Drug Design, Development and Therapy

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REVIEW

Clinical and pharmacological properties of incobotulinumtoxinA and its use in neurological disorders

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
1 April 2015
Number of times this article has been viewed

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Background: IncobotulinumtoxinA (Xeomin®) is a purified botulinum neurotoxin type A formulation, free from complexing proteins, with proven efficacy and good tolerability for the treatment of neurological conditions such as blepharospasm, cervical dystonia (CD), and post-stroke spasticity of the upper limb. This article provides a comprehensive overview of incobotulinumtoxinA based on randomized controlled trials and prospective clinical studies.

Summary: IncobotulinumtoxinA provides clinical efficacy in treating blepharospasm, CD, and upper-limb post-stroke spasticity based on randomized, double-blind, placebo-controlled trials with open-label extension periods (total study duration up to 89 weeks). Adverse events were generally mild or moderate. The most frequent adverse events, probably related to the injections, included eyelid ptosis and dry eye in the treatment of blepharospasm, dysphagia, neck pain, and muscular weakness in patients with CD, and injection site pain and muscular weakness when used for treating spasticity. In blepharospasm and CD, incobotulinumtoxinA was investigated in clinical trials permitting flexible intertreatment intervals based on the individual patient's clinical need; the safety profile of intervals shorter than 12 weeks was comparable to intervals of 12 weeks and longer. There were no cases of newly formed neutralizing antibodies during the Phase III and IV incobotulinumtoxinA trials. Phase III head-to-head trials of incobotulinumtoxinA versus onabotulinumtoxinA for the treatment of blepharospasm and CD have demonstrated therapeutic equivalence of both formulations. Additional Phase III trials of incobotulinumtoxinA in conditions such as lower-limb spasticity, spasticity in children with cerebral palsy, and sialorrhea in various neurological disorders are ongoing.

Conclusion: IncobotulinumtoxinA is an effective, well-tolerated botulinum neurotoxin type A formulation. Data from randomized clinical trials and further observational studies are expected to help physicians to optimize treatment by tailoring the choice of formulation, dose, and treatment intervals to the patient's clinical needs.

Keywords: blepharospasm, botulinum toxin, cervical dystonia, incobotulinumtoxinA, spasticity, Xeomin

Introduction

IncobotulinumtoxinA (Xeomin®; Merz Pharmaceuticals GmbH, Frankfurt, Germany) is a botulinum neurotoxin type A (BoNT/A) formulation, free from complexing proteins, that is indicated for the symptomatic treatment of neurological disorders such as blepharospasm, cervical dystonia (CD), and – in Europe – also for post-stroke spasticity of the upper limb.[1,2] Other BoNT/A products available in Europe and the US are onabotulinumtoxinA (Botox®; Allergan Inc., Irvine, CA, USA) and abobotulinumtoxinA (Dysport®; Ipsen, Slough, UK/Galderma, Paris, France).

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http://dx.doi.org/10.2147/DDDT.S79193

A comprehensive review of incobotulinumtoxinA clinical trial data was published in 2007.[3] Since then, new pivotal studies have been conducted in the indications blepharospasm, CD, and spasticity, leading to the approval of incobotulinumtoxinA in several countries. This review will provide an update of clinical data from these studies. Searches of PubMed and www.clinicaltrials.gov were performed up to October 2014. Not included were congress abstracts/posters, articles that were not peer-reviewed, articles not written in English, and case reports.

Pharmacological properties

The active component of commercially available BoNT/A products is the botulinum toxin derived from the Hall strain of *Clostridium botulinum*.[4] The onabotulinumtoxinA and abobotulinumtoxinA formulations contain the neurotoxin as part of a larger protein complex with complexing (accessory) proteins that are not required for the pharmacological activity of the neurotoxin. In the incobotulinumtoxinA formulation, the neurotoxin (150 kD) has been purified so that it is free from complexing proteins and thus has a high specific biological activity.[4] The complexing proteins do not affect the stability of the products and, in contrast to other BoNT/A formulations, unreconstituted incobotulinumtoxinA vials can be stored at room temperature.[5] Under physiological conditions, the complexing proteins are not associated with the neurotoxin.[6] Consequently, the complexing proteins do not affect the diffusion profile of the active neurotoxin.[7] Furthermore, animal studies have shown no significant differences in the diffusion profiles of the three BoNT/A products.[8] Whether the absence of complexing proteins confers a therapeutic advantage is not yet established.

Clinical efficacy and safety

Pivotal Phase III randomized clinical trials

Blepharospasm

The efficacy and safety of incobotulinumtoxinA in patients with blepharospasm was investigated in a double-blind, placebo-controlled, multicenter, single-dose trial (main period) followed by an open-label, repeated-dose extension period in which incobotulinumtoxinA was administered at flexible intervals ≥6 weeks (Table 1).[9,10] In the main period, 109 patients with bilateral blepharospasm were randomized in a 2:1 ratio to treatment with incobotulinumtoxinA (n=75) or placebo (n=34).[9] Patients in this trial had previously been treated with onabotulinumtoxinA and had moderate to severe blepharospasm, as indicated by the Jankovic Rating Scale (JRS) severity subscore ≥2 at baseline.[11] A significant difference in favor of incobotulinumtoxinA versus placebo was observed in the change in JRS severity subscore from administration to 6 weeks later (primary efficacy variable; $P<0.001$ versus placebo). All secondary outcome measures also favored incobotulinumtoxinA, including responder rates at 6 weeks (54.7% for incobotulinumtoxinA versus 14.7% for placebo; $P<0.001$; patients with an improvement in JRS severity subscore ≥1 point were classed as responders) and assessment of Blepharospasm Disability Index (BSDI) scores at 6 weeks (change from baseline: −0.4 for incobotulinumtoxinA versus 0.11 for placebo; $P=0.002$). At the 6-week visit, patients rated the mean therapeutic effect of incobotulinumtoxinA significantly greater than that of placebo (mean Patient Evaluation of Global Response 1.3 for incobotulinumtoxinA versus −0.6 for placebo).

