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STUDY REPORT SYNOPSIS

Study Title	**Prospective, single-arm, multicenter study to investigate the efficacy and safety of NT 201 (botulinum neurotoxin type A free of complexing proteins) and the duration of treatment effect after one injection session and in long-term treatment in subjects with cervical dystonia.**	
Name of Finished Product	NT 201 (botulinum neurotoxin type A [BoNT/A] free from complexing proteins, trade name Xeomin®)	
Name of Active Ingredient	[NT 101], BoNT A, 150 kD, free from complexing proteins, USAN: incobotulinumtoxinA)	
Coordinating Investigator(s)	[redacted] Germany Phone: [redacted] Fax: Email: [redacted]	
Total Number of Study Center(s)	17 active centers in Germany	
Publication (Reference)	None	
Study Period	Date of first enrolment:	28 SEP 2007
	Date when the last subject completed the Main Period:	01 AUG 2008
	Date when the last subject completed the Extension Period:	18 MAY 2010
Phase of Development	Phase IV	
Objective(s)	The primary objective, the safety and efficacy of NT 201 after one injection session in the treatment of subjects with cervical dystonia [CD], was determined in the Main Period. As secondary objectives, the efficacy and safety profile and the duration of treatment effect of NT 201 in long-term treatment with repeated injection sessions were	

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	determined in the Extension Period.
Methodology	This was a prospective, open-label, single-arm, multicenter Phase IV study. Seventy-six subjects aged 18 to 76 years suffering from CD, predominantly rotational spasmodic torticollis, and meeting the inclusion criteria after the assessment at Screening Visit (V1) were treated with NT 201. During the Main Period at Baseline (Visit 2), the subjects received one intramuscular (i.m.) NT 201 injection. The Main Period for each subject ended with a Control Visit (Visit 3) four weeks after baseline. Up to four additional injection sessions were applied during the Long-term Extension Period.
Number of Subjects (Planned and Analyzed)	Seventy-four subjects were planned to be enrolled into this study; 82 were screened and 76 subjects were treated.
Diagnosis and Main Criteria for Inclusion	**Diagnosis:** Cervical dystonia, predominantly rotational spasmodic torticollis **Main criteria for inclusion:** Treatment-naïve or pre-treated subjects of either sex aged between ≥18 to <76 years and with a clinical diagnosis of CD with a need for injection were eligible for the study. Other main inclusion criteria included: Toronto Western Spasmodic Torticollis Rating Scale [TWSTRS] total score at baseline ≥25 with TWSTRS severity score ≥10 and disability score ≥3. Pre-treated subjects had to have source documentation of the last two injection sessions, stable response directly prior to study entry and having received a dose of ≤ 300 units of Botox® or Xeomin®, or ≤ 1,200 units of Dysport® for treatment of CD in the most recent injection session. At least 10 weeks had to have passed between the most recent injection session and the Baseline Visit. After Visit 3 [V3], subjects continued study participation in the Extension Period, if at least 10 weeks had passed between the injection session of the Main Period and the second injection session.

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	~~For the full list of inclusion criteria and exclusion criteria, refer to section 9.3.1 and section 9.3.2 respectively~~.	
Investigational Product	Dose: Mode of administration: Batch number:	The total dose per injection session per subjects ranged from 50 to 300 units according to protocol. Intramuscular (i.m.) 6060836
Reference Product	Not applicable	
Duration of Treatment	Duration of the subject's study participation was approximately four weeks post study baseline plus the Screening Period (maximum of seven days), if subject did not enter the Long-term Extension Period, and up to 121 weeks (if subject did attend five injection sessions in total with a maximum duration of 24 weeks per injection cycle plus the Screening Period)	
Criteria for Evaluation **Efficacy Variables**	**Primary efficacy variable:** • TWSTRS total score: Change from Baseline Visit (V2) to week 4 (V3) after initial injection session. **Secondary efficacy variables:** • TWSTRS 1. Single interventional effect of one injection session by the change of the TWSTRS total, severity and disability scores from each cycle baseline (V4, V6, V8 and V10) to 4 weeks thereafter (V5, V7, V9, V11) within the Long-term Extension Period of the study, defined as: $\Delta TWSTRS^{cycle}_{i,\text{sin}\,gle} = TWSTRS^{cycle}_{i,week\,4} - TWSTRS^{cycle}_{i,baseline}$ 2. Overall interventional effect, measured by the change in the TWSTRS total, severity and disability	

