ORIGINAL REPORT

EFFICACY AND SAFETY OF TREATMENT WITH INCOBOTULINUM TOXIN A (BOTULINUM NEUROTOXIN TYPE A FREE FROM COMPLEXING PROTEINS; NT 201) IN POST-STROKE UPPER LIMB SPASTICITY

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Objective: To investigate the efficacy and safety of repeated treatment with incobotulinum toxin A (botulinum neurotoxin type A free from complexing proteins; NT 201) in post-stroke upper limb spasticity.

Patients and design: After completing a double-blind, placebo-controlled, multicentre study (up to 20 weeks), 145 patients received up to 5 additional sets of NT 201 injections for an open-label extension period of up to 69 weeks.

Methods: Upper limb muscle groups were treated as clinically indicated; injection intervals were ≥12 weeks. Outcome was assessed 4 weeks after each injection session and at the end of the study.

Results: Muscle tone (flexors of wrist, elbow, finger, and thumb, and forearm pronators) improved throughout the study (response rate: up to 80.6%, $p<0.0001$, Ashworth Scale). Continuous and significant improvements were also observed in disability ($p<0.05$, Disability Assessment Scale). The majority of investigators, patients and caregivers rated NT 201 efficacy as very good or good (56–84%). Adverse events considered treatment-related occurred in 11% of patients. Formation of neutralizing antibodies was not observed in any patient after repeated treatments.

Conclusion: Treatment with NT 201 showed sustained improvements in muscle tone and functionality (median dose 400 units) over a study duration of up to 89 weeks, and was well tolerated during repeated treatments for post-stroke upper limb spasticity.

Key words: botulinum toxin type A; repeated NT 201 treatment; stroke, spasticity.

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INTRODUCTION

Spasticity is estimated to occur in up to 38% of patients after stroke (1, 2). The common clinical picture of shortened overactive muscles, loss of fine motor control, paresis, stiffness, muscle spasms, and changes in limb posture (3) often interferes with activities of daily living, personal hygiene and ambulation, and can be associated with pain and significant discomfort (4, 5).

Botulinum neurotoxin type A (BoNT/A) has been shown to reduce upper and lower limb spasticity effectively and safely (6, 7), and has been recommended as a valuable tool in the management of focal adult spasticity by the American Academy of Neurology and the publication of the European consensus statement (3, 8).

NT 201 (Xeomin®, Merz Pharmaceuticals GmbH, Frankfurt, Germany) is a highly purified BoNT/A formulation free from complexing proteins and thus expected to be associated with a lower risk of immunogenicity compared with conventional BoNT/A complex products (9–11). To date, more than 86,000 patients have received NT 201 worldwide. Treatment efficacy and tolerability of NT 201 were comparable to a conventional BoNT/A complex product (Botox®, Allergan Inc., Irvine, USA) using a dose ratio of 1:1 in 2 phase I, 1 phase II, and 2 phase III clinical studies in patients with cervical dystonia and blepharospasm (12–15).

We recently reported a statistically significant reduction in muscle tone and improvement in functionality following a single set of NT 201 injections in 148 patients with post-stroke upper limb spasticity compared with placebo (16). All patients were allowed to receive concomitant stable anti-spastic treatment. Patients completing the 12–20-week main (single set of injections) study were invited to participate in an open-label extension period for up to 69 weeks. The objective of the open-label extension was to investigate the efficacy and safety of individually dosed, repeated injections of NT 201 over 1 year in patients with post-stroke spasticity of the upper limb. We describe here the efficacy and safety findings of the long-term repeated NT 201 treatment in upper limb spasticity.

METHODS

This prospective, non-randomized, repeated-treatment, open-label study was carried out at 23 European sites (in the Czech Republic,

Hungary and Poland) from September 2006 to May 2008 and conducted according to Good Clinical Practice and the Declaration of Helsinki. The study protocol was approved by the ethics committees responsible for each participating site, and all participating patients provided written informed consent before any study-related procedure took place. The trial was registered at www.clinicaltrials.gov (identifier: NCT00432666) and is the open-label extension of a preceding double-blind, placebo-controlled, single-treatment study with NT 201 in patients with post-stroke upper limb spasticity (16).

