



Spasticity in practice (SPACE): an international non-interventional study of botulinum neurotoxin type-A in treatment-naïve subjects with spasticity

Julian Harriss¹, Nicolas Roche², Carlos Cantú-Brito³, Svetlana Khatkova⁴, Patrik Säterö⁵, Susanne Heitmann⁶, Olivier Simon⁷, Christine Kliebe-Frisch⁸, Georg Comes⁸, Wolfgang H. Jost^{9,10}

¹IRMA: Independent Rehabilitation Medicine Assessment, London, United Kingdom

²Hôpital Raymond Poincaré, Garches, France

³Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico City, Mexico

⁴Federal State Hospital for Treatment and Rehabilitation, Ministry of Health, Moscow, Russia

⁵Sahlgrenska Universitetssjukhuset/Högsbo, Göteborg, Sweden

⁶DKD HELIOS clinic Wiesbaden, Wiesbaden, Germany

⁷formerly of Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany

⁸Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany

⁹Parkinson-Klinik Ortenau, Wolfach, Germany

¹⁰University of Freiburg, Freiburg/Breisgau, Germany

ABSTRACT

Aim of the study. SPACE, a prospective, non-interventional, open-label, multinational study, investigated physicians' and subjects' assessment of safety, efficacy, and health-related quality of life (HRQoL) following botulinum neurotoxin type-A (BoNT-A) treatment to understand real-world clinical usage for the management of focal and multifocal spasticity.

Clinical rationale for the study. Treatment guidelines recommend the use of BoNT-A for the management of spasticity in adults. This study assessed how physicians use BoNT-A therapy in real-world clinical practice, and provided evidence on long-term safety and efficacy over a period of up to 2 years.

Materials and methods. BoNT treatment-naïve adults with spasticity of any aetiology received any BoNT-A formulation at their physician's discretion, and were observed for ≤ 8 treatment cycles (≤ 2 years). Daily practice information, physician's global assessments of tolerability and efficacy, and HRQoL were documented. Incidences of adverse drug reactions or all adverse events were documented for non-Mexican subjects and for Mexican subjects, respectively, due to protocol differences based on local regulatory requirements.

Results. A total of 701 subjects were enrolled (safety population; nine countries). Physicians rated the tolerability of BoNT-A as 'very good' or 'good' for 88.2–97.4% of subjects throughout the study (subject numbers declined throughout this non-interventional study). Adverse drug reactions were reported for 16/600 (2.7%) of the non-Mexican subjects, with two considered to be 'definitely related' to treatment (injection-site haematoma, n = 1; botulism, n = 1). For 687 subjects, efficacy was rated 'very good' or 'good' by most physicians and subjects. Improvements in HRQoL were observed.

Conclusions and clinical implications. Throughout this 2-year study, BoNT-A treatment was generally well-tolerated, effective, and associated with an improved HRQoL. This study makes a valuable contribution to the broader understanding of how physicians use BoNT-A therapy to manage spasticity in real-world clinical practice.

Key words: botulinum neurotoxin A, rehabilitation, muscle spasticity, quality of life

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Address for correspondence: Dr Julian Harriss, IRMA, 10 Oakway, Bromley, BR2 0LJ, United Kingdom, e-mail: jharriss@doctors.org.uk

Introduction

European and US treatment guidelines and consensus statements recommend intramuscular botulinum neurotoxin type-A (BoNT-A) injections for the management of spasticity in adults [1–4]. At the time when this study was being conducted, three BoNT-A formulations were commercially available in North America and Europe: incobotulinumtoxinA (Xeomin[®]; Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany) [5, 6], onabotulinumtoxinA (Botox[®]; Allergan Inc., Irvine, CA, USA) [7, 8], and abobotulinumtoxinA (Dysport[®]; Ipsen Ltd, Boulogne-Billancourt, France) [9, 10]. Multiple controlled clinical trials have demonstrated the safety and efficacy of repeated BoNT-A injections for focal and multifocal spasticity [11–20]. However, less data exist regarding the long-term safety and efficacy outcomes in real-world clinical practice in subjects with spasticity [21–24].

The SPasticity in PractICE (SPACE) study is one of the most extensive non-interventional studies of BoNT-A in spasticity to date, enrolling subjects with spasticity of any aetiology and allowing the treatment of upper- and lower-limb spasticity simultaneously, according to the local approval status of the BoNT-A formulation and clinical setting in participating countries. The study was designed to investigate physicians' and subjects' assessment of safety, efficacy, and health-related quality of life (HRQoL) following BoNT-A treatment of treatment-naïve subjects in routine clinical practice, by collecting data on subjects' disease course and treatments, the treating physicians, and their treatment preferences.