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	scores, from study baseline (V2) to each examination 4 weeks after the injection sessions (V5, V7, V9, V11), defined as:
	$\Delta TWSTRS_{i,overall}^{cycle} = TWSTRS_{i,week4}^{cycle} - TWSTRS_{i,baseline}$
	• Global Assessment of Efficacy by Investigator [GAEI] at the end of each injection cycle prior to the next injection session or at the Study Termination Visit
	• Subject Evaluation of Global Response [PEGR] at the end of each injection cycle prior to the next injection session or at the Study Termination Visit.
	• Time (in days) from last injection session to onset of treatment effect as given by subjective subject assessment.
	• Time (in weeks) from last injection session to waning of treatment effect as rated by subjective subject assessment.
	• Duration of treatment effect defined as time period within an injection cycle from the day of the injection session until the day where the need for reinjection was indicated by the subject (if subject experienced an onset of treatment effect).
	• Dystonia Discomfort Scale [DDS] score (subject diary)
	  • Change from each injection session to four weeks thereafter given as difference of the score values (cycle baseline value minus Week 4 value) and by expressing the difference as percentage of the cycle baseline score value (quotient) – single interventional effect.
	  • Change from study baseline (first injection session) to four weeks after a repeated injection session given as difference of the score values (study baseline value minus cycle Week 4 value) and by expressing the difference as percentage of the study baseline score value (quotient) – overall interventional effect.
	  • Area under the curve [AUC] of DDS scores over time for the period from baseline to four weeks

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	thereafter – single interventional effect. • AUC of DDS scores over time for the period between two consecutive injection sessions divided by the length of time interval in days– single interventional effect. • AUC of DDS scores over time for the period from baseline (first injection session) to the day of a repeated injection session or the day of the Study Termination Visit divided by the length of time period in days– overall interventional effect. • Maximum absolute effect [aE_{max}] at the end of each injection cycle given as the difference between the cycle baseline score value and the lowest cycle score value (single interventional effect) and as the difference between the study baseline score value and the lowest overall score value (overall interventional effect). • Maximum relative effect [rE_{max}] at the end of each injection cycle described by expressing the maximum absolute effect aE_{max} as percentage of the pertinent baseline score value (cycle baseline score value to describe the single interventional effect, study baseline score value to describe the overall interventional effect). • Time [T_{max}] to achievement of aE_{max} at the end of each injection cycle (time since cycle baseline to describe the single interventional effect, time since study baseline to describe the overall interventional effect).
Safety Variables	• Adverse events [AEs]. • Standard clinical chemistry and hematology • Vital signs. • Physical and neurological examination. • Electrocardiogram [ECG] at screening. • Dysphagia Scale score. • Investigator's Global Assessment of Tolerability. • Results from botulinum neurotoxin type A antibody tests.

