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Upper Limb International Spasticity Study-II (ULIS-II): A large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management: Results

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Upper Limb International Spasticity Study-II (ULIS-II): A large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management: Results

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ABSTRACT

Objective: To describe real-life practice and person-centred outcomes in the treatment of post-stroke upper limb spasticity with botulinum toxin A (BoNT-A).

Design: Observational, prospective study.

Setting: 84 secondary care centres in 22 countries.

Participants: 456 adults (≥18 years) with post-stroke upper limb spasticity treated with one cycle of BoNT-A.

Methods/outcomes: Muscle selection, BoNT-A preparation, injection technique, and timing of follow up were conducted according to routine practice. Primary outcome: achievement of the patient's primary goal for treatment using goal-attainment scaling (GAS). Measurements of spasticity, standardised outcome measures and global benefits were also recorded.

Results: The median number of injected muscles was 5 (range 1−15) and the most frequently injected muscles were the long finger flexors, followed by biceps and brachioradialis. The median (range) follow-up time was 14 (2.6 to 32.3) weeks. Common primary treatment goals were pas passive function (132 [28.9%]) active function (104 [22.8%]) pain (61 [13.4%]), impairment (105 [23.0%]), involuntary movement (41 [9.0%]) and mobility (10 [2.2%]). Overall, 363 (79.6%) (95% CI: 75.6–83.2%) of patients achieved (or over-achieved) their primary goal and 355 (75.4%) (95% CI: 71.2–79.2%) achieved their secondary goal. Mean (SD) change from baseline in GAS T-scores was 17.6 (11.0) (95% CI: 16.4–18.8; p<0.001). GAS T-scores were strongly correlated with global benefit and other standard measures (correlations of 0.38 and 0.63, respectively; p<0.001).

Conclusion: BoNT-A demonstrated a clinically significant effect on goal attainment for the real-life management of upper limb spasticity following stroke. The study confirms the feasibility of a common international dataset to collect systematic prospective data, and of using GAS to capture person-centred outcomes relating to both passive and active function.

Registration: ClinicalTrials.gov identifier: NCT01020500

ARTICLE SUMMARY

Article focus

- A large international observational cohort study (the Upper Limb International Spasticity [ULIS]-II) to describe the use of BoNT-A for management of upper limb spasticity in the context of real-life clinical practice.
- To quantify and characterise the achievement of person centred goals following one BoNT-A injection cycle delivered in the context of routine clinical practice.
- To describe the variations in clinical practice and explore prognostic factors that may impact on outcome.

Key messages

- Despite wide variations in the approach to clinical practice, a large majority (80%) of the patients achieved their treatment goals, mainly in terms of passive and active functions and pain reduction.
- The results provide evidence that BoNT-A injections may contribute to an improvement in the daily life of patients and their carers beyond simply improvement of tone or spasticity.

Strengths and limitations of this study

- The wide geographical distribution of centres across three continents is a strength of this study, but recruitment of only 5–10 patients per site may not adequately reflect the patient population of each centre.
- The study lays the foundation for larger international longitudinal cohort studies to explore further the characteristics and treatment approaches that predict best outcomes in BoNT-A treatment of upper limb spasticity

INTRODUCTION

Spasticity is a common and distressing sequela of stroke, which interferes with upper limb movement and limits use of the limb for active functional tasks, as well as impacting on mobility and increasing the burden on caregivers.[1]

From the controlled clinical trials (CCTs) conducted to date,[2-10] it is established that botulinum toxin type A (BoNT-A) is safe and effective in reducing spasticity. However, functional gains have been harder to demonstrate, especially as there is wide diversity in the pattern of spasticity and goals for treatment.[11] As well as individual variation in response, we know that clinicians vary in their approach to treatment with respect to selection of muscle, injection technique, and follow-up therapy. These variations appear to have more to do with clinician bias and local availability of services than with patient presentation.[12]

It is now time to extend the field of investigation in this area to understand how BoNT-A is used in routine clinical practice around the world and gain better understanding of how to select patients most likely to respond to treatment. Establishing what treatment approaches work best based on clinical presentation would also be of great clinical value. To do this, we will need to build a consistent body of data that captures clinically important change at an individual level and is of sufficient size and generalisability to enable us to answer these critical questions.

The Upper Limb International Spasticity (ULIS) programme consists of a series of large, international observational studies to describe current clinical practice in the application of BoNT-A in this context, and to work towards the development of a common international dataset for prospective systematic recording of longitudinal outcomes.[13] Importantly, the programme incorporates elements of training in the use of agreed outcome measures, and development of electronic data-collection tools suitable for use by the wider international community.

Goal-attainment scaling (GAS) was chosen as the primary person-centred outcome measure to capture the diversity of treatment intentions that are important to the individual patient and their family/carers. First described by Kiresuk and Sherman in the 1960s,[14] GAS is increasingly used in the context of spasticity management[15, 16] and is shown to be sensitive to changes following focal intervention that are not detected by more global measures.[11] Although GAS provides a useful measure of achievement of treatment intention, it does not measure outcome *per se*, and therefore does not stand alone but is used alongside other standardised outcome measures.[17] It is therefore pertinent to understand the relationship between GAS and other outcome tools.

This second stage in the ULIS programme (ULIS-II) is a large, international, observational cohort study to describe real-life practice and outcomes in the treatment of post-stroke upper limb spasticity with BoNT-A. This is the first large international cohort study to use GAS as a primary outcome measure for the person-centred evaluation of treatment with BoNT-A for spasticity. In a separate paper, we have presented the rationale and methodology for ULIS-II in detail, and described the steps taken to ensure the validity of GAS as a measure of functional gains in this context.[13] Here we describe the baseline clinical characteristics, details of interventions, and the primary results in accordance with the STROBE guidelines for presentation of cohort studies.[18]

Aims and Objectives

The primary objective of the ULIS-II study was to assess the responder rate (as defined by the achievement of the primary goal from GAS) following one BoNT-A injection cycle delivered in the context of routine clinical practice.

Secondary objectives were to:

- Describe the baseline characteristics, including demographics, duration and pattern of spasticity, concomitant therapies/medication, etc
- Describe injection practices (muscle identification, dosage, dilution, etc)
- Assess achievement of secondary goals and evaluate the overall attainment of treatment goals using the GAS T-score as a patient-centred measure of outcome
- Document the use of standardised outcome measures and their results
- Assess the global benefits as perceived by the investigator and the patient.

Additional exploratory objectives, addressed through the analysis plan, were to:

- Describe the common goal areas for treatment and to identify those in which goals were most often achieved
- Examine the relationship between GAS and other standardised outcome measures
- Identify any prognostic factors for response.

Methods

Full details of the methodology are described elsewhere.[13] In brief, ULIS-II was an 18-month, post-marketing, international, multicentre, observational, prospective, before-and-after study, conducted in 84 centres in 22 countries spanning Europe, Pacific Asia and South America.

The study was conducted in compliance with Guidelines for Good Pharmacoepidemiology Practices (GPP). Marketing authorisation for the use of BoNT-A in this context was ensured for each participating country prior to the start of the study. Ethical approval and written informed consent to the recording of anonymous data was obtained in countries where this was required.

Recruitment took place between January 2010 and May 2011. To limit the potential bias from over-recruiting sites, the number of patients was limited to 5–12 patients per treatment centre. Centres included consecutive patients – or spaced inclusions in a pre-defined manner (e.g. one for every 2–3 patients) if necessary for pragmatic reasons – until their recruitment target was achieved.

Study population

The main inclusion criteria required patients to be consenting adults ≥18 years with post-stroke upper limb spasticity in whom a decision had already been made to inject BoNT-A, and who had had no previous treatment with BoNT-A or BoNT-B within the last 12-weeks. Agreement on an achievable goal set and ability to comply with the prescribed treatment were also required. The efficacy population analysed here included all subjects who received one BoNT-A injection and who underwent a post-injection visit including an assessment of GAS.

Study schedule

Baseline evaluation at Time 1 included:

- Demography and history of the stroke including type, location and time since onset.
- The pattern of impairment in the affected upper limb (modified Neurological Impairment Scale.[19, 20]
- Previous/concomitant treatments for upper limb spasticity.
- Clinical examination, including measurements of spasticity and other standardised outcome measures as routinely performed in that centre.
- Goal setting and GAS applied using the 'GAS-light' method,[21] as detailed in the rationale and methodology paper,[13] with emphasis on setting SMART (specific, measurable, achievable, realistic and timed) function-related goals agreed between investigator, the patient and the treating team.
- One primary and up to three secondary goals were set and assigned to one of seven goal categories.

Injection of BoNT-A

To reflect real-life practice in this non-interventional observational study, physicians were free to choose targeted muscles, BoNT-A preparation, injected doses, number of points and volume for each point, and use of

EMG/electrical stimulation in accordance with their usual practice, and with their local Summary of Product Characteristics and therapeutic guidelines.

The timing of follow up was at the discretion of the investigator, based on their usual practice and the nature of the goals set, usually between Month 3 and Month 5.

Follow-up evaluation at Time 2 included:

- Achievement of primary and secondary GAS goals rated on a 6-point verbal rating scale, and transcribed within the computer software to the 5-point numerical scale (range –2 to +2), and the GAS T-score.
- Any concomitant treatments for upper limb spasticity given since baseline.
- Clinical examination including measurements of spasticity as normally routinely performed.
- Global assessments of benefits were rated by the investigator and patient as: 'great benefit (+2)', 'some benefit (+1)', 'same (0)', 'worse (–1)', or 'much worse (–2)'.
- Change on any standardised measures performed was recorded on the same 5-point scale.
- The next therapeutic strategy – including any planned re-injection with BoNT-A – whether using the same agent and protocol or an adjusted one.

As this was a non-interventional study, reporting of related adverse events followed the standard regulations related to spontaneous adverse event reporting for marketed products.

Study size

The sample size calculation was based on an estimate that 60% of patients would achieve their primary goal following their first BoNT-A injection cycle. Using a 5% two-sided significance level, with a power of 80%, 450 patients were needed to allow estimation of this proportion with a precision of 4.5%. This sample size also allowed the detection of potential prognostic factors to response (based on detection of odds ratio larger or equal to 2).

Statistical analysis

Data were entered by the treating clinicians into an electronic case report form (eCRF). After cleaning and validation of the dataset, statistical evaluations were performed using Statistical Analysis System (SAS)® (version 9).

Analyses were conducted on the efficacy population. For the primary statistical analysis, 'Responders' were those who achieved their primary goal (GAS score 0, 1 or 2) (primary statistical analysis).

- Baseline characteristics and efficacy evaluations are presented as descriptive statistics, including 95% confidence intervals (95% CI) where relevant.
- Mean and standard deviation (SD) are reported for interval quality data, including long-ordinal data that fulfilled the criteria for normal distribution (e.g. Modified Ashworth Scale [MAS] total and GAS T-scores).
- Confidence intervals (95% CI) for percentage were calculated as p±1.96 x Standard Error. Standard errors were calculated as $\sqrt{(pq/n)}$, where p is the rate, q=1-rate and n=sample size.
- Short ordinal data are described by median and inter-quartile range (IQR) and analysed using non-parametric statistical techniques.

As originally described by Kiresuk and Sherman, the GAS T-score provides a composite score (the sum of the attainment levels × the relative weights [optional] for each goal) transformed into a standardised measure with a mean of 50 and standard deviation of 10. Several different scoring methods are currently used in the literature to account for partial achievement of goals in the GAS.[22] In this study, baseline scores were rated as −1 = 'some function' and –2 = 'no function' with respect to the goal. T-scores were calculated with weighting (importance), and partial achievement was rated as –0.5 to conserve the normal distribution of scores.[22]

MAS scores were recorded for the shoulder, elbow, wrist, fingers and thumb joints.
Scores of '1+' were entered as 1.5 in the calculation of the total MAS score and combined to composite scores as follows: MAS-Proximal = shoulder + elbow scores; MAS-Distal = wrist + fingers + thumb scores; MAS-total = composite sum of all five joints.

Relationships between GAS T-scores and other measures of outcome (e.g. measures of spasticity, global benefit and other standardised measures) were examined using Spearman rank correlation coefficients.

Stepwise logistic regression modelling was used to identify prognostic factors for achievement of the primary goal. Potential covariates included aetiology of the CVA, primary goal area, duration and severity of spasticity, time interval to follow-up, presence of confounding factors (including the presence of contractures; impaired motor, sensory, cognitive, emotional and cortical function, etc). A backward elimination analysis was followed using a significance level of 0.2 to retain variables in the model. The Hosmer and Lemeshow goodness-of-fit test[18] was used and 95% CI for the odds ratio (OR) estimated by the logistic model were calculated.

Results

Recruitment and participation

A total of 468 subjects were enrolled in this study of which 12 were excluded from the efficacy population (n=456). Eleven subjects were excluded because they did not attend their follow-up visit for assessment of GAS (n=5 lost to follow up, n=3 subject death unrelated to study medication and n=3 for other reasons). An additional subject was excluded as treatment was given in the lower (rather than the upper) limb. No subjects withdrew because of withdrawal of consent, lack of efficacy or adverse effect related to the BoNT-A treatment.

Demographics and disease characteristics

The geographic distribution and demographics of the efficacy population are described in detail elsewhere.[13] The mean (SD) age was 57 (13.5) years and mean (SD) time since onset of stroke was 61.4 (69.1) months. Fifty-eight percent of the population was male; 70% had had infarcts and 30% had haemorrhagic stroke. Left and right hemisphere localisation was approximately equal (47.1:51.1% respectively) and 3% had posterior circulation strokes.

Baseline characteristics are detailed in Table 1. Distal patterns of spasticity predominated. A quarter had evidence of fixed contractures and more than half had severe motor weakness. Over half of subjects (57.0%) had no useful hand function and 46% had sensory impairment. These findings confirm that the majority of subjects had chronic spasticity with severe impairment and therefore little potential for recovery of useful motor function. In contrast, cognitive and communication impairments were relatively uncommon and were mild for the most part.

Table 1. Baseline clinical characteristics of the efficacy population.

Parameter	Values	Range	n/missing or untestable
Distribution of spasticity (MAS ≥2), n (%)			
Shoulder	235 (55.7%)		422/34
Elbow	335 (75.1%)		446/10
Wrist	344 (77.8%)		442/14
Fingers	368 (82.9%)		444/12
Thumb	292 (66.8%)		437/19
Soft tissue shortening (limiting ≥half range), n (%)			456/0

Shoulder	156 (34.2%)		
Elbow	150 (32.9%)		
Wrist	179 (39.3 %)		
Hand	206 (45.2%)		
Motor paralysis (no useful function), n (%)			456
Proximal	95 (20.8%)		
Distal	260 (57.0%)		
Sensory, n (%)			447/9
Partial	208 (45.6%)		
Complete	20 (4.4%)		
Cognitive / communicative impairment, n (%)			
Cognitive	98 (21.5%)		455/1
Speech and language	159 (34.9%)		446/10
Neglect, dyspraxia or visuo-perceptual difficulties	60 (13.2%)		456/0
Other symptoms, which may impact on functional outcome, n (%)			456/0
Emotional / behavioural impairment	149 (32.7%)		
Pain*	78 (17.1%)		
Fatigue	48 (10.5%)		
Impairment scores (modified NIS)†	**Median (Q1–Q3)**	**Range**	**n/untestable**
Proximal upper limb motor score (arm raising / reaching)	2 (1–2)	0–3	456/0
Distal upper limb motor score (hand function)	3 (2–3)	0–3	456/0
Sensation	1 (0–2)	0–3	447/9
Communication impairment	0 (0–1)	0–3	455/1
Cognitive impairment	0 (0–0)	0–3	446/10
Spasticity (MAS)‡			**n/missing**
Distal composite MAS score	7.0 (6–9)	0–12	431/25
Proximal composite MAS score	4.0 (3–5)	0–8	422/34
Baseline outcome measures			
Total MAS score, mean (SD)	11.0 (3.3)	1–20	414/42

GAS weighted Score, mean (SD)	36.4 (7.7)	21.2–43.8	456/0

IQR, interquartile range; NIS, neurological impairment scale; SD, standard deviation

*Data extracted from injected segments at Baseline, when at least one muscle of the segment was injected.

†Modified NIS: The score range for each of the five domains is 0=none; 1=mild impairment affecting high-level function only; 2=significant impairment; 3=severe impairment, effectively preventing function. Further details are available from the corresponding author.

‡MAS composite scores: Proximal MAS score = shoulder + elbow scores; MAS-Distal = wrist + fingers + thumb scores; MAS-total = composite sum of all five joints.

As multiple answers were possible, the sum of some percentages in this table may exceed 100%.

