 1$ -point improvement) with incobotulinumtoxinA (69.6%) than with placebo (37.5%;  $P < 0.001$ ). Investigator's Global Impression of Change confirmed superiority of incobotulinumtoxinA vs. placebo ( $P = 0.003$ ). IncobotulinumtoxinA was associated with functional improvements, as demonstrated in responder rates for Disability Assessment Scale principal target at week 4 ( $P = 0.007$ ). Adverse events were mainly mild/moderate, and were reported by 22.4% (incobotulinumtoxinA) and 16.8% (placebo) of subjects. *Conclusions:* IncobotulinumtoxinA significantly improved upper-limb spasticity and associated disability, and was well-tolerated.

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## INTRODUCTION

The efficacy and safety of different formulations of botulinum toxin type A for the treatment of post-stroke spasticity of the upper-limb have been demonstrated in a number of randomized, placebo-controlled clinical studies.<sup>1–6</sup> On the basis of these clinical trial data, botulinum toxin injections are the recommended first-line treatment for

regional post-stroke spasticity affecting the upper-limb.<sup>7–10</sup>

In the USA and Europe, 3 formulations of botulinum toxin type A and 1 botulinum toxin type B product are commercially available: abobotulinumtoxinA (Dysport); incobotulinumtoxinA (Xeomin); onabotulinumtoxinA (Botox); and rimabotulinumtoxinB (NeuroBloc and Myobloc). While all 3 botulinum toxin type A products are approved for treatment of post-stroke upper-limb spasticity in Europe,<sup>11–13</sup> only onabotulinumtoxinA is currently licensed for this indication in the USA.<sup>14</sup>

IncobotulinumtoxinA is a purified form of botulinum toxin type A that was found to be therapeutically equivalent to onabotulinumtoxinA in the treatment of other neurological conditions, such as cervical dystonia and blepharospasm, when the same number of units were used.<sup>15–17</sup> IncobotulinumtoxinA does not contain accessory proteins (also designated neurotoxin-associated or complexing proteins) and has a high specific activity relative to other formulations.<sup>18</sup> A phase III trial of incobotulinumtoxinA that enrolled 148 subjects with post-stroke spasticity was performed previously in Europe.<sup>1,19</sup> In the randomized, placebo-controlled period of the trial, a single treatment with up to 400 units (U) of incobotulinumtoxinA led to significant improvements in muscle tone, spasticity-associated disability, and caregiver burden.<sup>1</sup> During an open-label extension period, improvements were sustained throughout the 5 additional treatment cycles, and no new adverse events (AEs) associated with repeated treatments were identified.<sup>19</sup>

Here we present results from the 12-week main period of a prospective, randomized, double-blind, placebo-controlled, phase III trial with an open-label extension period to further investigate the safety and efficacy of incobotulinumtoxinA for treatment of post-stroke spasticity of the upper-limb. The purpose of this study was to confirm the efficacy and safety of incobotulinumtoxinA for treatment of upper-limb spasticity.

Additional Supporting Information may be found in the online version of this article.

**Abbreviations:** AE, adverse event; AESI, adverse event of special interest; ANCOVA, analysis of covariance; AS, Ashworth Scale; BMI, body mass index; DAS, Disability Assessment Scale; FAS, full analysis set; FDA, U.S. Food and Drug Administration; LS mean, least-squares mean; PTCP, primary target clinical pattern; SES, safety evaluation set

**Key words:** botulinum toxins, type A; incobotulinumtoxinA; muscle spasticity; stroke; Xeomin

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## METHODS

**Study Design.** This prospective, multicenter study (NCT01392300, EudraCT 2010-023043-15) was a randomized, double-blind, placebo-controlled, parallel-group main period (12-week duration) with a single treatment of incobotulinumtoxinA 400 U or placebo. Subjects could continue into a 36-week, open-label extension to receive 3 further treatments with incobotulinumtoxinA 400 U at fixed 12-week intervals.