Clinical rationale for the study

With a paucity of data on the long-term safety and efficacy outcomes related to everyday use of BoNT-A in subjects with spasticity, the primary objective of this study was to investigate physicians' and subjects' assessment of safety, efficacy, and HRQoL in treatment-naïve subjects with multifocal spasticity who received BoNT-A in routine, real-world clinical practice over a treatment period of ≤ 2 years.

Materials and methods

Study design and participants

SPACE was a prospective, non-interventional, open-label, multicentre study conducted in nine countries: Canada, France, Germany, Italy, Mexico, Russia, Spain, Sweden, and the UK. Subjects ≥ 18 years of age were eligible if they had spasticity of any aetiology requiring BoNT-A injections and had never previously received BoNT-A or -B for any indication. Subjects were also required to have sufficient understanding of the primary local language to complete the study questionnaires and provide informed consent. Subjects already participating in an interventional study, or who were planning to participate in a study involving BoNT-A treatment, were ineligible.

Subjects could receive treatment for ≤ 2 years with any BoNT-A product available in their country, i.e. incobotulinumtoxinA, onabotulinumtoxinA or abobotulinumtoxinA, according to the local product approval status and the individual subject's needs, at the treating physician's discretion. Therefore, the visit schedule comprised ≤ 8 injection visits (treatment cycles) at intervals > 3 months, plus a final visit with no injection in subjects who returned for assessment at the end of the study. Doses (total and per-muscle), injection sites, injection techniques, and treatment intervals were determined by each physician based on clinical need.

The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with local regulatory requirements. Study documents were reviewed and approved by Ethics Committees and regulatory authorities according to local requirements in the participating countries. Subjects had to provide written informed consent, in the local language, for the use of their data or, if unable to sign the consent form, could consent verbally in the presence of a witness. The study protocol was registered with the Verband Forschender Pharma-Unternehmen Deutschland (the Association of Pharmaceutical Research Companies of Germany), https://www.vfa.de/de/arzneimittel-forschung/datenbanken-zu-arzneimitteln/nisdb/nis-details/_533.

Daily practice information

Information was captured on participating subjects, including history and current spasticity status (e.g. aetiology, topography, patterns of spasticity), details of each BoNT-A treatment (BoNT-A formulation used, muscles treated, injection sites/muscle, assessment scales used, injection guidance [e.g. electromyography with or without electrostimulation, ultrasound]), and concomitant treatment.

Data were also collected on treating physicians, including their medical speciality, years in clinical practice, previous experience with BoNT-A, and opinions on dosages.

Safety

Physicians rated each subject's tolerability of the medication at the end of each treatment cycle (i.e. at the next injection visit) on a 4-point scale from 1 (very good) to 4 (poor).

The incidence of adverse drug reactions (ADRs, defined as adverse events [AEs] for which a causal relationship to treatment cannot be excluded) was reported for all subjects enrolled, including subjects with no record of the BoNT-A product administered at the first injection, but for whom product data had been recorded at subsequent injections. In Mexico, due to local regulatory requirements, the incidence of all AEs (serious and non-serious, related or not), including ADRs, was recorded using a specific ADR/AE reporting form. As non-related AEs were recorded in addition to ADRs in Mexico, these were analysed separately from ADRs in non-Mexican countries.

Global assessment of efficacy

Physicians could document treatment efficacy using various impairment- or function-based scales (e.g. Ashworth Scale, Tardieu Scale, Rivermead Scale, Functional Ambulation Classification Scale). However, in this diverse, multinational study population, efficacy assessments were not consistently performed by all physicians in routine clinical practice. Therefore, global assessments of efficacy relevant to real-world clinical practice were assessed, and are reported here.

Physicians and subjects rated the efficacy of each treatment at the end of each treatment cycle (i.e. at the next injection visit) on a 4-point scale from 1 (very good) to 4 (poor). Responders were subjects with a score ≤ 3 (at least moderate efficacy).

HRQoL

HRQoL was assessed using the EuroQoL 5-dimension questionnaire (EQ-5D) visual analogue scale (VAS) [25], completed by the subjects at their study centres during each injection visit and at home 4 weeks post injection (i.e. during the assumed peak effect of treatment [26]). Subjects rated their current state of health on a quantitative scale from 0 (the worst imaginable) to 100 (the best imaginable).