BoNT-A injection history

Approximately two-thirds of subjects (n=307; 67.3%) had received a previous injection of BoNT-A in the upper limb. The mean (SD) time since the last injection was 8.0 (11.5) months and the median time was 5 months (IQR 3–5, range: 1−102 months). Some had had treatment spanning several years.

The median time since first injection was 24 months (range: 3−168 months), but two-thirds of subjects had had BoNT-A treatment for over 1 year. The median number of BoNT-A injections previously received by subjects was 4 (IQR 1–8; range: 1−45).

BoNT-A treatment

In this cohort, abobotulinumtoxinA (Dysport) was the most commonly used agent (70.4%), followed by Botox onabotulinumtoxinA (Botox) (21.5%) and incobotulinumtoxinA (Xeomin) (7.7%); two patients received another local BoNT-A preparation. The median number of injected muscles was 5.0 (range: 1−15). There was very wide variation in the total dose and dilution of BoNT-A (see Table 2).

Table 2. BoNT-A treatment.

Current injection:			
Agent*	**Dysport**	**Botox**	**Xeomin**
	n=321	**n=98**	**n=35**
	(70.4%)	**(21.5%)**	**(7.7%)**
No. of injected muscles			
Median (IQR)	5 (2)	5 (2)	5 (2)
Range	1–11	1–15	3–9

Dose and dilution			
Total dose range (units)	40–1900	50–500	100–600
Total dilution range (units/ml)	1–900	20–150	20–360
Localisation of injection (used for at least one muscle), n (%)			
EMG	91 (28.3%)	34 (34.7%)	6 (17.1%)
Electrical stimulation	145 (45.2%)	53 (54.1%)	9 (25.7%)

EMG, electromyography; IQR, interquartile range

*Two subjects received other BoNT-A preparations.

The most commonly injected muscles and doses, by treatment, are shown in Table 3. Most frequently injected were the long finger flexors, followed by biceps and brachioradialis. With the exception of pectoralis major (which was injected in 19.3% of patients), shoulder muscles were relatively rarely injected. Multiple injection points were most commonly used in the larger more proximal muscles, such as biceps and pectoralis major. Electrical stimulation was more commonly used to locate muscles than EMG (45.8% vs 29.2%), especially for the smaller muscles such as flexor pollicis longus.

At Visit 2, the median (range) follow-up time was 14 (2.6–32.3) weeks, further injection was planned in 361 (79.2%) subjects. Clinicians planned to inject the same muscles in 254 (70.4%) with the same dose in 227 (62.9%). In 134 (37.1%), a different dose was planned (increased in 26.3% and decreased in 10.8%), but only 10 (2.8%) planned to use a different agent.

Table 3. Most commonly injected muscles and technique within each upper limb segment.

Group / muscle	Total no. injected (%)*	No of units: median (IQR)			Range of units (min, max)			Multiple points	Use of EMG	Electrical stimulation
		Dysport	Botox	Xeomin	Dysport	Botox	Xeomin			
Shoulder	**N=147 (32.2%)**									
Pectoralis major	88 (19.3%)	200.0 (150.0)	30.0 (40.0)	70.0 (30.0)	30, 750	10, 100	20, 140	55 (62.5%)	11 (12.5%)	25 (28.4%)
Teres major	17 (3.7%)	75.0 (50.0)	10.0 (10.0)	50.0 (60.0)	50, 200	10, 50	40, 100	2 (11.8%)	8 (47.1%)	8 (47.1%)
Deltoideus	15 (3.3%)	100.0 (100.0)	50.0 (0.0)	N/A	50, 300	50, 50	N/A	1 (6.7%)	3 (20.0%)	7 (46.7%)
Subscapularis	14 (3.1%)	200.0 (100.0)	30.0 (0.0)	50.0 (0.0)	75, 320	20, 40	50, 50	3 (21.4%)	1 (7.1%)	11 (78.6%)
Latissimus dorsi	9 (2.0%)	120.0 (125.0)	55.0 (90.0)	40.0 (0.0)	75, 200	10, 100	40, 40	6 (66.7%)	4 (44.4%)	2 (22.2%)
Upper arm	**N=336 (73.7%)**									
Biceps brachii	270 (59.2%)	200.0 (150.0)	50.0 (10.0)	55.0 (40.0)	50, 750	20, 100	20, 100	208 (77.0%)	52 (19.3%)	70 (25.9%)
Brachialis	130 (28.5%)	150.0 (100.0)	50.0 (20.0)	60.0 (27.5)	20, 400	10, 100	30, 80	76 (58.5%)	30 (23.1%)	62 (47.7%)
Triceps brachii	18 (3.9%)	175.0 (100.0)	30.0 (25.0)	N/A	60, 300	20, 100	N/A	15 (83.3%)	8 (44.4%)	8 (44.4%)
Lower arm	**N=434 (95.2%)**									
Flexor digit. superficialis	325 (71.3%)	150.0 (100.0)	50.0 (35.0)	60.0 (37.5)	20, 500	15, 150	30, 100	195 (60.0%)	91 (28.0%)	151 (46.5%)
Flexor digit. profondus	265 (58.1%)	150.0 (100.0)	50.0 (30.0)	50.0 (20.0)	50, 600	15, 150	20, 200	142 (53.6%)	66 (24.9%)	114 (43.0%)
Flexor carpi radialis	262 (57.5%)	125.0 (100.0)	33.3 (25.0)	45.0 (40.0)	20, 350	5, 100	20, 80	83 (31.7%)	73 (27.9%)	99 (37.8%)
Brachioradialis	156 (34.2%)	112.5 (100.0)	40.0 (35.0)	50.0 (20.0)	25, 300	10, 75	20, 75	55 (35.3%)	29 (18.6%)	46 (29.5%)
Pronator teres	138 (30.3%)	100.0 (75.0)	40.0 (25.0)	40.0 (30.0)	25, 500	10, 100	10, 50	44 (31.9%)	26 (18.8%)	53 (38.4%)
Flexor pollicis longus	136 (29.8%)	100.0 (50.0)	25.0 (12.5)	35.0 (30.0)	20, 250	5, 50	10, 60	29 (21.3%)	31 (22.8%)	79 (58.1%)
Hand / fingers	**N=204 (44.7%)**									
Flexor pollicis brevis	47 (10.3%)	50.0 (50.0)	15.0 (12.5)	20.0 (0.0)	10, 200	5, 30	20, 40	7 (14.9%)	6 (12.8%)	19 (40.4%)
Adductor pollicis	37 (8.1%)	50.0 (22.5)	25.0 (15.0)	20.0 (20.0)	20, 125	10, 30	10, 30	0	8 (21.6%)	10 (27.0%)
Lumbricales	32 (7.0%)	100.0 (120.0)	25.0 (10.0)	40.0 (47.5)	50, 400	15, 40	20, 75	29 (90.6%)	8 (25.0%)	11 (34.4%)
Interossei dorsales	22 (4.8%)	150.0 (150.0)	25.0 (30.0)	N/A	50, 375	10, 80	N/A	20 (90.9%)	6 (27.3%)	9 (40.9%)
Opponens pollicis	18 (3.9%)	50.0 (50.0)	30.0 (20.0)	5.0 (0.0)	10, 120	20, 40	5, 5	0	3 (16.7%)	9 (50.0%)

Percentages are based on the number of subjects injected in the muscle, except * for which percentages are based on the number of subjects in the efficacy population.
EMG, electromyography; IQR, interquartile range

Concomitant treatments

Nearly two-thirds (61.6%) of patients were receiving physiotherapy in association with the BoNT-A treatment at follow up, and over a third (39.5%) of subjects also received occupational therapy. However, there was wide variation in the number of sessions received (see Table 4).

The types of concomitant treatments at baseline and follow up are shown in Table 4. At baseline, the frequency of concomitant treatments ranged from 18% (functional electrical stimulation) to 93% (passive stretching). By follow up, the overall frequency of concomitant therapies had diminished, although the range of modalities remained similar. Notably, the proportion of patents on antispasmodic medication fell from 46% to 28.5%.

Table 4. Concomitant treatments at baseline and follow up.

N (%)	Baseline	Visit 2
Physiotherapy		
1–4 sessions		33 (11.7%)
5–10 sessions		50 (17.8%)
11–20 sessions		74 (26.3%)
>20 sessions		120 (42.7%)
Unknown		4 (1.4%)
Occupational therapy		
1–4 sessions		34 (18.9%)
5–10 sessions		33 (18.3%)
11–20 sessions		46 (25.6%)
>20 sessions		63 (35.0%)
Unknown		4 (2.2%)
Splinting	188 (41.2%)	148 (32.5%)
Orthotics	114 (25.0%)	92 (20.2%)
Exercise	393 (86.2%)	360 (78.9%)
Passive stretching	423 (92.8%)	410 (89.9%)
Functional electrical stimulation	83 (18.2%)	58 (12.7%)
Positioning	266 (58.3%)	237 (52.0%)
Anti-spastic medication	210 (46.1%)	130 (28.5%)
No concomitant treatment	3 (0.7%)	12 (2.6%)

Primary and secondary goal areas

Primary and secondary goal areas set at baseline are shown in Table 5. Goals were most commonly set in the areas of passive function, impairment and active function followed by pain, and involuntary movement. Less commonly in this dataset, goals focused on mobility or other areas, such as cosmesis or supporting therapy interventions.

Overall, 363 (79.6%) (95% CI: 75.6–83.2) of patients achieved (or over-achieved) their primary goal with 355 (75.4%) (95% CI: 71.2–79.2%) achieving their secondary goal (see Table 5). Although the rate of achievement was lower (but not statistically significant) for active function goals in comparison with passive function and impairment goals, in this series, a total of 182 (primary and secondary) goals were set in relation to active function of which 122 (67.0%) were achieved, either as expected (73 [40.1%]) or beyond expectation (49 [26.9%]). Pain reduction was a goal for treatment in nearly one-third of patients (145 [31.8%]), and was achieved in 83.5%.

Table 5. Primary and secondary goal areas.

Goal area	Primary goals by area (n=456)			Secondary goals by area (n=471)		
	Goal set n (%)	Goal achieved n (%) (95% CI)	Partially achieved n (%)	Goal set n (%)	Goal achieved n (%) (95% CI%)	Partially achieved n (%)
Pain	61 (13.4%)	51(83.6%) (71.9–91.8%)	10 (16.4%)	84 (17.8%)	70 (83.3%) (73.6–90.6%)	6 (7.1%)
Passive function (Ease of care)	132 (29.0%)	113 (85.6%) (78.4–91.1%)	11 (8.3%)	109 (23.1%)	84 (77.1%) (68.0–84.6%)	15 (13.9%)
Active function (Active motor use of limb)	104 (22.8%)	75 (72.1%) (62.5–80.5%)	13 (12.5%)	78 (16.5%)	47 (60.3%) (48.5–71.2%)	18 (23.1%)
Mobility (balance, gait)	10 (2.2%)	7 (70.0%) (34.8–93.3%)	3 (30.0%)	19 (4.0%)	14 (73.7%) (48.8–90.9%)	2 (10.5%)
Involuntary movement (associated reaction)	41 (9.0%)	32 (78.0%) (62.4–89.4%)	5 (12.2%)	56 (11.9%)	45 (80.4%) (67.6–89.8%)	6 (10.7%)
Impairment (e.g. range of movement)	105 (23.0%)	82 (78.1%) (69.0–85.6%)	11 (10.5%)	117 (24.8%)	91 (77.8%) (69.2–84.9%)	13 (11.2%)
Other	3 (0.7%)	3 (100%) (29.2–100%)	0	5 (1.1%)	3 (60.0%) (14.7–94.7%)	2 (40.0%)
Total	456	363 (79.6%) (75.6–83.2%)	53 (11.6%)	471	355 (75.4%) (71.2–79.2%)	63 (13.4%)

Secondary outcomes

At follow-up, the mean (SD) weighted GAS T-score was 52.0 (10.1) (median 50.0, IQR 13.8), giving a mean (SD) change from baseline of 17.6 (11.0; 95% CI: 16.6–18.6) (p<0.001). Baseline and mean change from baseline in GAS T-scores were similar between BoNT-A preparations.

The mean (SD) MAS total score at follow up was 8.4 (3.4) giving a mean (SD) change from baseline of –2.6 (2.6; 95% CI: –2.9 to –2.4) (p<0.0001). Overall, 90.1% of investigators and 85.8% of patients considered BoNT-A treatment to be of benefit.

GAS T-scores correlated with changes in total MAS at follow up (Spearman rho 0.28; p<0.0001). This means positive goal attainment was related to reduction in spasticity and correlated positively with global assessment of benefit (Spearman rho 0.38; p<0.0001 for investigator assessment and 0.45; p<0.0001 for patient assessment).

Standardised measures of upper limb spasticity

Reflecting common impairment, the range of active (56.1%) and passive (54.4%) motion were the most commonly recorded standardised measures of upper limb spasticity used at baseline (Table 6). Approximately one-third (34.4%) of patients also used a visual analogue rating to reflect symptoms such as pain or carer burden. However, only a very small minority (7.2%) had a standardised measure of functional outcome recorded, such as the Arm Activity Scale (ArMA – a self-report measure of active and passive function) (5.9%) or the Leeds Adult Spasticity Impact Scale (LASIS – an investigator-reported measure of passive function) (1.3%). As shown in Table 6, the GAS T-score correlated strongly with change in these standardised measures wherever they were measured.

Table 6. Standardised measures to assess upper limb spasticity at baseline.

Standardised measure	Recorded at baseline	Recorded at follow up	No. showing change	Correlation with GAS T-Score	
	n (%)*	n (%)*	n (%)	rho	p-value
Impairment					
Tardieu	77 (16.9%)	62 (13.6%)	56 (90.3%)	0.43	<0.001
Active range of motion	256 (56.1%)	231 (50.7%)	137 (59.3%)	0.41	<0.001
Passive range of motion	248 (54.4%)	249 (54.6%)	172 (69.1%)	0.43	<0.001

Associated Reaction Rating Scale[25]	24 (5.3%)	26 (5.7%)	14 (53.8%)	0.76	<0.001
Symptoms/carer report					
Visual Analogue Scale[†]	157 (34.4%)	139 (30.5%)	109 (78.4%)	0.46	<0.001
Function					
Leeds Adult Spasticity Impact Scale[3]	6 (1.3%)[‡]	5 (1.1%)[‡]		–	–
Arm Activity Scale[26]	27 (5.9%)	27 (5.9%)	14 (51.9%)	0.63	<0.001

*Percentage of efficacy population.

[†]Parameters measured with VAS were not specified

[‡]Numbers too small to compute.

GAS, goal attainment scaling

Identification of potential prognostic factors

Potential predictors with a p-value <0.20 were the primary goal area, primary goal score at baseline, first administration of BoNT-A, and cortical function. These were entered into the multivariate logistic model. Results indicated that patients with impaired cortical function were half as likely to respond to treatment (OR 0.48 [95% CI: 0.26–0.89]). The most likely explanation for this is that patients with dyspraxia, neglect or poor visuospatial perception are more likely to have difficulty complying with and carrying through any treatment programme.

A non-significant trend was also seen for poorer goal achievement in patients receiving their first administration of BoNT-A, compared with those who had had previous injections (OR 0.69 (95% CI: 0.43–1.12). This may be due to the fact that patients who already received BoNT-A benefited from their prior experience to better define treatment goals.

Discussion

The findings from this large prospective international cohort study showed overall good response rates to BoNT-A injection delivered in the context of routine clinical practice for the management of upper limb spasticity. The study demonstrated wide variation in clinical practice with respect to the selection of muscles and approach to injection, highlighting the need for further systematic research into which approaches are likely to be most effective for which patients. Nevertheless, almost 80% of patients achieved their primary goal, as defined by the patients – together with their clinical team – at the start of treatment. The study also confirms the feasibility of collecting data across a large international community, using an eCRF.

Patient-reported outcomes are increasingly recognised as important indicators of quality of daily life for patients and/or their carers, and in this study GAS was selected as the primary endpoint in order to evaluate the benefits of treatment in terms of the attainment of individual person-centred goals. It also provides

important insight into the nature of goals that are chosen as priorities for treatment, and also those most likely to be achieved.

In keeping with findings from other studies,[11, 23] improvement in passive function was the most frequently selected primary goal area for treatment (29%), and primary goals were achieved in around 86% of cases. Goals for active function were also commonly set in nearly a quarter of patients (22%). Perhaps unsurprisingly in this population with chronic spasticity and severe motor impairment, the achievement rate was somewhat lower for active function. Nevertheless, 72% of patients achieved their primary active function goal. The third most commonly achieved primary goal area was pain (set in 13% of patients), where again achievement was around 84%. Functional goals relating to involuntary movements and mobility were less commonly set in this population but were nevertheless achieved at broadly similar rates overall. The wide diversity in treatment goals between patients, however, highlights the importance of defining the primary treatment intentions clearly and then evaluating outcome specifically in relation to those.