The randomization ratio of incobotulinumtoxinA to placebo was 2:1. Balanced randomization in blocks of  $n = 3$  and corresponding distribution of study drug and placebo to the investigation sites were achieved by using an interactive voice/web response system, ensuring an approximate treatment allocation rate of 2:1 at each study site. This system also provided for stratification by gender in each treatment group. The study sponsor's randomization officer allocated treatments to subjects using a computerized randomization program (RANCODE, version 3.6; IDV Datenanalyse und Versuchsplanung, Gauting, Germany). Site, subject, and sponsor remained blinded during the main period.

The study was conducted between September 2, 2011, and February 13, 2014, at 46 sites in the Czech Republic, Germany, Hungary, India, Poland, Russia, and the USA. The study protocol, informed consent documents, and any other appropriate study-related documents were reviewed and approved by the respective independent ethics committees and institutional review boards of each participating institution. The study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

**Subjects.** Adults (age 18–80 years) with spasticity of the upper-limb due to stroke ( $\geq 3$  months after the last stroke) were eligible for participation. Participants had to have a flexed elbow, flexed wrist, and clenched fist clinical pattern of spasticity with muscle tone  $\geq 2$  on the Ashworth scale (AS) at each site. Eligible subjects were required to have a clinical need for a total dose of 400 U of incobotulinumtoxinA into the affected upper-limb, according to the experience-based opinion of the investigator and could not have received treatment with any botulinum toxin formulation in any body region for any indication in the previous 12 months. This inclusion criterion ensured that subjects had significant spasticity at study entry. Main exclusion criteria were spasticity due to etiologies other than stroke; bilateral upper-limb paresis, paralysis, or tetraparesis; fixed contracture in the affected joints; severe atrophy in the target limb muscles; and previous treatment with phenol.

**Treatments.** At baseline, the investigator decided, based on his/her judgment and clinical experience, on 1 primary target clinical pattern (PTCP) that included flexed elbow, flexed wrist, or clenched fist. The PTCP was treated with a predefined fixed dose (flexed elbow, 200 U; flexed wrist, 150 U; clenched fist, 100 U). For the muscle groups other than the PTCP, investigators decided upon the dose and number of injection sites per muscle within predefined ranges (refer to Tables S1–S3 in the Supplementary Material, available online), based on their clinical judgment and the individual condition of the subject. Doses complied with the dose ranges approved for incobotulinumtoxinA in Europe.<sup>13</sup> The total dose was fixed at 400 U of incobotulinumtoxinA (using a 2.0 ml per 100 U dilution with preservative-free saline) or the corresponding volume of placebo (8.0 ml). The maximum injection volume per injection site was 1.0 ml, corresponding to 50 U of incobotulinumtoxinA. Injections were to be guided by electromyography and/or electrical nerve stimulation. Ultrasound guidance was allowed as a supplementary technique at the discretion of the investigator. All muscle groups with an AS score  $\geq 2$  and the corresponding clinical pattern had to be treated.

**Efficacy Assessments.** The primary outcome measure was the change from baseline of the AS score of the PTCP at week 4. This 5-point scale ranges from 0 (no increase in tone) to 4 (limb rigid in flexion or extension).<sup>20,21</sup> Assessments were performed by trained investigators, and the same investigator performed ratings at baseline and at week 4, and, preferably, at all other study visits.

A responder analysis was performed as a secondary outcome measure. Responders were defined as subjects with a  $\geq 1$ -point improvement in the AS score from baseline for any clinical pattern, including the PTCP. This improvement is considered to be clinically meaningful.<sup>3,22</sup>

The co-primary outcome was the Investigator's Global Impression of Change at week 4. Based on clinical experience, investigators rated the Global Impression of Change of each subject's upper-limb spasticity due to treatment compared with the condition before injection using a 7-point balanced Likert scale (–3, very much worse; –2, much worse; –1, minimally worse; 0, no change; +1, minimally improved; +2, much improved; +3, very much improved).

