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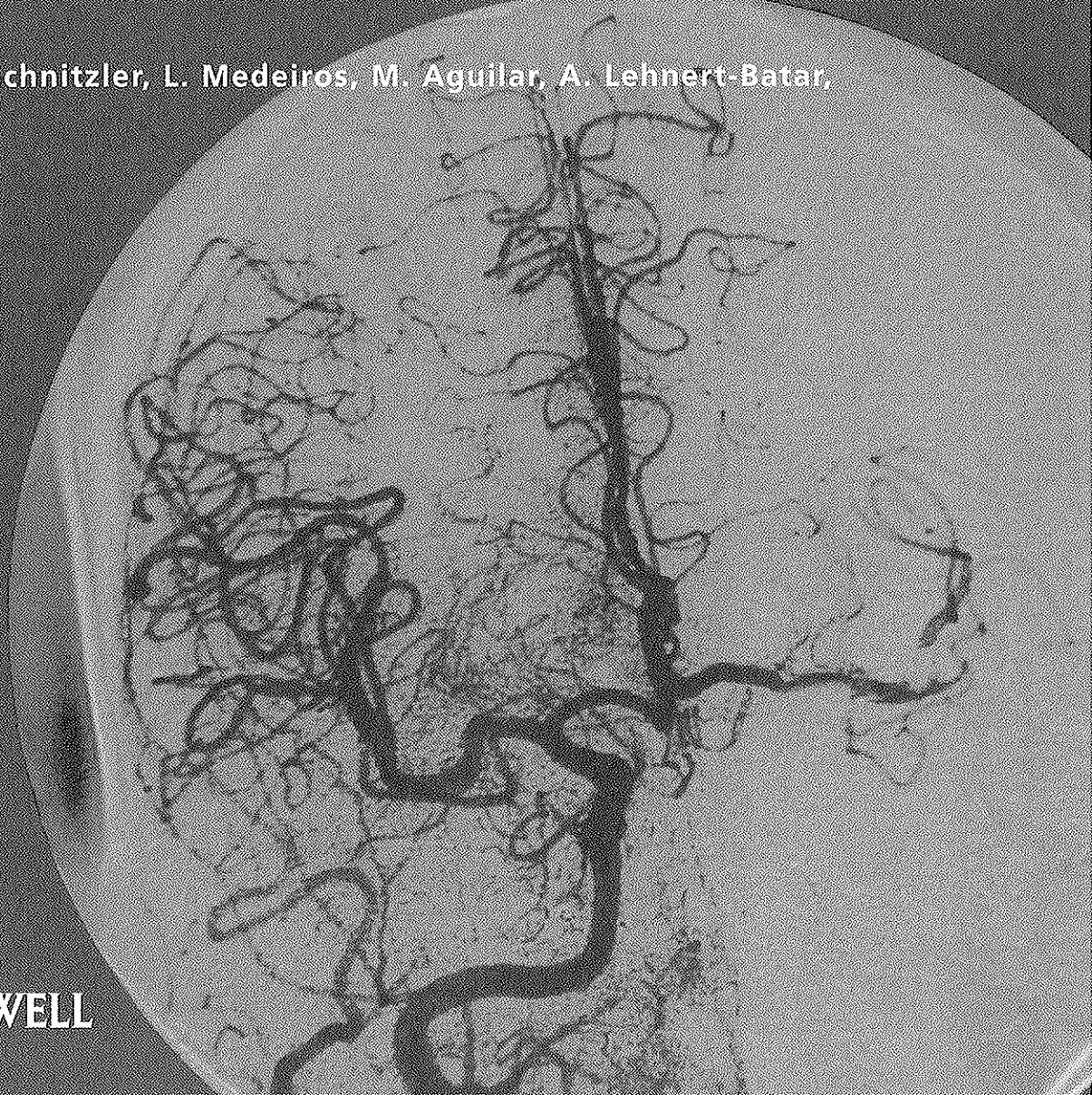

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ACTA NEUROLOGICA SCANDINAVICA

Efficacy and safety of NT 201 for upper limb spasticity of various etiologies – a randomized parallel-group study

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Acta Neurol Scand: 2010: 122: 295–302.