Subjects also selected the statement that best described their state of health on that day using the five dimensions of the EQ-5D descriptive system (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), and completed the 12-item Short-Form (SF-12) Health Survey to describe their perceived state of health (see Supplemental Methods).

Statistical analysis

Study data were summarised using descriptive statistics. All subjects enrolled were analysed for safety. All subjects with an available date of written informed consent and recorded information about the BoNT-A product administered at the first injection were analysed for efficacy and HRQoL. Subjects with no reported BoNT-A product at their first injection, who could not therefore be assigned to a treatment group (incobotulinumtoxinA, onabotulinumtoxinA, or abobotulinumtoxinA), were excluded from the efficacy and HRQoL analyses. Missing values were not imputed, and all analyses were conducted on observed cases.

Two post-hoc analyses were performed. One assessed differences in the proportion of non-Mexican subjects with ≥ 1 ADR or serious ADR (SADR) between treatment groups using Fisher's exact test. Another post-hoc analysis assessed change from Visit 1 (baseline) in EQ-5D VAS score using the Wilcoxon signed rank test; in this analysis, data following a switch between treatment groups was excluded.

Results

Daily practice information

Subjects

A total of 701 subjects were evaluated for safety; efficacy and HRQoL outcomes were assessed in 687 subjects with an available date of written consent and reported BoNT-A product administered at the first injection (Supplemental Fig. 1). Subjects' mean (standard deviation [SD]) age was 55.0 (15.5) years, and 61.3% were male (Tab. 1). The median (range) time since onset of spastic symptoms was 2.0 (0–79) years. Most participants had post-stroke spasticity and paresis most commonly presented as hemiplegia. At least one relevant concomitant medication was documented for 36.8% of subjects, among which antithrombotic agents (15.6%), muscle relaxants (13.4%), and lipid-modifying agents (13.0%) were the most frequently documented. At least one concomitant therapy was documented in 23.7% of subjects, with physiotherapy (20.7%) and occupational therapy (12.7%) the most frequently documented.

Overall, 205/701 (29.2%) subjects formally discontinued from the study prematurely, including four with no reported BoNT-A product at their first injection (Supplemental Fig. 1). The main reasons for discontinuation were: loss to follow-up (74/701, 10.6%), lack of efficacy (28/701, 4.0%), and another undocumented reason (79/701, 11.3%). The proportion of subjects attending at each injection visit also decreased throughout the study (Supplemental Tab. 1), although reasons were not documented.

The median (interquartile range; IQR) injection interval ranged from 3.5 (3.0–4.6) months at Visit 2 to 3.2 (3.0–3.7) months at Visit 8, with 22.8 (21.4–26.3) months between the first and last injections. The most frequently injected upper-limb muscles at Visit 1 were the flexor digitorum superficialis, biceps brachii, and flexor digitorum profundus (Supplemental Fig. 2a). The most frequently injected lower-limb muscles were the gastrocnemius caput mediale, soleus, gastrocnemius caput laterale, and tibialis posterior (Supplemental Fig. 2c). These remained among the most frequently injected muscles at Visit 8 (Supplemental Fig. 2b and d).

The median (IQR) total incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA doses administered at Visit 1 were 30 (20, 50) U, 50 (40, 75) U, and 125 (100, 200) U. Median doses administered into the most frequently injected muscles at Visit 1 are summarised in Table 1. The treating physician performed the BoNT-A injection for most subjects (67.9% of those with data recorded; 411/605) at Visit 1.

For 40.5% of subjects with data recorded, injections were administered without the use of guidance techniques at Visit 1 (47.6%, 19.0%, and 37.5% with incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, respectively). Electrostimulation was used in 18.6% (17.4%, 23.9%, and 16.3%, respectively), electromyography in 14.8% (12.4%, 17.6%, and