Over and above achievement of the primary goal, the GAS T-score provides an overall assimilation of attainment of primary and secondary goals regardless of the number of goals set. Some authors have cast doubt on the value of calculating a GAS T-score.[24] In this study, we went to considerable lengths to ensure that GAS was applied rigorously and goals were focused on functional gains,[13] so it is worth reflecting on the added value on the GAS T-score in this context.

- If goals are set in an unbiased fashion, and are neither over-ambitious or over-cautious, the mean GAS T-score should be around 50 (±SD 10).[21] Our mean (SD) GAS T-score at follow up of 52 (10.1) provides a useful quality check of the team's ability to set and negotiate achievable goals, neither over- nor under-estimating the expected outcome.
- Previous authors have recorded that GAS change scores >10 represent clinically meaningful change.[11, 17, 21] In this study, the mean improvement in GAS T-score from baseline to follow up was 17.6. This confirms findings from RCTs,[16] and provides supportive evidence that BoNT-A produces clinically meaningful change at a functional level in the treatment.
- Importantly, GAS T-scores provide a single numerical evaluation of overall goal achievement for comparison with other outcome measures. If the gains occur as a result of reduction in spasticity, a correlation with change in MAS score would be expected,[11, 16] and indeed this correlation was found. The significant correlations with other standardised measures (especially the Arm Activity Scale) provide further support for GAS as a meaningful person-centred measure of outcome in this context.

The findings of this study also give insight into the longer term treatment of upper limb spasticity. Many of the patients enrolled in this study had received several previous treatments, often over several years, suggesting that patients continue to receive benefit from repeat treatments, as indeed was shown by our findings. Additionally, the mean duration since last BoNT-A treatment was 8 months, suggesting that patients with upper limb spasticity may not require re-treatment as frequently as in other conditions (such as cervical dystonia). The reduction in use of other antispasmodic medication suggests that successful treatment may possibly have allowed the reduction or withdrawal of other systemic agents. Additional longitudinal studies are needed to confirm these observations and to better understand their clinical implications.

The authors recognise a number of limitations to this study:

- Although there was a wide geographical distribution of centres across three continents, the numerical representation in each region was by no means representative.
- The recruitment of just 5–10 patients per site may have been insufficient to ensure adequate representation of practice in each centre especially given the wide diversity of patients and goals for treatment.
- The relatively low frequency of reported impairments in cognitive and communicative function suggests either that there is selection bias (patients with these problems are less likely to be referred for treatment), or under-reporting (clinicians focussed on treating spasticity are not good at identifying associated impairments which may potentially impact on outcome).
- For pragmatic reasons, change on standardised outcome measures was recorded only subjectively on a standard scale of –2 to +2 and should therefore be interpreted with caution.
- The study was not sufficiently powered to perform a detailed investigation of prognostic factors for outcome, but has given some preliminary insights into potential prognostic factors within the baseline dataset.

Despite these limitations, the study provides useful information about the way that BoNT-A is used in clinical practice around the world, and demonstrates that its effectiveness in the management of post-stroke spasticity can be documented using individual person-centred goals. More importantly, a large majority of the patients achieved their treatment goals, mainly in terms of passive and active functions, demonstrating that BoNT-A injections contribute to an improvement in the daily life of the patients beyond improvement of tone or spasticity. Further secondary analyses will be presented separately to explore the impact of different treatment strategies including injection technique, early versus late treatment and the role of concomitant therapies. Further refinement of the tools and dataset are now underway to producing a concise Upper Limb

Spasticity Index that combines GAS with selected standardised measures targeted on the key goals for intervention in this context.

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Contributor statement

LTS wrote the first draft of this manuscript. LTS, KF and JJ were involved in data collection and assembly of data, manuscript review and critique, and final approval of manuscript. PM was involved in the concept and design, data analysis, manuscript writing, manuscript review and critique, and final approval of manuscript.

Competing interests:

LTS, KF and JJ all received honoraria and conference attendance fees from Ipsen for the undertaking of this research.

- LTS has a specific interest in outcomes evaluation and has published extensively on the use of GAS in this context, as well as a number of the other standardised measures (including the Associated Reaction Scale, the Arm Activity Scale and the Neurological Impairment Scale). All of these tools are freely available, however, and she has no personal financial interest in any of the material mentioned in this article.
- KF has a specific interest in outcomes evaluation and the use of the International Classification of Function in clinical settings. He has no personal financial interest in any of the material mentioned in this article.
- JJ has particular interest in spasticity clinical and instrumental evaluation methods, goal setting, treatment strategies/techniques and outcome measurement. He has no personal or financial interest in any of the material mentioned in this article.
- PM is an employee of Ipsen.

Previous publications:

Turner-Stokes L, Fheodoroff K, Jacinto J, Maisonobe P, Zakine B. Upper Limb International Spasticity Study: Rationale and protocol for a large international, multicentre prospective cohort study investigating management and goal attainment following treatment with botulinum toxin-A in real-life clinical practice. *BMJ Open* 2013 (In press).

References

1. RCP/BSRM. Spasticity in adults: Management using Botulinum Toxin. National Guidelines. London: Royal College of Physicians 2008.

2. Bakheit AM, Sawyer J. The effects of botulinum toxin treatment on associated reactions of the upper limb on hemiplegic gait--a pilot study. *Disabil Rehabil* 2002;24:519–22.

3. Bhakta BB, Cozens JA, Chamberlain MA, *et al*. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. *J Neurol Neurosurg Psychiatr* 2000;69:217–21.

4. Bhakta BB, Cozens JA, Bamford JM, *et al*. Use of botulinum toxin in stroke patients with severe upper limb spasticity. *J Neurol Neurosurg Psychiatr* 1996;61:30–5.

5. Brashear A, Gordon MF, Elovic E, *et al*. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Eng J Med* 2002;347:395–400.

6. Hesse S, Jahnke MT, Luecke D, *et al*. Short-term electrical stimulation enhances the effectiveness of Botulinum toxin in the treatment of lower limb spasticity in hemiparetic patients. *Neurosci Lett* 1995;201:37–40.

7. Richardson D, Edwards S, Sheean GL, *et al*. The effect of botulinum toxin on hand function after incomplete spinal cord injury at the level of C5/6: a case report. *Clin Rehabil* 1997;11:288–92.

8. Rodriquez AA, McGinn M, Chappell R. Botulinum toxin injection of spastic finger flexors in hemiplegic patients. *Am J Phys Med Rehabil* 2000;79:44–7.

9. Simpson DM, Alexander DN, O'Brien CF, *et al*. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996;46:1306–10.

10. Smith SJ, Ellis E, White S, *et al*. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin Rehabil* 2000;14:5–13.

11. Turner-Stokes L, Baguley I, De Graff S, *et al*. Goal attainment scaling in the evaluation of treatment of upper limb spasticity with botulinum toxin: a secondary analysis from a double blind placebo controlled randomised clinical trial. *J Rehabil Med* 2010;42:81–9.

12. Baguley IJ, Nott MT, Turner-Stokes L, *et al*. Investigating muscle selection for botulinum toxin-A injections in adults with post-stroke upper limb spasticity. *J Rehabil Med* 2011;43:1032–7.

13. Turner-Stokes L, Fheodoroff K, Jacinto J, *et al*. Upper Limb International Spasticity Study: Rationale and protocol for a large international, multicentre prospective cohort study investigating management and goal attainment following treatment with botulinum toxin-A in real-life clinical practice. *BMJ Open* 2013 (In press).

14. Kiresuk T, Sherman R. Goal attainment scaling: a general method of evaluating comprehensive mental health programmes. *Comm Ment Health J* 1968;4:443–53.

15. Ashford S, Turner-Stokes L. Goal attainment for spasticity management using botulinum toxin. *Physiother Res Int* 2006;11:24–34.

16. McCrory P, Turner-Stokes L, Baguley IJ, *et al*. Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomised placebo-controlled study of the effects on quality of life and other person-centred outcomes. *J Rehabil Med* 2009;41:536–44.

17. Turner-Stokes L, Williams H, Johnson J. Goal Attainment Scaling: does it provide added value as a person-centred measure for evaluation outcome in neurorehabilitation following acquired brain injury? *J Rehabil Med* 2009;41:528–35.

18. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.

19. Thu A, Casey R, Turner-Stokes L, Williams H. Inter-rater Reliability of the Neurological Impairment Scale (NIS): A Standard Impairment Set for Neurorehabilitation Populations (AAPMR Annual Assembly Poster 44). *Phys Med Rehabil* 2011;3(10 Suppl.):S191.

20. Turner-Stokes L, Siegert RJ, Thu A, *et al*. The Neurological Impairment Scale: reliability and validity as a predictor of functional outcome in neurorehabilitation. *Disabil Rehabil* 2013 (In press).

21. Turner-Stokes L. Goal attainment scaling in rehabilitation; a practical guide. *Clin Rehabil* 2009;23:362–70.

22. Turner-Stokes L, Williams H. Goal attainment scaling: a direct comparison of alternative rating methods. *Clin Rehabil* 2010;24:66–73.

23. Bakheit AM, Zakine B, Maisonobe P, *et al*. The profile of patients and current practice of treatment of upper limb muscle spasticity with botulinum toxin type A: an international survey. *Int J Rehabil Res* 2010;33:199–204.

24. Tennant A. Goal attainment scaling: current methodological challenges. *Disabil Rehabil* 2007;29:1583–8.

25. Macfarlane A, Turner-Stokes L, De Souza L. The associated reaction rating scale: a clinical tool to measure associated reactions in the hemiplegic upper limb. *Clin Rehabil* 2002;16:726–35.

26. Ashford S, Turner-Stokes L, Siegert RJ,*et al*. Initial psychometric evaluation of the Arm Activity Measure (ArmA): a measure of activity in the hemiparetic arm. *Clin Rehabil* 2013 (In press).

Upper Limb International Spasticity Study-II (ULIS-II): A large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management: Results

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Upper Limb International Spasticity Study-II (ULIS-II): A large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management: Results

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ABSTRACT

Objective: To describe real-life practice and person-centred outcomes in the treatment of post-stroke upper limb spasticity with botulinum toxin A (BoNT-A).

Design: Observational, prospective study.

Setting: 84 secondary care centres in 22 countries.

Participants: 456 adults (≥18 years) with post-stroke upper limb spasticity treated with one cycle of BoNT-A.

Methods/outcomes: Muscle selection, BoNT-A preparation, injection technique, and timing of follow up were conducted according to routine practice. Primary outcome: achievement of the patient's primary goal for treatment using goal-attainment scaling (GAS). Measurements of spasticity, standardised outcome measures and global benefits were also recorded.

Results: The median number of injected muscles was 5 (range 1−15) and the most frequently injected muscles were the long finger flexors, followed by biceps and brachioradialis. The median (range) follow-up time was 14 (2.6 to 32.3) weeks. Common primary treatment goals were passive function (132 [28.9%]) active function (104 [22.8%]) pain (61 [13.4%]), impairment (105 [23.0%]), involuntary movement (41 [9.0%]) and mobility (10 [2.2%]). Overall, 363 (79.6%) (95% CI: 75.6–83.2%) of patients achieved (or over-achieved) their primary goal and 355 (75.4%) (95% CI: 71.2–79.2%) achieved their secondary goal. Mean (SD) change from baseline in GAS T-scores was 17.6 (11.0) (95% CI: 16.4–18.8; p<0.001). GAS T-scores were strongly correlated with global benefit and other standard measures (correlations of 0.38 and 0.63, respectively; p<0.001).

Conclusion: BoNT-A demonstrated a clinically significant effect on goal attainment for the real-life management of upper limb spasticity following stroke. The study confirms the feasibility of a common international dataset to collect systematic prospective data, and of using GAS to capture person-centred outcomes relating to passive and active function, and to pain.

Registration: ClinicalTrials.gov identifier: NCT01020500

ARTICLE SUMMARY

Article focus

- A large international observational cohort study (the Upper Limb International Spasticity [ULIS]-II) to describe the use of BoNT-A for management of upper limb spasticity in the context of real-life clinical practice.
- To quantify and characterise the achievement of person centred goals following one BoNT-A injection cycle delivered in the context of routine clinical practice.
- To describe the variations in clinical practice and explore prognostic factors that may impact on outcome.

Key messages

- Despite wide variations in the approach to clinical practice, a large majority (80%) of the patients achieved their treatment goals, mainly in terms of passive and active functions and pain reduction.
- The results provide evidence that BoNT-A injections may contribute to an improvement in the daily life of patients and their carers beyond simply improvement of tone or spasticity.

Strengths and limitations of this study

- The wide geographical distribution of centres across three continents is a strength of this study, but recruitment of only 5–12 patients per site may not adequately reflect the patient population of each centre.
- The study lays the foundation for larger international longitudinal cohort studies to explore further the characteristics and treatment approaches that predict best outcomes in BoNT-A treatment of upper limb spasticity

INTRODUCTION

Spasticity is a common and distressing sequela of stroke, which interferes with upper limb movement and limits use of the limb for active functional tasks, as well as impacting on mobility and increasing the burden on caregivers.[1]

From controlled clinical trials (CCTs) conducted to date,[2-9] it is established that botulinum toxin type A (BoNT-A) is safe and effective in reducing spasticity. However, functional gains have been harder to demonstrate,[10] especially as there is wide diversity in the pattern of spasticity and goals for treatment.[11] As well as individual variation in response, we know that clinicians vary in their approach to treatment with respect to selection of muscle, injection technique, and follow-up therapy. These variations appear to have more to do with clinician bias and local availability of services than with patient presentation.[12]

It is now time to extend the field of investigation in this area to understand how BoNT-A is used in routine clinical practice around the world and gain better understanding of how to select patients most likely to respond to treatment. Establishing what treatment approaches work best based on clinical presentation would also be of great clinical value. To do this, we will need to build a consistent body of data that captures clinically important change at an individual level and is of sufficient size and generalisability to enable us to answer these critical questions.

The Upper Limb International Spasticity (ULIS) programme consists of a series of large, international observational studies to describe current clinical practice in the application of BoNT-A in this context, and to work towards the development of a common international dataset for prospective systematic recording of longitudinal outcomes.[13] Importantly, the programme incorporates elements of training in the use of agreed outcome measures, and development of electronic data-collection tools suitable for use by the wider international community.

Goal-attainment scaling (GAS) was chosen as the primary person-centred outcome measure to capture the diversity of treatment intentions that are important to the individual patient and their family/carers. First described by Kiresuk and Sherman in the 1960s,[14] GAS is increasingly used in the context of spasticity management[15, 16] and is shown to be sensitive to changes following focal intervention that are not detected by more global measures.[11] Although GAS provides a useful measure of achievement of treatment intention, it does not measure outcome *per se*, and therefore does not stand alone but is used alongside other standardised outcome measures.[17] It is therefore pertinent to understand the relationship between GAS and other outcome tools.

This second stage in the ULIS programme (ULIS-II) is a large, international, observational cohort study to describe real-life practice and outcomes in the treatment of post-stroke upper limb spasticity with BoNT-A. This is the first large international cohort study to use GAS as a primary outcome measure for the person-centred evaluation of treatment with BoNT-A for spasticity. In a separate paper, we have presented the rationale and methodology for ULIS-II in detail, and described the steps taken to ensure the validity of GAS as a measure of functional gains in this context.[13] Here we describe the baseline clinical characteristics, details of interventions, and the primary results in accordance with the STROBE guidelines for presentation of cohort studies.[18]

Aims and Objectives

The primary objective of the ULIS-II study was to assess the responder rate (as defined by the achievement of the primary goal from GAS) following one BoNT-A injection cycle delivered in the context of routine clinical practice.

Secondary objectives were to:

- Describe the baseline characteristics, including demographics, duration and pattern of spasticity, concomitant therapies/medication, etc
- Describe injection practices (muscle identification, dosage, dilution, etc)
- Assess achievement of secondary goals and evaluate the overall attainment of treatment goals using the GAS T-score as a patient-centred measure of outcome
- Document the use of standardised outcome measures and their results
- Assess the global benefits as perceived by the investigator and the patient.

Additional exploratory objectives, addressed through the analysis plan, were to:

- Describe the common goal areas for treatment and to identify those in which goals were most often achieved
- Examine the relationship between GAS and other standardised outcome measures
- Identify any prognostic factors for response.

Methods

Full details of the methodology are described elsewhere.[13] In brief, ULIS-II was an 18-month, post-marketing, international, multicentre, observational, prospective, before-and-after study, conducted in 84 centres in 22 countries spanning Europe, Pacific Asia and South America.