The Disability Assessment Scale (DAS) was a secondary outcome variable. Based on subject interviews, investigators determined the extent of functional impairment within 4 domains that included a subject's hygiene, dressing, limb position, and pain according to a 4-point scale (0, no disability; 1, mild

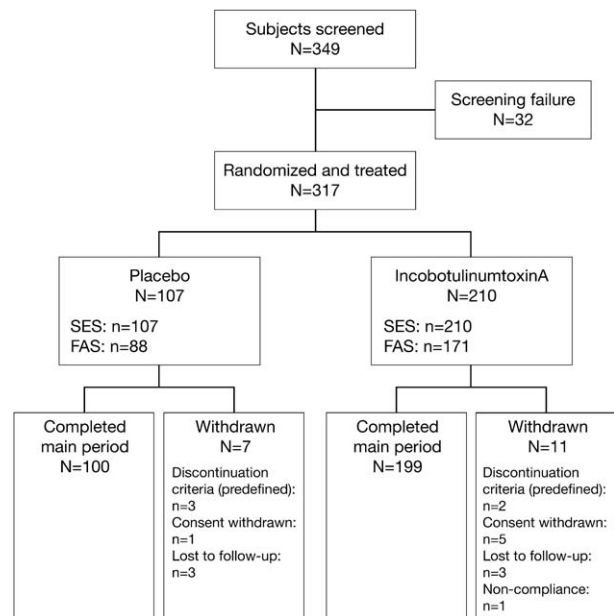
disability; 2, moderate disability; 3, severe disability). Each subject selected a principal target domain at the screening visit. Responders were defined as subjects with a  $\geq 1$ -point improvement in the DAS score from baseline for the principal target domain.

**Safety Assessments.** Subjects were instructed to report all AEs to the investigator or clinic staff and were requested specifically to report AEs at each visit or telephone contact. An AE of special interest (AESI) was defined as an AE occurring after treatment that may indicate toxin spread; investigators actively asked subjects about such events at each clinic visit using a pre-specified list of questions to elicit such complications. In addition, standard safety assessments (vital signs, physical and neurologic examinations, clinical chemistry and hematology measurements, and pregnancy testing) were performed throughout the study.

**Protocol Amendment.** The original study protocol was amended in response to a special protocol assessment by the U.S. Food and Drug Administration (FDA). The protocol amendment stipulated a predefined fixed dose for the PTCP, as detailed above. The remainder of the 400 U, fixed total dose per subject had to be distributed among the other clinical patterns as medically indicated. Moreover, the co-primary efficacy variable, Investigator's Global Impression of Change, was added. Recruitment was monitored to ensure an even distribution of subjects representing each of the 3 PTCPs.

The amendment came into effect after the first 58 participants had been randomized. In this article we describe efficacy results in the full analysis set (FAS), which only includes subjects who were randomized after the amendment came into effect. However, because the 58 subjects who were randomized prior to the amendment received the same fixed total dose as those randomized thereafter, they were included in the safety evaluation set (SES).

**Statistical Analysis.** Based on an assumed treatment difference between incobotulinumtoxinA and placebo of 0.45 points on the AS scale and of 0.8 points on the Investigator's Global Impression of Change scale and a 2:1 randomization ratio, it was estimated that a total of 222 subjects (incobotulinumtoxinA,  $n = 148$ ; placebo,  $n = 74$ ) would provide a combined power of 95.5% to show a statistically significant difference between incobotulinumtoxinA and placebo in both co-primary efficacy variables. However, allowing for a premature discontinuation rate of 20% for the entire study and in order to generate a sufficiently large database with long-term safety data, the enrollment



**FIGURE 1.** Subject flow diagram. FAS indicates full analysis set; SES indicates safety evaluation set.

target was increased to 300 subjects (incobotulinumtoxinA,  $n = 200$ ; placebo,  $n = 100$ ).