Table 1. Subject baseline demographics and characteristics

Characteristic	Incobotulinum-toxinA n = 465	Onabotulinum-toxinA n = 142	Abobotulinum-toxinA n = 80	Study population n = 687
Male sex, n (%)	283 (60.9)	83 (58.5)	55 (68.8)	421 (61.3)
Age, years; mean (SD)	54.6 (15.6)	55.6 (15.3)	56.2 (15.3)	55.0 (15.5)
BMI, kg/m ² ; mean (SD)	25.8 (5.1)	25.6 (5.7)	25.7 (4.6)	25.7 (5.1)
Time since spasticity-causing event, years; median (range)	2.0 (0–63)	2.0 (0–52)	2.0 (0–55)	2.0 (0–63)
Time since onset of spastic symptoms, years; median (range)	2.0 (0–59)	2.0 (0–51)	2.0 (0–79)	2.0 (0–79)
Aetiology of spasticity, n (%)^a				
Stroke	310 (66.7)	85 (59.9)	49 (61.3)	444 (64.6)
Brain injury	33 (7.1)	4 (2.8)	4 (5.0)	41 (6.0)
Multiple sclerosis	36 (7.7)	19 (13.4)	9 (11.3)	64 (9.3)
Spinal-cord injury	19 (4.1)	8 (5.6)	3 (3.8)	30 (4.4)
Cerebral palsy	10 (2.2)	4 (2.8)	4 (5.0)	18 (2.6)
Other	48 (10.3)	18 (12.7)	11 (13.8)	77 (11.2)
Missing	2 (0.4)	0	0	2 (0.3)
Topographical distribution of paresis, n (%)				
Hemiplegia	377 (81.1)	106 (74.6)	58 (72.5)	541 (78.7)
Diplegia	44 (9.5)	23 (16.2)	12 (15.0)	79 (11.5)
Quadriplegia	41 (8.8)	9 (6.3)	8 (10.0)	58 (8.4)
Missing	3 (0.6)	4 (2.8)	2 (2.5)	9 (1.3)
BoNT-A dose in most frequently injected muscles at Visit 1, median (IQR)				
Overall, median (IQR) [n]	30 (20, 50) [2,899]	50 (40, 75) [676]	125 (100, 200) [476]	NA
Upper limb				NA
Flexor digitorum superficialis; L, R	30 (25, 50), 30 (25, 50)	55 (40, 77.5), 60 (50, 75)	175 (100, 250), 150 (100, 200)	
Biceps brachii; L, R	60 (40, 75), 50 (40, 75)	50 (50, 75), 55 (50, 77.5)	225 (150, 300), 150 (100, 200)	
Flexor digitorum profundus; L, R	30 (20, 40), 25 (20, 40)	50 (50, 70), 50 (50, 60)	150 (100, 200), 100 (50, 200)	
Lower limb				NA
Gastrocnemius caput mediale; L, R	50 (40, 55), 50 (35, 50)	50 (40, 75), 50 (40, 75)	150 (100, 250), 125 (100, 150)	
Soleus; L, R	50 (40, 70), 50 (50, 75)	60 (50, 85), 70 (50, 80)	200 (150, 200), 150 (125, 200)	
Gastrocnemius caput laterale; L, R	50 (40, 50), 50 (35, 50)	50 (40, 75), 50 (40, 75)	100 (80, 125), 125 (50, 150)	

^aMultiple entries were possible. Percentages based on total subject populations

BMI — body mass index; BoNT-A — botulinum neurotoxin type-A; IQR — interquartile range; L — left; n — number of observations; N — total number of subjects; NA — not applicable; R — right; SD — standard deviation; U — units

23.8%, respectively), and ultrasound in 13.6% (14.6%, 11.3%, and 12.5%, respectively) of subjects.

Physicians

Of the 171 participating physicians, 54 (31.6%) were from Germany, 33 (19.3%) from France, 28 (16.4%) from Italy, 14 (8.2%) from the UK, 11 (6.4%) from Russia, 11 (6.4%) from Spain, 10 (5.8%) from Canada, seven (4.1%) from Mexico, and three (1.8%) from Sweden. Most were neurologists (47.4%) or physiatrists (28.1%). The physicians had a mean (SD) of 15.7 (8.7) years of experience in medical practice and a mean (SD) of 9.2 (5.8) years of

experience with BoNT injections; 59.1% stated that they would like to inject higher doses of BoNT-A than permitted by current product labelling. The mean (SD; IQR) higher doses these physicians would like to inject were incobotulinumtoxinA 651.8 U (191.6; 600–800), onabotulinumtoxinA 640.3 U (170.4; 500–800), and abobotulinumtoxinA 1,751.9 U (844.2; 1,500–2,000).

