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1) Name and Address of Sponsor/Company and Marketing Authorization Holder Merz Pharmaceuticals GmbH Eckenheimer Landstrasse 100 60318 Frankfurt/M, Germany	**AMG §42b Synopsis** (15-JUN-2012) of Clinical Study Report MRZ-60201-0520/1
2) Name of Finished Product NT 201	**4) Individual Study Table Referring to Part of the Dossier** Volume: Page:
3) Name of Active Substance NT 201 containing 100 mouse LD_{50}-units NT 101 (*Clostridium botulinum* neurotoxin type A [150 kDa], free of complexing proteins)	

SYNOPSIS

Study identifier MRZ-60201-0520/1

5) Title of study

A prospective, randomized, double-blind, placebo-controlled, multicenter trial with an open-label extension period to investigate the efficacy and safety of NT 201, free of complexing proteins, in the treatment of glabellar frown lines

- 2nd protocol amendment, substantial: version 3.0, 01 Nov 2006
- 1st protocol amendment, non-substantial: version 2.0, 11 Sep 2006
- initial version: final version, 05 Jul 2006

6-7) Investigator(s) and study site(s)

- Clinic for Dermatology, Campus Charité Mitte, Berlin, Germany
- Universitätsklinikum des Saarlandes, Department of Dermatology, Homburg/Saar, Germany
- Rosenparkklinik, Darmstadt, Germany
- Krankenhaus Dresden-Friedrichstadt, Department of Dermatology, Dresden, Germany
- Johann Wolfgang Goethe-Universität, Centre for Dermatology, Frankfurt am Main, Germany
- Universität Hamburg, Specialization: cosmetics and personal hygienics, Hamburg, Germany
- Private Practice for Dermatology, Mahlow, Germany
- SCIderm GmbH, Hamburg, Germany
- Private Practice for Dermatology, Wuppertal, Germany
- Private Practice for Dermatology, München, Germany
- Praxisklinik for Dermatology, Starnberg, Germany (no subjects enrolled)

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8) Publication (reference)

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9) Study period	First subject enrolled:	10 Oct 2006	**10) Phase:**
	Last subject completed:	29 Nov 2007	**III**

Study on hold: -

Early Termination: -

11) Objectives

To investigate the efficacy and safety of NT 201 versus placebo in the treatment of glabellar frown lines.

12) Study design and methodology

A prospective, multicenter, Phase III clinical trial comprised of a 120-day Main Period and a 120-day OLEX Period. The Main Period was randomized, double-blind, and placebo controlled, with a parallel group design. In the Main Period, subjects were randomized to receive treatment with NT 201 or placebo using a 2:1 (NT 201:placebo) randomization ratio. NT 201 or placebo treatment was administered at Visit 1 (Day 0). Subjects were then followed up for 120 days. The OLEX Period used an open label, non-controlled group design. NT 201 treatment was administered at Visit 6 part 2 and subjects were followed up for 120 days. This Integrated Clinical and Statistical Study Report [CSR] describes the Main and OLEX Periods of the study.

13) Number of subjects (planned and analyzed)

Planned: the planned number of subjects to be randomized was 255 (2:1 randomization ratio: 170 subjects NT 201, 85 subjects placebo).
Analyzed (Main Period): 364 subjects were screened. Of these, 108 subjects were dropouts during screening and 256 subjects were randomized and treated with study medication (NT 201: 169 subjects; placebo: 87 subjects). All 256 subjects were included

in the Full Analysis Set [FAS] and the Safety Evaluation Set [SES]. The FAS consisted of all randomized subjects (Intention-to-Treat principle). Of these, 225 subjects (87.9%) were included in the Per-Protocol Set [PPS]. A total of 10 subjects (5.9%) and 4 subjects (4.6%) in the NT 201 and placebo groups, respectively, prematurely withdrew from the study during the Main Period.