The study was conducted in compliance with Guidelines for Good Pharmacoepidemiology Practices (GPP). Marketing authorisation for the use of BoNT-A in this context was ensured for each participating country prior to the start of the study. Ethical approval and written informed consent to the recording of anonymous data was obtained in countries where this was required.

Recruitment took place between January 2010 and May 2011. To limit the potential bias from over-recruiting sites, the number of patients was limited to 5–12 patients per treatment centre. All centres recruited at least 5 patients, but 25 of the more experienced centres (which were usually also larger) could recruit up to 12 patients. This was allowed to try to ensure a representative sample from clinicians with experience in this area of practice. It also offers the opportunity for future sub-analysis of the differences between experienced and less experienced injectors.

Centres included consecutive patients – or spaced inclusions in a pre-defined manner (e.g. one for every 2–3 patients) if necessary for pragmatic reasons – until their recruitment target was achieved.

Study population

The main inclusion criteria required patients to be consenting adults ≥18 years with post-stroke upper limb spasticity in whom a decision had already been made to inject BoNT-A, and who had had no previous treatment with BoNT-A or BoNT-B within the last 12-weeks. Agreement on an achievable goal set and ability to comply with the prescribed treatment were also required. The efficacy population analysed here included all subjects who received one BoNT-A injection and who underwent a post-injection visit including an assessment of GAS.

Study schedule

Baseline evaluation at Time 1 included:

- Demography and history of the stroke including type, location and time since onset.
- The pattern of impairment in the affected upper limb (modified Neurological Impairment Scale.[19, 20]
- Previous/concomitant treatments for upper limb spasticity.
- Clinical examination, including measurements of spasticity and other standardised outcome measures as routinely performed in that centre.
- Goal setting and GAS applied using the 'GAS-light' method,[21] as detailed in the rationale and methodology paper,[13] with emphasis on setting SMART (specific, measurable, achievable, realistic and timed) function-related goals agreed between investigator, the patient and the treating team.

- One primary and up to three secondary goals were set and assigned to one of seven goal categories.

Injection of BoNT-A

To reflect real-life practice in this observational study, physicians were free to choose targeted muscles, BoNT-A preparation, injected doses, number of points and volume for each point, and use of EMG/electrical stimulation in accordance with their usual practice, and with their local Summary of Product Characteristics and therapeutic guidelines. The timing of follow up was at the discretion of the investigator, based on their usual practice and the nature of the goals set, usually between Month 3 and Month 5.

Follow-up evaluation at Time 2 included:

- Achievement of primary and secondary GAS goals rated on a 6-point verbal rating scale, and transcribed within the computer software to the 5-point numerical scale (range –2 to +2), and the GAS T-score.
- Any concomitant treatments for upper limb spasticity given since baseline.
- Clinical examination including measurements of spasticity as normally routinely performed.
- Global assessments of benefits were rated by the investigator and patient as: 'great benefit (+2)', 'some benefit (+1)', 'same (0)', 'worse (–1)', or 'much worse (–2)'.
- Change on any standardised measures performed was recorded on the same 5-point scale.
- The next therapeutic strategy – including any planned re-injection with BoNT-A – whether using the same agent and protocol or an adjusted one.

As this was an observational study, reporting of related adverse events followed the standard regulations related to spontaneous adverse event reporting for marketed products.

Study size

The sample size calculation was based on an estimate that 60% of patients would achieve their primary goal following their first BoNT-A injection cycle. Using a 5% two-sided significance level, with a power of 80%, 450 patients were needed to allow estimation of this proportion with a precision of 4.5%. This sample size also allowed the detection of potential prognostic factors to response (based on detection of odds ratio larger or equal to 2).

Statistical analysis

Data were entered by the treating clinicians into an electronic case report form (eCRF). After cleaning and validation of the dataset, statistical evaluations were performed using Statistical Analysis System (SAS)® (version 9).

Analyses were conducted on the efficacy population. For the primary statistical analysis, 'Responders' were those who achieved their primary goal (GAS score 0, 1 or 2) (primary statistical analysis).

- Baseline characteristics and efficacy evaluations are presented as descriptive statistics, including 95% confidence intervals (95% CI) where relevant.
- Mean and standard deviation (SD) are reported for interval quality data, including long-ordinal data that fulfilled the criteria for normal distribution (e.g. Modified Ashworth Scale [MAS] total and GAS T-scores).
- Confidence intervals (95% CI) for percentage were calculated as p±1.96 x Standard Error. Standard errors were calculated as $\sqrt{(pq/n)}$, where p is the rate, q=1-rate and n=sample size.
- Short ordinal data are described by median and inter-quartile range (IQR) and analysed using non-parametric statistical techniques.

As originally described by Kiresuk and Sherman, the GAS T-score provides a composite score (the sum of the attainment levels × the relative weights [optional] for each goal) transformed into a standardised measure with a mean of 50 and standard deviation of 10. Several different scoring methods are currently used in the literature to account for partial achievement of goals in the GAS.[22] In this study, baseline scores were rated as −1 = 'some function' and –2 = 'no function' with respect to the goal. T-scores were calculated with weighting (importance), and partial achievement was rated as –1 to conserve the normal distribution of scores.[22]

MAS scores were recorded for the shoulder, elbow, wrist, fingers and thumb joints.
Scores of '1+' were entered as 1.5 in the calculation of the total MAS score and combined to composite scores as follows: MAS-Proximal = shoulder + elbow scores; MAS-Distal = wrist + fingers + thumb scores; MAS-total = composite sum of all five joints.

Relationships between GAS T-scores and other measures of outcome (e.g. measures of spasticity, global benefit and other standardised measures) were examined using Spearman rank correlation coefficients.

Stepwise logistic regression modelling was used to identify prognostic factors for achievement of the primary goal. Potential covariates included stroke aetiology, primary goal area, duration and severity of spasticity, time interval to follow-up, presence of confounding factors (including the presence of contractures; impaired motor, sensory, cognitive, emotional and cortical function (ie, neglect, dyspraxia, visuo-spatial deficits, etc). A backward elimination analysis was followed using a significance level of 0.2 to retain variables in the model.

The Hosmer and Lemeshow goodness-of-fit test[18] was used and 95% CI for the odds ratio (OR) estimated by the logistic model were calculated.

Results

Recruitment and participation

A total of 468 subjects were enrolled in this study of which 12 were excluded from the efficacy population (n=456). Eleven subjects were excluded because they did not attend their follow-up visit for assessment of GAS (n=5 lost to follow up, n=3 subject death unrelated to study medication and n=3 for other reasons). An additional subject was excluded as treatment was given in the lower (rather than the upper) limb. No subjects withdrew because of withdrawal of consent, lack of efficacy or adverse effect related to the BoNT-A treatment.

Demographics and disease characteristics

The geographic distribution and demographics of the efficacy population are described in detail elsewhere.[13] The mean (SD) age was 57 (13.5) years and mean (SD) time since onset of stroke was 61.4 (69.1) months. Fifty-eight percent of the population was male; 70% had had infarcts and 30% had haemorrhagic stroke. Left and right hemisphere localisation was approximately equal (47.1:51.1% respectively) and 3% had posterior circulation strokes.

Baseline characteristics are detailed in Table 1. Distal patterns of spasticity predominated. A quarter had evidence of fixed contractures and more than half had severe motor weakness. Over half of subjects (57.0%) had no useful hand function and 46% had sensory impairment. These findings confirm that the majority of subjects had chronic spasticity with severe impairment and therefore little potential for recovery of useful motor function. In contrast, cognitive and communication impairments were relatively uncommon and were mild for the most part.

Table 1. Baseline clinical characteristics of the efficacy population.

Parameter	Values	Range	n/missing or untestable
Distribution of spasticity (MAS ≥2), n (%)			
Shoulder	235 (55.7%)		422/34
Elbow	335 (75.1%)		446/10
Wrist	344 (77.8%)		442/14
Fingers	368 (82.9%)		444/12

Thumb	292 (66.8%)		437/19
Soft tissue shortening (limiting ≥half range), n (%)			456/0
Shoulder	156 (34.2%)		
Elbow	150 (32.9%)		
Wrist	179 (39.3 %)		
Hand	206 (45.2%)		
Motor paralysis (no useful function), n (%)			456
Proximal	95 (20.8%)		
Distal	260 (57.0%)		
Sensory, n (%)			447/9
Partial	208 (45.6%)		
Complete	20 (4.4%)		
Cognitive / communicative impairment, n (%)			
Cognitive	98 (21.5%)		455/1
Speech and language	159 (34.9%)		446/10
Neglect, dyspraxia or visuo-perceptual difficulties	60 (13.2%)		456/0
Other symptoms, which may impact on functional outcome, n (%)			456/0
Emotional / behavioural impairment	149 (32.7%)		
Pain*	78 (17.1%)		
Fatigue	48 (10.5%)		
Impairment scores (modified NIS)†	**Median (Q1–Q3)**	**Range**	**n/untestable**
Proximal upper limb motor score (arm raising / reaching)	2 (1–2)	0–3	456/0
Distal upper limb motor score (hand function)	3 (2–3)	0–3	456/0
Sensation	1 (0–2)	0–3	447/9
Communication impairment	0 (0–1)	0–3	455/1
Cognitive impairment	0 (0–0)	0–3	446/10
Spasticity (MAS)‡			**n/missing**
Distal composite MAS score	7.0 (6–9)	0–12	431/25

Proximal composite MAS score	4.0 (3–5)	0–8	422/34
Baseline outcome measures			
Total MAS score, mean (SD)	11.0 (3.3)	1–20	414/42
GAS weighted Score, mean (SD)	36.4 (7.7)	21.2–43.8	456/0

IQR, interquartile range; NIS, neurological impairment scale; SD, standard deviation

*Data extracted from injected segments at Baseline, when at least one muscle of the segment was injected.

†Modified NIS: The score range for each of the five domains is 0=none; 1=mild impairment affecting high-level function only; 2=significant impairment; 3=severe impairment, effectively preventing function. Further details are available from the corresponding author.

‡MAS composite scores: Proximal MAS score = shoulder + elbow scores; MAS-Distal = wrist + fingers + thumb scores; MAS-total = composite sum of all five joints. (Total composite scores were only calculated if individual MAS scores were recorded at all five joints.)

As multiple answers were possible, the sum of some percentages in this table may exceed 100%.

BoNT-A injection history

Approximately two-thirds of subjects (n=307; 67.3%) had received a previous injection of BoNT-A in the upper limb. The mean (SD) time since the last injection was 8.0 (11.5) months and the median time was 5 months (IQR 3–5, range: 1–102 months). Some had had treatment spanning several years.

The median time since first injection was 24 months (range: 3–168 months), but two-thirds of subjects had had BoNT-A treatment for over 1 year. The median number of BoNT-A injections previously received by subjects was 4 (IQR 1–8; range: 1–45).

BoNT-A treatment

In this cohort, abobotulinumtoxinA (Dysport) was the most commonly used agent (70.4%), followed by Botox onabotulinumtoxinA (Botox) (21.5%) and incobotulinumtoxinA (Xeomin) (7.7%); two patients received another local BoNT-A preparation. The median number of injected muscles was 5.0 (range: 1–15). There was very wide variation in the total dose of BoNT-A (see Table 2).

Table 2. BoNT-A treatment.

Current injection:			
Agent*	**Dysport**	**Botox**	**Xeomin**
	n=321	**n=98**	**n=35**
	(70.4%)	**(21.5%)**	**(7.7%)**

No. of injected muscles			
Median (IQR)	5 (2)	5 (2)	5 (2)
Range	1–11	1–15	3–9
Dose			
Total dose range (units)	40–1900	50–500	100–600
Localisation of injection (used for at least one muscle), n (%)			
EMG	91 (28.3%)	34 (34.7%)	6 (17.1%)
Electrical stimulation	145 (45.2%)	53 (54.1%)	9 (25.7%)

EMG, electromyography; IQR, interquartile range

*Two subjects received other BoNT-A preparations.

The most commonly injected muscles and doses, by treatment, are shown in Table 3. Most frequently injected were the long finger flexors, followed by biceps and brachioradialis. With the exception of pectoralis major (which was injected in 19.3% of patients), shoulder muscles were relatively rarely injected. Multiple injection points were most commonly used in the larger more proximal muscles, such as biceps and pectoralis major. Electrical stimulation was more commonly used to locate muscles than EMG (45.8% vs 29.2%), especially for the smaller muscles such as flexor pollicis longus.

At Visit 2, the median (range) follow-up time was 14 (2.6–32.3) weeks, further injection was planned in 361 (79.2%) subjects. Clinicians planned to inject the same muscles in 254 (70.4%) with the same dose in 227 (62.9%). In 134 (37.1%), a different dose was planned (increased in 26.3% and decreased in 10.8%), but only 10 (2.8%) planned to use a different agent.

Table 3. Most commonly injected muscles and technique within each upper limb segment.

Group / muscle	Total no. injected (%)*	No of units: median (IQR)			Range of units (min, max)			Multiple points	Use of EMG	Electrical stimulation
		Dysport	Botox	Xeomin	Dysport	Botox	Xeomin			
Shoulder	**N=147 (32.2%)**									
Pectoralis major	88 (19.3%)	200.0 (150.0)	30.0 (40.0)	70.0 (30.0)	30, 750	10, 100	20, 140	55 (62.5%)	11 (12.5%)	25 (28.4%)
Teres major	17 (3.7%)	75.0 (50.0)	10.0 (10.0)	50.0 (60.0)	50, 200	10, 50	40, 100	2 (11.8%)	8 (47.1%)	8 (47.1%)
Deltoideus	15 (3.3%)	100.0 (100.0)	50.0 (0.0)	N/A	50, 300	50, 50	N/A	1 (6.7%)	3 (20.0%)	7 (46.7%)
Subscapularis	14 (3.1%)	200.0 (100.0)	30.0 (0.0)	50.0 (0.0)	75, 320	20, 40	50, 50	3 (21.4%)	1 (7.1%)	11 (78.6%)
Latissimus dorsi	9 (2.0%)	120.0 (125.0)	55.0 (90.0)	40.0 (0.0)	75, 200	10, 100	40, 40	6 (66.7%)	4 (44.4%)	2 (22.2%)
Upper arm	**N=336 (73.7%)**									
Biceps brachii	270 (59.2%)	200.0 (150.0)	50.0 (10.0)	55.0 (40.0)	50, 750	20, 100	20, 100	208 (77.0%)	52 (19.3%)	70 (25.9%)
Brachialis	130 (28.5%)	150.0 (100.0)	50.0 (20.0)	60.0 (27.5)	20, 400	10, 100	30, 80	76 (58.5%)	30 (23.1%)	62 (47.7%)
Triceps brachii	18 (3.9%)	175.0 (100.0)	30.0 (25.0)	N/A	60, 300	20, 100	N/A	15 (83.3%)	8 (44.4%)	8 (44.4%)
Lower arm	**N=434 (95.2%)**									
Flexor digit. superficialis	325 (71.3%)	150.0 (100.0)	50.0 (35.0)	60.0 (37.5)	20, 500	15, 150	30, 100	195 (60.0%)	91 (28.0%)	151 (46.5%)
Flexor digit. profondus	265 (58.1%)	150.0 (100.0)	50.0 (30.0)	50.0 (20.0)	50, 600	15, 150	20, 200	142 (53.6%)	66 (24.9%)	114 (43.0%)
Flexor carpi radialis	262 (57.5%)	125.0 (100.0)	33.3 (25.0)	45.0 (40.0)	20, 350	5, 100	20, 80	83 (31.7%)	73 (27.9%)	99 (37.8%)
Brachioradialis	156 (34.2%)	112.5 (100.0)	40.0 (35.0)	50.0 (20.0)	25, 300	10, 75	20, 75	55 (35.3%)	29 (18.6%)	46 (29.5%)
Pronator teres	138 (30.3%)	100.0 (75.0)	40.0 (25.0)	40.0 (30.0)	25, 500	10, 100	10, 50	44 (31.9%)	26 (18.8%)	53 (38.4%)
Flexor pollicis longus	136 (29.8%)	100.0 (50.0)	25.0 (12.5)	35.0 (30.0)	20, 250	5, 50	10, 60	29 (21.3%)	31 (22.8%)	79 (58.1%)
Hand / fingers	**N=204 (44.7%)**									
Flexor pollicis brevis	47 (10.3%)	50.0 (50.0)	15.0 (12.5)	20.0 (0.0)	10, 200	5, 30	20, 40	7 (14.9%)	6 (12.8%)	19 (40.4%)
Adductor pollicis	37 (8.1%)	50.0 (22.5)	25.0 (15.0)	20.0 (20.0)	20, 125	10, 30	10, 30	0	8 (21.6%)	10 (27.0%)
Lumbricales	32 (7.0%)	100.0 (120.0)	25.0 (10.0)	40.0 (47.5)	50, 400	15, 40	20, 75	29 (90.6%)	8 (25.0%)	11 (34.4%)
Interossei dorsales	22 (4.8%)	150.0 (150.0)	25.0 (30.0)	N/A	50, 375	10, 80	N/A	20 (90.9%)	6 (27.3%)	9 (40.9%)
Opponens pollicis	18 (3.9%)	50.0 (50.0)	30.0 (20.0)	5.0 (0.0)	10, 120	20, 40	5, 5	0	3 (16.7%)	9 (50.0%)

Percentages are based on the number of subjects injected in the muscle, except * for which percentages are based on the number of subjects in the efficacy population.
EMG, electromyography; IQR, interquartile range

Concomitant treatments

Nearly two-thirds (61.6%) of patients were receiving physiotherapy in association with the BoNT-A treatment at follow up, and over a third (39.5%) of subjects also received occupational therapy. However, there was wide variation in the number of sessions received (see Table 4).