Objective – To assess efficacy and safety of two dilutions of botulinum neurotoxin type A NT 201 (Xeomin®) in patients with upper limb spasticity of diverse etiology. *Methods* – Changes in functional disability and muscle tone from baseline to week 4 after NT 201 treatment. *Results* – One hundred ninety-two patients with stroke, brain injury, multiple sclerosis, or cerebral palsy were randomized to either 50 or 20 U/ml NT 201 dilutions. The maximum total NT 201 dose was 495 units. Four weeks post-injection, a ≥ 1-point reduction was observed on the Disability Assessment Scale in 57.1%, and on the Ashworth scale in ≥ 62.2% of patients. The 20 U/ml NT 201 dilution was non-inferior to the 50 U/ml NT 201 dilution. Global improvement was rated high by patients (80.2%) and investigators (89.0%). *Conclusions* – NT 201 improved functional disability and muscle tone and was well tolerated in patients with upper limb spasticity of diverse etiology in both dilutions.

M. Barnes[1], A. Schnitzler[2], L. Medeiros[3], M. Aguilar[4], A. Lehnert-Batar[5], P. Minnasch[5]

[1]14 Rake House Farm, North Shields, UK; [2]Hôpital Raymond Poincaré, Service de Médecine Physique et Réadaptation, Garches, France; [3]Centro Hospitalar de Lisboa Central, Unidade de Neurologia e Neurofisiologia, Lisbon, Portugal; [4]Hospital Mútua de Terrassa, Terrassa, Spain; [5]Merz Pharmaceuticals GmbH, Frankfurt/Main, Germany

Key words: botulinum neurotoxin type A; etiology; functional disability; muscle tone; NT 201; upper limb spasticity; Xeomin

Michael Barnes, MD, 14 Rake House Farm Rake Lane North Shields NE29 8EQ, UK
Tel/Fax.: +44 1 912195690
e-mail: m.p.barnes@btinternet.com

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Introduction

Spasticity can be caused by various diseases affecting the central nervous system such as stroke, brain injury, multiple sclerosis, spinal cord injuries, or cerebral palsy (1). Botulinum neurotoxin (BoNT) has been recommended by two expert panels as a valuable treatment option for upper and lower limb spasticity in adult patients (2, 3).

NT 201 (Xeomin®; Merz Pharmaceuticals GmbH, Frankfurt, Germany), a highly purified BoNT/A formulation, is free from complexing proteins and thus expected to be associated with a lower risk of immunogenicity and reduced numbers of secondary non-responders. Efficacy and tolerability of NT 201 were comparable with a different BoNT/A formulation (Botox®; Allergan Inc., Marlow, UK) in two clinical phase I studies (4, 5) and two clinical phase III studies in patients with cervical dystonia (6) and blepharospasm (7) when used in a dose ratio of 1:1. In the treatment of spasticity, NT 201 was recently demonstrated to produce a significant reduction in muscle tone and functional disability in patients with post-stroke upper limb spasticity compared with placebo (8).

This study assessed efficacy and safety of a set of intramuscular NT 201 injections in the treatment of upper limb spasticity of diverse etiology using two different dilutions of the formulation. The study was powered sufficiently to test non-inferiority of the high volume dilution of 20 U/ml NT 201 to the low volume dilution of 50 U/ml NT 201.

Patients and methods

This prospective, randomized, observer-blind, parallel-group, multi-center study assessed the efficacy and safety of two NT 201 dilutions (20 and 50 U/ml) in patients with upper limb spasticity of diverse etiology. The study was conducted at 32 sites in eight Western European countries from February 2007 to May 2008 according to the Declaration of Helsinki and

assistance)' and '3 = severe disability (normal activities are limited)'. Changes in muscle tone were evaluated by the investigator using the five-point Ashworth Scale (0 = no increase in tone, 4 = limb rigid in flexion or extension). For both DAS and Ashworth scale, patients with a ≥ 1-point reduction from baseline were rated responsive to treatment. Global assessment of treatment response (nine-point scale ranging from +4 = very marked improvement to −4 = very marked worsening) was evaluated separately by investigators and patients at week 4.

Safety assessments throughout the study included adverse event (AE) monitoring, changes in vital signs, physical, and neurological examination and standard laboratory parameters. A 12-lead ECG was performed as a screening measure.