All patients who completed the preceding double-blind treatment period could participate in the extension study. The main inclusion criteria for the double-blind study were a history of stroke (at least 6 months prior to enrolment) resulting in focal spasticity of wrist and finger flexors (as demonstrated by the presence of the respective clinical patterns and a score ≥ 2 on the Ashworth Scale (17)), and a score ≥ 2 on the Disability Assessment Scale (DAS) in 1 of 4 domains (dressing, limb position, pain and hygiene) chosen as the principal therapeutic target (18). Detailed inclusion and exclusion criteria for the double-blind study have been published elsewhere (16).

Merz Pharmaceuticals GmbH, Frankfurt, Germany was responsible for the funding, conduct, data collection and statistical analysis of the study. The authors had full access to all study data.

Treatment

All patients in the double-blind treatment period were to enter the open-label extension; therefore, the final assessment visit of the double-blind study was regarded as the start of the open-label extension study. Patients had received 1 set of injections during the double-blind period (first injection) and could receive a maximum of 5 additional sets of NT 201 injections during the open-label period (second to sixth injections), with at least 12 weeks between injection sessions (Fig. 1). If the patient did not require a new injection at the final visit of the double-blind period, he or she was to attend as soon as there was a need for a new injection. The need for a re-injection was communally agreed upon by investigator and patient, taking into account Ashworth scores and clinical impression of the patient as assessed by the investigator. Once patient and investigator agreed upon the need for re-injection, each muscle group with an Ashworth score ≥ 2 and the presence of the corresponding clinical pattern, i.e. flexed elbow, pronated forearm, flexed wrist, thumb-in-palm, clenched fist, was treated. In all other cases (e.g. improvement on the Ashworth Scale in some of the upper limb flexors/forearm pronators), the investigator could decide upon the need for a new injection based upon the clinical impression and his or her experience. Four weeks after each injection session, patients attended a control visit for the assessment of outcome measures. Investigators additionally telephoned patients 1 week after each injection visit for a safety follow-up. Patients were observed for up to 20 weeks following their final NT 201 injection session. At the end of the safety observation period a trial termination visit was performed.

Except for in those patients with implanted electronic devices, injections were performed under electrical stimulation control in almost all patients and under electromyography control in some patients. As the clinical development programme for NT 201 indicated a dose ratio of 1:1 for NT 201 to another conventional BoNT/A complex product (Botox®(19)), treatment of the affected muscles was based on dose recommendations provided by the WE MOVE Spasticity Study Group for this formulation (20). Based on their clinical experience in the treatment of spasticity and on consideration of "dose modifiers" (e.g. muscle bulk, patient weight, Ashworth score) the investigator was to choose the appropriate dose for the corresponding spastic muscle within the recommended dose range (Table I) (20). Patients were to receive a maximum of 400 units (U) NT 201 per injection session.

Efficacy assessment

The primary efficacy endpoint defined in the trial protocol related to the placebo-controlled period (16). During the open-label extension period of the study, reported here, the following efficacy measures were evaluated.

Ashworth Scale. The tone of wrist, finger, elbow, and thumb flexors and forearm pronators was rated at each visit using the 5-point Ashworth Scale, ranging from 0 (no increase in tone) to 4 (limb rigid in flexion or extension) (17). Investigators were permitted 3 trials to assess muscle tone for each joint.

Response rates were evaluated based on the improvement in Ashworth scores for the treated muscle groups at week 4 after each injection. As in the main study, responders were defined as patients with ≥ 1-point improvement (reduction) from baseline; this reduction is considered clinically meaningful (21, 22). A pre-trial training session was conducted and a standardized method for assessments on the Ashworth Scale was used (23). Assessments on the Ashworth Scale were to be performed by the same investigator at the control visit and the preceding injection visit, in order to minimize a potential bias that might have been caused by change of assessors.