In this study, patients were directly questioned about the occurrence of adverse events (AEs) that might indicate potential toxin spread. The most frequently reported AEs were eyelid ptosis (18.9% for incobotulinumtoxinA versus 5.9% for placebo), dry eye (18.9% for incobotulinumtoxinA versus 11.8% for placebo), and dry mouth (14.9% for incobotulinumtoxinA versus 2.9% placebo). Investigators rated the treatment tolerability as "good/very good" for 91.9% of patients who received incobotulinumtoxinA and for 85.2% of patients who received placebo.[9]

Most patients (102/109) who participated in the double-blind main period continued into the 69-week, open-label extension, and 82 patients completed the trial (Table 1).[10] During the extension period, patients could receive a maximum of five incobotulinumtoxinA injections at flexible doses and injection intervals (≥6 weeks; first registration trial in blepharospasm that evaluated flexible BoNT/A injection intervals), based upon patients' request for reinjection and clinical need, as assessed by a JRS severity subscore ≥2. Efficacy results confirmed observations from the main period. Throughout the open-label extension period, mean JRS sum scores, and JRS severity and frequency subscores, improved significantly from each injection visit to the respective control visit 6 weeks later ($P<0.001$ for all visits and scores).[10] JRS sum and subscores and patient-rated BSDI scores remained significantly improved at trial completion compared with the first injection visit ($P<0.05$ for all), demonstrating the sustained efficacy of long-term treatment with flexible intervals.[9,10]

As in the placebo-controlled main period, patients were directly questioned about the occurrence of specific AEs; the most frequently reported AEs during the ≤69-week extension period were eyelid ptosis (31.4%) and dry eye

Table 1 Prospective clinical trials with incobotulinumtoxinA in blepharospasm

Study design	Patients	Treatment cycles/study duration	Dose	Key efficacy outcomes
Randomized, placebo-controlled, parallel-group, multicenter, double-blind trial[9] followed by an open-label extension.[10]	Adult patients. JRS severity subscore ≥2. Previously treated with onabotulinumtoxinA. Main period: n=109. Open-label extension: n=102.	Injections permitted every ≥6 weeks. Main period: one treatment with incobotulinumtoxinA or placebo. Observation period: ≤20 weeks. Open-label extension: ≤5 incobotulinumtoxinA treatments. Total study duration: ≤89 weeks.	≤50 U per eye	Mean change in JRS severity subscore from baseline to 6 weeks post-treatment: −0.83 for incobotulinumtoxinA, +0.21 for placebo ($P<0.001$). Change in mean JRS sum scores and mean BSDI scores improved significantly from each injection visit to respective 6-week control visit ($P<0.001$ for all).
Randomized, double-blind, noninferiority, multicenter trial.[33]	Adult patients. Previously treated with onabotulinumtoxinA. n=300.	One treatment with incobotulinumtoxinA or onabotulinumtoxinA.	≤50 U per eye	Change from baseline to 3 weeks post-injectionin mean JRS sum scores: −2.90 for incobotulinumtoxinA and −2.67 for onabotulinumtoxinA ($P<0.0001$ for both). Confirmed noninferiority of incobotulinumtoxinA versus onabotulinumtoxinA.
Randomized, double-blind, parallel-group trial.[34]	Adult patients. JRS sum score >2. Previously treated with onabotulinumtoxinA. n=65.	One treatment with incobotulinumtoxinA or onabotulinumtoxinA.	≤45 U per eye	Change from baseline to 4 weeks post-injectionin mean total BSDI scores: −1.3 for incobotulinumtoxinA and −2.8 for onabotulinumtoxinA. No statistical difference between formulations.
Randomized, double-blind, split-face study.[32]	Adult patients. Previously treated with onabotulinumtoxinA. n=48.	Four treatments with incobotulinumtoxinA or onabotulinumtoxinA to either side of face.	Doses based on previous onabotulinumtoxinA treatments.	No statistical difference between formulations in BSDI ($P=0.8161$) or JRS scores ($P=0.2314$). No statistical difference between formulations in relation to patient preferences.

Abbreviations: BSDI, Blepharospasm Disability Index; JRS, Jankovic Rating Scale.

symptoms (17.6%). Investigators rated the tolerability of incobotulinumtoxinA as "good/very good" for ≥96.4% of patients after each treatment cycle.[10]

A detailed post hoc analysis of the safety of flexible incobotulinumtoxinA injection intervals included all incobotulinumtoxinA treatments that were administered at intervals of 6 to 20 weeks during the placebo-controlled main period and the open-label extension of the above trial.[12] Overall, 461 incobotulinumtoxinA treatments were analyzed; 207 (44.9%) were given at intervals <12 weeks. Irrespective of injection interval, the most frequent AEs were eyelid ptosis, dry eyes, and dry mouth. The frequency of AEs was similar for injection intervals <12 weeks and ≥12 weeks, even for intervals as short as 6 weeks, leading the authors to conclude that there were no additional safety concerns with a more frequent, patient-orientated dosing schedule.[12]

As a result of more recent randomized, controlled trials, including the incobotulinumtoxinA trial summarized here, a 2013 evidence-based review assigned level A recommendation for the treatment of blepharospasm with incobotulinumtoxinA and onabotulinumtoxinA,[13] thus superseding the previous level B recommendation of botulinum neurotoxin (BoNT) for blepharospasm by the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology.[14]

Cervical dystonia

The efficacy and safety of incobotulinumtoxinA for the treatment of CD was explored in a randomized, placebo-controlled, double-blind, single-dose trial (main period) followed by a randomized, double-blind, repeated-dose extension period in which incobotulinumtoxinA was administered at flexible intervals ≥6 weeks based on patients' needs[15,16] (Table 2). This trial included BoNT/A-treatment-naïve patients with CD as well as patients who had previously received other formulations of BoNT/A.[15]

In the main period, 233 patients with CD predominantly manifested by torticollis (head rotation) were randomized in a 1:1:1 ratio to receive one treatment with placebo, incobotulinumtoxinA 120 U, or incobotulinumtoxinA 240 U, regardless of their disease severity or previous BoNT/A treatment history. Improvements in Toronto Western Spasmodic Torticollis Rating Scale (TWSTRS)-total scores at week 4 (primary outcome) were significantly greater with incobotulinumtoxinA (120 U group, −9.9; 240 U group, −10.9) versus placebo (−2.2; $P<0.001$ for both doses versus placebo). The study was not designed or powered to detect statistically significant differences between the incobotulinumtoxinA dose groups. Secondary efficacy measures, including the change from baseline in TWSTRS-severity, -disability, and -pain subscores at week 4, were significantly improved for both incobotulinumtoxinA dose groups compared with placebo ($P\leq0.003$ for both doses and all subscores). Direct questioning about the occurrence of specific AEs revealed that the most frequently reported treatment-related AEs in the incobotulinumtoxinA groups were dysphagia, neck pain, and muscular weakness, which were mostly mild or moderate in intensity. Investigators rated the tolerability of study treatment as good/very good for 88.5% of patients in the 120 U dose group, 91.4% of patients in the 240 U dose group, and 85.1% of patients in the placebo group.[15]