The primary efficacy variable (change from baseline to week 4 in the AS score of the PTCP) was analyzed using analysis of covariance (ANCOVA; 2-sided, significance level  $\alpha = 0.05$ ) in the FAS with comparison of least squares (LS) mean and missing values imputed according to the last observation carried forward approach, with baseline AS score of the PTCP as covariate and treatment, gender, and pooled study site as fixed factors. The co-primary efficacy variable, Investigator's Global Impression of Change at week 4, was also analyzed using ANCOVA (2-sided, significance level  $\alpha = 0.05$ ) in the FAS with comparison of LS mean and the median baseline AS score of all 3 possible PTCPs as covariate and treatment, gender, and pooled site as fixed factors, imputing for missing values with 0 (no change). Superiority of incobotulinumtoxinA compared with placebo was proven if both the primary efficacy variable and the co-primary efficacy variable showed a statistically significant result. DAS was also analyzed using ANCOVA (2-sided, significance level  $\alpha = 0.05$ ) in the FAS with comparison of LS mean and the baseline AS score as covariate and last observation carried forward approach for missing values. Safety variables were assessed using descriptive summary statistics.

## RESULTS

**Subjects.** A total of 349 subjects were screened. The SES included 317 participants who were randomized and received incobotulinumtoxinA ( $n = 210$ ) or placebo ( $n = 107$ ). The majority ( $n = 259$ ) were randomized after the amended

**Table 1.** Subject demographics and baseline disease characteristics (full analysis set).

Characteristic	IncobotulinumtoxinA ( <i>n</i> = 171)	Placebo ( <i>n</i> = 88)
Men, <i>n</i> (%)	97 (56.7)	50 (56.8)
Mean (SD) age, years	55.4 (11.7)	57.1 (10.8)
Race, <i>n</i> (%)		
White	136 (79.5)	73 (83.0)
Black or African American	6 (3.5)	2 (2.3)
Asian	27 (15.8)	13 (14.8)
Other	2 (1.2)	0
Mean (SD) BMI, kg/m <sup>2</sup>	27.0 (4.5)	27.0 (3.9)
Median (range) time since last stroke leading to spasticity, months	28.0 (4–277)	27.8 (3–412)
Median (range) time since first diagnosis of upper-limb spasticity, months	11.8 (0–270)	12.0 (0–257)
Clinical pattern(s) of upper limb spasticity, <i>n</i> (%)		
Adducted or internally rotated shoulder	87 (50.9)	49 (55.7)
Flexed elbow	171 (100.0)	88 (100.0)
Pronated forearm	151 (88.3)	75 (85.2)
Flexed wrist	171 (100.0)	88 (100.0)
Thumb-in-palm	104 (60.8)	52 (59.1)
Clenched fist	171 (100.0)	88 (100.0)
Intrinsic plus hand	22 (12.9)	5 (5.7)

BMI, body mass index; SD, standard deviation.

protocol came into effect and were included in the FAS (incobotulinumtoxinA, *n* = 171; placebo, *n* = 88). The disposition of subjects (Fig. 1) showed that overall discontinuation rates were comparable for both treatment groups (incobotulinumtoxinA, 5.2%; placebo, 6.5%; total, 5.7%). No subjects withdrew due to AEs or lack of efficacy. A total of 5 subjects from a single study site were withdrawn at the final main period visit because the investigator did not perceive a clinical need for another injection of 400 U of incobotulinumtoxinA, which was a predefined discontinuation criterion. The majority of participants were White or Asian (including Indian subjects). Overall, subject baseline characteristics were balanced between the treatment groups; subjects who received incobotulinumtoxinA were, on average, slightly younger than subjects in the placebo group (Table 1). The majority of subjects [220 of 259 (84.9%)] had not received botulinum toxin treatment for upper-limb spasticity prior to participation in this study.