Statistical analysis

The statistical analysis was performed with SAS version 8.2 (SAS Institute, Cary, NC, USA). The primary efficacy analysis of the study was performed using the per-protocol population (PP, all randomized patients [full analysis set, FAS] who had no major protocol deviations) in accordance to ICH guidelines; the FAS was used for supportive sensitivity analyses.

The primary objective of the study was to show non-inferiority of a 20 U/ml NT 201 dilution to 50 U/ml NT 201 with respect to the DAS response 4 weeks after injection. To compare the groups, a two-sided 95% Newcombe–Wilson confidence interval (CI) for the difference in response rates between groups was calculated. All secondary efficacy analyses were descriptive. Using the FAS population, missing post-baseline values of all secondary efficacy variables were set to the median value of the corresponding treatment group at that visit, assuming a median effect for these subjects. Baseline missing values were not imputed.

With 77 subjects in each treatment group, the lower limit of the observed one-sided 97.5% CI for the difference in response rates between groups on the DAS primary therapeutic target was expected to exceed -25% (non-inferiority margin) with 90% power when the response rates in the treatment groups were exactly identical and both amounted to 62.5%. A 62.5% responder rate for the 50 U/ml dilution of NT 201 at week 4 was assumed to be the same as the response rate for Botox® at week 6. The non-inferiority margin of -25% was viewed to be medically justifiable as the resulting response rate would be higher than the possible placebo effect reported in the literature. To account for a withdrawal/protocol violation rate of 23% during the first four study weeks, a total of 100 patients per treatment group were needed for randomization. Sample size calculation was based on 10,000 simulations using the Newcombe–Wilson score method to construct CIs.

All randomized patients receiving the study medication were included in the safety analysis. AEs were coded according to MedDRA, version 11. Safety data were analyzed descriptively.

Results

A total of 192 patients received NT 201 treatment. Ninety-seven and 95 patients were randomized to receive doses diluted either as 20 or 50 U/ml (FAS; Fig. 1). One of the patients randomized to the 20 U/ml NT 201 group was instead administered the low volume injection and was therefore included in the 50 U/ml group for safety analysis (n = 96 for each group). All 192 patients were included in FAS and safety analyses set; data of 165 patients (85.9%) were available for PP assessments as major protocol violations were documented for 27 patients. Deviations to the injection procedure were the most common protocol violation; of these, most deviations implied a lack of a compulsory injection into all muscles of patterns rated with an Ashworth of ≥ 2. Twelve patients (6.3%) discontinued prematurely from the study after treatment (Fig. 1); there were no withdrawals owing to reported lack of efficacy. The baseline characteristics of the study population (FAS) are listed in Table 1; similar characteristics were observed in the PP population (data not shown). Patients had been diagnosed with upper limb spasticity for an average of more than 6 years; the most common etiology was stroke (88%). In addition to the clinical pattern 'flexed wrist', the majority of patients also presented with 'flexed elbow' (93.2%) and 'pronated forearm' (85.9%). A total of 127 patients (66.1%) had been pretreated with BoNT/A injections for upper limb spasticity. Baseline characteristics showed no notable differences between the two groups except for a larger proportion of male patients in the 50 U/ml group.

The median administered NT 201 dose was 300 units. Two patients received a higher than the maximum recommended dose of 400 units (440 and 495 units by using a NT 201 vial that was additionally supplied with the study medication). Table 2 lists the mean administered doses for individual muscles.

A total of 64 patients had reported non-trial BoNT injections during follow-up. Of these patients most had their reinjection during week 12 and 13.

