Clinical Study Report Synopsis for Public Disclosure

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2. SYNOPSIS

Study Title	Prospective, randomized, double-blind, placebo-controlled multicenter pilot trial to investigate the impact of an early use of NT 201 in patients with an acute cerebrovascular event on the development of upper limb spasticity
Name of Finished Product	NT 201 powder for solution or placebo reconstituted with sodium chloride for intramuscular injection
Name of Active Ingredient	NT 101, *Clostridium botulinum* neurotoxin type A free of complexing proteins
Investigator(s)	[redacted]
Total Number of Study Center(s)	2 centers in Germany
Publication (reference)	NA.
Study Period	Date of first enrolment: July 2006 Date when the last patient completed the study: September 2008 (planned: March 2009)
Phase of Development	Phase II
Objective(s)	To assess the impact of an early treatment of NT 201 in patients with beginning upper limb spasticity caused by an acute cerebrovascular event on the development of spasticity
Methodology	Assessment of reduction of muscle tone in wrist flexors using the Modified Ashworth Scale [MAS] 48 weeks after baseline visit
Number of Patients (planned and analyzed)	Planned: 54 patients to be enrolled Screened: 11 patients Treated: 10 patients Completed: 2 patients
Diagnosis and Main Criteria for Inclusion	Patients with beginning upper limb spasticity caused by an acute cerebrovascular event • Female or male patients ≥ 18 years.

	• Acute cerebrovascular event (e.g., any kind of stroke or cerebral hemorrhage). • Necessity for rehabilitation measure. • Newly developed focal spasticity in upper limb. • Spasticity with ≥ 1 point on the MAS in the wrist flexors or spasticity with ≥ 1 point on the MAS in the wrist flexors and elbow flexors. • Start of injection of trial medication within 3 to 30 days after the event.	
Investigational Product	Dose:	100 units NT 201 for wrist flexors (incl. Mm. flexores digitorum longi) or 100 units NT 201 for wrist flexors (incl. Mm. flexores digitorum longi) and 100 units for elbow flexors.
	Mode of Administration:	Dose was kept constant for the first and second injection. For the other injections dose could be reduced by 25% to 100% if no further signs of spasticity (i.e.,, MAS of 0 points for wrist and/or elbow flexors) remained.
	Batch Number:	60203
Reference Product	Dose: Mode of Administration:	Placebo, volume injected per patient corresponded to the volume of NT 201
	Batch Number:	60202
Duration of Treatment	Up to 9 days of screening, 48 weeks of treatment period (injection of NT 201 or placebo at baseline visit, day 0, and repeated injections of NT 201 or placebo at weeks 12, 24 and 36) and 8 weeks of safety follow-up after visit 11 at week 48.	

Criteria for Evaluation	
Efficacy:	Primary parameter: • Change in MAS for wrist flexors from baseline to 48 weeks after baseline. Secondary parameter: • Change in MAS for wrist flexors from baseline over time. • Change in MAS for elbow flexors (if treated) from baseline over time. • Change in Activity of Daily Living [ADL] score (Barthel Index) from baseline over time. • Change in Disability Assessment Scale [DAS] from baseline over time. • Change in passive range of motion [PROM] for wrist from baseline over time. • Change in pain intensity in the upper limb from baseline over time as assessed by Visual Analogue Scale [VAS]. • Investigator's and patient's global assessment of efficacy of treatment at week 48. Due to the low number of randomized patients, the analysis of efficacy was carried out descriptively.
Safety	• Adverse events [AEs]. • Standard clinical chemistry and hematology. • Vital signs. • Electrocardiogram [ECG]. • Neutralizing antibodies against Botulinum neurotoxin type A. • Physical and neurological examinations.
Statistical Methods	Descriptive and explorative data analysis. The primary efficacy hypothesis was analyzed using a two-sided Wilcoxon rank sum test with α set to 5%. It was based on the Full Analysis Set [FAS], which was defined as all randomized patients. The Last Observation Carried Forward [LOCF] principle was used to handle missing values.

	For sensitivity reasons, the primary and all secondary efficacy variables were evaluated on the FAS as well as on the Per Protocol Set [PPS]. The PPS contains all the patients of the FAS who had no relevant deviations from the study protocol. All safety parameters were analyzed on the Safety Evaluation Set [SES], which is defined as all treated patients.
Summary / Conclusions	
Efficacy Results	On the MAS, no patient maintained a reduced wrist flexor spasticity at 48 weeks. Two patients relapsed to the baseline score for wrist flexors at week 48. For most other scales tested ADL, DAS, PROM, pain intensity, the results over time were more or less stable or indicated an improvement of the patients' situation. Most patients and investigators who rated the outcome of treatment after 48 weeks were of the opinion that the treatment had produced "good" results.
Safety Results	8 patients were reported to have AEs, in 3 of them serious adverse events [SAEs] occurred. None of the AEs were classified as AEs of special interest. Most AEs were of mild intensity, but some moderate and few severe cases occurred. Most AEs resolved until study termination. AEs that did not resolve until the end of the study originated in diseases not related to study treatment (especially cardiovascular diseases), or to the cardiovascular event itself. None of the AEs were assessed to be treatment-related. One clinically significant abnormal laboratory value was found after baseline, which was not treatment-related. All other values of clinical chemistry, hematology as well as vital signs over time were not alarming.
Conclusion	Due to the low number of observations documented in this study, no reliable conclusions regarding efficacy of early NT 201 administration in patients with wrist and elbow flexor spasticity after a cerebrovascular event can be drawn. This is the reason why only an abbreviated report was written for this trial. The safety data from this study did not reveal any new concerns to the known safety profile of NT 201.