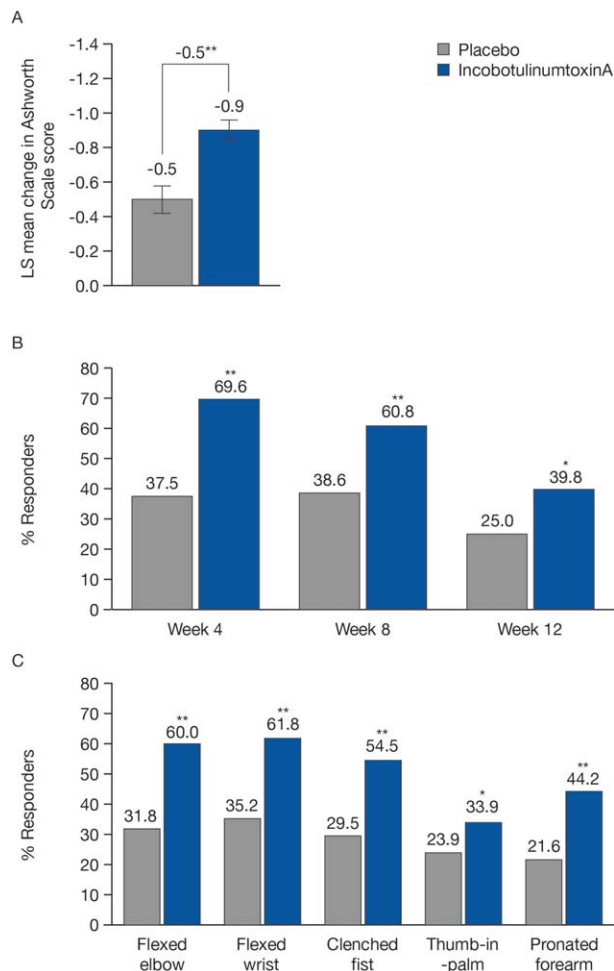
**Treatment Compliance.** In all but 1 case, subjects received 400 U of incobotulinumtoxinA or the corresponding volume of placebo (8.0 ml). In deviation from the protocol, 1 subject was injected with 7.5 ml of incobotulinumtoxinA (375 U).

**Treatment Efficacy.** *AS Scores.* Treatment with incobotulinumtoxinA (total dose of 400 U) led to significant improvements in AS scores for the PTCP overall from baseline to week 4 compared with placebo. The LS mean change (standard error; SE)

was  $-0.9$  (0.06) for incobotulinumtoxinA vs.  $-0.5$  (0.08) for placebo ( $P < 0.001$ ; Fig. 2A). Significant superiority of incobotulinumtoxinA, as measured by improvements in overall PTCP AS scores, was maintained at weeks 8 ( $P < 0.001$ ) and 12 ( $P = 0.041$ ). The ANCOVA did not show a significant effect of pooled study site (country) on the mean change in AS score from baseline to week 4 ( $P = 0.171$ ).

At week 4, 119 of 171 subjects (69.6%) who received incobotulinumtoxinA had a  $\geq 1$ -point improvement on the AS score for the PTCP compared with 33 of 88 subjects (37.5%) who received placebo ( $P < 0.001$ ). Significant superiority of incobotulinumtoxinA vs. placebo in the AS responder rates for the PTCP was maintained at weeks 8 and 12 (Fig. 2B). Responder rates at week 4 for each clinical pattern group, irrespective of whether or not this was the PTCP for a given subject, were significantly higher for incobotulinumtoxinA than for placebo (Fig. 2C). Similar changes in AS scores were observed for the 58 subjects who were randomized and treated before the protocol amendment and excluded from the FAS (data not shown).