Most patients (217/233) were willing to continue into the double-blind extension period, and 214 patients were rerandomized to receive either 120 U or 240 U of incobotulinumtoxinA, regardless of the main period of randomization; 169 patients completed the extension. Patients could receive up to five treatments with flexible injection intervals of ≥6 weeks over a treatment period of up to 48 weeks, followed by an observation period of up to 20 weeks.[16] Injection intervals were based upon patient request and clinical need, as assessed by a TWSTRS-total score ≥20. Throughout the extension period, both incobotulinumtoxinA doses provided statistically significant and clinically relevant improvements in mean TWSTRS-total scores, and -severity, -disability, and -pain subscores from each injection session to the respective 4-week follow-up visit ($P<0.001$ for TWSTRS-total and $P<0.05$ for all subscores). The most frequently reported adverse drug reaction for all injection intervals during the extension period was dysphagia (23.4% in the 240 U dose group and 10.7% in the 120 U dose group). After each treatment cycle, investigators rated the tolerability of incobotulinumtoxinA as good/very good for ≥92.2% of patients in the 240 U dose group and for ≥91.5% of patients in the 120 U dose group.[16]

A detailed post hoc analysis of the safety of the flexible incobotulinumtoxinA injection scheme for CD included all incobotulinumtoxinA treatments that were administered at 6- to 20-week intervals during the placebo-controlled main period and the double-blind extension of the above trial.[12] Of the 821 incobotulinumtoxinA treatment cycles included in the analysis, 369 (44.9%) were given at intervals <12 weeks. Irrespective of injection interval, the most frequent AEs were dysphagia, muscular weakness, and neck pain. The frequency of AEs was similar for incobotulinumtoxinA injection intervals <12 weeks and ≥12 weeks, even for intervals as short as 6 weeks.[12]

Table 2 Prospective clinical trials with incobotulinumtoxinA in cervical dystonia

Study design	Patients	Treatment cycles/study duration	Dose	Key efficacy outcomes
Randomized, placebo-controlled, double-blind, multicenter trial[15] followed by a randomized double-blind, repeated dose extension.[16]	Adult patients. TWSTRS-total score ≥20. Treatment-naïve and previously treated with onabotulinumtoxinA. Main period: n=233. Double-blind extension period: n=217.	Injections permitted every ≥6 weeks. Main period: one treatment with incobotulinumtoxinA or placebo. Observation period: ≤20 weeks. Extension period: ≤5 incobotulinumtoxinA treatments. Total study duration: ≤88 weeks.	Fixed doses of 120 U or 240 U incobotulinumtoxinA.	Change in TWSTRS-total score from baseline to week 4: −2.2 for placebo, −9.9 for 120 U dose, −10.9 for 240 U dose ($P<0.001$ versus placebo for both doses). Significant improvements in TWSTRS-total scores and subscores from all injection sessions to their respective 4-week follow-up visits for both doses ($P<0.05$ for all).
Open-label, single-arm, repeated dose, multicenter, real-world clinical practice study.[26]	Adult patients. Baseline TWSTRS-total score ≥25. Treatment-naïve and previously treated with BoNT. n=76.	≤5 incobotulinumtoxinA treatments. Flexible 10–24-week intervals. Study duration: 51–121 weeks.	≤50 U per injection site; total ≤300 U	Significant mean change in TWSTRS-total score from injection session one to the control visit 4 weeks later: −11.7. Maintenance of significant improvements after subsequent injection sessions.
Randomized, double-blind, active-controlled, parallel-group, multicenter, noninferiority trial.[31]	Adult patients. Baseline TWSTRS-severity score ≥10. n=463.	One treatment with incobotulinumtoxinA or onabotulinumtoxinA. Study duration: 16 weeks.	70–300 U	Change from baseline to day 28 in mean TWSTRS-severity score: −6.6 for incobotulinumtoxinA and −6.4 for onabotulinumtoxinA ($P<0.0001$ for both formulations). Confirmed noninferiority of incobotulinumtoxinA versus onabotulinumtoxinA.
Prospective, observational, multicenter, real-world clinical practice study.[24]	Adult patients with cervical dystonia or blepharospasm. Treatment-naïve and previously treated with BoNT. n=145 (cervical dystonia only, interim analysis).	Two treatments with incobotulinumtoxinA at ≥6-week intervals.	Dosing according to US prescribing information for incobotulinumtoxinA.	Interim data: total CDIP-58 scores improved significantly from baseline (46.0) to 4 weeks after the first injection (36.2; $P<0.0001$).

Abbreviations: BoNT, botulinum neurotoxin; CDIP-58, Cervical Dystonia Impact Profile; TWSTRS, Toronto Western Spasmodic Torticollis Rating Scale.

This was the first randomized trial to evaluate flexible injection intervals of BoNT/A for repeated treatment of CD in the setting of a registration trial.[16] The use of flexible injection intervals enabled treatment to be tailored to the individual patient, and of those who received more than two incobotulinumtoxinA injections in the extension period, 47.1% and 22.5% of patients had median injection intervals of ≤12 weeks and ≤10 weeks, respectively.[16] The treatment intervals observed during this trial reflect the findings of a recent patient survey, which revealed that 45.6% of patients who received abobotulinumtoxinA or onabotulinumtoxinA for the treatment of CD would prefer BoNT/A treatment at intervals of ≤10 weeks.[17]

IncobotulinumtoxinA for BoNT treatment-naïve patients with CD

A considerable proportion of patients with CD (38.6%) were naïve to BoNT prior to participation in the trial, allowing a subgroup analysis comparing incobotulinumtoxinA efficacy and safety data in patients who were naïve to BoNT with those who had previously been treated with BoNT.[18] Significant improvements from baseline in TWSTRS-total scores were observed at 4 weeks in both pretreated and BoNT-naïve patients compared with placebo ($P \leq 0.002$ versus placebo for all patients receiving either dose), confirming that incobotulinumtoxinA was effective regardless of prior BoNT treatment. In the 240 U dose group, the incidence of AEs was higher in BoNT-naïve patients (71.0%) than in previously treated patients (48.0%; statistical analyses of AE data were not included in this report). In the 120 U dose group, the incidence of AEs was similar for BoNT-naïve (54.8%) and previously treated patients (55.3%).[18]