Analyzed (OLEX Period): of the 242 subjects that completed the Main Period, 6 subjects did not enter the OLEX Period [redacted]. 236 subjects were treated with study medication (Main Period NT 201: 153 subjects; Main Period placebo: 83 subjects). All 236 subjects were included in the FAS and SES. Of these, 161 subjects (68.2%) were included in the PPS. A total of 11 subjects (4.7%) prematurely withdrew from the study during the OLEX Period.

14) Diagnosis and main criteria for in- and exclusion

Diagnosis: moderate to severe glabellar frown lines.

Main criteria for inclusion: females and males fulfilling the following criteria were to be eligible for inclusion:

- Moderate to severe glabellar frown lines *at maximum frown* (severity score of 2 or 3 on the Facial Wrinkle Scale [FWS]) as assessed by the investigator's rating:
  0 = 'none', 1 = 'mild', 2 = 'moderate', 3 = 'severe'
- Stable medical condition
- 18 years of age or older
- Sum score below cut-off in evaluation based on the quality of life, skin and cosmetics questionnaire 'Fragebogen zur Lebensqualität, Haut und Kosmetik' [FLQA-k]

Main criteria for exclusion:

Subjects who presented any of the following exclusion criteria were to be excluded from the study enrollment at Screening:

- Previous treatment with Botulinum toxin of any serotype or with biodegradable fillers in the glabellar area within the last 12 months
- Any previous insertion of permanent material in the glabellar area (regardless of the time between previous treatment and this study)
- Previous treatment with any facial cosmetic procedure (e.g. dermal filling, chemical peeling, photo rejuvenation) in the glabellar area within the last 12 months
- Planned treatment with Botulinum toxin of any serotype in any body region during the study period

- Any other planned facial cosmetic procedure during the trial period
- Inability to substantially lessen glabellar frown lines even by physically spreading them apart
- Any surgery in the glabellar area including surgical removal of the corrugator, procerus, or depressor supercilli muscles or a combination of these, or scars in the glabellar area
- Marked facial asymmetry or ptosis of eyelid and/or eyebrow
- Any infection in the area of the injection sites
- History of facial nerve palsy

15) Test product, dose and mode of administration, batch number

NT 201 (*Clostidium Botulinum* neurotoxin type A [150 kDa] free of complexing proteins)

Dose: 20 Units [U]

Mode of administration: of the total injection volume (0.5 mL), equal aliquots were administered intramuscularly to 5 injection sites: procerus muscle; each side in the central part of the corrugator muscle approximately 1 cm above the bony orbital rim; and each side in the middle part of the corrugator muscle at least 1.5 cm above the bony orbital rim.

Batch number: 60506

16) Duration of treatment

The duration of treatment during the Main Period of the study was 120 days plus the individual duration of screening (3 to 14 days). Eligible subjects received 1 application of study treatment during the Main Period at Visit 1 (Day 0).
The duration of treatment during the OLEX Period of the study was 120 days plus up to 30 days for eligibility reassessments for entering the OLEX Period. Eligible subjects received 1 application of study treatment during the OLEX Period at Visit 6 part 2 (Day 0).

17) Reference therapy

Lyophilized placebo solution only containing the excipients of NT 201

Mode of administration: same as for NT 201

Batch number: 60202

18) Criteria for evaluation

Efficacy

Primary parameters (Main Period only):

- Percentage of responders *at maximum frown* at Day 30 of the Main Period, as assessed by the investigator according to the FWS, i.e. FWS score of none (0) or mild (1).
- Percentage of responders at Day 30 of the Main Period, as assessed by the subject's global assessment of change in appearance of glabellar frown lines, i.e. a score of at least +2 (equivalent to a moderate improvement).

Secondary parameters in the Main Period and OLEX Period:

- Percentage of responders *at maximum frown* on Days 7, 60, 90, and 120 of the Main Period, as assessed by the investigator's rating according to the FWS.
- Percentage of responders on Days 7, 60, 90, and 120 of the Main Period, as assessed by the subject's global assessment of change in appearance of glabellar frown lines.
- Percentage of responders *at maximum frown* on Days 7, 30, 75, and 120 of the OLEX Period, as assessed by the investigator's rating according to the FWS
- Percentage of responders on Days 7, 30, 75, and 120 of the OLEX Period, as assessed by the subject's global assessment of change in appearance of glabellar frown lines.