*Investigator's Global Impression of Change.* The Investigator's Global Impression of Change at week 4 for the PTCP confirmed that incobotulinumtoxinA was superior to placebo ( $P = 0.003$ ; Fig. 3A). Differences in the corresponding frequency distribution were also significant ( $P = 0.001$ , Wilcoxon rank-sum test; Fig. 3B). In the incobotulinumtoxinA group, 73 subjects (42.7%)



**FIGURE 2.** Ashworth scale scores. LS mean indicates least-squares mean. **(A)** Change from baseline to week 4 for the primary target clinical pattern (PTCP, full analysis set, last observation carried forward). Error bars show the standard error. **\*\*** $P < 0.001$  for incobotulinumtoxinA vs. placebo. **(B)** Responder analysis for the PTCP over time (full analysis set, worst case imputation). Subjects with an improvement (reduction) of  $\geq 1$  point on the Ashworth scale were classified as responders. **\*\*** $P < 0.001$ ,  $*P = 0.004$  for incobotulinumtoxinA vs. placebo. **(C)** Responder analysis for each clinical pattern group at week 4 (full analysis set, observed cases). Subjects with an improvement (reduction) of  $\geq 1$  point on the Ashworth scale were classified as responders. **\*\*** $P \leq 0.001$ ,  $*P = 0.028$  for incobotulinumtoxinA vs. placebo.

reached a score  $\geq +2$  (much improved or very much improved) for the PTCP compared with 20 subjects (22.7%) in the placebo group (Fig. 3B).

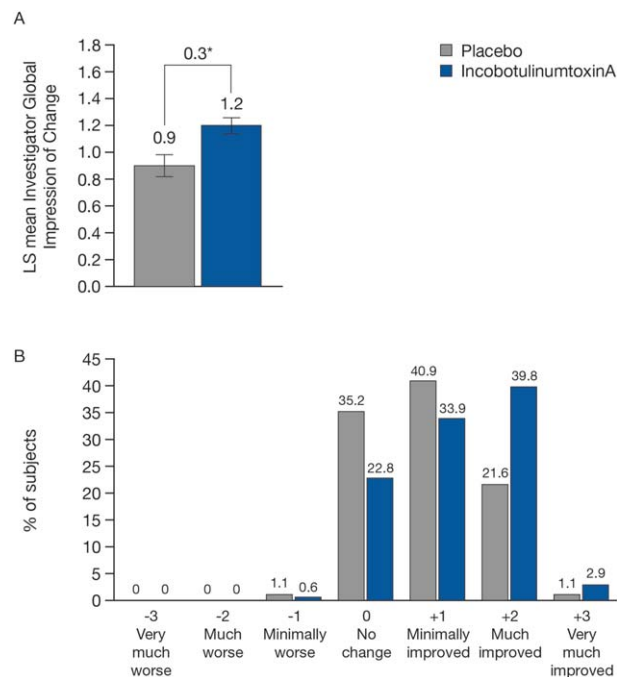
**DAS Scores.** A higher proportion of subjects in the incobotulinumtoxinA group (79 of 171; 46.2%) were DAS responders at week 4 (subjects with  $\geq 1$ -point improvement on the DAS score of the principal target domain) than in the placebo group (25 of 88; 28.4%;  $P = 0.007$ , Wilcoxon rank-sum test).

**Safety.** AEs were reported by 47 of 210 subjects (22.4%) in the incobotulinumtoxinA group and 18 of 107 subjects (16.8%) in the placebo group.

AESIs were reported by 7 subjects (3.3%) in the incobotulinumtoxinA group and 3 subjects (2.8%) in the placebo group. The most frequent AESI was dry mouth (Table 2), seen in 4 subjects in the incobotulinumtoxinA group and 1 subject in the placebo group. Of these, 3 events in the incobotulinumtoxinA group and 1 event in the placebo group were considered to have been related to treatment. There were no serious treatment-related AEs and no study discontinuations due to AEs. Further details of AEs are summarized in Table 2.