Safety

Safety analyses were performed for all 701 subjects across the entire study duration (≤ 2 years). The tolerability of all BoNT-A formulations was rated as 'very good' or 'good' by

Table 2. Frequency of non-Mexican subjects with ADRs

System organ class	Incobotulinum-toxinA n = 369	Onabotulinum-toxinA n = 142	Abobotulinum-toxinA n = 75	Total n = 600
Subjects with ≥ 1 ADR, n (%)	11 (3.0)	3 (2.1)	2 (2.7)	16 (2.7)
General disorders and administration-site conditions	3 (0.8)	1 (0.7)	1 (1.3)	5 (0.8)
Nervous system disorders	4 (1.1)	1 (0.7)	0 (0.0)	5 (0.8)
Gastrointestinal disorders	1 (0.3)	0 (0.0)	1 (1.3)	2 (0.3)
Infections and infestations	1 (0.3)	0 (0.0)	1 (1.3)	2 (0.3)
Eye disorders	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.2)
Injury, poisoning, and procedural complications	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Investigations	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	0 (0.0)	1 (0.7)	0 (0.0)	1 (0.2)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (1.3)	1 (0.2)
Respiratory, thoracic, and mediastinal disorders	1 (0.3)	0 (0.0)	0 (0.0)	1 (0.2)

Data shown for non-Mexican subject population, where incidence of ADRs was documented. In Mexico, the incidences of ADRs and all other AEs, regardless of their relationship with the study treatment, were recorded. Total population includes those with no reported injection in first treatment cycle. Medical terms are as per the Medical Dictionary for Regulatory Activities version 16.0. ADR — adverse drug reaction; AE — adverse event; n — number of subjects; N — total number of subjects

physicians for the large majority of subjects (88.2–97.4%) throughout the study (Supplemental Fig. 3).

In most countries, the incidence of ADRs was recorded except in Mexico, where non-related AEs were recorded in addition to ADRs. Therefore, safety outcomes for Mexican (n = 101) and non-Mexican (n = 600) subjects were analysed separately. Among the 600 non-Mexican subjects, over the entire duration of the study, there were only 27 ADRs reported by 16 subjects (Tab. 2). The most frequent system organ classes affected were ‘general disorders and administration site conditions’ and ‘nervous system disorders’. The proportion of subjects with ADRs was similar across the BoNT-A treatment groups (Tab. 2), and post-hoc analysis did not reveal a significant difference ($p \geq 0.7666$ for comparisons between treatment groups).

For 8/600 (1.3%) non-Mexican subjects, at least one ADR was considered ‘unlikely to be related’, for 2/600 (0.3%) ‘possibly related’, for 4/600 (0.7%) ‘probably related’, and for 2/600 (0.3%) ‘definitely related’ to the study medication. The ADRs considered ‘definitely related’ to the study medication were injection-site haematoma (n = 1) and botulism (n = 1) that was further described as asthenia, generalised weakness, and a decrease in the activities of daily living.

SADRs were reported for eight subjects; in four subjects these were classed as ‘nervous system disorders’. All reported SADRs were considered ‘unlikely to be related’ to BoNT-A treatment. SADRs included abdominal pain, anxiety, astrocytoma, bipolar disorder, cerebrovascular accident, chronic obstructive pulmonary disease (COPD), death, epilepsy, fall, hemiparesis, hemiplegia, patella fracture, radius fracture, and subarachnoid haemorrhage. The percentage of subjects with SADRs was similar across the three treatment groups

(incobotulinumtoxinA, 5/369 subjects [1.4%]; onabotulinumtoxinA, 2/142 subjects [1.4%]; abobotulinumtoxinA, 1/75 subjects [1.3%]), and post-hoc analysis did not reveal significant differences (all $p = 1.000$).

Within the Mexican subject population, 17/101 subjects (16.8%) experienced an AE without causal relationship; most events were classed as ‘infections and infestations’ (n = 6) or ‘cardiac disorders’ (n = 5). One subject experienced two ADRs (urinary tract infection and lower respiratory tract infection) that were both classed as SADRs; however, the relationship to the study treatment was considered ‘not assessable’. ADRs/AEs were recorded as serious in 14/17 subjects, with most classed as ‘cardiac disorders’ (n = 5), ‘infections and infestations’ (n = 5), or ‘respiratory, thoracic, and mediastinal disorders’ (n = 3). A small cluster of serious cases of pneumonia (n = 6 subjects) was observed.

Nine subjects died while participating in the study (one subject in the non-Mexican population and eight in the Mexican population; Supplemental Tab. 2). These subjects had received BoNT-A doses of 40–620 U for the treatment of upper- and lower-limb spasticity. Deaths occurred between 10 days and 7–8 months after treatment. All eight Mexican subjects who died had poor health and multiple comorbidities, including high blood pressure, type 2 diabetes mellitus, COPD, heart disease, HIV infection, and cancer, which were strong confounding factors. In all cases, the cause of death was considered to be unrelated to BoNT-A treatment.