Spasticity

The safety and efficacy of incobotulinumtoxinA in the treatment of spasticity have been explored in a randomized, double-blind, placebo-controlled, multicenter trial with an open-label extension period (total trial duration up to 89 weeks)[19,20] (Table 3). In the double-blind, placebo-controlled main period of the trial, 148 patients with post-stroke upper-limb spasticity were randomized to a single treatment session with incobotulinumtoxinA (maximum dose 400 U) or placebo and followed for ≤20 weeks. Four weeks after the injections, significantly more patients treated with incobotulinumtoxinA (68.5%) were responders (defined as an improvement of ≥1 point in the 5-point Ashworth Scale [AS] score of the wrist flexor muscles) compared with patients who received placebo (37.3%; $P<0.001$, primary efficacy outcome). Responder rates for other muscle flexor groups were also significantly improved with incobotulinumtoxinA versus placebo (4 weeks after treatment; $P<0.009$). For forearm pronators, the responder rate approached but did not reach statistical significance for incobotulinumtoxinA versus placebo ($P=0.057$). Disability Assessment Scale (DAS) scores showed significant improvements from baseline in the principal therapeutic target (dressing, limb position, hygiene, or pain) at all post-treatment visits (2, 4, 8, and 12 weeks) for incobotulinumtoxinA versus placebo ($P \leq 0.005$). The global assessment of treatment benefit of incobotulinumtoxinA was rated significantly better than placebo by investigators, patients, and caregivers ($P \leq 0.001$ for all). The proportion of patients who experienced AEs was similar in both treatment groups (28.8% for incobotulinumtoxinA and 26.7% for placebo), with most events being mild in intensity. AEs related to treatment with either incobotulinumtoxinA or placebo were feeling hot (four events); headache (three events); and one event each of dysesthesia, hypoesthesia, dysphagia, injection site pain, and injection site hematoma. Investigators rated the treatment tolerability as good/very good for 96.7% of patients, with no significant differences between the placebo and incobotulinumtoxinA treatment groups.[19]

Most patients (145/148) who participated in the placebo-controlled phase of the trial continued into the open-label extension period with up to 69-weeks' duration and received a maximum of five additional sets of incobotulinumtoxinA injections with ≥12-week intervals.[20] One hundred and twenty patients completed the extension period. Muscle tone of the wrist, elbow, finger and thumb flexors, and the forearm pronators improved significantly from each injection session to the control visit 4 weeks later (AS response rate: ≤80.6%; $P<0.0001$). Changes in the DAS score for the principal therapeutic target from each injection session to the control visit 4 weeks later were also significant for all injection intervals (response rate: ≤56.3%; $P<0.05$). Most investigators, patients, and caregivers consistently rated the efficacy of incobotulinumtoxinA as good/very good throughout the open-label period (56.3%–83.8%). Treatment-related AEs were reported in 11% of patients and included muscular weakness (3.4%), injection site pain (2.8%), dysphagia (1.4%), and pain in the extremity (1.4%). Investigators rated the tolerability of incobotulinumtoxinA as good/very good for ≥90% of patients after each treatment cycle.[20]

A prospective, randomized, Phase III, observer-blind, noninferiority trial evaluated the efficacy and safety of two dilutions of incobotulinumtoxinA (50 or 20 U/mL) in patients with upper-limb spasticity.[21] Most of the 192 patients in this

Table 3 Prospective clinical trials with incobotulinumtoxinA in spasticity

Study design	Patients	Treatment cycles/study duration	Dose	Key efficacy outcomes
Randomized, double-blind, placebo-controlled, multicenter trial[19] followed by an open-label, repeat-treatment extension.[20]	Adults patients ≥6 months post-stroke. Wrist and finger flexor AS score ≥2 and moderate disability (DAS ≥2 in the principal therapeutic target). Main period: n=148. Open-label extension period: n=145.	Injections permitted every ≥12 weeks. Main period: one treatment with incobotulinumtoxinA or placebo. Observation period: ≤20 weeks. Extension period: ≤5 incobotulinumtoxinA treatments. Total study duration: ≤89 weeks.	≤400 U	Responder rates at 4 weeks post-treatment (defined as improvement of ≥1 point in AS score of wrist flexors): 68.5% for incobotulinumtoxinA versus 37.3% for placebo ($P<0.001$). AS responder rates in all muscle groups 48.8%–80.6% after each injection session in the open-label phase.
Randomized, observer-blind, multicenter trial.[21]	Adult patients. Focal spasticity of wrist flexors or wrist flexors AS score ≥2. n=192.	One treatment with incobotulinumtoxinA. Observation period: ≤20 weeks.	≤400 U total dose 20 or 50 U/mL dilutions.	At 4 weeks post-injection, response defined as ≥1-point reduction on the DAS or ≥1-point reduction on the AS occurred in 57.6% and 62.2% of patients, respectively. The 20 U/mL dilution was noninferior to the 50 U/mL dilution.
Prospective, open-label study.[27]	Adult patients. Upper-limb post-stroke spasticity. n=20.	Multiple treatments with retreatment permitted at 12 weeks after prior treatment. Study duration: 1 year.	Total dose for first treatment: 160–450 U; total dose for last treatment: 120–350 U.	MAS scores, DAS scores, and spasm frequency were significantly reduced at all time points assessed ($P\leq0.001$ for all).
Prospective, open-label study.[28]	Adult patients. Lower-limb post-stroke spasticity. MAS=2 for ankle plantar flexor muscles. No previous botulinum toxin treatment. n=71.	One treatment. Assessments at 30 and 90 days after treatment.	25–100 U per muscle	MAS was statistically reduced at 30 days and 90 days post-treatment ($P=0.0000$ for all).
Prospective, open-label, nonrandomized study.[29]	Adult patients. Upper- and lower-limb post-stroke spasticity. AS score ≥2 for elbow, wrist, finger, and ankle flexors. n=25.	One treatment. Assessments at 30 and 90 days after treatment.	Total ≤840 U	Spasticity (AS) and pain (Visual Analog Scale) and disability (DAS) were significantly reduced at 30 days and at 90 days after injections versus baseline ($P=0.0000$ for all).