## DISCUSSION

The results of this randomized, placebo-controlled study confirmed the efficacy and safety of incobotulinumtoxinA for treatment of adults with upper-limb post-stroke spasticity, based on the improvement of muscle tone in the PTCP (primary outcome) and the Investigator's Global Impression of Change (co-primary outcome). Both efficacy variables showed significant superiority using 400 U of incobotulinumtoxinA vs. placebo. In addition, significant superiority vs. placebo in the AS responder rate was sustained to weeks 8 and 12 post-treatment for the PTCP overall. Moreover, the study showed that the improvements in muscle tone after incobotulinumtoxinA injections led to



**FIGURE 3.** Investigator's Global Impression of Change. LS mean indicates least-squares mean. **(A)** Mean scores for the primary target clinical pattern (PTCP) at week 4 (full analysis set, worst case imputation). Error bars show the standard error.  $*P < 0.05$  for incobotulinumtoxinA vs. placebo. **(B)** Frequency distribution for the PTCP 4 weeks after treatment (full analysis set, worst case imputation).  $P = 0.001$  (Wilcoxon rank-sum test).

**Table 2.** Summary of AEs, AESIs, and serious AEs (safety evaluation set).

Number of subjects (%)	IncobotulinumtoxinA (n = 210)	Placebo (n = 107)
Any AE	47 (22.4)	18 (16.8)
Any AE related to treatment	8 (3.8)	2 (1.9)
Any AESI*	7 (3.3)	3 (2.8)
Dry mouth	4 (1.9)	1 (0.9)
Muscular weakness	1 (0.5)	1 (0.9)
Urinary retention	1 (0.5)	1 (0.9)
Blurred vision	1 (0.5)	0
Bradycardia	1 (0.5)	0
Constipation	1 (0.5)	0
Diplopia	1 (0.5)	0
Hypoglossal nerve paresis	0	1 (0.9)
Any AESI related to treatment	4 (1.9)	2 (1.9)
Any serious AE*	7 (3.3)	2 (1.9)
Peripheral ischemia <sup>†</sup>	2 (1.0)	0
Biliary colic	1 (0.5)	0
Bladder calculus	0	1 (0.9)
Epilepsy	1 (0.5)	0
Pancreatic enlargement	1 (0.5)	0
Pneumonia	1 (0.5)	0
Renal cancer	0	1 (0.9)
Urinary tract infection	1 (0.5)	0
Urosepsis	1 (0.5)	0
Any serious AE related to treatment	0	0
Any fatal AE	0	0

AE, adverse event; AESI, adverse event of special interest.

\*By overall frequency and by preferred term.

<sup>†</sup>Both participants had ischemia of the left lower limb that was not related to treatment.

significant functional improvements of spasticity-associated disability, as determined by improvements of the DAS scores for the principal target domain at week 4.

The observed AS responder rates were generally comparable with those of a previous randomized, placebo-controlled study of incobotulinumtoxinA for treatment of upper-limb post-stroke spasticity.<sup>1</sup> That study, by Kanovský *et al.*, was designed with a maximum total dose of 400 U of incobotulinumtoxinA rather than a fixed total dose as in the study presented here. In addition, mean doses administered to the flexed wrist and clenched fist patterns were lower than in our study, and treatment of the flexed elbow pattern was not mandatory. AS responder rates for individual patterns ranged from 54.3% to 68.5% in the incobotulinumtoxinA group and from 31.6% to 38.2% in the placebo group.<sup>1</sup>

A noticeable placebo effect was observed in this study, consistent with observations from a previous placebo-controlled study of incobotulinumtoxinA<sup>1</sup> and studies of other botulinum toxin A formulations in upper-limb spasticity.<sup>2–4,6,23,24</sup> Yablon *et al.* carried out a pooled data analysis of 7 placebo-controlled studies of onabotulinumtoxinA in upper-limb post-stroke spasticity. In their analysis,

which included a total of 544 subjects, mean changes in AS score from baseline to week 6 for elbow, finger, and wrist flexors ranged from –0.4 to –0.5 for placebo and from –0.5 to –1.6 for onabotulinumtoxinA (various doses),<sup>22</sup> which are similar to the changes in AS score from baseline to week 4 for the PTCP in our study (–0.5 for placebo and –0.9 for incobotulinumtoxinA).