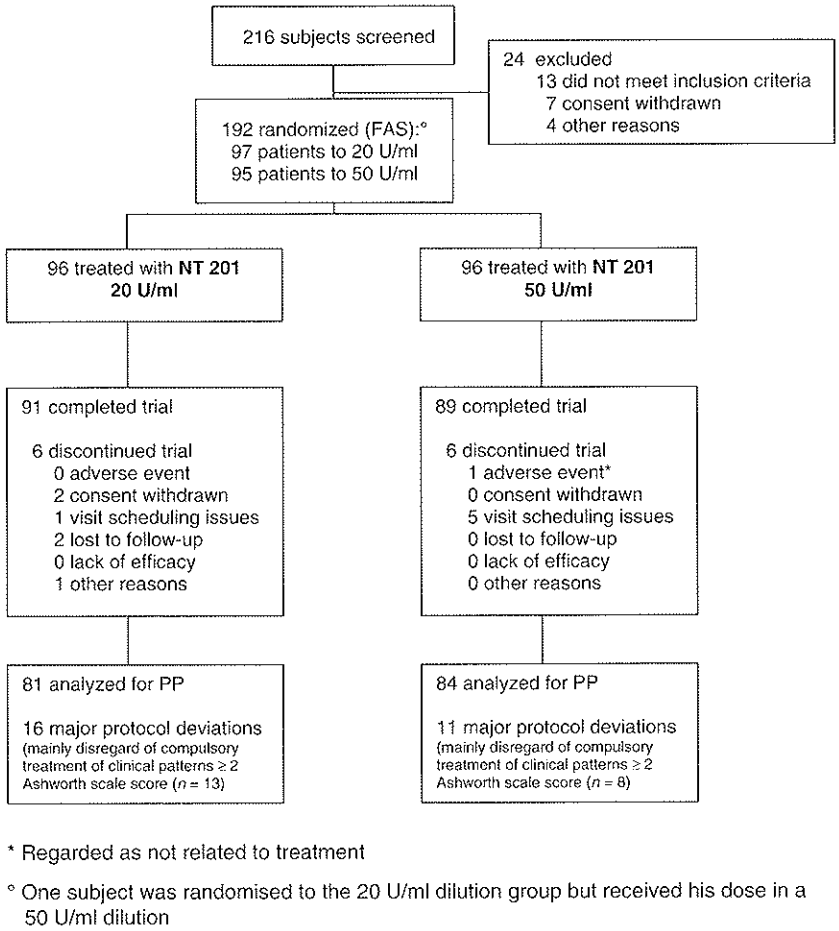

Figure 1. CONSORT flow chart.

Functional disability

The majority of patients chose limb position (63%, PP) as the primary therapeutic target on the DAS followed by dressing (23.6%), hygiene (7.9%) and pain (5.5%). A treatment response was observed at week 4 for 95 of PP patients (57.6%; n = 165). The improvement was experienced by 51 patients (63%) in the 20 U/ml group and 44 patients (52.4%) in the 50 U/ml group. The response was similar in the FAS population (data not shown). The difference in proportion of responders between the two treatment groups was 10.6% (95% CI: -4.4, 24.9). As the lower CI boundary clearly exceeds the non-inferiority margin of -25%, non-inferiority of the 20 U/ml dilution over the 50 U/ml dilution could be shown. The FAS analysis with a difference in proportion of responders between the two treatment groups of 11.2% (95% CI: -2.9, 24.6) supports this finding. The response continued to week 12 for 43.6% of the PP patients.

Within the individual primary therapeutic target, more patients of the PP group achieved an improvement in dressing and limb position in the 20 U/ml group (49.9% of patients for dressing and 71.4% for limb position) compared with the 50 U/ml group (17.7% of patients for dressing and 58.2% for limb position). Hygiene and pain were chosen as primary therapeutic targets by 18 and 12 patients, respectively. Because of small numbers the interpretation is limited.

Muscle tone assessments

At week 4, treatment response (1-point improvement on the Ashworth scale) of 62.2% and more was observed in the treated muscles groups of patients in the FAS study population. Figure 2 summarizes the treatment response for all five upper limb clinical patterns at week 4 and week 12. After 12 weeks 44%–56.8% of patients were still responders in all treated muscle groups.

Global assessment of treatment response

Four weeks after treatment, the majority of patients and investigators (80.2% and 89.0%, respectively) rated the patients' condition as

Table 1 Baseline characteristics of the study population (full analysis set)