Global assessment of efficacy

At all visits, most subjects in all three treatment groups were classed as responders according to the physicians’ and the subjects’ global assessment of efficacy. At Visit 2 following the first treatment cycle, for those with available data

treated with incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, physician-assessed response rates were 95.5% (359/376 subjects), 91.3% (95/104 subjects), and 98.4% (63/64 subjects), respectively. Similarly, subject-assessed response rates were 92.9% (353/380 subjects), 86.5% (96/111 subjects), and 93.7% (59/63 subjects), respectively.

Although the number of subjects with global efficacy assessment data reduced substantially from Visit 2 to the final visit, both physician-assessed and subject-assessed response rates in the recorded data remained high. Among subjects treated with incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, physician-assessed response rates at the final visit were 97.4% (147/151 subjects), 87.0% (20/23 subjects), and 100% (18/18 subjects), respectively; with similar subject-assessed response rates of 97.4% (149/153 subjects), 81.8% (18/22 subjects), and 100% (18/18 subjects), respectively.

At Visit 2 and at the final visit, most physicians and subjects rated the efficacy of BoNT-A as 'very good' or 'good', regardless of BoNT-A formulation. However, these ratings were recorded for fewer subjects at the final visit (Fig. 1).

HRQoL

Treatment with all three BoNT-A formulations was associated with an improvement in HRQoL from injection Visit 1 (baseline), as measured on the EQ-5D VAS (Fig. 2). In subjects receiving incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, respectively, the mean (SD) EQ-5D VAS score was 53.4 (18.66), 56.1 (20.32), and 52.6 (18.75) at injection Visit 1, and 71.1 (20.35), 65.7 (18.52), and 67.0 (15.64) at the final visit.

A post-hoc analysis of the change in EQ-5D VAS score from injection Visit 1 revealed statistically significant improvements for pooled data across all formulations, and for incobotulinumtoxinA ($p < 0.0001$ from Visit 1 at each subsequent visit). For onabotulinumtoxinA and abobotulinumtoxinA, statistical significance was less consistent. In those receiving incobotulinumtoxinA, onabotulinumtoxinA, and abobotulinumtoxinA, respectively, the mean (SD) change in EQ-5D VAS score was 6.2 (16.19), 3.2 (16.49), and 2.4 (17.33) at Visit 2, and 18.6 (20.13), 5.9 (16.57), and 18.2 (19.65) at the final visit.

In general, compared to Visit 2, the percentage of subjects reporting their condition as 'normal (no problems)' increased, and those reporting 'severe impairment (extreme problems)' decreased with all three BoNT-A formulations across all dimensions of the EQ-5D at the final visit (Supplemental Fig. 4). Also, from Visit 1 until 4 weeks post injection, subjects treated with incobotulinumtoxinA showed improvements in mean composite SF-12 physical and mental health scores, with less data available for meaningful analysis in onabotulinumtoxinA- and abobotulinumtoxinA-treated subjects (Supplemental Tab. 3).

Discussion

This non-interventional study investigated how BoNT-A is used to treat spasticity in treatment-naïve subjects in routine clinical practice settings in nine countries worldwide during up to eight treatment cycles, for up to 2 years. Over the entire study duration, the incidence of ADRs was low, and the rate was similar across all three BoNT-A treatment groups. Of the 16/600 non-Mexican subjects reporting ADRs, two subjects had ADRs considered by the treating physician to be 'definitely related' to BoNT-A treatment, but of a non-serious nature; however, half of the subjects had ADRs that, while a causal relationship to treatment could not be ruled out, were assessed by the treating physician as 'unlikely to be related' to BoNT-A treatment, including all reported SADR. Eight of nine deaths reported during the study occurred in Mexican subjects. In all cases, these subjects had a history of poor health, the deaths were deemed to be unrelated to BoNT-A treatment, and multiple co-morbidities and strong confounding factors were present.

Physicians were able to document treatment efficacy using various impairment or function-based scales (e.g. Ashworth Scale, Tardieu Scale, Rivermead Scale, Functional Ambulation Classification Scale). However, many of these assessments are of academic value and are not performed in routine clinical practice, or only performed occasionally. For this reason, and to alleviate the potential effects of multinational differences in approval status for BoNT-A dose and indication, efficacy was evaluated using global assessments of more relevance to real-world clinical practice.