The safety profile was comparable to the profile observed in studies of other botulinum toxin type A formulations in the treatment of post-stroke upper-limb spasticity.<sup>2–5,23–25</sup> No new or unexpected AEs were identified in our study, confirming the favorable safety profile of incobotulinumtoxinA for the treatment of post-stroke upper-limb spasticity as ascertained from previous studies and clinical experience.<sup>1,19,26–28</sup> AEs, serious AEs, and AESIs occurred numerically more often in the incobotulinumtoxinA group than in the placebo group. However, differences between the treatment groups were small, and the overall occurrence of AESIs was low. Dry mouth, the most frequent AESI in the incobotulinumtoxinA group, is a known undesirable effect of botulinum toxin type A formulations in patients with upper-limb spasticity and other indications.<sup>11–14,29,30</sup>

Limitations of the study design were the fixed dose and the fixed injection interval. The PTCP had to be treated with a fixed dose (200 U for a flexed elbow, 150 U for a flexed wrist, and 100 U for a clenched fist), and the total dose had to be 400 U of incobotulinumtoxinA. This approach did not take into account that the clinical picture and severity of upper-limb spasticity can be heterogeneous among individual patients. However, investigators were allowed some flexibility in their decision of which muscle group (out of those with the required level of severity) to treat as the PTCP and the distribution of the remaining dose. The fixed 12-week injection interval applied during the open-label extension did not take into account patients' individual medical needs. A recent survey showed that many physicians who treat patients with post-stroke spasticity find that flexibility in treatment intervals and dosing may improve therapy outcomes.<sup>31</sup> Another limitation was that stratification for the PTCP was by monitoring the distribution of subjects regarding their PTCP rather than by stratified randomization, as the FDA-requested protocol amendments came into effect after the study had already started. Also, an active comparator, such as another botulinum toxin formulation, was not included.

A strength of the study design was that subjects were required to have muscle tone with an AS score  $\geq 2$  in all arm regions and that a substantial dose of 400 U of incobotulinumtoxinA was

used to treat this significant spasticity, which is similar to how these patients would be treated in clinical practice.

In conclusion, the results of this large, randomized, placebo-controlled study confirm that incobotulinumtoxinA improves muscle tone and disability associated with spasticity and is an effective and well-tolerated treatment for patients with post-stroke spasticity of the upper-limb.

The principal study investigators in the trial included: *Czech Republic*: Michal Bar, Martin Bares, Edvard Ehler, Robert Jech, Petr Kaňovský, Radim Mazanec, Stanislav Vohanka, Oldřich Vysata; *Germany*: Reiner Benecke; *France*: Dominique Mazevet; *Hungary*: Csilla Rozsa, Zoltan Denes, Peter Dioszeghy, Laszlo Vecsei; *India*: Asad Abbas, Madhuri Behari, Mohit Bhatt, Shamsheer Dwivedee, R. Srinivasa, Cannigaiper U. Velmurugendran, Krishnan Vijayan; *Poland*: Andrzej Bogucki, Anna Czlonkowska, Pawel Jan Polrola, Monika Rudzinska, Jaroslaw W. Slawek, Zbigniew Stelmasiak, Adam Stepień, Andrzej Tutaj, Jaroslaw Wronka, Jacek Zaborski; *Russia*: Igor Boyev, Elena Kostenko, Dmitry Pokhobov, Denis Zakharov; *USA*: Ziyad Ayyoub, David Bowers, Allison Brashear, Andrew Dubin, Elie P. Elovic (coordinating investigator), Stanley Fisher, Richard Harvey, Richard T. Jermyn, Michael Y. Lee, Ian B. Maitin, Christina Marciniak, Shyamal H. Mehta, Michael C. Munin, Atul T. Patel, Bruce S. Rubin, Daniel D. Truong.

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