	20 U/ml (n = 97)	50 U/ml (n = 95)	Total (n = 192)
Gender, n (%)			
Female	48 (49.5%)	33 (34.7%)	81 (42.2%)
Male	49 (50.5%)	62 (65.3%)	111 (57.8%)
Age (years), mean (SD)	55.3 (14.9)	55.5 (13.7)	55.4 (14.3)
Body mass index (kg/m^2), mean (SD)	26.4 (4.5)	25.9 (3.5)	26.2 (4.0)
Etiology of spasticity, n (%)			
Stroke	84 (86.6%)	85 (89.5%)	169 (88%)
Brain injury	5 (5.2%)	6 (6.3%)	11 (5.7%)
Multiple sclerosis	1 (1%)	0	1 (0.5%)
Cerebral palsy	3 (3.1%)	0	3 (1.6%)
Other	4 (4.1%)	4 (4.2%)	8 (4.2%)
Duration of upper limb spasticity (months), mean (SD)	77.9 (85.0)	72.2 (70.1)	75.0 (77.8)
Clinical pattern of spasticity, n (%)			
Flexed wrist	97 (100%)	94 (98.9%)*	191 (99.5%)*
Flexed elbow	90 (92.8%)	89 (93.7%)	179 (93.2%)
Pronated forearm	86 (88.7%)	79 (83.2%)	165 (85.9%)
Thumb-in-palm	57 (58.8%)	53 (55.8%)	110 (57.3%)
Clenched fist	53 (54.6%)	50 (52.6%)	103 (53.6%)
Internally rotated shoulder	46 (47.4%)	48 (50.5%)	94 (49%)
Adducted shoulder	44 (45.4%)	38 (40%)	82 (42.7%)
Intrinsic plus hand	15 (15.5%)	18 (18.9%)	33 (17.2%)
Botulinum toxin type A pretreatment for upper limb spasticity, n (%)†	66 (68.8%)	61 (63.5%)	127 (66.1%)

*Mandatory wrist spasticity not 100% as one patient violated an inclusion criterion by lacking flexed wrist pattern.
†Based on safety analysis set.

Table 2 Mean NT 201 doses (units ± SD) administered to individual muscles (safety population)

	Total NT 201 units injected		
Clinical pattern Muscle treated	20 U/ml (n = 96)	50 U/ml (n = 96)	Total (n = 192)
Flexed wrist			
Flexor carpi radialis	47.4 ± 17.7	46.7 ± 11.1	47.1 ± 14.9
Flexor carpi ulnaris	44.3 ± 18.8	40.8 ± 14.2	42.5 ± 16.6
Flexed elbow			
Biceps	71.8 ± 24.8	75.9 ± 32.3	73.9 ± 28.8
Brachioradialis	43.5 ± 16.4	48.3 ± 14.6	46.0 ± 15.6
Brachialis	47.6 ± 17.1	54.3 ± 20.9	51.1 ± 19.3
Clenched fist			
Flexor digitorum superficialis	46.2 ± 23.6	45.8 ± 24.2	46.0 ± 23.8
Flexor digitorum profundus	39.6 ± 18.8	38.1 ± 16.5	38.8 ± 17.1
Pronated forearm	42.6 ± 21.1	44.1 ± 19.9	43.4 ± 20.4
Pronator teres	25.0 ± 15.7	27.5 ± 7.8	26.3 ± 12.0
Pronator quadratus	34.7 ± 25.3	31.8 ± 20.4	33.3 ± 23.0
Other			

mildly to very markedly improved. Of those, patients as well as investigators rated 15.6% of patients as showing a marked or very marked improvement. There were only minor differences in the results between patients and investigators (Fig. 3) as well as between the 20 and 50 U/ml group (data not shown).

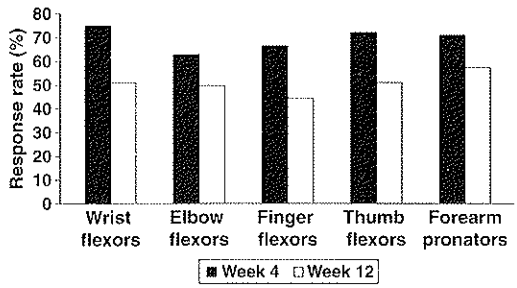

Figure 2. Proportion of patients with ≥ 1-point improvement (reduction) from baseline on the Ashworth score at weeks 4 and 12 (full analysis set).

Safety

One of the patients randomized to the 20 U/ml NT 201 group was instead administered the low volume injection and was therefore included in the 50 U/ml group for safety analysis set (n = 96 for each group).