The types of concomitant treatments at baseline and follow up are shown in Table 4. At baseline, the frequency of concomitant treatments ranged from 18% (functional electrical stimulation) to 93% (passive stretching). By follow up, the overall frequency of concomitant therapies had diminished, although the range of modalities remained similar. Notably, the proportion of patents on antispasmodic medication fell from 46% to 28.5%.

Table 4. Concomitant treatments at baseline and follow up.

N (%)	Baseline	Visit 2
Physiotherapy		
1–4 sessions		33 (11.7%)
5–10 sessions		50 (17.8%)
11–20 sessions		74 (26.3%)
>20 sessions		120 (42.7%)
Unknown		4 (1.4%)
Occupational therapy		
1–4 sessions		34 (18.9%)
5–10 sessions		33 (18.3%)
11–20 sessions		46 (25.6%)
>20 sessions		63 (35.0%)
Unknown		4 (2.2%)
Splinting	188 (41.2%)	148 (32.5%)
Orthotics	114 (25.0%)	92 (20.2%)
Exercise	393 (86.2%)	360 (78.9%)
Passive stretching	423 (92.8%)	410 (89.9%)
Functional electrical stimulation	83 (18.2%)	58 (12.7%)
Positioning	266 (58.3%)	237 (52.0%)
Oral anti-spastic medication	210 (46.1%)	130 (28.5%)
No concomitant treatment	3 (0.7%)	12 (2.6%)

Primary and secondary goal areas

Primary and secondary goal areas set at baseline are shown in Table 5. Goals were most commonly set in the areas of passive function, impairment and active function followed by pain, and involuntary movement. Less commonly in this dataset, goals focused on mobility (ie, improvement in balance or gait quality by restoring freedom of upper limb movement) or other areas, such as cosmesis or supporting therapy interventions.

Overall, 363 (79.6%) (95% CI: 75.6–83.2) of patients achieved (or over-achieved) their primary goal with 355 (75.4%) (95% CI: 71.2–79.2%) achieving their secondary goal (see Table 5). Although the rate of achievement was lower (but not statistically significant) for active function goals in comparison with passive function and impairment goals, in this series, a total of 182 (primary and secondary) goals were set in relation to active function of which 122 (67.0%) were achieved, either as expected (73 [40.1%]) or beyond expectation (49 [26.9%]). Pain reduction was a goal for treatment in nearly one-third of patients (145 [31.8%]), and was achieved in 83.5%.

Table 5. Primary and secondary goal areas.

Goal area	Primary goals by area (n=456)			Secondary goals by area (n=471)		
	Goal set n (%)	Goal achieved n (%) (95% CI)	Partially achieved n (%)	Goal set n (%)	Goal achieved n (%) (95% CI%)	Partially achieved n (%)
Pain	61 (13.4%)	51(83.6%) (71.9–91.8%)	10 (16.4%)	84 (17.8%)	70 (83.3%) (73.6–90.6%)	6 (7.1%)
Passive function (Ease of care)	132 (29.0%)	113 (85.6%) (78.4–91.1%)	11 (8.3%)	109 (23.1%)	84 (77.1%) (68.0–84.6%)	15 (13.9%)
Active function (Active motor use of limb)	104 (22.8%)	75 (72.1%) (62.5–80.5%)	13 (12.5%)	78 (16.5%)	47 (60.3%) (48.5–71.2%)	18 (23.1%)
Mobility (balance, gait)	10 (2.2%)	7 (70.0%) (34.8–93.3%)	3 (30.0%)	19 (4.0%)	14 (73.7%) (48.8–90.9%)	2 (10.5%)
Involuntary movement (associated reaction)	41 (9.0%)	32 (78.0%) (62.4–89.4%)	5 (12.2%)	56 (11.9%)	45 (80.4%) (67.6–89.8%)	6 (10.7%)
Impairment (e.g. range of movement)	105 (23.0%)	82 (78.1%) (69.0–85.6%)	11 (10.5%)	117 (24.8%)	91 (77.8%) (69.2–84.9%)	13 (11.2%)
Other	3 (0.7%)	3 (100%) (29.2–100%)	0	5 (1.1%)	3 (60.0%) (14.7–94.7%)	2 (40.0%)
Total	456	363 (79.6%) (75.6–83.2%)	53 (11.6%)	471	355 (75.4%) (71.2–79.2%)	63 (13.4%)

Secondary outcomes

At follow-up, the mean (SD) weighted GAS T-score was 52.0 (10.1) (median 50.0, IQR 13.8), giving a mean (SD) change from baseline of 17.6 (11.0; 95% CI: 16.6–18.6) (p<0.001). Baseline and mean change from baseline in GAS T-scores were similar between BoNT-A preparations.

The mean (SD) MAS total score at follow up was 8.4 (3.4) giving a mean (SD) change from baseline of –2.6 (2.6; 95% CI: –2.9 to –2.4) (p<0.0001). Overall, 90.1% of investigators and 85.8% of patients considered BoNT-A treatment to be of benefit.

GAS T-scores correlated, albeit rather weakly, with reduction in total MAS at follow up (Spearman rho 0.28; p<0.0001). They correlated more strongly, however, with global assessment of benefit (Spearman rho 0.38; p<0.0001 for investigator assessment and 0.45; p<0.0001 for patient assessment).

Standardised measures of upper limb spasticity

Reflecting common impairment, the range of active (56.1%) and passive (54.4%) motion were the most commonly recorded standardised measures of upper limb spasticity used at baseline (Table 6). Approximately one-third (34.4%) of patients also used a visual analogue rating to reflect symptoms such as pain or carer burden. However, only a very small minority (7.2%) had a standardised measure of functional outcome recorded, such as the Arm Activity Scale (ArMA – a self-report measure of active and passive function) (5.9%) or the Leeds Adult Spasticity Impact Scale (LASIS – an investigator-reported measure of passive function) (1.3%). As shown in Table 6, the GAS T-score correlated strongly with change in these standardised measures wherever they were measured.

Table 6. Standardised measures to assess upper limb spasticity at baseline.

Standardised measure	Recorded at baseline	Recorded at follow up	No. showing change	Correlation with GAS T-Score	
	n (%)*	n (%)*	n (%)	rho	p-value
Impairment					
Tardieu	77 (16.9%)	62 (13.6%)	56 (90.3%)	0.43	<0.001
Active range of motion	256 (56.1%)	231 (50.7%)	137 (59.3%)	0.41	<0.001
Passive range of motion	248 (54.4%)	249 (54.6%)	172 (69.1%)	0.43	<0.001
Associated Reaction Rating Scale[23]	24 (5.3%)	26 (5.7%)	14 (53.8%)	0.76	<0.001
Symptoms/carer report					
Visual Analogue Scale†	157 (34.4%)	139 (30.5%)	109 (78.4%)	0.46	<0.001

Function					
Leeds Adult Spasticity Impact Scale[3]	6 (1.3%)‡	5 (1.1%)‡		–	–
Arm Activity Scale[24]	27 (5.9%)	27 (5.9%)	14 (51.9%)	0.63	<0.001

*Percentage of efficacy population.

†Parameters measured with VAS were not specified

‡Numbers too small to compute.

GAS, goal attainment scaling

Identification of potential prognostic factors

Potential predictors with a p-value <0.20 were the primary goal area, primary goal score at baseline, first administration of BoNT-A, and cortical function. These were entered into the multivariate logistic model. Results indicated that patients with impaired cortical function were half as likely to respond to treatment (OR 0.48 [95% CI: 0.26–0.89]). The most likely explanation for this is that patients with dyspraxia, neglect or poor visuospatial perception are more likely to have difficulty complying with and carrying through any treatment programme.

A non-significant trend was also seen for poorer goal achievement in patients receiving their first administration of BoNT-A, compared with those who had had previous injections (OR 0.69 (95% CI: 0.43–1.12). Possible explanations for this may be that dose-ranging and muscle selection had been optimised through previous injections, or that patients benefited from their prior experience to better define their treatment goals.

Discussion

The findings from this large prospective international cohort study showed overall good response rates to BoNT-A injection delivered in the context of routine clinical practice for the management of upper limb spasticity. The study demonstrated wide variation in clinical practice with respect to the selection of muscles and approach to injection, highlighting the need for further systematic research into which approaches are likely to be most effective for which patients. Nevertheless, almost 80% of patients achieved their primary goal, as defined by the patients – together with their clinical team – at the start of treatment. The study also confirms the feasibility of collecting data across a large international community, using an eCRF.

Patient-reported outcomes are increasingly recognised as important indicators of quality of daily life for patients and/or their carers, and in this study GAS was selected as the primary endpoint in order to evaluate the benefits of treatment in terms of the attainment of individual person-centred goals. It also provides

important insight into the nature of goals that are chosen as priorities for treatment, and also those most likely to be achieved.

In keeping with findings from other studies,[11, 25] improvement in passive function was the most frequently selected primary goal area for treatment (29%), and primary goals were achieved in around 86% of cases. Goals for active function were also commonly set in nearly a quarter of patients (22%). Perhaps unsurprisingly in this population with chronic spasticity and severe motor impairment, the achievement rate was somewhat lower for active function. Nevertheless, 72% of patients achieved their primary active function goal. The second most commonly achieved primary goal area was pain (set in 13% of patients), where again achievement was around 84%. Functional goals relating to involuntary movements and mobility were less commonly set in this population but were nevertheless achieved at broadly similar rates overall. The wide diversity in treatment goals between patients, however, highlights the importance of defining the primary treatment intentions clearly and then evaluating outcome specifically in relation to those.

Over and above achievement of the primary goal, the GAS T-score provides an overall assimilation of attainment of primary and secondary goals regardless of the number of goals set. Some authors have cast doubt on the value of calculating a GAS T-score.[26] In this study, we went to considerable lengths to ensure that GAS was applied rigorously and goals were focused on functional gains,[13] so it is worth reflecting on the added value on the GAS T-score in this context.

- If goals are set in an unbiased fashion, and are neither over-ambitious or over-cautious, the mean GAS T-score should be around 50 (±SD 10).[21] Our mean (SD) GAS T-score at follow up of 52 (10.1) provides a useful quality check of the team's ability to set and negotiate achievable goals, neither over- nor under-estimating the expected outcome.
- Previous authors have recorded that GAS change scores >10 represent clinically meaningful change.[11, 17, 21] In this study, the mean improvement in GAS T-score from baseline to follow up was 17.6. This confirms findings from one RCT,[16] and provides supportive evidence that BoNT-A produces clinically meaningful change at a functional level in the treatment.
- Importantly, GAS T-scores provide a single numerical evaluation of overall goal achievement for comparison with other outcome measures. If the gains occur as a result of reduction in spasticity, some correlation with change in MAS score would be expected, even though the relationship may not necessarily be very strong [11, 16] and indeed this was found. The significant correlations with other standardised measures (especially the Arm Activity Scale) provide further support for GAS as a meaningful person-centred measure of outcome in this context.

The findings of this study also give insight into the longer term treatment of upper limb spasticity. Many of the patients enrolled in this study had received several previous BoNT-A injections, often over several years, suggesting that patients continue to receive benefit from repeat treatments, as indeed was shown by our findings. Additionally, the mean duration since last BoNT-A treatment was 8 months, suggesting that patients with upper limb spasticity may not require re-treatment as frequently as in other conditions (such as cervical dystonia). The reduction in use of other antispasmodic medication suggests that successful treatment may possibly have allowed the reduction or withdrawal of other systemic agents. Many patients were receiving other concomitant therapies at the time of their injection (eg, therapy, splinting home exercise, etc). It is possible that these interventions play a role in reducing the frequency of BoNT-A injections, but insufficient detail regarding the frequency, duration and content of therapies was collected in this study to examine this possibility in great detail. Further longitudinal studies with systematic recording of concomitant interventions are needed to confirm these observations and to 'open the black box' of a holistic approach to spasticity management.

The authors recognise a number of limitations to this study:

- Although there was a wide geographical distribution of centres across three continents, the numerical representation in each region was by no means representative. The recruitment of just 5–12 patients per site may have been insufficient to ensure adequate representation of practice in each centre, especially given the wide diversity of patients and goals for treatment.
- The relatively low frequency of reported impairments in cognitive and communicative function suggests either that there is selection bias (patients with these problems are less likely to be referred for treatment), or under-reporting (clinicians focussed on treating spasticity are not good at identifying associated impairments which may potentially impact on outcome).
- For pragmatic reasons, change on standardised outcome measures was recorded only subjectively on a standard scale of –2 to +2 and should therefore be interpreted with caution.
- The study was not sufficiently powered to perform a detailed investigation of prognostic factors for outcome, but has given some preliminary insights into potential prognostic factors within the baseline dataset.

Despite these limitations, the study provides useful information about the way that BoNT-A is used in clinical practice around the world, and demonstrates that its effectiveness in the management of post-stroke spasticity can be documented using individual person-centred goals. More importantly, a large majority of the patients achieved their treatment goals, mainly in terms of passive and active functions, demonstrating that BoNT-A injections contribute to an improvement in the daily life of the patients beyond improvement of tone

or spasticity. Further secondary analyses will be presented separately to explore the impact of different treatment strategies including injection technique, early versus late treatment and the role of concomitant therapies. Further refinement of the tools and dataset are now in train to produce a concise Upper Limb Spasticity Index that combines GAS with selected standardised measures targeted on the key goals for intervention (including the GAS evaluation of outcome in upper limb spasticity [GAS-EOUS] tool).[27] Tools have also been developed for recording systematically the nature and content of any concomitant treatments provided in routine clinical practice. These tools will be used in the next phase of the ULIS programme (ULIS-III) to expand the cohort and to capture the benefits of integrated spasticity management in a fully generalisable sample recorded longitudinally over several cycles of BoNT-A treatment.

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Contributor statement

LTS wrote the first draft of this manuscript. LTS, KF and JJ were involved in data collection and assembly of data, manuscript review and critique, and final approval of manuscript. PM was involved in the concept and design, data analysis, manuscript writing, manuscript review and critique, and final approval of manuscript.

Competing interests:

LTS, KF and JJ all received honoraria and conference attendance fees from Ipsen for the undertaking of this research.

- LTS has a specific interest in outcomes evaluation and has published extensively on the use of GAS in this context, as well as a number of the other standardised measures (including the Associated Reaction Scale, the Arm Activity Scale and the Neurological Impairment Scale). All of these tools are freely available, however, and she has no personal financial interest in any of the material mentioned in this article.

- KF has a specific interest in outcomes evaluation and the use of the International Classification of Function in clinical settings. He has no personal financial interest in any of the material mentioned in this article.
- JJ has particular interest in spasticity clinical and instrumental evaluation methods, goal setting, treatment strategies/techniques and outcome measurement. He has no personal or financial interest in any of the material mentioned in this article.
- PM is an employee of Ipsen.

Previous publications:

Turner-Stokes L, Fheodoroff K, Jacinto J, Maisonobe P, Zakine B. Upper Limb International Spasticity Study: Rationale and protocol for a large international, multicentre prospective cohort study investigating management and goal attainment following treatment with botulinum toxin-A in real-life clinical practice. *BMJ Open* 2013;3(3):e002230.

Data sharing:

No additional data available.

References

1. RCP/BSRM. Spasticity in adults: Management using Botulinum Toxin. National Guidelines. London: Royal College of Physicians 2008.

2. Bakheit AM, Sawyer J. The effects of botulinum toxin treatment on associated reactions of the upper limb on hemiplegic gait--a pilot study. *Disabil Rehabil* 2002;24:519–22.

3. Bhakta BB, Cozens JA, Chamberlain MA, *et al*. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. *J Neurol Neurosurg Psychiatr* 2000;69:217–21.