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	• Pregnancy test.
Statistical Methods	Enrolled and treated subjects with a baseline TWSTRS measurement were included in the Full Analysis Set [FAS]. The Per Protocol Set [PPS] consisted of all subjects of the FAS for whom no major protocol violations were reported. Major protocol violations were defined during the Data Review Meeting of the study before final database closure. Efficacy analyses were performed on both the FAS and the PPS. The results of both analyses (FAS/PPS) were compared and any different outcomes or considerable deviations were described. Safety analyses were based on the Safety Evaluation Set [SES] only (all treated subjects). For the primary efficacy parameter, defined as the mean change in the TWSTRS total score from baseline to week 4 after the initial injection session, a 95% confidence interval [CI] was calculated (for FAS using LOCF, median imputation and observed cases; for PPS using observed cases). In addition, to evaluate the influence of possible risk factors, an analysis of covariance [ANCOVA] was performed using the change from baseline in TWSTRS total score as dependent variable and baseline TWSTRS total score, gender, age, center and pre-treatment situation (treatment-naïve/pre-treated) as covariates. As secondary efficacy endpoints with respect to the TWSTRS total score, two different approaches were used. The first endpoint measured the single interventional effect of one injection session by the change of the TWSTRS total score from each baseline cycle (V4, V6, V8 and V10) to four weeks thereafter (V5, V7, V9 and V11) within the Long-term Extension Period of the study. The overall interventional effect was measured by the change in the TWSTRS total score from study baseline (V2) to each examination four weeks after the injection sessions (V5, V7, V9 and V11). Additionally, the TWSTRS total score baseline values, as well as gender, age, body mass index [BMI], center, and

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	the pre-treatment situation at screening were taken as adjusting covariates.
	All described analysis of the total TWSTRS total score were furthermore repeated for the TWSTRS severity and disability scores. The GAEI was documented at the end of each injection cycle. A frequency table displaying results for this variable over the injection cycles was given. The PEGR was documented at the end of each injection cycle. A table displaying the frequency distribution of the PEGR for each injection cycle was given. Furthermore, a response analysis was performed wherein Cochran's Q-test was used to analyze the difference in response rates between injection cycles. The time to event endpoints (time to onset of treatment effect, time to waning of treatment effect, and duration of treatment effect) were analyzed using the Kaplan-Meier approach for survival data. The DDS scores were used to investigate the NT 201 treatment effects for each injection cycle enabling a comparison between the treatment cycles. In addition this secondary efficacy variable was used to assess the impact of repeated injection sessions on the functional status of CD patients. Point estimates and parametric 95% confidence intervals were provided for each of these secondary efficacy parameters at the end of each injection cycle. A repeated measures model was additionally estimated analogously for the single interventional and the overall interventional effect with DDS scores at cycle baseline or the DDS scores at study baseline, injection cycle, center, age, gender, BMI and the pre-treatment situation included in the model as factors and covariates, respectively. Furthermore a correlation analysis between the DDS and the TWSTRS total score as well as between the DDS and the TWSTRS severity, disability and pain scores was applied.

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	Safety variables with continuous outcomes (e.g. vital signs and laboratory parameters) were analyzed using descriptive summary statistics including sample size, number of missing observations, mean and standard deviation [SD], median, minimum and maximum. Categorical safety data (e.g. AEs and laboratory parameters with reference to normal ranges) were analyzed using frequency tables and, if applicable, shift tables.
Summary / Conclusions **Efficacy Results**	**Primary Efficacy Endpoint** *Change in TWSTRS total score* The primary efficacy endpoint is defined as the change in the TWSTRS total score from Baseline Visit to 4 weeks thereafter. At the Baseline Visit, subjects had a mean TWSTRS total score of 39. Four weeks after the injection of NT 201, the TWSTRS total score was reduced by 11.7 points to a mean value of 27.4 (analysis on FAS with missing values imputed according to last observation carried forward [LOCF] strategy). **Secondary Efficacy Endpoints** *Change in TWSTRS total score* As a secondary efficacy endpoint the single interventional effect, i.e. the change of the TWSTRS total score from each injection session to 4 weeks thereafter for all injection cycles, was analyzed for the FAS using LOCF for missing values. The change in the TWSTRS total score progressionally decreased from the first injection cycle to the fifth injection cycle, with a mean (±SD) change of -11.7 (9.8) at V3 and of -6.5 (8.9) at V11. In parallel, the TWSTRS total score at cycle baselines (visits V2, V4, V6, V8, and V10) progressionally decreased from the first injection cycle to the fifth injection cycle, with a mean (±SD) score of 39.2 (10.1) at V3 and of 32.2 (11.2) at V11. The secondary efficacy endpoint with respect to the TWSTRS total score was also assessed by