Abbreviations: AS, Ashworth Scale; DAS, Disability Assessment Scale; MAS, modified Ashworth Scale.

trial (88.0%) had post-stroke spasticity; other etiologies included cerebral palsy, multiple sclerosis, and brain injury. Clinical patterns treated included flexed wrist, flexed elbow, and clenched fist. Although dosing was flexible and adapted to patients' needs, the mean total doses injected were similar for both treatment groups. At 4 weeks post-injection, response to treatment defined as ≥1-point reduction on the DAS for the primary therapeutic target was reported in 57.6% of patients (primary efficacy outcome) and in ≥62.2% of patients when response was defined as ≥1-point reduction on the AS. Statistical analysis of the primary outcome measure showed that the 20 U/mL dilution was noninferior to the 50 U/mL dilution, suggesting that when a similar number of units was injected, a higher injection volume was not less effective than a lower injection volume. Most patients (80.2%) and investigators (89.0%) reported the patients' condition as having "mildly to very markedly" improved 4 weeks after treatment.[21]

Most clinical trials of botulinum toxin in post-stroke spasticity have been conducted in patients with chronic spasticity, usually at least 6 months after the stroke. Hesse et al conducted a randomized, single-blind, pilot study in patients with beginning elevated finger flexor tone, 4 to 6 weeks after a stroke. The 18 participants received either 150 U incobotulinumtoxinA into the finger and wrist flexors or no injections. All patients then received a comprehensive rehabilitation program. One month after treatment, the muscle tone of the finger flexors, measured on the modified AS (MAS), was significantly lower in patients who received incobotulinumtoxinA than in patients who had not received any injections. Importantly, significant incobotulinumtoxinA treatment effects were still seen 6 months after the injections. The authors concluded that early treatment with incobotulinumtoxinA could potentially reduce the development of contractures in the longer term and that further placebo-controlled studies are warranted.[22]

Phase IV and open-label studies

In their 2008 series of evidence-based reviews of BoNT treatment for movement disorders and spasticity, the American Academy of Neurology Therapeutics and Technology Assessment Subcommittee called for more research on the use of BoNT using study designs that allow for individualized choice of target muscles and doses at the investigators' discretion, which are more likely to reflect clinical practice, as well as further studies assessing the safety and efficacy of repeated and long-term injections of BoNT.[23] The committee recognized that practicability and ethical issues mean that a placebo-controlled design may not be feasible for this type of study,[14] but such data have now become available from prospective, longer-term interventional and observational incobotulinumtoxinA studies.

Blepharospasm

The recently completed large, prospective observational XCiDaBLE study (NCT01287247) was designed to collect, evaluate, and report observational data regarding the clinical use of incobotulinumtoxinA for the treatment of CD and blepharospasm in a "real-world" therapeutic setting in the US.[24,25] The trial enrolled 688 patients with blepharospasm or CD, who received two incobotulinumtoxinA treatments with dosing, treatment intervals, dilutions, target muscles, and choice of guidance techniques used at the discretion of the treating investigator. Interim analysis of data from the first 170 patients with blepharospasm confirmed the efficacy of incobotulinumtoxinA in this setting, based on significant improvements in self-administered JRS assessments 4 weeks after treatment (sum score of 4.9 versus 3.2, respectively; $P<0.0001$). In addition, 78.0% of patients reported an improvement (minimal, much or very much improved) using a 7-point Subject Global Impressions of Improvement Scale.[25] The average total dose of incobotulinumtoxinA (71.5 U) was similar to the doses administered in the pivotal Phase III trial.[9,10] Nearly all patients (96.5%) had been treated with BoNT prior to study participation. AEs were reported by eight patients and included entropion, ulcerative keratitis, contusion, dry eye, and lagophthalmos.[25]

Cervical dystonia

The XCiDaBLE study also enrolled patients with CD. In an interim analysis of data from the first 145 participants with CD, less than one-quarter (22.8%) of patients were BoNT-naïve.[24] For these patients, the mean total dose of incobotulinumtoxinA administered at their first ever BoNT treatment (159.2 U) was considerably lower than for previously treated patients (244.7 U). The mean total Cervical Dystonia Impact Profile score was significantly improved 4 weeks after the first incobotulinumtoxinA treatment compared to baseline (36.2 versus 46.0, respectively; $P<0.0001$). Based on the Subject Global Impressions of Improvement Scale, 73.7% of patients reported an improvement of their CD. Only seven patients reported any AEs, with decreased joint range of motion, musculoskeletal pain, neck pain, and localized swelling identified as definitely or probably related to treatment.[24]

A long-term, Phase IV, open-label, multicenter trial performed in Germany evaluated incobotulinumtoxinA treatment in 76 patients with CD who received five injections of incobotulinumtoxinA in a setting similar to real-world clinical practice.[26] Treatment intervals were flexible and ranged from 10 to 24 weeks, in line with the 10-week minimum interval according to the current label for incobotulinumtoxinA in Europe. Patients received individualized dosing (total dose ≤300 U) determined by the investigator based on physical and neurological examinations. The primary efficacy outcome, the mean improvement in TWSTRS-total score from injection session one (baseline) to the control visit 4 weeks later, showed significant improvements (−11.7, standard deviation 9.8; 95% confidence interval [CI] −13.9 to −9.4). Furthermore, the significant improvements in TWSTRS-total scores from baseline to the control visit 4 weeks after each injection session were maintained after the four subsequent treatments. Up to 81.6% of investigators rated the efficacy of each incobotulinumtoxinA injection session as good/very good, while up to 78.9% of patients rated their response to treatment as "improved." The mean total doses ranged from 151.4 U at injection session one to 192.2 U at injection session five. For each treatment cycle, the most common AEs were dysphagia (≤18%), nasopharyngitis (≤17%), and headache (≤22%).[26]

Spasticity

The positive safety and efficacy profile of incobotulinumtoxinA in post-stroke spasticity Phase III clinical trials has been consistently demonstrated in subsequent prospective, open-label studies. One of these studies explored the safety and efficacy of incobotulinumtoxinA in upper-limb post-stroke spasticity over a 1-year period in 20 patients who could receive retreatment every 12 weeks.[27] One year after the initial incobotulinumtoxinA treatment, muscle tone, determined using the MAS, was significantly reduced in all muscle groups treated ($P<0.001$). In addition, DAS scores and daily spasm frequency were also significantly reduced ($P<0.001$ for all). The authors reported no AEs in these patients.[27]

While incobotulinumtoxinA is, according to the European product label, currently approved for treating post-stroke spasticity of the upper limb, the use of incobotulinumtoxinA to treat lower-limb spasticity has also been described. In an open-label study, 71 BoNT/A-naïve patients with post-stroke spasticity in their ankle plantar flexor muscles received incobotulinumtoxinA treatment (dose range 25–100 U for each muscle; maximum total dose 180 U), leading to significant improvements in muscle tone, rated by MAS assessed at 30 days and 90 days after treatment ($P=0.0000$ for both time points).[28] In addition, there was a significant reduction in the frequency of spasms at 30 days and 90 days after treatment ($P\leq0.0001$ for both time points). Both patients and investigators considered treatment with incobotulinumtoxinA to be effective. Two weeks after treatment, AEs were reported by eight (11%) patients (injection site pain, n=3; muscular weakness, n=5), which were all mild in intensity and resolved shortly after the treatment.[28]