Seventy-three patients (38.0%) experienced treatment-emergent adverse events (AEs). AEs occurring in ≥ 2% of the patients were epilepsy (3.1%), nausea (2.1%), and injection site hematoma (2.1%). All patients reporting an epilepsy event had a medical history of the disease; no epilepsy event was related to treatment. Most AEs were mild or moderate in intensity and were resolved by the end of the study period. Four patients (2.1%) reported five severe AEs (appendicitis, implant site infection following osteosynthesis, diarrhoea, arthralgia, eye pain), none of them treatment-related. In 18 patients (9.4%), a relationship to NT 201 treatment was assumed (8.3% of patients in the 20 U/ml group, 10.4% in the 50 U/ml group). NT 201 related AEs occurring in ≥ 2% of the patients were injection site hematoma (2.1%), injection site pain (1.0%), muscular weakness (1.6%), nausea (1.0%), and hematoma (1.0%). Twelve patients experienced 17 serious AEs, none of them treatment-related; one patient had to withdraw during the study. No fatal AE occurred. There were no notable findings regarding standard clinical and hematological laboratory parameters, physical and neurological findings and vital signs.

Two patients had received higher than the intended maximum NT 201 dose of 400 units. No treatment-related AE was documented for the patient receiving 495 units of study medication. Mild asthenia and mild nausea (both considered

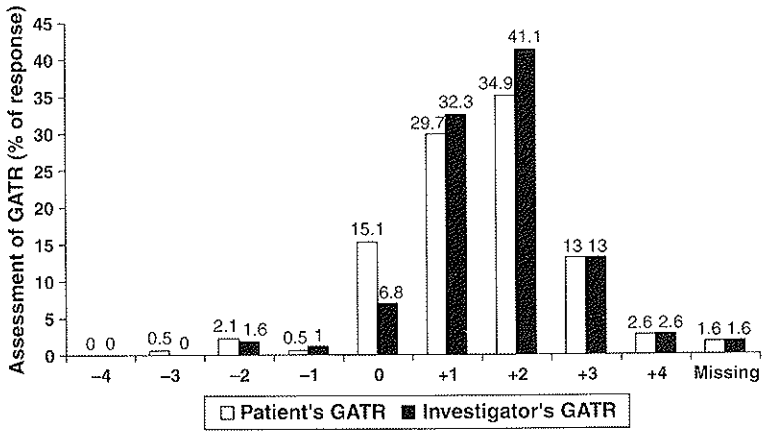

Figure 3. Patient's and investigator's global assessment of treatment response at week 4 compared with baseline (full analysis set). GATR scale: −4 = very marked worsening, −3 = marked worsening, −2 = moderate worsening, −1 = mild worsening, 0 = no change, +1 = mild improvement, +2 = moderate improvement, +3 = marked improvement, +4 = very marked improvement.

related to treatment by the investigator, resolved 3 days after onset) were reported for the patient administered 440 units NT 201 as injection of 50 U/ml dilution.

Discussion

This study confirms the previous finding that one set of intramuscular NT 201 injections can improve functional disability and muscle tone in patients with upper limb spasticity (8). Four weeks after treatment, more than 57.1% of patients in this large study were treatment responders with improved functional disability in their primary therapeutic target on the DAS.

The DAS is a tool for the measurement of functional disability in patients with spasticity (10). The scale was used in a double-blind trial assessing BoNT/A treatment for upper limb post-stroke spasticity; the trial showed significant improvements in the chosen primary therapeutic target following BoNT/A treatment compared with placebo (13). In a recent NT 201 study, statistically significant correlation between changes in mean Ashworth score for the treated muscle groups wrist, finger, elbow, thumb, and forearm pronator and changes in the DAS primary therapeutic target score has been demonstrated for week 4 (8). In this study, the DAS documented an improved functional disability in the chosen primary therapeutic target after NT 201 treatment with maintained effect at 12 weeks. The majority of both patients and investigators (≥80%) rated the patients' condition as improved by their global assessment of treatment response. Overall, NT 201 treatment was effective and led to improvement in function and muscle tone.

The proportion of treatment responders with improved muscle tone on the Ashworth scale at week 4 was also high: 74% for wrist, 62% for elbow, 66% for finger and 72% for thumb flexors, and 71% for forearm pronators. The clinical effect was maintained for about half of patients until 12 weeks after treatment.