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	the overall interventional effect measured by the change in the TWSTRS total score from study baseline (V2) to each examination 4 weeks after the injection sessions (visits 5, 7, 9, and 11) for the FAS using LOCF for missing values. The change in the TWSTRS total score progressionally decreased from the study baseline to the fifth injection cycle, with a mean (±SD) change of -11.7 (9.8) at V3 and of -14.3 (13.1) at V11. The TWSTRS baseline score or the score at the injection visit, center, and pre-treatment status of the subjects showed a significant influence on the changes of the TWSTRS total score for the overall and single interventional effect. Subjects with higher TWSTRS severity score at the injection visit showed a lower reduction in TWSTRS severity score. Pre-treated subjects achieved a higher reduction in the TWSTRS total score compared to treatment-naïve subjects. *Change in TWSTRS Severity Score* The single interventionel (change from injection) in the TWSTRS severity score progressionally decreased from the first injection cycle to the fifth injection cycle, with a mean (±SD) change of -5.5 (4.2) at V3 and of -3.2 (3.8) at V11 (FAS using LOCF). In parallel, the TWSTRS severity score at cycle baselines (visits V2, V4, V6, V8, and V10) progressionally decreased from the first injection cycle to the fifth injection cycle, with a mean (±SD) score of 18.4 (3.7) at V3 and of 15.2 (4.4) at V11. The overall interventionel effect (change from study baseline) in the TWSTRS severity score progressionally decreased from the first to the fifth injection cycle, with a mean (±SD) change of -5.5 (4.2) at V3 and -6.5 (5.3) at V11 (FAS using LOCF). The TWSTRS cycle baseline score and center of the subjects showed a significant influence on the changes of the TWSTRS severity score. Subjects with higher TWSTRS severity score at the injection visit showed a lower reduction in TWSTRS severity score.

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	Change in TWSTRS Disability Score The single interventional effect (change from injection) in the TWSTRS disability score progressionally decreased from the first injection cycle to the fifth injection cycle, with a mean (±SD) change of -3.7 (4.6) at V3 and of -1.8 (3.7) at V11 (FAS using LOCF). In parallel, the TWSTRS disability score at cycle baselines (V2, 4, 6, 8, and 10) progressionally decreased from the first injection cycle to the fifth injection cycle, with a mean (±SD) score of 11.3 (5.1) at V3 and of 8.9 (4.9) at V11. The overall interventional effect (change from study baseline) in the change in the TWSTRS disability score progressionally decreased from the study baseline to the fifth injection cycle, with a mean (±SD) change of -3.7 (4.6) at V3 and -4.5 (5.9) at V11 (FAS using LOCF). Results of a linear regression analysis showed that the TWSTRS cycle baseline score, center, and pre-treatment status of the subjects had a significant influence on the changes of the TWSTRS disability score for the single and overall interventional effect. Additionally the injection cycle had significant influence for the single interventional effect. Subjects with higher TWSTRS disability baseline score showed a lower reduction in TWSTRS disbility score. Pre-treated subjects achieved a higher reduction in the TWSTRS disability score compared to treatment-naïve subjects. Subjects showed a higher reduction in the TWSTRS disability score in cycle 2 compared to reference cycle 5 for the single interventional effect. Sensitivity analyses of the TWSTRS total, severity and disability score on the FAS with complete cases and median imputation and on the PPS showed similar results. *Global Assessment of Efficacy by Investigator* Most investigators rated the efficacy of an injection as good across all injection cycles during the study in the FAS. The highest incidence of investigators reported a good efficacy during cycle 5 (60.5%), followed by cycle 1 and 4 (50.0%). The trend over cycles shows excellent results at cycle 1, slightly poorer results at cycle 2 with improving results of over the rest of cycles. The best