The European incobotulinumtoxinA product label recommends a maximum dose of 400 U for the treatment of upper-limb post-stroke spasticity. However, higher doses of incobotulinumtoxinA were recently evaluated in two different studies.[29,30]

In a prospective, open-label study, 25 consecutive patients with upper- and lower-limb post-stroke spasticity received up to 840 U of incobotulinumtoxinA.[29] At 30 days after treatment, muscle tone (measured on the AS), pain (measured on a Visual Analog Scale), and disability (measured on the DAS) were significantly reduced compared with baseline ($P=0.0000$ for all). IncobotulinumtoxinA treatment effects were still significant at 90 days of follow-up ($P=0.0000$ for all). AEs, monitored 2 weeks after treatment, were reported in four (16%) patients (injection site pain in one patient and muscular weakness in four patients) and were mild in intensity, resolving within days of the injection.[29] However, as a major limitation, the report does not detail whether muscular weakness in these patients was focal or generalized, which could be an indication of systemic spread of BoNT.

In a noninterventional study, Dressler et al evaluated safety outcomes in a randomly selected population of 130 patients with dystonia or spasticity. Patients who had received incobotulinumtoxinA as "high-dose" therapy (n=100, single dose ≥400 U) were compared to patients who had received "regular-dose" therapy (n=30, single dose ≤200 U).[30] Outcomes assessed included a systemic toxicity patient questionnaire, neurological examination for motor or autonomic systemic adverse effects, laboratory screening, and the occurrence of antibody-induced treatment failure. Patients in the high-dose group received 400–1,200 U of incobotulinumtoxinA (mean 570.1 U) during four to 37 treatment cycles (mean 10.2 cycles). In the low-dose group, patients were treated with 60–200 U of incobotulinumtoxinA (mean 153.2 U) during four to 63 treatment cycles (mean 11.8 cycles). The systemic toxicity questionnaire and neurological examinations did not show any signs of motor or autonomic dysfunction distant from the target muscles that were

attributable to incobotulinumtoxinA treatment; laboratory screening did not reveal any remarkable abnormalities, and no patient developed secondary treatment failure. The authors concluded that further studies are required to explore the threshold dose of incobotulinumtoxinA for clinically detectable systemic toxicity.[30]

Trials of incobotulinumtoxinA with active comparator control

IncobotulinumtoxinA and onabotulinumtoxinA have been investigated in several randomized, double-blind, head-to-head trials in patients with CD or blepharospasm, respectively (Tables 1 and 2). None of these trials identified differences in the efficacy of incobotulinumtoxinA and onabotulinumtoxinA with regard to the respective primary outcome measure or clinically relevant differences in the AE profile of the formulations.[3,31–34]

Blepharospasm

In a large Phase III head-to-head trial, the efficacy and safety of incobotulinumtoxinA and onabotulinumtoxinA were explored in patients (n=300) with blepharospasm who had received at least two previous onabotulinumtoxinA injections.[33] Doses administered were based on those the patients had received at their previous two onabotulinumtoxinA treatments; the maximum dose per eye was 50 U. At 3 weeks after treatment, patients in both treatment groups had significant improvements from baseline in all efficacy variables assessed ($P<0.0001$, all variables for both treatment groups). The primary efficacy variable was the change from baseline in JRS sum score (adjusted mean change: incobotulinumtoxinA, −2.90; onabotulinumtoxinA, −2.67). The least-square mean difference between the treatment groups was −0.23 (95% CI −0.68 to 0.22), confirming noninferiority of incobotulinumtoxinA to onabotulinumtoxinA because the upper confidence limit of the mean treatment difference (0.22) was below the predefined noninferiority margin $\Delta=0.8$. In addition, the CI of the mean difference was within the predefined equivalence range (−0.8 to 0.8), showing that, in the administered dose range at a 1:1 unit dosing ratio, incobotulinumtoxinA and onabotulinumtoxinA were therapeutically equivalent in treating blepharospasm.

Furthermore, no statistically significant difference was evident between the treatments for any of the secondary efficacy outcomes assessed, including BSDI and patient and investigator global assessments of efficacy. The time to onset of effect, waning of effect, and duration of treatment effect (median of 110 days for both treatment groups) were similar between incobotulinumtoxinA and onabotulinumtoxinA. Both treatments were well tolerated, and the most common AEs were ptosis (6.1% and 4.5%), abnormal vision (1.4% and 3.2%), and back pain (1.4% and 2.6%) in the incobotulinumtoxinA and onabotulinumtoxinA groups, respectively.[33]

In another head-to-head, double-blind, randomized trial of incobotulinumtoxinA and onabotulinumtoxinA in 65 patients with blepharospasm, both formulations reduced total BSDI scores at 4 weeks (primary endpoint) and 8 weeks after treatment.[34] After 4 weeks, the mean improvement in total BSDI score was not significantly different between the incobotulinumtoxinA group (1.3 points) and the onabotulinumtoxinA group (2.8 points). Secondary efficacy outcomes, including JRS assessments and Patient Global Assessment of efficacy, showed improvements at 4 weeks after treatment in both groups, without significant differences between the treatment groups. The duration of treatment effect did not differ between treatment groups (median of 13 weeks for both groups). An additional post hoc responder analysis in 43 patients with a baseline total BSDI score ≥4 showed differences between the two formulations in favor of onabotulinumtoxinA (responders were defined as patients with ≥4-point reduction in the total BSDI score 4 weeks after treatment). Both treatments were well tolerated and the proportion of patients in each treatment group who reported AEs did not differ significantly. The most commonly reported AEs were periorbital hematoma, headache, and eyelid ptosis.[34]

Another direct comparison of incobotulinumtoxinA and onabotulinumtoxinA was made in a prospective, randomized, double-blind, split-face trial in 48 patients who had previously received onabotulinumtoxinA treatment for blepharospasm (Table 1).[32] Patients received four injections of each formulation to either side of the face, using the same number of dose units for incobotulinumtoxinA and onabotulinumtoxinA. No significant difference was found between incobotulinumtoxinA and onabotulinumtoxinA in the changes from baseline in BSDI scores ($P=0.8161$) or JRS scores ($P=0.2314$). Patients did not show a preference for one formulation over the other.[32]