4. Bhakta BB, Cozens JA, Bamford JM, *et al*. Use of botulinum toxin in stroke patients with severe upper limb spasticity. *J Neurol Neurosurg Psychiatr* 1996;61:30–5.

5. Brashear A, Gordon MF, Elovic E, *et al*. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Eng J Med* 2002;347:395–400.

6. Rodriquez AA, McGinn M, Chappell R. Botulinum toxin injection of spastic finger flexors in hemiplegic patients. *Am J Phys Med Rehabil* 2000;79:44–7.

7. Simpson DM, Alexander DN, O'Brien CF, *et al*. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996;46:1306–10.

8. Smith SJ, Ellis E, White S, *et al*. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin Rehabil* 2000;14:5–13

9. Shaw L, Rodgers H, Price C, *et al*. BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. *Health Technol Assess* 2010;14:1–113, iii–iv.

10. Teasell R, Foley N, Pereira S, *et al*. Evidence to practice: botulinum toxin in the treatment of spasticity post stroke. *Top Stroke Rehabil* 2012;19:115–21.

11. Turner-Stokes L, Baguley I, De Graff S, *et al*. Goal attainment scaling in the evaluation of treatment of upper limb spasticity with botulinum toxin: a secondary analysis from a double blind placebo controlled randomised clinical trial. *J Rehabil Med* 2010;42:81–9.

12. Baguley IJ, Nott MT, Turner-Stokes L, *et al*. Investigating muscle selection for botulinum toxin-A injections in adults with post-stroke upper limb spasticity. *J Rehabil Med* 2011;43:1032–7.

13. Turner-Stokes L, Fheodoroff K, Jacinto J, *et al*. Upper Limb International Spasticity Study: Rationale and protocol for a large international, multicentre prospective cohort study investigating management and goal attainment following treatment with botulinum toxin-A in real-life clinical practice. *BMJ Open* 2013;3:e002230.

14. Kiresuk T, Sherman R. Goal attainment scaling: a general method of evaluating comprehensive mental health programmes. *Comm Ment Health J* 1968;4:443–53.

15. Ashford S, Turner-Stokes L. Goal attainment for spasticity management using botulinum toxin. *Physiother Res Int* 2006;11:24–34.

16. McCrory P, Turner-Stokes L, Baguley IJ, *et al*. Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomised placebo-controlled study of the effects on quality of life and other person-centred outcomes. *J Rehabil Med* 2009;41:536–44.

17. Turner-Stokes L, Williams H, Johnson J. Goal Attainment Scaling: does it provide added value as a person-centred measure for evaluation outcome in neurorehabilitation following acquired brain injury? *J Rehabil Med* 2009;41:528–35.

18. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.

19. Thu A, Casey R, Turner-Stokes L, et al. Inter-rater Reliability of the Neurological Impairment Scale (NIS): A Standard Impairment Set for Neurorehabilitation Populations (AAPMR Annual Assembly Poster 44). *Phys Med Rehabil* 2011;3(10 Suppl.):S191.

20. Turner-Stokes L, Siegert RJ, Thu A, *et al*. The Neurological Impairment Scale: reliability and validity as a predictor of functional outcome in neurorehabilitation. *Disabil Rehabil* 2013 (In press).

21. Turner-Stokes L. Goal attainment scaling in rehabilitation; a practical guide. *Clin Rehabil* 2009;23:362–70.

22. Turner-Stokes L, Williams H. Goal attainment scaling: a direct comparison of alternative rating methods. *Clin Rehabil* 2010;24:66–73.

23. Macfarlane A, Turner-Stokes L, De Souza L. The associated reaction rating scale: a clinical tool to measure associated reactions in the hemiplegic upper limb. *Clin Rehabil* 2002;16:726–35.

24. Ashford S, Turner-Stokes L, Siegert RJ, *et al*. Initial psychometric evaluation of the Arm Activity Measure (ArmA): a measure of activity in the hemiparetic arm. *Clin Rehabil* 2013;20 Feb [Epub ahead of print].

25. Bakheit AM, Zakine B, Maisonobe P, *et al*. The profile of patients and current practice of treatment of upper limb muscle spasticity with botulinum toxin type A: an international survey. *Int J Rehabil Res* 2010;33:199–204.

26. Tennant A. Goal attainment scaling: current methodological challenges. *Disabil Rehabil* 2007;29:1583–8.

27. Turner-Stokes L, Ashford S, De Graaff S, *et al*. The GAS-EOUS tool – a framework for evaluation of outcome in upper limb spasticity. *Neurorehabil Neural Repair* 2012;26:695–804 (Abstract 200).

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Upper Limb International Spasticity Study-II (ULIS-II): A large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management: Results

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ABSTRACT

Objective: To describe real-life practice and person-centred outcomes in the treatment of post-stroke upper limb spasticity with botulinum toxin A (BoNT-A).

Design: Observational, prospective study.

Setting: 84 secondary care centres in 22 countries.

Participants: 456 adults (≥18 years) with post-stroke upper limb spasticity treated with one cycle of BoNT-A.

Methods/outcomes: Muscle selection, BoNT-A preparation, injection technique, and timing of follow up were conducted according to routine practice. Primary outcome: achievement of the patient's primary goal for treatment using goal-attainment scaling (GAS). Measurements of spasticity, standardised outcome measures and global benefits were also recorded.

Results: The median number of injected muscles was 5 (range 1−15) and the most frequently injected muscles were the long finger flexors, followed by biceps and brachioradialis. The median (range) follow-up time was 14 (2.6 to 32.3) weeks. Common primary treatment goals were passive function (132 [28.9%]) active function (104 [22.8%]) pain (61 [13.4%]), impairment (105 [23.0%]), involuntary movement (41 [9.0%]) and mobility (10 [2.2%]). Overall, 363 (79.6%) (95% CI: 75.6–83.2%) of patients achieved (or over-achieved) their primary goal and 355 (75.4%) (95% CI: 71.2–79.2%) achieved their secondary goal. Mean (SD) change from baseline in GAS T-scores was 17.6 (11.0) (95% CI: 16.4–18.8; p<0.001). GAS T-scores were strongly correlated with global benefit and other standard measures (correlations of 0.38 and 0.63, respectively; p<0.001).

Conclusion: BoNT-A demonstrated a clinically significant effect on goal attainment for the real-life management of upper limb spasticity following stroke. The study confirms the feasibility of a common international dataset to collect systematic prospective data, and of using GAS to capture person-centred outcomes relating to passive and active function, and to pain.

Registration: ClinicalTrials.gov identifier: NCT01020500

ARTICLE SUMMARY

Article focus

- A large international observational cohort study (the Upper Limb International Spasticity [ULIS]-II) to describe the use of BoNT-A for management of upper limb spasticity in the context of real-life clinical practice.
- To quantify and characterise the achievement of person centred goals following one BoNT-A injection cycle delivered in the context of routine clinical practice.
- To describe the variations in clinical practice and explore prognostic factors that may impact on outcome.

Key messages

- Despite wide variations in the approach to clinical practice, a large majority (80%) of the patients achieved their treatment goals, mainly in terms of passive and active functions and pain reduction.
- The results provide evidence that BoNT-A injections may contribute to an improvement in the daily life of patients and their carers beyond simply improvement of tone or spasticity.

Strengths and limitations of this study

- The wide geographical distribution of centres across three continents is a strength of this study, but recruitment of only 5–12 patients per site may not adequately reflect the patient population of each centre.
- The study lays the foundation for larger international longitudinal cohort studies to explore further the characteristics and treatment approaches that predict best outcomes in BoNT-A treatment of upper limb spasticity

INTRODUCTION

Spasticity is a common and distressing sequela of stroke, which interferes with upper limb movement and limits use of the limb for active functional tasks, as well as impacting on mobility and increasing the burden on caregivers.[1]

From controlled clinical trials (CCTs) conducted to date,[2-9] it is established that botulinum toxin type A (BoNT-A) is safe and effective in reducing spasticity. However, functional gains have been harder to demonstrate,[10] especially as there is wide diversity in the pattern of spasticity and goals for treatment.[11] As well as individual variation in response, we know that clinicians vary in their approach to treatment with respect to selection of muscle, injection technique, and follow-up therapy. These variations appear to have more to do with clinician bias and local availability of services than with patient presentation.[12]

It is now time to extend the field of investigation in this area to understand how BoNT-A is used in routine clinical practice around the world and gain better understanding of how to select patients most likely to respond to treatment. Establishing what treatment approaches work best based on clinical presentation would also be of great clinical value. To do this, we will need to build a consistent body of data that captures clinically important change at an individual level and is of sufficient size and generalisability to enable us to answer these critical questions.

The Upper Limb International Spasticity (ULIS) programme consists of a series of large, international observational studies to describe current clinical practice in the application of BoNT-A in this context, and to work towards the development of a common international dataset for prospective systematic recording of longitudinal outcomes.[13] Importantly, the programme incorporates elements of training in the use of agreed outcome measures, and development of electronic data-collection tools suitable for use by the wider international community.

Goal-attainment scaling (GAS) was chosen as the primary person-centred outcome measure to capture the diversity of treatment intentions that are important to the individual patient and their family/carers. First described by Kiresuk and Sherman in the 1960s,[14] GAS is increasingly used in the context of spasticity management[15, 16] and is shown to be sensitive to changes following focal intervention that are not detected by more global measures.[11] Although GAS provides a useful measure of achievement of treatment intention, it does not measure outcome *per se*, and therefore does not stand alone but is used alongside other standardised outcome measures.[17] It is therefore pertinent to understand the relationship between GAS and other outcome tools.

This second stage in the ULIS programme (ULIS-II) is a large, international, observational cohort study to describe real-life practice and outcomes in the treatment of post-stroke upper limb spasticity with BoNT-A. This is the first large international cohort study to use GAS as a primary outcome measure for the person-centred evaluation of treatment with BoNT-A for spasticity. In a separate paper, we have presented the rationale and methodology for ULIS-II in detail, and described the steps taken to ensure the validity of GAS as a measure of functional gains in this context.[13] Here we describe the baseline clinical characteristics, details of interventions, and the primary results in accordance with the STROBE guidelines for presentation of cohort studies.[18]

Aims and Objectives

The primary objective of the ULIS-II study was to assess the responder rate (as defined by the achievement of the primary goal from GAS) following one BoNT-A injection cycle delivered in the context of routine clinical practice.

Secondary objectives were to:

- Describe the baseline characteristics, including demographics, duration and pattern of spasticity, concomitant therapies/medication, etc
- Describe injection practices (muscle identification, dosage, dilution, etc)
- Assess achievement of secondary goals and evaluate the overall attainment of treatment goals using the GAS T-score as a patient-centred measure of outcome
- Document the use of standardised outcome measures and their results
- Assess the global benefits as perceived by the investigator and the patient.

Additional exploratory objectives, addressed through the analysis plan, were to:

- Describe the common goal areas for treatment and to identify those in which goals were most often achieved
- Examine the relationship between GAS and other standardised outcome measures
- Identify any prognostic factors for response.

Methods

Full details of the methodology are described elsewhere.[13] In brief, ULIS-II was an 18-month, post-marketing, international, multicentre, observational, prospective, before-and-after study, conducted in 84 centres in 22 countries spanning Europe, Pacific Asia and South America.

The study was conducted in compliance with Guidelines for Good Pharmacoepidemiology Practices (GPP). Marketing authorisation for the use of BoNT-A in this context was ensured for each participating country prior to the start of the study. Ethical approval and written informed consent to the recording of anonymous data was obtained in countries where this was required.

Recruitment took place between January 2010 and May 2011. To limit the potential bias from over-recruiting sites, the number of patients was limited to 5–12 patients per treatment centre. All centres recruited at least 5 patients, but 25 of the more experienced centres (which were usually also larger) could recruit up to 12 patients. This was allowed to try to ensure a representative sample from clinicians with experience in this area of practice. It also offers the opportunity for future sub-analysis of the differences between experienced and less experienced injectors.

Centres included consecutive patients – or spaced inclusions in a pre-defined manner (e.g. one for every 2–3 patients) if necessary for pragmatic reasons – until their recruitment target was achieved.

Study population

The main inclusion criteria required patients to be consenting adults ≥18 years with post-stroke upper limb spasticity in whom a decision had already been made to inject BoNT-A, and who had had no previous treatment with BoNT-A or BoNT-B within the last 12-weeks. Agreement on an achievable goal set and ability to comply with the prescribed treatment were also required. The efficacy population analysed here included all subjects who received one BoNT-A injection and who underwent a post-injection visit including an assessment of GAS.

Study schedule

Baseline evaluation at Time 1 included:

- Demography and history of the stroke including type, location and time since onset.
- The pattern of impairment in the affected upper limb (modified Neurological Impairment Scale.[19, 20]
- Previous/concomitant treatments for upper limb spasticity.
- Clinical examination, including measurements of spasticity and other standardised outcome measures as routinely performed in that centre.
- Goal setting and GAS applied using the 'GAS-light' method,[21] as detailed in the rationale and methodology paper,[13] with emphasis on setting SMART (specific, measurable, achievable, realistic and timed) function-related goals agreed between investigator, the patient and the treating team.

- One primary and up to three secondary goals were set and assigned to one of seven goal categories.

Injection of BoNT-A

To reflect real-life practice in this observational study, physicians were free to choose targeted muscles, BoNT-A preparation, injected doses, number of points and volume for each point, and use of EMG/electrical stimulation in accordance with their usual practice, and with their local Summary of Product Characteristics and therapeutic guidelines. The timing of follow up was at the discretion of the investigator, based on their usual practice and the nature of the goals set, usually between Month 3 and Month 5.

Follow-up evaluation at Time 2 included:

- Achievement of primary and secondary GAS goals rated on a 6-point verbal rating scale, and transcribed within the computer software to the 5-point numerical scale (range –2 to +2), and the GAS T-score.
- Any concomitant treatments for upper limb spasticity given since baseline.
- Clinical examination including measurements of spasticity as normally routinely performed.
- Global assessments of benefits were rated by the investigator and patient as: 'great benefit (+2)', 'some benefit (+1)', 'same (0)', 'worse (–1)', or 'much worse (–2)'.
- Change on any standardised measures performed was recorded on the same 5-point scale.
- The next therapeutic strategy – including any planned re-injection with BoNT-A – whether using the same agent and protocol or an adjusted one.

As this was an observational study, reporting of related adverse events followed the standard regulations related to spontaneous adverse event reporting for marketed products.

Study size

The sample size calculation was based on an estimate that 60% of patients would achieve their primary goal following their first BoNT-A injection cycle. Using a 5% two-sided significance level, with a power of 80%, 450 patients were needed to allow estimation of this proportion with a precision of 4.5%. This sample size also allowed the detection of potential prognostic factors to response (based on detection of odds ratio larger or equal to 2).

Statistical analysis

Data were entered by the treating clinicians into an electronic case report form (eCRF). After cleaning and validation of the dataset, statistical evaluations were performed using Statistical Analysis System (SAS)® (version 9).

Analyses were conducted on the efficacy population. For the primary statistical analysis, 'Responders' were those who achieved their primary goal (GAS score 0, 1 or 2) (primary statistical analysis).

- Baseline characteristics and efficacy evaluations are presented as descriptive statistics, including 95% confidence intervals (95% CI) where relevant.
- Mean and standard deviation (SD) are reported for interval quality data, including long-ordinal data that fulfilled the criteria for normal distribution (e.g. Modified Ashworth Scale [MAS] total and GAS T-scores).
- Confidence intervals (95% CI) for percentage were calculated as p±1.96 x Standard Error. Standard errors were calculated as √(pq/n), where p is the rate, q=1-rate and n=sample size.
- Short ordinal data are described by median and inter-quartile range (IQR) and analysed using non-parametric statistical techniques.

As originally described by Kiresuk and Sherman, the GAS T-score provides a composite score (the sum of the attainment levels × the relative weights [optional] for each goal) transformed into a standardised measure with a mean of 50 and standard deviation of 10. Several different scoring methods are currently used in the literature to account for partial achievement of goals in the GAS.[22] In this study, baseline scores were rated as −1 = 'some function' and –2 = 'no function' with respect to the goal. T-scores were calculated with weighting (importance), and partial achievement was rated as –1 to conserve the normal distribution of scores.[22]

MAS scores were recorded for the shoulder, elbow, wrist, fingers and thumb joints.
Scores of '1+' were entered as 1.5 in the calculation of the total MAS score and combined to composite scores as follows: MAS-Proximal = shoulder + elbow scores; MAS-Distal = wrist + fingers + thumb scores; MAS-total = composite sum of all five joints.

Relationships between GAS T-scores and other measures of outcome (e.g. measures of spasticity, global benefit and other standardised measures) were examined using Spearman rank correlation coefficients.