Our results compare well with the findings of a recent meta-analysis of double-blind, randomized, placebo-controlled trials which found a significantly higher improvement in muscle tone in upper limb spasticity for BoNT/A treated patients compared with placebo patients at 3–6 weeks and even after 9–12 weeks after treatment (14). Most studies investigating BoNT treatment of the upper limb focus on wrist, elbow, and finger spasticity but few studies report treatment results of thumb flexors (13, 15, 16). In this study, a high responder rate for improvement of muscle tone in thumb flexors (72%) was observed at week 4 similar to a previous NT 201 study (8). As the thumb plays a leading role for hand function and grip this effect may provide for improvement of muscle tone balance of thumb flexors and extensors as basis for functional improvements. It remains for future studies to further investigate functional improvement of the thumb.

Two previous randomized studies investigated the effect of BoNT/A dilution on upper limb spasticity in adults in a small sample size (17, 18). A trend but no statistically significant evidence towards larger improvements in wrist and finger flexor hypertonia was observed in stroke or traumatic brain injury patients receiving BoNT/A in 50 U/ml dilution compared with 100 U/ml dilution (17). Recently, high volume BoNT/A injections (dilution of 20 U/ml) achieved greater

spasticity reduction than low volume injections (dilution of 100 U/ml [18]). This study demonstrated non-inferiority of a high volume NT 201 dilution of 20 U/ml to a low volume dilution of 50 U/ml in improving functional disability. There was a trend towards a higher responder rate of the high volume dilution. Although better efficacy with a higher volume dilution for larger muscles has been hypothesized among the experts, the trend in the present study was also obvious for smaller muscles. We currently have no explanation for this finding.

Previous studies comparing NT 201 to an active BoNT/A comparator have demonstrated a similar safety profile for both agents (4–7). In this study, the median NT 201 dose of 300 units was well tolerated. Two patients received doses higher than 400 units NT 201 (440 and 495 units). AEs considered related by the investigator, mild nausea and mild asthenia, were reported for the patient who received 440 units, whereas no related AE was reported in the patient who received 495 units. The incidence of treatment-related side effects was low (9.4%) and similar for the two NT 201 dilutions. These safety results are comparable with a pooled safety analysis of BoNT/A treatment of post-stroke spasticity (19).

A limitation of the study is the relatively high number of major protocol violations which resulted in the exclusion of 14.1% of the patients from the PP analysis. Lack of a compulsory injection into all muscles of patterns rated with an Ashworth of ≥ 2 was the most common deviation. The very restrictive design applied in this study probably explains this high number.

In conclusion, the administration of one set of NT 201 injections resulted in substantial improvements in functional disability and muscle tone. This study supports the treatment of upper limb spasticity with NT 201 regardless of etiology.

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Author roles

M.B. was involved in design and conduct of the study, writing of the manuscript and critical revision of further versions. A.S., L.M., and M.A. participated in the execution of the research project and critical revision of the manuscript. A.L.B. conducted the statistical analysis for the study. P.M. supervised the study and provided critical revision of the manuscript.

Conflict of interest

M.B. received lecture fees and honoraria for serving on advisory boards for the sponsor. A.S. received compensation for the conduct of the study and honoraria for serving on advisory boards for the sponsor. L.M. and M.A. received compensation for the conduct of the study. A.L.B. and P.M. are employees of the study sponsor.

List of principal study investigators (in alphabetical order)

Miquel Aguilar (Spain), Alberto Albanese (Italy), Eduard Auff (Austria), Abdel Magid Osman Bakheit (United Kingdom), Reiner Benecke (Germany), Christian Brenneis (Austria), Roberto Eleopra (Italy), Giovanni Fabbrini (Italy), Joaquin Ferreira (Portugal), Klemens Fheodoroff (Austria), Philippe Gallien (France), Paolo Girlanda (Italy), Francisco Grandas (Spain), Bernhard Haslinger (Germany), Harald Hefter (Germany), Alain Kaelin (Switzerland), Ruth Kent (United Kingdom), Andreas Kupsch (Germany), Eva López Valdes (Spain), Fernando Martins (Portugal), Luisa Medeiros (Portugal), Gianfranco Megna (Italy), Francesc Miquel (Spain), Franco Molteni (Italy), Peter Moore (United Kingdom), Renato Nunes (Portugal), Heinz-Dieter Oelmann (Germany), Bernard Parratte (France), Marc Rousseaux (France), Hauke Schneider (Germany), Alexis Schnitzler (France), Aurelio Tobon (Switzerland), Francisco Vivancos Matellano (Spain), Jörg Wissel (Germany), Alain Yelnik (France).

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