Disability Assessment Scale. The extent of disability was rated at each visit by patients and investigators on the 4-point DAS (0 = no disability; 3 = severe disability, normal activities limited) in the 4 domains hygiene, dressing, limb position, and pain (18). At each injection visit, patients (in consultation with the investigator) were asked to select 1 of the 4 disability domains as their personal principal therapeutic target. Responders were defined as patients with ≥ 1-point improvement (reduction) from baseline.

Global assessment of efficacy. Investigators, patients, and carers rated the efficacy of the previous injection cycle at each following injection visit and at study termination visit using a 4-point Likert scale ranging from 1 = very good to 4 = poor.

Fig. 1. Study design.

Table I. *Potential NT 201 doses for clinical patterns in the open-label extension period*

| Clinical pattern	Potential muscles for treatment	NT 201, units	Calculated volume, ml	Injection sites, *n*
Flexed elbow	Brachioradialis	25–100	0.5–2.0	1–3
	Biceps	75–200	1.5–4.0	2–4
	Brachialis	40–150	0.8–3.0	1–2
Pronated forearm	Pronator quadratus	10–50	0.2–1.0	1
	Pronator teres	25–75	0.5–1.5	1–2
Flexed wrist	Flexor carpi radialis	25–100	0.5–2.0	1–2
	Flexor carpi ulnaris	20–100	0.4–2.0	1–2
Thumb-in-palm	Flexor pollicis longus	10–50	0.2–1.0	1
	Adductor pollicis	5–30	0.1–0.6	1
	Flexor pollicis brevis/opponens	5–30	0.1–0.6	1
Clenched fist	Flexor digitorum superficialis	40–100	0.8–2.0	2
	Flexor digitorum profundus	40–100	0.8–2.0	2
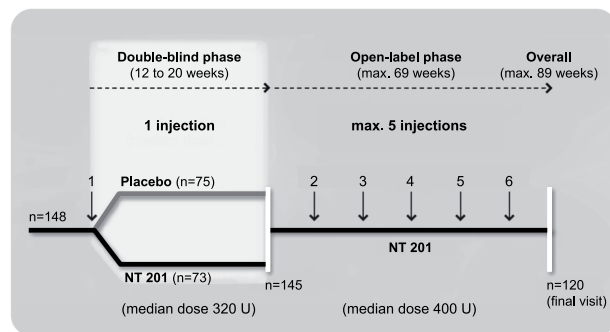
Duration of treatment effect. Duration of treatment effect was defined as the time between 2 injection sessions for patients who experienced a treatment effect.

Safety assessment

Safety was assessed throughout the study by adverse event (AE) monitoring, vital signs, and standard clinical and haematological laboratory testing. A physical and neurological examination was performed at the second and fourth injection visit and at study termination visit. Investigators were asked to rate the patients' overall treatment tolerability for the previous injection cycle (1 = very good to 4 = poor) at all injection visits and at study termination.

Blood samples for botulinum toxin antibody testing were collected at all injection visits, the control visit after the third injection, and at study termination visit. Assessments were performed using a fluorescence immunoassay in a microplate format. Positive samples were subsequently tested with the mouse hemidiaphragm assay (HDA) for neutralizing antibodies (24).

Statistical analyses

Statistical analyses were performed using SAS version 8.2 (SAS Institute, Cary, NC, USA). Full analysis set (FAS) efficacy analysis and safety analysis included all patients who had received study medication. A further efficacy analysis using the FAS patients without major protocol violations (per-protocol population) was planned. As no major protocol violations were reported, the 2 populations are identical.

Efficacy data were analysed descriptively and considered exploratory; there was no imputation of missing data (observed case analysis). For analysis of change in Ashworth and in DAS scores, data were tested using Wilcoxon signed-rank test for paired samples.

Safety data were analysed descriptively. AEs were coded according to MedDRA, version 9.1.