Stepwise logistic regression modelling was used to identify prognostic factors for achievement of the primary goal. Potential covariates included stroke aetiology, primary goal area, duration and severity of spasticity, time interval to follow-up, presence of confounding factors (including the presence of contractures; impaired motor, sensory, cognitive, emotional and cortical function (ie, neglect, dyspraxia, visuo-spatial deficits, etc). A backward elimination analysis was followed using a significance level of 0.2 to retain variables in the model.

The Hosmer and Lemeshow goodness-of-fit test[18] was used and 95% CI for the odds ratio (OR) estimated by the logistic model were calculated.

Results

Recruitment and participation

A total of 468 subjects were enrolled in this study of which 12 were excluded from the efficacy population (n=456). Eleven subjects were excluded because they did not attend their follow-up visit for assessment of GAS (n=5 lost to follow up, n=3 subject death unrelated to study medication and n=3 for other reasons). An additional subject was excluded as treatment was given in the lower (rather than the upper) limb. No subjects withdrew because of withdrawal of consent, lack of efficacy or adverse effect related to the BoNT-A treatment.

Demographics and disease characteristics

The geographic distribution and demographics of the efficacy population are described in detail elsewhere.[13] The mean (SD) age was 57 (13.5) years and mean (SD) time since onset of stroke was 61.4 (69.1) months. Fifty-eight percent of the population was male; 70% had had infarcts and 30% had haemorrhagic stroke. Left and right hemisphere localisation was approximately equal (47.1:51.1% respectively) and 3% had posterior circulation strokes.

Baseline characteristics are detailed in Table 1. Distal patterns of spasticity predominated. A quarter had evidence of fixed contractures and more than half had severe motor weakness. Over half of subjects (57.0%) had no useful hand function and 46% had sensory impairment. These findings confirm that the majority of subjects had chronic spasticity with severe impairment and therefore little potential for recovery of useful motor function. In contrast, cognitive and communication impairments were relatively uncommon and were mild for the most part.

Table 1. Baseline clinical characteristics of the efficacy population.

Parameter	Values	Range	n/missing or untestable
Distribution of spasticity (MAS ≥2), n (%)			
Shoulder	235 (55.7%)		422/34
Elbow	335 (75.1%)		446/10
Wrist	344 (77.8%)		442/14
Fingers	368 (82.9%)		444/12

Thumb	292 (66.8%)		437/19
Soft tissue shortening (limiting ≥half range), n (%)			456/0
Shoulder	156 (34.2%)		
Elbow	150 (32.9%)		
Wrist	179 (39.3 %)		
Hand	206 (45.2%)		
Motor paralysis (no useful function), n (%)			456
Proximal	95 (20.8%)		
Distal	260 (57.0%)		
Sensory, n (%)			447/9
Partial	208 (45.6%)		
Complete	20 (4.4%)		
Cognitive / communicative impairment, n (%)			
Cognitive	98 (21.5%)		455/1
Speech and language	159 (34.9%)		446/10
Neglect, dyspraxia or visuo-perceptual difficulties	60 (13.2%)		456/0
Other symptoms, which may impact on functional outcome, n (%)			456/0
Emotional / behavioural impairment	149 (32.7%)		
Pain*	78 (17.1%)		
Fatigue	48 (10.5%)		
Impairment scores (modified NIS)†	**Median (Q1–Q3)**	**Range**	**n/untestable**
Proximal upper limb motor score (arm raising / reaching)	2 (1–2)	0–3	456/0
Distal upper limb motor score (hand function)	3 (2–3)	0–3	456/0
Sensation	1 (0–2)	0–3	447/9
Communication impairment	0 (0–1)	0–3	455/1
Cognitive impairment	0 (0–0)	0–3	446/10
Spasticity (MAS)‡			**n/missing**
Distal composite MAS score	7.0 (6–9)	0–12	431/25

Proximal composite MAS score	4.0 (3–5)	0–8	422/34
Baseline outcome measures			
Total MAS score, mean (SD)	11.0 (3.3)	1–20	414/42
GAS weighted Score, mean (SD)	36.4 (7.7)	21.2–43.8	456/0

IQR, interquartile range; NIS, neurological impairment scale; SD, standard deviation

*Data extracted from injected segments at Baseline, when at least one muscle of the segment was injected.

†Modified NIS: The score range for each of the five domains is 0=none; 1=mild impairment affecting high-level function only; 2=significant impairment; 3=severe impairment, effectively preventing function. Further details are available from the corresponding author.

‡MAS composite scores: Proximal MAS score = shoulder + elbow scores; MAS-Distal = wrist + fingers + thumb scores; MAS-total = composite sum of all five joints. (Total composite scores were only calculated if individual MAS scores were recorded at all five joints.)

As multiple answers were possible, the sum of some percentages in this table may exceed 100%.

BoNT-A injection history

Approximately two-thirds of subjects (n=307; 67.3%) had received a previous injection of BoNT-A in the upper limb. The mean (SD) time since the last injection was 8.0 (11.5) months and the median time was 5 months (IQR 3–5, range: 1–102 months). Some had had treatment spanning several years.

The median time since first injection was 24 months (range: 3–168 months), but two-thirds of subjects had had BoNT-A treatment for over 1 year. The median number of BoNT-A injections previously received by subjects was 4 (IQR 1–8; range: 1–45).

BoNT-A treatment

In this cohort, abobotulinumtoxinA (Dysport) was the most commonly used agent (70.4%), followed by Botox onabotulinumtoxinA (Botox) (21.5%) and incobotulinumtoxinA (Xeomin) (7.7%); two patients received another local BoNT-A preparation. The median number of injected muscles was 5.0 (range: 1–15). There was very wide variation in the total dose of BoNT-A (see Table 2).

Table 2. BoNT-A treatment.

Current injection:			
Agent*	**Dysport**	**Botox**	**Xeomin**
	n=321	**n=98**	**n=35**
	(70.4%)	**(21.5%)**	**(7.7%)**

No. of injected muscles			
Median (IQR)	5 (2)	5 (2)	5 (2)
Range	1–11	1–15	3–9
Dose			
Total dose range (units)	40–1900	50–500	100–600
Localisation of injection (used for at least one muscle), n (%)			
EMG	91 (28.3%)	34 (34.7%)	6 (17.1%)
Electrical stimulation	145 (45.2%)	53 (54.1%)	9 (25.7%)

EMG, electromyography; IQR, interquartile range

*Two subjects received other BoNT-A preparations.

The most commonly injected muscles and doses, by treatment, are shown in Table 3. Most frequently injected were the long finger flexors, followed by biceps and brachioradialis. With the exception of pectoralis major (which was injected in 19.3% of patients), shoulder muscles were relatively rarely injected. Multiple injection points were most commonly used in the larger more proximal muscles, such as biceps and pectoralis major. Electrical stimulation was more commonly used to locate muscles than EMG (45.8% vs 29.2%), especially for the smaller muscles such as flexor pollicis longus.

At Visit 2, the median (range) follow-up time was 14 (2.6–32.3) weeks, further injection was planned in 361 (79.2%) subjects. Clinicians planned to inject the same muscles in 254 (70.4%) with the same dose in 227 (62.9%). In 134 (37.1%), a different dose was planned (increased in 26.3% and decreased in 10.8%), but only 10 (2.8%) planned to use a different agent.

Table 3. Most commonly injected muscles and technique within each upper limb segment.

Group / muscle	Total no. injected (%)*	No of units: median (IQR)			Range of units (min, max)			Multiple points	Use of EMG	Electrical stimulation
		Dysport	Botox	Xeomin	Dysport	Botox	Xeomin			
Shoulder	**N=147 (32.2%)**									
Pectoralis major	88 (19.3%)	200.0 (150.0)	30.0 (40.0)	70.0 (30.0)	30, 750	10, 100	20, 140	55 (62.5%)	11 (12.5%)	25 (28.4%)
Teres major	17 (3.7%)	75.0 (50.0)	10.0 (10.0)	50.0 (60.0)	50, 200	10, 50	40, 100	2 (11.8%)	8 (47.1%)	8 (47.1%)
Deltoideus	15 (3.3%)	100.0 (100.0)	50.0 (0.0)	N/A	50, 300	50, 50	N/A	1 (6.7%)	3 (20.0%)	7 (46.7%)
Subscapularis	14 (3.1%)	200.0 (100.0)	30.0 (0.0)	50.0 (0.0)	75, 320	20, 40	50, 50	3 (21.4%)	1 (7.1%)	11 (78.6%)
Latissimus dorsi	9 (2.0%)	120.0 (125.0)	55.0 (90.0)	40.0 (0.0)	75, 200	10, 100	40, 40	6 (66.7%)	4 (44.4%)	2 (22.2%)
Upper arm	**N=336 (73.7%)**									
Biceps brachii	270 (59.2%)	200.0 (150.0)	50.0 (10.0)	55.0 (40.0)	50, 750	20, 100	20, 100	208 (77.0%)	52 (19.3%)	70 (25.9%)
Brachialis	130 (28.5%)	150.0 (100.0)	50.0 (20.0)	60.0 (27.5)	20, 400	10, 100	30, 80	76 (58.5%)	30 (23.1%)	62 (47.7%)
Triceps brachii	18 (3.9%)	175.0 (100.0)	30.0 (25.0)	N/A	60, 300	20, 100	N/A	15 (83.3%)	8 (44.4%)	8 (44.4%)
Lower arm	**N=434 (95.2%)**									
Flexor digit. superficialis	325 (71.3%)	150.0 (100.0)	50.0 (35.0)	60.0 (37.5)	20, 500	15, 150	30, 100	195 (60.0%)	91 (28.0%)	151 (46.5%)
Flexor digit. profondus	265 (58.1%)	150.0 (100.0)	50.0 (30.0)	50.0 (20.0)	50, 600	15, 150	20, 200	142 (53.6%)	66 (24.9%)	114 (43.0%)
Flexor carpi radialis	262 (57.5%)	125.0 (100.0)	33.3 (25.0)	45.0 (40.0)	20, 350	5, 100	20, 80	83 (31.7%)	73 (27.9%)	99 (37.8%)
Brachioradialis	156 (34.2%)	112.5 (100.0)	40.0 (35.0)	50.0 (20.0)	25, 300	10, 75	20, 75	55 (35.3%)	29 (18.6%)	46 (29.5%)
Pronator teres	138 (30.3%)	100.0 (75.0)	40.0 (25.0)	40.0 (30.0)	25, 500	10, 100	10, 50	44 (31.9%)	26 (18.8%)	53 (38.4%)
Flexor pollicis longus	136 (29.8%)	100.0 (50.0)	25.0 (12.5)	35.0 (30.0)	20, 250	5, 50	10, 60	29 (21.3%)	31 (22.8%)	79 (58.1%)
Hand / fingers	**N=204 (44.7%)**									
Flexor pollicis brevis	47 (10.3%)	50.0 (50.0)	15.0 (12.5)	20.0 (0.0)	10, 200	5, 30	20, 40	7 (14.9%)	6 (12.8%)	19 (40.4%)
Adductor pollicis	37 (8.1%)	50.0 (22.5)	25.0 (15.0)	20.0 (20.0)	20, 125	10, 30	10, 30	0	8 (21.6%)	10 (27.0%)
Lumbricales	32 (7.0%)	100.0 (120.0)	25.0 (10.0)	40.0 (47.5)	50, 400	15, 40	20, 75	29 (90.6%)	8 (25.0%)	11 (34.4%)
Interossei dorsales	22 (4.8%)	150.0 (150.0)	25.0 (30.0)	N/A	50, 375	10, 80	N/A	20 (90.9%)	6 (27.3%)	9 (40.9%)
Opponens pollicis	18 (3.9%)	50.0 (50.0)	30.0 (20.0)	5.0 (0.0)	10, 120	20, 40	5, 5	0	3 (16.7%)	9 (50.0%)

Percentages are based on the number of subjects injected in the muscle, except * for which percentages are based on the number of subjects in the efficacy population.
EMG, electromyography; IQR, interquartile range

Concomitant treatments

Nearly two-thirds (61.6%) of patients were receiving physiotherapy in association with the BoNT-A treatment at follow up, and over a third (39.5%) of subjects also received occupational therapy. However, there was wide variation in the number of sessions received (see Table 4).

The types of concomitant treatments at baseline and follow up are shown in Table 4. At baseline, the frequency of concomitant treatments ranged from 18% (functional electrical stimulation) to 93% (passive stretching). By follow up, the overall frequency of concomitant therapies had diminished, although the range of modalities remained similar. Notably, the proportion of patents on antispasmodic medication fell from 46% to 28.5%.

Table 4. Concomitant treatments at baseline and follow up.

N (%)	Baseline	Visit 2
Physiotherapy		
1–4 sessions		33 (11.7%)
5–10 sessions		50 (17.8%)
11–20 sessions		74 (26.3%)
>20 sessions		120 (42.7%)
Unknown		4 (1.4%)
Occupational therapy		
1–4 sessions		34 (18.9%)
5–10 sessions		33 (18.3%)
11–20 sessions		46 (25.6%)
>20 sessions		63 (35.0%)
Unknown		4 (2.2%)
Splinting	188 (41.2%)	148 (32.5%)
Orthotics	114 (25.0%)	92 (20.2%)
Exercise	393 (86.2%)	360 (78.9%)
Passive stretching	423 (92.8%)	410 (89.9%)
Functional electrical stimulation	83 (18.2%)	58 (12.7%)
Positioning	266 (58.3%)	237 (52.0%)
Oral anti-spastic medication	210 (46.1%)	130 (28.5%)
No concomitant treatment	3 (0.7%)	12 (2.6%)

Primary and secondary goal areas

Primary and secondary goal areas set at baseline are shown in Table 5. Goals were most commonly set in the areas of passive function, impairment and active function followed by pain, and involuntary movement. Less commonly in this dataset, goals focused on mobility (ie, improvement in balance or gait quality by restoring freedom of upper limb movement) or other areas, such as cosmesis or supporting therapy interventions.

Overall, 363 (79.6%) (95% CI: 75.6–83.2) of patients achieved (or over-achieved) their primary goal with 355 (75.4%) (95% CI: 71.2–79.2%) achieving their secondary goal (see Table 5). Although the rate of achievement was lower (but not statistically significant) for active function goals in comparison with passive function and impairment goals, in this series, a total of 182 (primary and secondary) goals were set in relation to active function of which 122 (67.0%) were achieved, either as expected (73 [40.1%]) or beyond expectation (49 [26.9%]). Pain reduction was a goal for treatment in nearly one-third of patients (145 [31.8%]), and was achieved in 83.5%.

Table 5. Primary and secondary goal areas.

Goal area	Primary goals by area (n=456)			Secondary goals by area (n=471)		
	Goal set n (%)	Goal achieved n (%) (95% CI)	Partially achieved n (%)	Goal set n (%)	Goal achieved n (%) (95% CI%)	Partially achieved n (%)
Pain	61 (13.4%)	51(83.6%) (71.9–91.8%)	10 (16.4%)	84 (17.8%)	70 (83.3%) (73.6–90.6%)	6 (7.1%)
Passive function (Ease of care)	132 (29.0%)	113 (85.6%) (78.4–91.1%)	11 (8.3%)	109 (23.1%)	84 (77.1%) (68.0–84.6%)	15 (13.9%)
Active function (Active motor use of limb)	104 (22.8%)	75 (72.1%) (62.5–80.5%)	13 (12.5%)	78 (16.5%)	47 (60.3%) (48.5–71.2%)	18 (23.1%)
Mobility (balance, gait)	10 (2.2%)	7 (70.0%) (34.8–93.3%)	3 (30.0%)	19 (4.0%)	14 (73.7%) (48.8–90.9%)	2 (10.5%)
Involuntary movement (associated reaction)	41 (9.0%)	32 (78.0%) (62.4–89.4%)	5 (12.2%)	56 (11.9%)	45 (80.4%) (67.6–89.8%)	6 (10.7%)
Impairment (e.g. range of movement)	105 (23.0%)	82 (78.1%) (69.0–85.6%)	11 (10.5%)	117 (24.8%)	91 (77.8%) (69.2–84.9%)	13 (11.2%)
Other	3 (0.7%)	3 (100%) (29.2–100%)	0	5 (1.1%)	3 (60.0%) (14.7–94.7%)	2 (40.0%)
Total	456	363 (79.6%) (75.6–83.2%)	53 (11.6%)	471	355 (75.4%) (71.2–79.2%)	63 (13.4%)

Secondary outcomes

At follow-up, the mean (SD) weighted GAS T-score was 52.0 (10.1) (median 50.0, IQR 13.8), giving a mean (SD) change from baseline of 17.6 (11.0; 95% CI: 16.6–18.6) (p<0.001). Baseline and mean change from baseline in GAS T-scores were similar between BoNT-A preparations.