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	performance was observed in cycle 5. In the overall best global assessment of efficacy by investigator, the investigator rated the response of 53.9% of the subjects as good followed by 42.1% who were rated with very good response; only 1.3% subjects were evaluated with a poor response in efficacy. *Patient Evaluation of Global Response* Most of the subjects rated the efficacy of the previous injection session across all the injection cycles during the study as +3 (marked improvement). The highest incidence of subjects reported a score of +3 during injection cycle 1 (51.3%), followed by injection cycle 5 (50%). 2.6% of the subjects reported a PEGR score of +4 (complete abolishment of signs and symptoms) during injection cycles 2 and 4. *Time to Onset, Time to Waning, and Duration of Treatment Effect* The Kaplan-Meier analysis of the time to onset of the treatment effect showed that the median time to onset for subjects in the FAS was 7 days for injection cycle 1 up to a maximum of 10 days for injection cycle 2. The minimal and maximum observed number of days to onset varied between the 5 injection cycles with a minimum of 1 day and a maximum of 49 days. Thus, approximately 50% of the subjects reported an onset of the treatment effect which was equal to or less than 7 days across the 5 injection cycles. The Kaplan-Meier analysis of the time to waning of the treatment effect showed that the median time to waning for subjects in the FAS was 7 weeks across the 5 injection cycles. The range for the number of weeks to waning varied across the 5 injection cycles, with a minimum of 13 weeks in injection cycle 1 and a maximum of 24 weeks in cycle 2. The Kaplan-Meier analysis of the duration of treatment effect showed that the median time of duration of treatment effect for subjects in the FAS was 8 weeks for

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	injection cycle 1 and 10 weeks for the remaining injection cycles. The range for the duration of treatment effect varied across the 5 injection cycles, with a minimum of 20 weeks in cycle 3 and a maximum of 24 weeks in cycles 2 and 5 respectively. *Change in Dystonia Discomfort Scale* A total of 71 subjects had a DDS baseline score and these subjects diaries could be analysed for overall changes. The mean (±SD) baseline value of the DDS score was 72.7 (±26.2). On the day of V3 the patient diary was filled out by 75 subjects, yielding a mean (±SD) DDS of 51.8 (±25.8) after 4 weeks. On average, the mean (±SD) single absolute change in the DDS score was reported as 21.1 (±23.9) from baseline to Week 4, with the 95% confidence interval for this absolute change reported as (15.4; 26.8). The median value of the corresponding relative change in the DDS score was 29%. The mean (±SD) AUC for the DDS score for the time period from V2 to V3 was 1697.3 (±685.9) (95% CI, 1538.4; 1856.2) in the FAS. The AUC of the DDS level over time from each injection session to 4 weeks thereafter, was comparable across the 5 injection cycles in the FAS. A similar single interventional effect was observed for the AUC of the DDS level over time in the PPS. The mean (±SD) AUC for the DDS score for the time period from V2 to V3 was 57.5 (±22.7) (95% CI, 52.3; 62.8), while the mean (±SD) AUC for the DDS score at V11 was 54.7 (±21.2) (95% CI, 49.2; 60.3). The mean maximum absolute effect and the maximum relative effect aEmax and rEmax values from baseline injection cycle within each injection cycle measured the single interventional effect by one injection session. The mean (±SD) aEmax for the time period from V2 to V4 was 32.6 (±21.0) (95% CI, 27.6; 37.6) and the mean (±SD) rEmax for the time period from V2 to V4 was 42.6 (±48.5) (95% CI, 31.1; 54.2) in the FAS. The mean aEmax and rEmax values from study baseline to the current injection session measured the overall