Tertiary parameters in the Main Period and OLEX Period:

- Percentage of responders *at rest* on Days 7, 30, 60, 90 and 120 of the Main Period, and on Days 7, 30, 75, and 120 of the OLEX Period, as assessed by the investigator's rating according to the FWS.
- Subject's assessment on a 4-point scale *at rest* and *at maximum frown* at all visits except at Screening
- Onset of effect after each treatment.

Safety

Safety parameters in the Main Period and OLEX Period:

- Incidence of adverse events [AEs] during the Main Period of the trial (4 months duration)
- Incidence of AEs during the Overall Period of the trial (8 months duration)

- Clinical biochemistry and hematology at Screening, Day 120 of the Main Period, and Day 120 of the OLEX Period
- Botulinum neurotoxin type A [BoNT/A] antibody tests (Fluorescence immunoassay-antibody [FIA-AB] and, if positive, Hemidiaphragm Assay [HDA]) at Screening, Days 30 and 120 of the Main Period, and Days 30 and 120 of the OLEX Period
- Vital signs (heart rate, blood pressure [BP]) at all visits
- 12-lead electrocardiogram [ECG] at Screening, Day 30 of the Main Period and Day 30 of the OLEX Period
- Physical examination at Screening, Day 120 of the Main Period, and Day 120 of the OLEX Period
- Concomitant medications at all visits
- Concomitant treatments at all visits.

19) Statistical methods

In the primary efficacy analysis, the FAS was used for the confirmatory analysis. Missing values were imputed using the last observation carried forward principle. If there were no values available until Day 30, the subject was analyzed as a non-responder. The confirmatory analysis of both primary efficacy parameters was performed using the Cochran-Mantel-Haenszel [CMH] Method to compare the responder rates in the treatment and placebo groups at Day 30 (Visit 3) after first treatment, with center as the stratification variable (significance level of $\alpha = 0.0125$, one sided). Both primary efficacy parameters had to show significant p-values simultaneously to confirm the efficacy of the treatment. All other p-values and confidence intervals [CI] were descriptive. Subgroup analyses were performed for gender and age. Safety analyses were based upon the SES, which was identical to the FAS.

20) Summary – Conclusions

Study subjects

Main Period:

256 subjects were randomized and treated with study medication (NT 201: 169 subjects; placebo: 87 subjects).

OLEX Period:

Of the 242 subjects that completed the Main Period, 6 subjects did not enter the OLEX Period. 236 subjects were treated with study medication in OLEX (Main Period NT 201: 153 subjects; Main Period placebo: 83 subjects).

Efficacy results

Main Period: At Day 0, 79.9% of subjects in the NT 201 group (FAS) had severe glabellar frown lines (FWS of 3) *at maximum frown*; the remaining 20.1% subjects had moderate. Severe glabellar frown lines were also found in 34.9% of subjects in the NT 201 group *at rest*; 53.8% had moderate and 11.2% had mild. Similar patterns were also observed in the placebo group. The efficacy of NT 201, as assessed by the percentages of responders *at maximum frown* at Day 30 in the investigator's assessment and in the subject's global assessment of change in appearance of glabellar frown lines, was highly significantly superior to placebo ($p < 0.0001$), i.e. the primary efficacy criterion was fulfilled. The responder rate in the NT 201 group at Day 30 was higher in the subject's global assessment (67.5%) compared with the investigator's assessment (51.5%), whereas the responder rates in the placebo group were negligible (1.1% and 0%, respectively). These data (FAS) were supported by the findings in the PPS. The results of the secondary and tertiary endpoints (responder rates over time in the various subgroups; *at rest* as assessed by the investigator; *at maximum frown* and *at rest* as assessed by subjects) were consistent with the data observed for the co-primary endpoints. A higher response rate for NT 201 was observed in female subjects relative to male subjects as well as in subjects ≤ 50 years relative to subjects > 50 years, indicating that the effect was more pronounced in females aged ≤ 50 years. A clear time course of action for NT 201 in the treatment of glabellar frown lines was evident: the effect was apparent on Day 7, reached a maximum on Day 30 and declined slowly thereafter.