The mean (SD) MAS total score at follow up was 8.4 (3.4) giving a mean (SD) change from baseline of –2.6 (2.6; 95% CI: –2.9 to –2.4) (p<0.0001). Overall, 90.1% of investigators and 85.8% of patients considered BoNT-A treatment to be of benefit.

GAS T-scores correlated, albeit rather weakly, with reduction in total MAS at follow up (Spearman rho 0.28; p<0.0001). They correlated more strongly, however, with global assessment of benefit (Spearman rho 0.38; p<0.0001 for investigator assessment and 0.45; p<0.0001 for patient assessment).

Standardised measures of upper limb spasticity

Reflecting common impairment, the range of active (56.1%) and passive (54.4%) motion were the most commonly recorded standardised measures of upper limb spasticity used at baseline (Table 6). Approximately one-third (34.4%) of patients also used a visual analogue rating to reflect symptoms such as pain or carer burden. However, only a very small minority (7.2%) had a standardised measure of functional outcome recorded, such as the Arm Activity Scale (ArMA – a self-report measure of active and passive function) (5.9%) or the Leeds Adult Spasticity Impact Scale (LASIS – an investigator-reported measure of passive function) (1.3%). As shown in Table 6, the GAS T-score correlated strongly with change in these standardised measures wherever they were measured.

Table 6. Standardised measures to assess upper limb spasticity at baseline.

Standardised measure	Recorded at baseline	Recorded at follow up	No. showing change	Correlation with GAS T-Score	
	n (%)*	n (%)*	n (%)	rho	p-value
Impairment					
Tardieu	77 (16.9%)	62 (13.6%)	56 (90.3%)	0.43	<0.001
Active range of motion	256 (56.1%)	231 (50.7%)	137 (59.3%)	0.41	<0.001
Passive range of motion	248 (54.4%)	249 (54.6%)	172 (69.1%)	0.43	<0.001
Associated Reaction Rating Scale[23]	24 (5.3%)	26 (5.7%)	14 (53.8%)	0.76	<0.001
Symptoms/carer report					
Visual Analogue Scale†	157 (34.4%)	139 (30.5%)	109 (78.4%)	0.46	<0.001

Function					
Leeds Adult Spasticity Impact Scale[3]	6 (1.3%)‡	5 (1.1%)‡		–	–
Arm Activity Scale[24]	27 (5.9%)	27 (5.9%)	14 (51.9%)	0.63	<0.001

*Percentage of efficacy population.

†Parameters measured with VAS were not specified

‡Numbers too small to compute.

GAS, goal attainment scaling

Identification of potential prognostic factors

Potential predictors with a p-value <0.20 were the primary goal area, primary goal score at baseline, first administration of BoNT-A, and cortical function. These were entered into the multivariate logistic model. Results indicated that patients with impaired cortical function were half as likely to respond to treatment (OR 0.48 [95% CI: 0.26–0.89]). The most likely explanation for this is that patients with dyspraxia, neglect or poor visuospatial perception are more likely to have difficulty complying with and carrying through any treatment programme.

A non-significant trend was also seen for poorer goal achievement in patients receiving their first administration of BoNT-A, compared with those who had had previous injections (OR 0.69 (95% CI: 0.43–1.12). Possible explanations for this may be that dose-ranging and muscle selection had been optimised through previous injections, or that patients benefited from their prior experience to better define their treatment goals.

Discussion

The findings from this large prospective international cohort study showed overall good response rates to BoNT-A injection delivered in the context of routine clinical practice for the management of upper limb spasticity. The study demonstrated wide variation in clinical practice with respect to the selection of muscles and approach to injection, highlighting the need for further systematic research into which approaches are likely to be most effective for which patients. Nevertheless, almost 80% of patients achieved their primary goal, as defined by the patients – together with their clinical team – at the start of treatment. The study also confirms the feasibility of collecting data across a large international community, using an eCRF.

Patient-reported outcomes are increasingly recognised as important indicators of quality of daily life for patients and/or their carers, and in this study GAS was selected as the primary endpoint in order to evaluate the benefits of treatment in terms of the attainment of individual person-centred goals. It also provides

important insight into the nature of goals that are chosen as priorities for treatment, and also those most likely to be achieved.

In keeping with findings from other studies,[11, 25] improvement in passive function was the most frequently selected primary goal area for treatment (29%), and primary goals were achieved in around 86% of cases. Goals for active function were also commonly set in nearly a quarter of patients (22%). Perhaps unsurprisingly in this population with chronic spasticity and severe motor impairment, the achievement rate was somewhat lower for active function. Nevertheless, 72% of patients achieved their primary active function goal. The second most commonly achieved primary goal area was pain (set in 13% of patients), where again achievement was around 84%. Functional goals relating to involuntary movements and mobility were less commonly set in this population but were nevertheless achieved at broadly similar rates overall. The wide diversity in treatment goals between patients, however, highlights the importance of defining the primary treatment intentions clearly and then evaluating outcome specifically in relation to those.

Over and above achievement of the primary goal, the GAS T-score provides an overall assimilation of attainment of primary and secondary goals regardless of the number of goals set. Some authors have cast doubt on the value of calculating a GAS T-score.[26] In this study, we went to considerable lengths to ensure that GAS was applied rigorously and goals were focused on functional gains,[13] so it is worth reflecting on the added value on the GAS T-score in this context.

- If goals are set in an unbiased fashion, and are neither over-ambitious or over-cautious, the mean GAS T-score should be around 50 (±SD 10).[21] Our mean (SD) GAS T-score at follow up of 52 (10.1) provides a useful quality check of the team's ability to set and negotiate achievable goals, neither over- nor under-estimating the expected outcome.
- Previous authors have recorded that GAS change scores >10 represent clinically meaningful change.[11, 17, 21] In this study, the mean improvement in GAS T-score from baseline to follow up was 17.6. This confirms findings from one RCT,[16] and provides supportive evidence that BoNT-A produces clinically meaningful change at a functional level in the treatment.
- Importantly, GAS T-scores provide a single numerical evaluation of overall goal achievement for comparison with other outcome measures. If the gains occur as a result of reduction in spasticity, some correlation with change in MAS score would be expected, even though the relationship may not necessarily be very strong [11, 16] and indeed this was found. The significant correlations with other standardised measures (especially the Arm Activity Scale) provide further support for GAS as a meaningful person-centred measure of outcome in this context.

The findings of this study also give insight into the longer term treatment of upper limb spasticity. Many of the patients enrolled in this study had received several previous BoNT-A injections, often over several years, suggesting that patients continue to receive benefit from repeat treatments, as indeed was shown by our findings. Additionally, the mean duration since last BoNT-A treatment was 8 months, suggesting that patients with upper limb spasticity may not require re-treatment as frequently as in other conditions (such as cervical dystonia). The reduction in use of other antispasmodic medication suggests that successful treatment may possibly have allowed the reduction or withdrawal of other systemic agents. Many patients were receiving other concomitant therapies at the time of their injection (eg, therapy, splinting home exercise, etc). It is possible that these interventions play a role in reducing the frequency of BoNT-A injections, but insufficient detail regarding the frequency, duration and content of therapies was collected in this study to examine this possibility in great detail. Further longitudinal studies with systematic recording of concomitant interventions are needed to confirm these observations and to 'open the black box' of a holistic approach to spasticity management.

The authors recognise a number of limitations to this study:

- Although there was a wide geographical distribution of centres across three continents, the numerical representation in each region was by no means representative. The recruitment of just 5–12 patients per site may have been insufficient to ensure adequate representation of practice in each centre, especially given the wide diversity of patients and goals for treatment.
- The relatively low frequency of reported impairments in cognitive and communicative function suggests either that there is selection bias (patients with these problems are less likely to be referred for treatment), or under-reporting (clinicians focussed on treating spasticity are not good at identifying associated impairments which may potentially impact on outcome).
- For pragmatic reasons, change on standardised outcome measures was recorded only subjectively on a standard scale of –2 to +2 and should therefore be interpreted with caution.
- The study was not sufficiently powered to perform a detailed investigation of prognostic factors for outcome, but has given some preliminary insights into potential prognostic factors within the baseline dataset.

Despite these limitations, the study provides useful information about the way that BoNT-A is used in clinical practice around the world, and demonstrates that its effectiveness in the management of post-stroke spasticity can be documented using individual person-centred goals. More importantly, a large majority of the patients achieved their treatment goals, mainly in terms of passive and active functions, demonstrating that BoNT-A injections contribute to an improvement in the daily life of the patients beyond improvement of tone

or spasticity. Further secondary analyses will be presented separately to explore the impact of different treatment strategies including injection technique, early versus late treatment and the role of concomitant therapies. Further refinement of the tools and dataset are now in train to produce a concise Upper Limb Spasticity Index that combines GAS with selected standardised measures targeted on the key goals for intervention (including the GAS evaluation of outcome in upper limb spasticity [GAS-EOUS] tool).[27] Tools have also been developed for recording systematically the nature and content of any concomitant treatments provided in routine clinical practice. These tools will be used in the next phase of the ULIS programme (ULIS-III) to expand the cohort and to capture the benefits of integrated spasticity management in a fully generalisable sample recorded longitudinally over several cycles of BoNT-A treatment.

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Contributor statement

LTS wrote the first draft of this manuscript. LTS, KF and JJ were involved in data collection and assembly of data, manuscript review and critique, and final approval of manuscript. PM was involved in the concept and design, data analysis, manuscript writing, manuscript review and critique, and final approval of manuscript.

Competing interests:

LTS, KF and JJ all received honoraria and conference attendance fees from Ipsen for the undertaking of this research.

- LTS has a specific interest in outcomes evaluation and has published extensively on the use of GAS in this context, as well as a number of the other standardised measures (including the Associated Reaction Scale, the Arm Activity Scale and the Neurological Impairment Scale). All of these tools are freely available, however, and she has no personal financial interest in any of the material mentioned in this article.

- KF has a specific interest in outcomes evaluation and the use of the International Classification of Function in clinical settings. He has no personal financial interest in any of the material mentioned in this article.
- JJ has particular interest in spasticity clinical and instrumental evaluation methods, goal setting, treatment strategies/techniques and outcome measurement. He has no personal or financial interest in any of the material mentioned in this article.
- PM is an employee of Ipsen.

Previous publications:

Turner-Stokes L, Fheodoroff K, Jacinto J, Maisonobe P, Zakine B. Upper Limb International Spasticity Study: Rationale and protocol for a large international, multicentre prospective cohort study investigating management and goal attainment following treatment with botulinum toxin-A in real-life clinical practice. *BMJ Open* 2013;3(3):e002230.

References

1. RCP/BSRM. Spasticity in adults: Management using Botulinum Toxin. National Guidelines. London: Royal College of Physicians 2008.

2. Bakheit AM, Sawyer J. The effects of botulinum toxin treatment on associated reactions of the upper limb on hemiplegic gait--a pilot study. *Disabil Rehabil* 2002;24:519–22.

3. Bhakta BB, Cozens JA, Chamberlain MA, *et al*. Impact of botulinum toxin type A on disability and carer burden due to arm spasticity after stroke: a randomised double blind placebo controlled trial. *J Neurol Neurosurg Psychiatr* 2000;69:217–21.

4. Bhakta BB, Cozens JA, Bamford JM, *et al*. Use of botulinum toxin in stroke patients with severe upper limb spasticity. *J Neurol Neurosurg Psychiatr* 1996;61:30–5.

5. Brashear A, Gordon MF, Elovic E, *et al*. Intramuscular injection of botulinum toxin for the treatment of wrist and finger spasticity after a stroke. *N Eng J Med* 2002;347:395–400.

6. Rodriquez AA, McGinn M, Chappell R. Botulinum toxin injection of spastic finger flexors in hemiplegic patients. *Am J Phys Med Rehabil* 2000;79:44–7.

7. Simpson DM, Alexander DN, O'Brien CF, *et al*. Botulinum toxin type A in the treatment of upper extremity spasticity: a randomized, double-blind, placebo-controlled trial. *Neurology* 1996;46:1306–10.

8. Smith SJ, Ellis E, White S, *et al*. A double-blind placebo-controlled study of botulinum toxin in upper limb spasticity after stroke or head injury. *Clin Rehabil* 2000;14:5–13

9. Shaw L, Rodgers H, Price C, *et al*. BoTULS: a multicentre randomised controlled trial to evaluate the clinical effectiveness and cost-effectiveness of treating upper limb spasticity due to stroke with botulinum toxin type A. *Health Technol Assess* 2010;14:1–113, iii–iv.

10. Teasell R, Foley N, Pereira S, *et al*. Evidence to practice: botulinum toxin in the treatment of spasticity post stroke. *Top Stroke Rehabil* 2012;19:115–21.

11. Turner-Stokes L, Baguley I, De Graff S, *et al*. Goal attainment scaling in the evaluation of treatment of upper limb spasticity with botulinum toxin: a secondary analysis from a double blind placebo controlled randomised clinical trial. *J Rehabil Med* 2010;42:81–9.

12. Baguley IJ, Nott MT, Turner-Stokes L, *et al*. Investigating muscle selection for botulinum toxin-A injections in adults with post-stroke upper limb spasticity. *J Rehabil Med* 2011;43:1032–7.

13. Turner-Stokes L, Fheodoroff K, Jacinto J, *et al*. Upper Limb International Spasticity Study: Rationale and protocol for a large international, multicentre prospective cohort study investigating management and goal attainment following treatment with botulinum toxin-A in real-life clinical practice. *BMJ Open* 2013;3:e002230.

14. Kiresuk T, Sherman R. Goal attainment scaling: a general method of evaluating comprehensive mental health programmes. *Comm Ment Health J* 1968;4:443–53.

15. Ashford S, Turner-Stokes L. Goal attainment for spasticity management using botulinum toxin. *Physiother Res Int* 2006;11:24–34.

16. McCrory P, Turner-Stokes L, Baguley IJ, *et al*. Botulinum toxin A for treatment of upper limb spasticity following stroke: a multi-centre randomised placebo-controlled study of the effects on quality of life and other person-centred outcomes. *J Rehabil Med* 2009;41:536–44.

17. Turner-Stokes L, Williams H, Johnson J. Goal Attainment Scaling: does it provide added value as a person-centred measure for evaluation outcome in neurorehabilitation following acquired brain injury? *J Rehabil Med* 2009;41:528–35.

18. von Elm E, Altman DG, Egger M, *et al*. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement: guidelines for reporting observational studies. *J Clin Epidemiol* 2008;61:344–9.

19. Thu A, Casey R, Turner-Stokes L, Williams H. Inter-rater Reliability of the Neurological Impairment Scale (NIS): A Standard Impairment Set for Neurorehabilitation Populations (AAPMR Annual Assembly Poster 44). *Phys Med Rehabil* 2011;3(10 Suppl.):S191.

20. Turner-Stokes L, Siegert RJ, Thu A, *et al*. The Neurological Impairment Scale: reliability and validity as a predictor of functional outcome in neurorehabilitation. *Disabil Rehabil* 2013 (In press).

21. Turner-Stokes L. Goal attainment scaling in rehabilitation; a practical guide. *Clin Rehabil* 2009;23:362–70.

22. Turner-Stokes L, Williams H. Goal attainment scaling: a direct comparison of alternative rating methods. *Clin Rehabil* 2010;24:66–73.

23. Macfarlane A, Turner-Stokes L, De Souza L. The associated reaction rating scale: a clinical tool to measure associated reactions in the hemiplegic upper limb. *Clin Rehabil* 2002;16:726–35.

24. Ashford S, Turner-Stokes L, Siegert RJ, *et al*. Initial psychometric evaluation of the Arm Activity Measure (ArmA): a measure of activity in the hemiparetic arm. *Clin Rehabil* 2013;20 Feb [Epub ahead of print].

25. Bakheit AM, Zakine B, Maisonobe P, *et al*. The profile of patients and current practice of treatment of upper limb muscle spasticity with botulinum toxin type A: an international survey. *Int J Rehabil Res* 2010;33:199–204.

26. Tennant A. Goal attainment scaling: current methodological challenges. *Disabil Rehabil* 2007;29:1583–8.

27. Turner-Stokes L, Ashford S, De Graaff S, *et al*. The GAS-EOUS tool – a framework for evaluation of outcome in upper limb spasticity. *Neurorehabil Neural Repair* 2012;26:695–804 (Abstract 200).

Correction

Turner-Stokes L, Fheodoroff K, Jacinto J, *et al*. Results from the Upper Limb International Spasticity Study-II (ULIS-II): a large, international, prospective cohort study investigating practice and goal attainment following treatment with botulinum toxin A in real-life clinical management. *BMJ Open* 2013;**3**:e002771.

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