Clinical Study Report Synopsis for Public Disclosure

This Clinical Study Report Synopsis is provided to the public for informational purposes only in accordance with legal requirements. Being part of the clinical study report it had been prepared according to legal/regulatory requirements and best practice at the time of study completion.

The study listed may include information about approved and non-approved uses, doses, formulations or treatment regimens. The results reported in any single study may not reflect the overall results obtained on studies of a product. Patients should always seek medical advice before making any decisions on their treatment. Healthcare professionals should always refer to the specific prescribing information approved for the patient's country or region.

Page numbering in the Clinical Study Report Synopsis may be inconsistent due to the fact that it is part of a comprehensive clinical study report. Information not relevant for the Clinical Study Report Synopsis is crossed-out. Information in the Clinical Study Report Synopsis may have been redacted (blacked out) to fulfill legal requirements (e.g. statutory obligations on protection of personal data) or to protect commercially confidential information of Merz Pharmaceuticals GmbH.

2. SYNOPSIS

Study Title	A prospective, open-label, international, multicenter trial to investigate the efficacy and safety of NT 201, free of complexing proteins, in the treatment of glabellar frown lines	
Name of Finished Product	NT 201	
Name of Active Ingredient	*Clostridium Botulinum* neurotoxin type A [150 kDa], free of complexing proteins.	
Investigator(s)	[redacted] Germany [redacted] Russia [redacted] Russia	
Total Number of Study Center(s)	Two sites in Russia and one site in Germany that were experienced in treatment of glabellar frown lines with Botulinum neurotoxin type A.	
Publication (Reference)	Not applicable.	
Study Period	Date of first enrolment: Date of completion:	26 May 2008 02 February 2009
Phase of Development	Phase III	
Objective(s)	To investigate the efficacy and safety of NT 201 in the treatment of glabellar frown lines.	
Methodology	Assessment of the FWS at maximum frown by the investigator.	
Number of Subjects (planned and analyzed)	Planned: 101 subjects. Analyzed: screened: 108 subjects, treated: 105 subjects, study completed: 104 subjects	
Diagnosis and Main Criteria for Inclusion	**Diagnosis:** Moderate to severe glabellar frown lines. **Main criteria for inclusion:** Females and males fulfilling the following criteria were eligible: • Moderate to severe glabellar frown lines at maximum frown (severity score of 2 or 3 on Facial Wrinkle Scale [FWS]) as assessed by the investigator's rating: 0 = 'none', 1 = 'mild', 2 = 'moderate', 3 = 'severe'. • Stable medical condition. • Age: between 18 and 65 years (inclusively).	

Study Title	A prospective, open-label, international, multicenter trial to investigate the efficacy and safety of NT 201, free of complexing proteins, in the treatment of glabellar frown lines	
Investigational Product	NT 201 Dose: Mode of administration: Batch number:	Active ingredient: Botulinum neurotoxin type A, free of complexing proteins. A total dose of 20 U NT 201 was administered at Visit 2 (Day 0 of the study period). Of the 0.5 ml total injection volume, equal aliquots of 0.1 ml were administered to five injection sites. 0802019036
Reference Product	Not applicable.	
Duration of Treatment	The planned duration was 84 ±7 days plus individual duration of screening (7 days ±3) for each subject. All subjects adhered to the scheduled time points.	
Criteria for Evaluation **Efficacy**	<u>Primary efficacy endpoint:</u> • The primary efficacy endpoint was the response to the treatment with respect to the FWS at maximum frown as rated by the investigator at Visit 3 (Day 28), defined as an improvement of the FWS of at least one point from Visit 2 (Day 0) to Visit 3 (Day 28). <u>Secondary efficacy endpoints:</u> • Response to the treatment with respect to the FWS at maximum frown as rated by the investigator at Visit 4 (Day 84), defined as an improvement of the FWS of at least one point from Visit 2 (Day 0) to Visit 4 (Day 84). • Response to the treatment with respect to the FWS at rest as rated by the investigator at Visit 3 (Day 28). • Response to the treatment with respect to the FWS at rest as rated by the investigator at Visit 4 (Day 84). • Response to the treatment with respect to the patient's assessment at maximum frown at Visit 3 (Day 28), defined as an improvement of the patient's assessment of at least one point from Visit 2 (Day 0) to Visit 3 (Day 28). • Response to the treatment with respect to the	