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	interventional effect by several repeated injection sessions. The mean (±SD) aEmax from V2 to V4 was 32.6 (±21.0) (95% CI, 27.6; 37.6) and the mean (±SD) aEmax at V12 was 43.3 (±26.1) (95% CI, 36.2; 50.5) in the FAS. *Correlation of Dystonia Discomfort Scale Score and TWSTRS Score over time.* The results of DDS score and TWSTRS score over time suggested that there is a positive moderate relationship between DDS score and TWSTRS total score (Bravais-Pearson coefficient 0.5482, Spearman coefficient 0.5146).
Safety Results	The subjects in the SES received a mean body dose ranging between 151 units (cycled 1) and 192 units (cycle 5). Of the 76 subjects in the SES, a total of 72 subjects (94.7%) experienced at least 1 treatment emergent adverse event [TEAE]. Frequently reported TEAEs during the study by system organ class [SOC] (incidence rate ≥25% within SOC) were, "Infections and infestations" 50 (65.8%), "Gastrointestinal disorders" 46 (60.5%), "Musculoskeletal and connective tissue disorder" 39 (51.3%), and "Nervous system disorders" 34 (44.7%). Frequently observed TEAEs according to their preferred term were nasopharyngitis 35 (46.1%), dysphagia 29 (38.2%), headache 22 (28.9%), and neck pain 15 (19.7%). The majority of subjects (67 [88.2%]) in the SES reported TEAEs that were categorized as mild. The majority of subjects reported TEAEs (71 [93.4%] of 76 subjects) as "not related" to the study drug. The majority of TEAEs considered as related to study drug were of mild intensity (27 subjects [35.5%]) and few were of moderate intensity (14 subjects [18.4%]). Only 1 subject reported a related TEAE (muscular weakness) of severe intensity. Thirty-seven subjects reported at least 1 TEAE that were

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	categorized as TEAEs of special interest. No fatal or drug-related serious adverse events [SAEs] were reported during the study. Twelve subjects of the SES experienced at least 1 serious TEAE. All the reported SAEs were considered as "not related" to the study drug. Three subjects experienced AEs leading to dropout [ADOs] (Myocardial Infarction, Dysphagia, and Hodgkin's Disease) of which one ADO (Dysphagia) was categorized as "related to treatment". No notable treatment-related changes were observed in the mean laboratory parameter results or vital signs over time. The majority of the subjects (61 [80.3%] of 76) did not have any swallowing difficulties at baseline. A similar trend was observed across the remaining visits during the study. Few subjects (7 [9.2%] of 76 subjects) reported mild swallowing difficulties. The frequency of mild swallowing difficulties was comparable across the remaining visits (V4, V6, V8, and V10) during the study. Two subjects reported severe swallowing difficulties once during the study. The Global Assessment of Tolerability by Investigator in the overall study was reported as 'very good' or 'good' for most of the subjects and 'moderate' for few subjects. Most of the subjects tested negative for BoNT/A antibodies at screening and at the Study Termination Visit by the fluorescence immunoassay for antibodies [FIA-AB], which was used for pre-screening purposes. Three subjects (2.3 %) tested positive at screening and at V12 with the FIA-AB and also tested positive with the mouse ex-vivo hemidiaphragm assay [HDA] for neutralizing BoNT/A antibodies. Three subjects tested positive with FIA-AB at screening only. Repeated injections with NT 201 do not result in the new formation of neutralizing antibodies during the study.
Conclusion	In both the FAS and PPS, the reductions in the TWSTRS total score and TWSTRS severity and disability scores show that all subjects experienced improvement after the

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	injection of NT 201 from study baseline to 4 weeks theraftер. Moreover, reductions in the TWSTRS total score, TWSTRS severity, and TWSTRS disability score from each injection session (V4, V6, V8, and V10) to 4 weeks thereafter (V5, V7, V9, and V11); and from study baseline (V2) to 4 weeks after each injection session (V5, V7, V9, and V11) were also observed. Pre-treatment showed a significant impact on the decreases of the TWSTRS total score. The median time to onset of the treatment effect was 7 days, the median time to waning of the treatment effect was 7 weeks and the median duration of treatment effect was 8 weeks for injection cycle 1 and 10 weeks for the remaining injection cycles. On average the DDS score was reduced indicating improvement of the subjects' well-being. Adverse events were predominantly of mild intensity and considered as not related to the study treatment. TESAEs were reported in 15.8% subjects. No fatal or drug-related SAEs were reported during the study and there were 3 subjects who were discontinued from the study due to AEs. No unknown AEs were observed in the study. No subject developed neutralizing antibodies. The study drug was generally well tolerated in this study population Overall, NT 201 was found to be efficacious and safe in subjects with CD under long-term treatment.