Global assessments of efficacy and tolerability showed that BoNT-A spasticity treatment was effective and well-tolerated, confirming the positive findings from previous clinical studies of BoNT-A injections for spasticity treatment, including randomised controlled trials [11–20]. No formal statistical analyses of the data were conducted; however, there did not appear to be any major differences in efficacy between BoNT-A formulations. Most subjects and physicians rated the efficacy of the first and last treatments as 'very good' or 'good' in all three BoNT-A treatment groups, with no noticeable reduction in perceived benefit with repeated treatment over time. Also, assessment of HRQoL, based on EQ-5D VAS, suggested that BoNT-A treatment improved HRQoL for the duration of the study, i.e. up to 2 years. However, when considering the apparent gradual increase in HRQoL scores over time, the effects of selection bias, resulting from the diminishing analysis population, should be taken into account.

It is worth underlining that physicians were given complete freedom to choose the BoNT-A formulation, dose and interval between injections, diagnostic and treatment procedures, and concomitant medications for each subject. The majority of participating physicians (59.1%) stated that they would like to inject higher doses of BoNT-A than is permitted by current product labelling, suggesting that many felt that current

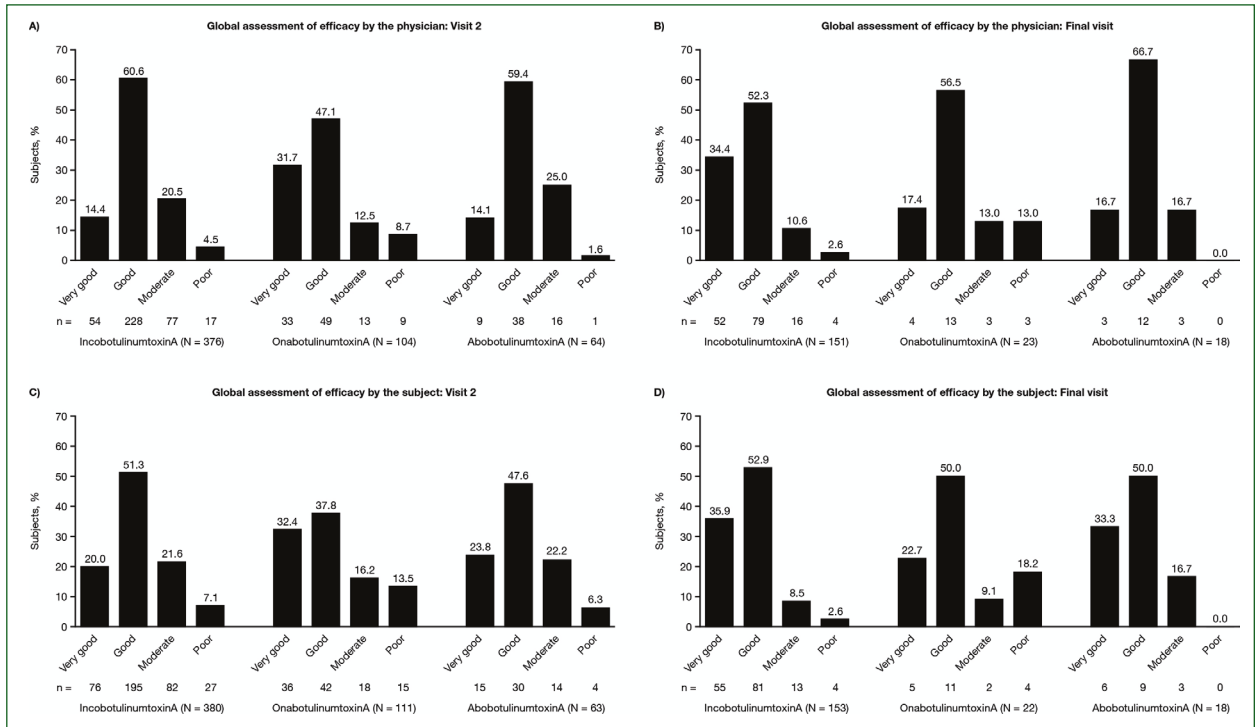


Figure 1. Proportion of subjects with very good, good, moderate, or poor global assessment of efficacy ratings according to physician at A) Visit 2 (evaluation of treatment cycle 1) and B) final visit^a (evaluation of treatment cycle 8), and according to subject at C) Visit 2 and D) final visit^a