Study Title	A prospective, open-label, international, multicenter trial to investigate the efficacy and safety of NT 201, free of complexing proteins, in the treatment of glabellar frown lines
	patient's assessment at rest at Visit 3 (Day 28), defined as an improvement of the patient's assessment of at least one point from Visit 2 (Day 0) to Visit 3 (Day 28). • Response to the treatment with respect to the patient's assessment at maximum frown at Visit 4 (Day 84). • Response to the treatment with respect to the patient's assessment at rest at Visit 4 (Day 84). • Response to the treatment with respect to the patient's global assessment [PGA] at Visit 3 (Day 28), defined as a score of at least +2 in the PGA at Visit 3 (Day 28). • Response to the treatment with respect to the PGA at Visit 4 (Day 84), defined as a score of at least +2 in the PGA at Visit 4 (Day 84).
Safety	• Incidence of adverse events [AEs] over 3 months duration of trial. • AEs of special interest [AESIs] and all other signs and symptoms, which the investigator considers to indicate toxin spread. • Clinical biochemistry and hematology at Screening and Day 84. • Botulinum neurotoxin type A antibody tests (fluorescence immunoassay [FIA-AB] and, if positive, Hemidiaphragm Assay [HDA]) at Screening and Day 84. • Vital signs (pulse rate [PR], blood pressure [BP]) at Screening and Day 84. • Physical examination at Screening and Day 84. • Concomitant medication and concomitant treatments at all visits.
Statistical Methods	**Efficacy Analysis:** All enrolled and treated subjects with a baseline measurement of the FWS at maximum frown as assessed by the investigator were included in the Full Analysis Set

Study Title	A prospective, open-label, international, multicenter trial to investigate the efficacy and safety of NT 201, free of complexing proteins, in the treatment of glabellar frown lines
	[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. The 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 in this Clinical Study Report. *Primary efficacy analysis:* The primary efficacy variable was analyzed by frequency tables and shift tables. For the primary efficacy endpoint a parametric 95% confidence interval was estimated. This confirmatory analysis was based on the FAS with missing values imputed either by the respective baseline value of the FWS at maximum frown (if the FWS value was missing at Visit 4), or by applying a next-observation-carried-backwards strategy (if the FWS value was observed at Visit 4, the missing value at Visit 3 was imputed by the respective value of Visit 4). Sensitivity analysis was conducted by repeating the primary efficacy analysis on the FAS with observed cases only, as well as on the PPS. *Secondary efficacy analysis:* All statistical procedures performed on the secondary efficacy variables were descriptive and had to be treated as exploratory. All secondary efficacy variables were analyzed using frequency tables and shift tables. Additionally, parametric 95% confidence intervals were estimated for all secondary efficacy endpoints. The analysis of the secondary endpoints based on the FWS at maximum frown and the FWS at rest was performed on the FAS and the PPS with imputed values and observed cases, respectively. For all other secondary efficacy endpoints based on the patient's assessment at maximum frown and at rest as well as PGA missing values were not imputed, but the analysis was based on the FAS and the PPS with observed cases only.