RESULTS

Of the 148 patients who participated in the preceding double-blind, placebo-controlled study (16), 145 patients completed that period and entered the open-label extension. Seventy-one patients (49%) had received NT 201 treatment and 74 patients (51%) had been treated with placebo during the preceding double-blind period. A total of 120 patients (82.8%) completed the open-label extension. Reasons for discontinuation were patients' withdrawal of consent (6.9%), insufficient efficacy of the study medication (4.1%), and AEs (3.4%). The majority of patients who participated in the placebo-controlled study were classified as treatment-naïve (75.7%). Pretreated patients had received a mean of 3.4 BoNT injections since first diagnosis

Table II. *Baseline characteristics of the study population entering the open-label extension period*

Characteristics	Baseline value
Patients, *n*	145
Male/female, %	64.1/35.9
Age, years, mean (SD)	55.7 (12.1)
Body mass index, kg/m², mean (SD)	26.5 (4.1)
Time since first diagnosis of spasticity[a], months, mean (SD)	55.0 (48.7)
Treatment in preceding double-blind study, *n* (%)	
NT 201	71 (49)
Placebo	74 (51)
Concomitant diseases *n* (%)	
Nervous system	145 (100)
Vascular	105 (72.4)
Metabolism and nutrition	87 (60)
Psychiatric	52 (35.9)
Cardiac	35 (24.1)

[a]At baseline of preceding double-blind study (16).
SD: standard deviation.

(16). Table II summarizes the baseline characteristics of the open-label study population.

A total of 111 patients (76.6%) received at least 3 injections and 72 (49.7%) had 4 injections during the open-label extension period. The study termination visit was attended by most patients (94.5%).

More than 90% of all attending patients were treated for the clinical patterns flexed wrist and clenched fist at all injection visits. Table III shows the mean NT 201 doses administered to the muscle groups of the 5 clinical patterns over the course of the study. Patients received comparable mean NT 201 total doses at each injection session; the median dose was 400 U per injection session, with the exception of the first injection cycle in which the median dose was 385 U. The mean cumulative NT 201 exposure during the open-label treatment period was 1197.0 ± 450.8 U.

Efficacy

Ashworth Scale. A high proportion of treatment responders (defined as ≥ 1-point improvement on the Ashworth Scale) was consistently observed and statistically significant for all clinical patterns in the open-label phase ($p < 0.0001$) (all *p*-values calculated for change from baseline) (Fig. 2).

Table III. *Mean NT 201 doses administered to the muscle groups of the 5 clinical patterns in the extension phase (by treatment session). The injection session during the double-blind study phase (16) was regarded as the first injection session*

Clinical pattern	Injection session										Cumulative dose	
	2		3		4		5		6			
	n	Units (SD)	*n*	Units (SD)	*n*	Units (SD)	*n*	Units (SD)	*n*	Units (SD)	*n*	Units (SD)
Total dose	145	351.3 (64.7)	129	356.0 (68.8)	111	363.1 (67.9)	88	352.0 (75.7)	16	339.4 (87.8)	145	1197.0 (450.8)
Flexed wrist	142	97.7 (27.5)	122	101.3 (33.9)	102	105.7 (38.1)	82	107.4 (41.8)	16	107.2 (25.8)	144	330.2 (159.8)
Clenched fist	140	100.6 (28.4)	120	109.3 (33.1)	103	120.9 (40.7)	81	118.3 (39.3)	16	113.1 (34.2)	142	359.4 (168.0)
Flexed elbow	124	133.9 (35.0)	109	138.3 (49.0)	89	137.5 (52.9)	67	132.2 (45.7)	7	159.3 (44.4)	133	405.1 (200.4)
Pronated forearm	78	54.2 (22.6)	65	49.6 (19.5)	54	52.3 (21.5)	42	54.0 (20.7)	8	58.8 (22.0)	87	149.7 (93.0)
Thumb-in-palm	60	35.6 (18.5)	60	36.1 (17.6)	50	40.2 (22.0)	40	36.5 (18.2)	8	40.0 (17.9)	85	95.2 (71.0)

SD: standard deviation.