Cervical dystonia

In a Phase III, head-to-head trial, 463 patients with moderate to severe CD were randomized and received one treatment with 70–300 U of incobotulinumtoxinA or onabotulinumtoxinA.[31] All patients had previously received onabotulinumtoxinA, and the dose of incobotulinumtoxinA was based on the onabotulinumtoxinA doses given at the last two treatments before the trial. At the day 28 control visit, the

TWSTRS-severity score had improved by a mean −6.6 points in the incobotulinumtoxinA and a mean −6.4 points in the onabotulinumtoxinA group (primary efficacy outcome). The least-square mean difference between the treatment groups was −0.33 (95% CI −1.05 to 0.38). The study confirmed noninferiority of incobotulinumtoxinA to onabotulinumtoxinA as the upper confidence limit of the mean treatment difference (0.38) was below the predefined noninferiority margin Δ=1.3. In addition, the CI of the mean difference was within the predefined equivalence range (−1.3 to 1.3), showing that incobotulinumtoxinA and onabotulinumtoxinA were therapeutically equivalent in treating CD at a 1:1 unit dosing ratio in the administered dose range.

There were no significant differences in any secondary efficacy outcomes assessed, including TWSTRS-pain subscores at the control and final visits. The time to onset of effect, waning of effect, and duration of treatment effect (median of 110 days for incobotulinumtoxinA and 109.5 days for onabotulinumtoxinA) were also similar for both groups. The most frequent AEs were dysphagia and skeletal pain in both treatment groups, occurring in 10.8% and 3.5% of patients in the incobotulinumtoxinA group and 8.2% and 2.2% of patients in the onabotulinumtoxinA group, respectively.[31]

Switching between formulations

A prospective, open-label, cross-over study of 40 patients with CD explored the duration of BoNT/A treatment effect and injection intervals for at least four treatments after switching from onabotulinumtoxinA to incobotulinumtoxinA in a 1:1 dosing ratio.[35] The mean duration of treatment effect was similar for both formulations (11.2 weeks for onabotulinumtoxinA and 11.4 weeks for incobotulinumtoxinA). The mean interval between injections was 14.7 weeks for onabotulinumtoxinA and 15.0 weeks for incobotulinumtoxinA, which confirmed the equivalent efficacy of both formulations administered at the 1:1 dose ratio, at an average dose of 296 U incobotulinumtoxinA or onabotulinumtoxinA per treatment.[35]

Switching from abobotulinumtoxinA to incobotulinumtoxinA has been described in a recent chart review.[36] A total of 257 patients with focal dystonia (CD, blepharospasm, hemifacial spasm, or segmental/generalized dystonia) were switched from established abobotulinumtoxinA therapy to incobotulinumtoxinA at a 4:1 unit ratio, and 251 patients were followed for at least 1 year after the switch (52–219 weeks, a mean of 8.3 injection cycles). After switching, incobotulinumtoxinA dose requirements and treatment intervals (mean interval 12.9 weeks) remained stable throughout the follow-up period. Most patients (84.1%) rated the efficacy of incobotulinumtoxinA injections as "excellent/very good" and 93.6% rated the duration of its treatment effect as "excellent/good." IncobotulinumtoxinA was generally well tolerated, with 45 patients reporting injection-site pain and four patients reporting bruising throughout the follow-up period. The authors also reported that in their clinic, switching from abobotulinumtoxinA to incobotulinumtoxinA was associated with a reduction in the mean expenditure for botulinum toxin per patient per year to 76.7% of the cost prior to switching.[36]

Analysis of patient preferences of patients with blepharospasm who switched between BoNT/A formulations showed that, overall, patients perceived the different formulations as being equivalent. A recent retrospective review of 128 patients who received onabotulinumtoxinA treatment for blepharospasm included 50 patients who were switched to treatment with incobotulinumtoxinA.[37] The proportion of patients who preferred incobotulinumtoxinA (52%) was similar to the proportion that preferred onabotulinumtoxinA (48%). Intriguingly, the reasons patients gave for their preferences were similar for patients who preferred incobotulinumtoxinA and those who preferred onabotulinumtoxinA. The reasons for a preference for incobotulinumtoxinA (26 patients) included "overall more effective" (n=10); "longer duration" (n=9); "faster effect" (n=5); and "less dry eye symptoms" (n=4). The reasons for a preference for onabotulinumtoxinA (24 patients) included longer duration (n=11); overall more effective (n=10); and less dry eye symptoms (n=4).[37]

Immunological findings with incobotulinumtoxinA

Due to its high specific biological activity, incobotulinumtoxinA may be associated with a low risk of immunogenicity. Immunological testing using a highly sensitive mouse hemidiaphragm assay[38] in the Phase III clinical trials program in blepharospasm, CD, and spasticity showed that no treatment-naïve patients developed new neutralizing antibodies while being treated with incobotulinumtoxinA.[9,10,15,16,19,20] Notably, in the Phase III blepharospasm and CD trials, patients could receive up to six treatments at flexible ≥6-week injection intervals based on patient needs, and in both of these trials, 44.9% of treatments were administered at intervals <12 weeks,[12] more frequently than currently recommended for any BoNT/A formulation.

In the Phase IV trial of 76 patients with CD, no patient developed new neutralizing antibodies during the course of

the trial based on testing using the mouse hemidiaphragm assay. Three patients had neutralizing antibodies at screening (prior to treatment with incobotulinumtoxinA), two of whom experienced no loss of treatment effect (defined by an improvement in TWSTRS-total score 4 weeks after repeated injections of incobotulinumtoxinA), while a third patient did experience a loss of treatment effect after the second and subsequent incobotulinumtoxinA injections.[26]

In a prospective, blinded cohort study, 37 patients with CD who had developed neutralizing antibodies and partial secondary nonresponse to prior therapy with abobotulinumtoxinA or onabotulinumtoxinA received continuous treatment with incobotulinumtoxinA for up to 50 months. Ten patients (27%) in this cohort of patients with evidence of preexisting neutralizing antibodies had a transient increase in titers of such antibodies in the first 24 months of treatment with incobotulinumtoxinA. However, for the majority of patients (84%), antibody titers declined to levels below the initial titer ($P<0.001$). At the end of the study, tests for neutralizing antibodies were either negative or below the lower detection limit in 23 patients (62%). However, it is unclear if the patients whose antibody titers decreased regained complete treatment benefit.[39]

Further studies are required to explore the association of low titers of neutralizing antibodies with clinical response to BoNT/A treatment and the potential of incobotulinumtoxinA for patients who developed secondary nonresponse after treatment with other formulations. Longer-term observations in a larger number of patients are required to further characterize the immunological properties of incobotulinumtoxinA.