Study Title	A prospective, open-label, international, multicenter trial to investigate the efficacy and safety of NT 201, free of complexing proteins, in the treatment of glabellar frown lines
	Safety Analysis: All subjects who had received study medication were part of the Safety Evaluation Set [SES]. Safety analysis was based on the SES only. 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, upper and lower quartiles, 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**	The response to the treatment with NT 201, with respect to the FWS at maximum frown as rated by the investigator at Visit 3 (Day 28), was the primary efficacy endpoint of this study. The primary efficacy parameter was the expected proportion of responders at Visit 3. Overall, 103 (98.1%) subjects of the FAS (imputed values) were responders at maximum frown and Visit 3. After 12 weeks (Visit 4, imputed values), the response rate was with 80.0% still quite high. At rest, 99 (94.3%) subjects responded to the treatment after 4 weeks (Visit 3, imputed values) and dropped to 81.9% after 12 weeks (Visit 4). A further objective of the trial was to evaluate the subject's self assessment of the treatment success. At Visit 3 and maximum frown, 99.0% of subjects were responders. The response rate at Visit 4 and maximum frown was still 76.0%. With regard to the glabellar frown lines at rest, the response rate was slightly lower (93.3%) at Visit 3 and 81.7% at Visit 4, respectively. Additionally, the PGA of change in appearance of glabellar frown lines compared with the situation immediately before the NT 201 injection, was evaluated. At Visit 3, 98.1% of subjects were responders and of

Study Title	A prospective, open-label, international, multicenter trial to investigate the efficacy and safety of NT 201, free of complexing proteins, in the treatment of glabellar frown lines
	85.6% of subjects, the treatment effect was still visible at Visit 4. The results of the subgroups (subjects aged ≤ 50 years and > 50 years) were comparable after 4 weeks (Visit 3) of treatment with respect to the FWS and the patient's assessment at maximum frown and the PGA. In contrast, the response rates after 4 weeks at rest according to the FWS as well as the patient's assessment were clearly higher of subjects aged ≤ 50 years than subjects aged > 50. After 12 weeks (Visit 4), subjects aged ≤ 50 years were better responders to the treatment with NT 201 than subjects aged > 50 years according to all assessed scales.
Safety Results	Safety of NT 201 was evaluated in 105 subjects. No subject died during the course of this study. In total, 25 (23.8%) out of 105 subjects of the SES suffered from AEs. Seven (6.7%) subjects had non-TEAEs and 21 (20.0%) subjects had TEAEs. Fourteen (13.3%) subjects of the SES suffered from TEAEs assessed as 'mild', 6 (5.7%) subjects had moderate and 1 (1.0%) subject severe TEAEs. No TEAE that occurred during this study was of special interest, and no TEAE led to any drop-out. Four (3.8%) subjects experienced TEAEs that were considered 'related to treatment' and classified as 'nervous system disorder' ('headache' and 'carotid artery stenosis'). Most TEAEs were allocated to 'nervous system disorders' and occurred in 7 (6.7%) subjects, followed by 'infections and infestations' and 'respiratory, thoracic and mediastinal disorders' (affecting 2.9% of subjects each). Six (5.7%) subjects experienced 'headache' and 3 (2.9%) subjects reported 'respiratory disorder'. All other TEAEs (for example 'acute tonsillitis' or 'bronchitis') affected 1 (1.0%) subject each. The overall profile of most frequent TEAEs occurring in this study is not unexpected under NT 201 treatment. One TESAE ('fibroadenoma of breast') occurred in 1 (1.0%) subject of the SES during the study. This TESAE was assessed as 'not related' to study medication and 'moderate'. Among the non-TEAEs, 2 subjects experienced 'headache' and 1 subject experienced 'migraine'. This

Study Title	A prospective, open-label, international, multicenter trial to investigate the efficacy and safety of NT 201, free of complexing proteins, in the treatment of glabellar frown lines
Conclusion	corresponds to headache being the most frequent reported TEAE. Two subjects were documented to have clinically significant clinical chemistry values. Clinically significant hematology parameters were reported for 3 subjects. None of the vital signs showed systematic or clinically relevant changes during the course of the study. Overall, analyses of clinical laboratory data and vital signs raised no safety concerns. No subject experienced the formation of neutralizing antibodies during the study. In conclusion, NT 201 was well tolerated and safe. The current study did not reveal any suspicion of unknown risks related to the treatment of glabellar frown lines with NT 201. This study demonstrated, that 20 U NT 201 can be considered [redacted] effective in the treatment of glabellar frown lines. The investigators' assessments of the [redacted] treatment success at maximum frown as well as at rest were supported by the treated subjects themselves. Additionally, NT 201 was well tolerated and safe.