Double-blind	Wrist Flexors	Finger Flexors	Elbow Flexors	Thumb Flexors	Forearm Pronators
1st interval, n (%)	50/73 (68.5)	50/73 (68.5)	34/54 (63.0)	17/26 (65.4)	19/35 (54.3)
Open-label					
2nd interval, n (%)	103/141 (73.0)	112/139 (80.6)	84/123 (68.3)	46/59 (78.0)	61/78 (78.2)
3rd interval, n (%)	90/121 (74.4)	86/118 (72.9)	63/107 (58.9)	38/58 (65.5)	38/65 (58.5)
4th interval, n (%)	77/102 (75.5)	74/103 (71.8)	52/89 (58.4)	37/50 (74.0)	41/54 (75.9)
5th interval, n (%)	53/80 (66.3)	60/78 (76.9)	39/65 (60.0)	24/37 (64.9)	20/41 (48.8)

Fig. 2. Proportion of patients with Ashworth score improvement ≥1 point (treatment responders) for all treated muscle groups during injection intervals (from injection session to control visit 4 weeks later). Data for NT 201 patients from the first injection interval (double-blind study (16)) are added for completeness. *$p < 0.0001$ (Wilcoxon signed-rank test for change from injection to control visit). The low number of patients ($n = 16$) for whom a fifth injection during the open-label period (sixth overall injection) was clinically indicated, does not allow meaningful analysis for this interval. In the table, the proportions of patients with an improvement are given (number of treatment responders/number of treated subjects; percentages shown in parentheses).

Disability Assessment Scale. The most frequently selected principal therapeutic target at all 5 injection sessions in the open-label phase was dressing (40.3–45.9% of patients), followed by limb position (25–37.5%), hygiene (18–31.3%), and pain (0–3.4%). When excluding the sixth injection administered to only 16 patients, the frequency of the therapeutic target changed to 32.4–37.5% for limb position, 18–23.4% for hygiene, and 1.6–3.4% for pain; while frequency for dressing remained the same. Changes in DAS for the principal therapeutic target were statistically significant for all injection intervals (response rate up to 56.3%, $p < 0.05$); when omitting the sixth injection interval, the *p*-value was $p < 0.0001$ (change from baseline; Fig. 3).

There was a consistent, highly significant improvement in DAS in the secondary targets in the first 4 injection intervals of the open-label phase in the DAS domains hygiene, dressing and limb position, and in the first 3 intervals for the domain pain ($p < 0.0001$).

Improvement in health status. A comparison of the Ashworth sum scores at the start of the open-label phase and the termination visit at which patients left the study (approximately 20 weeks after their final injection) was conducted to investigate a prolonged treatment effect of repeated injections. A reduction in muscle tone was still observed at termination visit in 37.5% of patients for wrist flexors ($p < 0.0001$), 32.8% for finger flexors ($p = 0.0003$), 36% for elbow flexors ($p = 0.0002$), 26.6% for thumb flexors ($p = 0.47$) and 47.5% for forearm pronators ($p < 0.0001$) in comparison with the time point when patients entered the extension period.

Global assessments of treatment benefit. Efficacy was rated consistently as good or very good by the majority of investigators, patients and caregivers throughout the open-label period (79.8%, 83.8%, 80.7%, 56.3%, 77.4% of investigators, 69.8%, 75.7%, 72.7%, 68.8%, 59.2% of patients, and 75.8%,

84.0%, 80.0%, 62.5%, 64.6% of caregivers (assessment only for patients with a carer) for injection interval 2, 3, 4, 5 and the final visit of the open-label phase).

Duration of treatment effect. Except for 1 patient, all patients who had received a subsequent injection to their first NT 201 injection experienced a treatment effect during the study period. The overall median duration of treatment effect for all injection intervals was 99 days (95% confidence interval 95.7, 108.7).
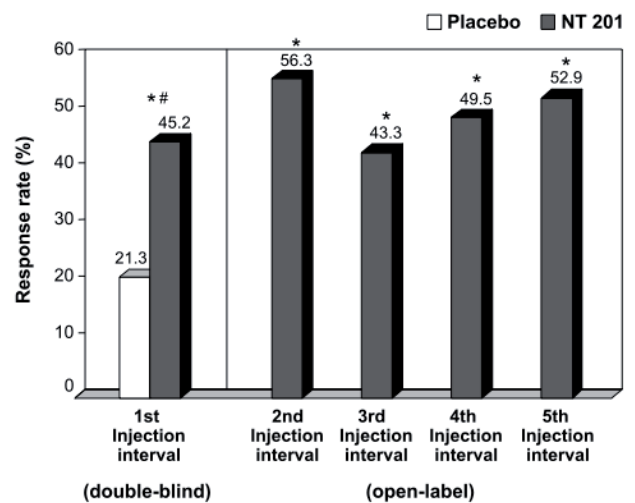