Current research and future directions

Ongoing clinical trials in approved indications

Ongoing Phase III and IV trials will add to the body of evidence for incobotulinumtoxinA in the currently approved indications of CD, blepharospasm, and spasticity. The CD-FLEX study (NCT01486264) investigates the efficacy of shorter treatment intervals compared with standard treatment intervals for the treatment of CD. A randomized, placebo-controlled Phase III trial is currently being conducted in Europe and Asia to substantiate the incobotulinumtoxinA efficacy and safety database in the blepharospasm indication (NCT01896895). In the spasticity indication, a placebo-controlled Phase III trial investigating incobotulinumtoxinA for treating post-stroke upper-limb spasticity has recently been completed (PURE trial, NCT01392300), and a placebo-controlled Phase III trial in lower-limb spasticity after stroke is currently ongoing (PLUS trial, NCT01464307). The TOWER trial (NCT01603459) explores the safety and efficacy of titrated doses of incobotulinumtoxinA (up to 800 U) for the treatment of upper- and lower-limb spasticity in patients who are deemed to require higher doses than those currently approved. The trial enrolled 150 patients at 33 sites throughout Europe, Canada, and the US. In addition, the Spasticity in Practice (SPACE) noninterventional study is ongoing and designed to explore BoNT/A use (including incobotulinumtoxinA and other formulations) in an open-label, observational setting in BoNT/A-naïve patients with spasticity.

Other indications

A large clinical trial program consisting of three Phase III trials will explore the safety and efficacy of incobotulinumtoxinA in the pediatric setting (NCT01893411, NCT02002884, and NCT01905683). These trials are enrolling children and adolescents with lower-limb spasticity and combined lower- and upper-limb spasticity due to cerebral palsy. Three placebo-controlled Phase II or III trials investigating incobotulinumtoxinA for troublesome sialorrhea (hypersalivation) are ongoing in adults with various neurological conditions (NCT02091739), adults with Parkinson's disease/parkinsonism (NCT01653132), and in children and adolescents (2–17 years of age) with neurological disorders and/or intellectual disability (NCT02270736). Ongoing pilot studies are also underway in other indications, such as plantar fasciitis (NCT01678001); restless leg syndrome (NCT01931878); focal cancer pain after surgery and/or radiation (NCT01931865); and rosacea (NCT01614743). In addition, a Phase II multicenter trial of incobotulinumtoxinA for the treatment of moderate to marked essential tremor of the upper limb, using quantitative tremor recordings to guide injections, has recently begun recruiting (NCT02207946). Another randomized, placebo-controlled Phase II trial will assess incobotulinumtoxinA as a treatment for focal task-specific dystonia of the musician's hand (NCT02107261).

Discussion and conclusion

IncobotulinumtoxinA is a well-tolerated therapy with proven efficacy in the treatment of blepharospasm, CD, and spasticity. Recent surveys of patients with CD or post-stroke spasticity reveal that many patients would prefer to receive BoNT treatment at intervals ≤10 weeks.[17,40] However, there is a lack of clinical trial data with treatment intervals ≤12 weeks.

The incobotulinumtoxinA registration trials in blepharospasm and CD permitted flexible injection intervals ≥6 weeks that could be adapted to patients' clinical needs. The trials with an overall duration of maximal 89 weeks showed that dosing intervals shorter than the recommended minimum interval of 12 weeks (as short as 6 weeks) were well tolerated and not associated with increased safety concerns, allowing a more patient-orientated treatment approach with incobotulinumtoxinA. In the spasticity indication, many patients with complex multifocal spasticity require higher BoNT doses than those that are currently recommended, and the TOWER trial is investigating the safety of high-dose therapy in this patient population.

Further studies are underway to investigate incobotulinumtoxinA in not yet systematically evaluated clinical indications. For instance, clinical trials are ongoing for incobotulinumtoxinA in the treatment of children with spasticity, and in children and adults with sialorrhea.

Large head-to-head trials and physician experience support the therapeutic equivalence of incobotulinumtoxinA and onabotulinumtoxinA. Patients who are switched from one botulinum toxin formulation to another report no difference in preference for one formulation over another, citing efficacy and duration of effect as being equivalent between formulations.

Treatment with incobotulinumtoxinA did not trigger the new development of neutralizing antibodies in any of the patients during the Phase III and IV trials. However, longer-term data from a large number of patients are required to further explore the immunogenic potential of incobotulinumtoxinA.

Currently, large observational studies are collecting data on how incobotulinumtoxinA and other BoNT/A formulations are used to treat blepharospasm, CD, and spasticity in daily clinical practice. These observational studies incorporate patients in a real-world setting, accumulating evidence on administration and outcomes for patients for whom physicians have chosen BoNT/A therapy outside the confines of a clinical trial setting. Data from these studies will aid physicians in optimizing treatment for their patients by tailoring the choice of formulation, dose, and treatment intervals to suit the patient's individual symptoms.

Acknowledgments

Merz Pharmaceuticals had the opportunity to review the manuscript from a medical and data accuracy perspective. Editorial support was provided by Rhian Harper Owen, PhD, on behalf of Complete Medical Communications and financed by Merz Pharmaceuticals.

Disclosure

WHJ received speaker honoraria and is a consultant for Pharm Allergan, Ipsen Pharma, and Merz Pharmaceuticals. RB and DH report no conflicts of interest in this work. JJ received research grants from Allergan, Inc., Ipsen Pharma, and Merz Pharmaceuticals, and served as a consultant for Allergan, Inc. and Merz Pharmaceuticals. PK has received honoraria for lectures and training from Medtronic, Abbvie, Merz Pharmaceuticals, Ipsen Pharma, Allergan, and Novartis, and has received commercial support for research from Biogen, Medtronic, and Ipsen Pharma. PR received research funding to his university from Merz Pharmaceuticals and Allergan, Inc. DMS received research grants from and served as a consultant for Allergan, Inc., Ipsen Pharma, and Merz Pharmaceuticals. CLC received research funding to her university from Merz Pharmaceuticals, Allergan, Inc., and Ipsen Pharma. She received consulting fees from Merz Pharmaceuticals, Allergan, Inc., Ipsen Pharma, and Medtronic. The authors report no other conflicts of interest in this work.

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