^aFinal visit occurred at end of study, subjects did not receive an injection at this point and only those who returned for assessment were included in analysis

Percentages are based on non-missing values; N – total number of subjects assessed

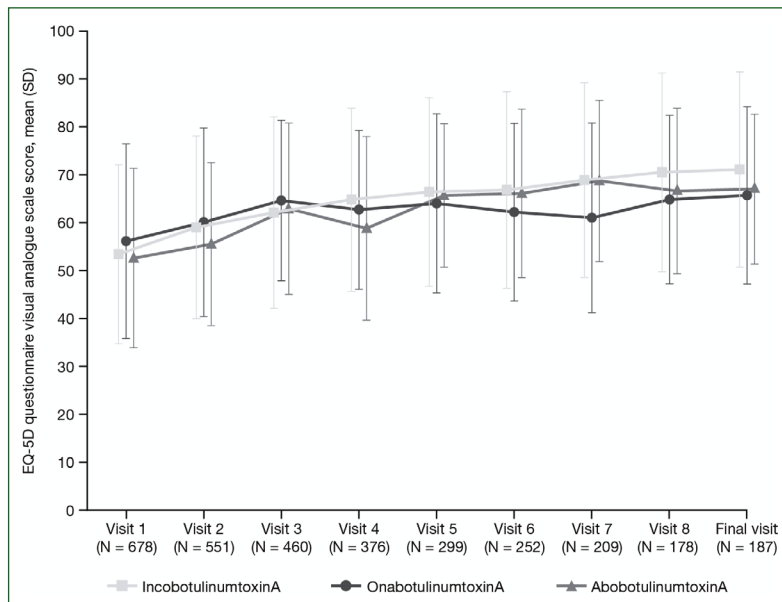


Figure 2. Mean (SD) HRQoL (EQ-5D visual analogue scale score)

Final visit occurred at end of study, subjects did not receive an injection at this point and only those who returned for assessment were included in analysis

EQ-5D — EuroQoL 5-dimensions; HRQoL — health-related quality of life

maximum dose recommendations might be too restrictive for some subjects' needs (see relevant prescribing information for details of current indicated doses of BoNT-A products [5–10]). This is consistent with a survey reporting that a physician-estimated 24.6% of individuals could benefit from higher doses of BoNT-A, and that lifting dosing and interval restrictions could improve therapy outcomes and treatment satisfaction [27]. A prospective, dose-titration study investigated the safety and efficacy of escalating incobotulinumtoxinA doses in subjects with upper- and lower-limb spasticity [20]. IncobotulinumtoxinA doses up to 800 U were well tolerated and allowed the treatment of a greater number of muscles and clinical patterns in a single treatment cycle, which may alleviate physicians' requirements to prioritise clinical patterns for treatment.

The strengths of this study include the large population (n = 701 for the safety analysis) from nine countries worldwide, the long duration (up to 2 years), and the fact that all participating subjects were treatment-naïve at study entry.

However, the representation of routine clinical practice across nine countries with different licenced indications and recommendations could also be viewed as a limitation. Further limitations include the lack of subject-reported safety information, and the gradual attrition of subject information and the resulting convenience sampling at later treatment cycles. Such attrition may seem discordant with the reported efficacy; additional studies are needed to investigate the factors contributing to treatment discontinuation in those who experience efficacy with BoNT-A. Although not reported in this study, reasons for attrition in such non-interventional studies can include subjects being lost to follow-up, either because they do not return for treatment or because the physician no longer documents the data, as well as when subjects experience treatment dissatisfaction, or indeed improvement in their symptoms, and do not require further treatment.

Conclusion

These results support the routine use of BoNT-A therapy in adults with spasticity. Throughout this 2-year real-world study, BoNT-A treatment was well tolerated, effective, and associated with an improved HRQoL.

Clinical implications/future directions

The results of the SPACE study make a valuable contribution to the broader understanding of how physicians use BoNT-A therapy to manage spasticity in real-world clinical practice. Further studies are required to investigate any correlations in practice and outcomes across the participating countries, including the effects of guidance techniques known to influence the efficacy of BoNT treatment [28].

Furthermore, research would be welcomed that brings clinicians closer to a consensus about objective outcome measures which could be used to capture the diverse range of

benefits in subjects with spasticity, including the evaluation of goal attainment and functional improvements included in previous trials [20, 24, 29].

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