Fig. 3. Proportion of patients with Disability Assessment Scale (DAS) score improvement ≥1 point in the principal therapeutic target during injection intervals (from injection session to control visit 4 weeks later). Data for NT 201 and placebo patients from the first injection interval (double-blind study (16)) are added for completeness. ns indicate the numbers of patients with non-missing data. *$p < 0.0001$ (Wilcoxon signed-rank test for change from injection to control visit); #$p = 0.002$ vs. placebo. The low number of patients ($n = 16$) for whom a fifth injection during the open-label period (sixth overall injection) was clinically indicated, does not allow meaningful analysis for this interval.

Safety

Safety was analysed for the 145 patients who entered the open-label phase. For this population, safety data ere as follow: Eighty-two patients (56.6%) experienced at least one AE during the extension period. The majority of incidences occurred during the first 2 injection intervals (in 31.7% of patients during the first injection interval and 31% of patients during the second injection interval). Most AEs were mild or moderate in intensity. Severe AEs occurred in 7.6% of these patients; none was considered related to treatment. AEs considered related by the investigator were reported in 11% ($n = 16$) of the patients (Table IV). These included 1 event of dysphagia during the extension period, which led to discontinuation as described below. Serious adverse events (SAEs) were experienced by 17.2% of these patients; none was considered related to treatment. Eight patients (5.5%) were prematurely discontinued owing to an AE; they were related to treatment in 3 patients (injection site pain 2, dysphagia 1). The AE of dysphagia, which led to discontinuation, occurred in a 74-year-old male patient with a history of an ischaemic stroke; at entry to the open-label period, 1 of the concomitant conditions ongoing in this patient was hypoglossal nerve paresis. The patient received a total of 3 sets of injections of NT 201, consisting of 330, 310 and 325 U, in the upper left limb for the treatment of flexed wrist, clenched fist, flexed elbow and thumb in palm (first injection only), and experienced dysphagia 1 day after the final administration of NT 201 (325 U). The dysphagia was classified as mild and the patient recovered.

No clinically relevant trends were apparent in clinical laboratory parameters, vital signs, and physical and neurological examinations.

The investigators rated treatment tolerability as good or very good for > 95% of patients in the first 4 injection intervals of the open-label extension, and for > 90% of patients at trial termination, after the final injection interval.

Neutralizing antibodies

HDA testing did not detect NT 201 neutralizing antibodies for any patient at any treatment interval during this study or at study termination.

DISCUSSION

In this large open-label extension study of up to 69 weeks' duration, repeated NT 201 injection sessions resulted in

significant and sustained improvements in muscle tone and disability in patients with post-stroke upper limb spasticity. As almost all patients (98%) participating in the preceding double-blind trial phase (maximum duration 20 weeks (16)) entered this open-label extension, the beneficial effects of repeated NT 201 treatment could be demonstrated for a study duration of up to 89 weeks.

Significant improvements in the tone of all 5 assessed muscle groups (wrist, elbow, finger and thumb flexors, and forearm pronators) were sustained throughout the open-label extension. The proportion of responders was consistently high for all muscles groups after all repeated injections (all values $p < 0.0001$). This finding confirms the improvements observed after administration of a single set of NT 201 injections in the preceding double-blind treatment period: odds ratios (NT 201/placebo) from 3.12 to 13.43 in the 4 flexor groups were all significantly in favour of NT 201 ($p < 0.009$ (16)). This is, to our knowledge, the first study investigating the effect of repeated BoNT/A treatment on muscle tone of the 4 flexor muscle groups and forearm pronators. Similar to a previous BoNT/A study (25), repeated NT 201 treatment provided sustained improvements in wrist, elbow, finger and thumb flexor tone but additionally showed a high response rate to forearm pronator treatment for the first 4 open-label injection intervals. Forearm pronators in post-stroke patients are commonly affected by spasticity, leading to inability to place the forearm in a neutral position, which is a prerequisite for performing functional tasks. Treatment of all affected upper limb muscle groups, including forearm pronators, can be expected to significantly contribute to upper limb functionality.

Indeed, NT 201 led to an amelioration of disability associated with post-stroke spasticity as measured by the DAS. The improvements in disability were consistently maintained during the repeated injections in the open-label phase of the trial (all $p < 0.05$) and confirm the results observed with a single NT 201 treatment in the double-blind study period (16). Compared with placebo, the improvements in the principal therapeutic target were statistically significant at all post-injection visits until week 12 ($p < 0.005$ (16)). The open-label data also indicate an effective reduction in disability owing to pain in patients with pain caused by post-stroke upper limb spasticity.

These results are comparable to findings in another phase III study with NT 201 for the indication of upper limb spasticity (26).

Prolonged treatment with NT 201 provides long-term improvement for patients with upper limb spasticity. Comparison of muscle tone status at the beginning of the extension study with that at the termination visit approximately 20 weeks after the final injection shows a reduction in muscle tone (Ashworth Scale) at the termination visit in 27–38% of patients for the 4 flexor muscle groups and in 47.5% of patients for forearm pronators.

Global assessments of efficacy by investigator, patient and carer were also performed and efficacy was rated as very good or good by the majority of investigators, patients and carers throughout the whole extension period. Again, these results were similar to those observed in the double-blind period (16).

Table IV. *Adverse events during the open-label period considered by the investigator (*n = 145) to be related to NT 201

Adverse event	n (%)
Injection site pain	4 (2.8)
Muscular weakness	5 (3.4)
Dysphagia	2 (1.4)
Pain in extremity	2 (1.4)
Oedema, peripheral	1 (0.7)
Cough	1 (0.7)
Myalgia	1 (0.7)
Dry mouth	1 (0.7)

Our study design permitted physicians to be flexible in their choices for the treatment of individual muscle groups, taking into account the heterogeneity of the clinical picture of upper limb spasticity. Injections were administered depending on the medical need, as agreed by patient and investigator. The investigator was free to make a decision and select the appropriate dose within a dose range, based on muscle tone status and clinical impression. Although dose recommendations for individual muscle groups were provided, appropriate doses for individual patients were at the investigators' discretion.

Administration of up to 5 NT 201 treatments during the open-label period was safe and well tolerated (median dose 400 U). The overall incidence of AEs was low considering the long-term observation period and mainly older and multi-morbid patient population. Only 11% of patients experienced AEs considered by the investigator to be related to NT 201 treatment, which is comparable to similar BoNT/A studies in post-stroke spasticity (25, 27, 28). None of these AEs were rated severe or serious. The most frequent NT 201-related AEs were injection site pain, muscular weakness and dysphagia. All 3 have been reported in repeated BoNT/A treatment of upper limb spasticity (25, 27, 28). A completer rate of 82.8% and only 3 treatment-related AEs among the reasons for premature discontinuation also underline the favourable safety profile.

No patient developed neutralizing antibodies during the entire open-label study period plus the preceding single-treatment double-blind period (up to 6 injection sessions).

Limitations of the extension period of the study included the lack of a comparison group. However, it would not have been ethical to include a placebo-comparator arm in such a long-term study. In addition, the maximum dose per injection session was limited to 400 U; for a number of patients it is possible that higher doses would have been deemed appropriate by the investigator had they been available.

In conclusion, the study demonstrated that repeated treatments with NT 201 (Xeomin®; BoNT/A free from complexing proteins) resulted in significant and sustained improvements in muscle tone and disability for a study duration of up to 89 weeks. The treatment was well tolerated, and did not induce neutralizing antibodies in any patient.

ACKNOWLEDGEMENTS

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