OLEX Period: At Day 0, 69.1% of subjects overall (FAS) had severe glabellar frown lines (FWS of 3) *at maximum frown*; the remaining 30.9% subjects had moderate. Severe glabellar frown lines were also found in 30.1% of subjects overall *at rest*; 51.7% had moderate, 17.8% had mild and 0.4% had none. At baseline of the OLEX Period the severity of glabellar frown lines was generally worse in subjects who had received placebo during the Main Period of the study as opposed to NT 201. The results of the secondary and tertiary endpoints (responder rates *at maximum frown* and *at rest* in the investigator and subjects' assessments) demonstrated a clear time course of action for NT 201 in the treatment of glabellar frown lines: the effect was apparent on Day 7, reached a maximum on Day 30 and declined slowly thereafter. An onset of treatment effect was apparent on Day 1 (day of study drug administration) and the median time to onset of treatment effect was 4 days which includes the day of injection. Higher response

rates were observed in the assessments that were performed by the subjects, in contrast with the assessments performed by the investigators. In the investigators' assessments and subject's global assessment, greater proportions of subjects in the Main Period NT 201 group were responders at each time point; conversely, in the subjects' assessments, greater proportions of subjects in the Main Period placebo group were responders at each time point.

Safety results

Main Period: No subjects were withdrawn during the Main Period of the study as a result of a TEAE. Four subjects overall, all in the NT 201 group, experienced a total of 5 SAEs [redacted] None of the SAEs were fatal or "expected" according to the IB (Version VIII) or were considered to be related to the study medication. Only 1 TEAE was reported as an AESI: mild eyelid ptosis, which resolved 4 days after onset. The event was "expected" according to the IB and related to the study drug in the opinions of both the investigator and the sponsor. Other TEAEs (headache [14.1%] and nasopharyngitis [12.9%] were the most frequently reported) were well balanced with regard to incidence and type of TEAEs; any differences between groups were minimal and not clinically relevant. Neutralizing antibodies for BoNT/A were only observed in 1 subject at Screening and 2 additional subjects at Day 30 in subjects in the NT 201 group. However, no positive HDA results were observed at Day 120.

OLEX Period: No subjects were withdrawn during the OLEX Period of the study as a result of a TEAE. Five subjects overall, all in the Main Period NT 201 group, experienced a total of 6 SAEs [redacted] None of the SAEs were fatal or "expected" according to the IB (Version VIII) or were considered to be related to the study medication. Only 2 TEAEs of mild eyelid ptosis were reported as AESIs, which resolved 25 and 4 days after onset, respectively. These events were "expected" according to the IB and related to the study drug in the opinions of both the investigator and the sponsor. Other TEAEs (headache [8.1%] and nasopharyngitis [8.1%] were the most frequently reported) were well balanced with regard to the incidence and type of TEAEs reported. No major changes were observed in terms of vital signs, physical examinations and ECG data. Overall, abnormal clinically significant laboratory results were rarely observed (2.5%). As a consequence of the abnormal laboratory data observed, 6 TEAEs were diagnosed in 5 subjects (2.1%). Neutralizing antibodies for

BoNT/A were only observed in 1 subject (Day 30). However, no positive HDA results were observed at Day 120. In the study as a whole (Main and OLEX Periods), TEAEs were reported in a higher proportion of subjects after treatment with NT 201 (55.2%) than after treatment with placebo (46.0%).

Conclusions

- Subjects with moderate to severe glabellar frown lines *at maximum frown* were selected for this study
- The efficacy of NT 201 in correcting the appearance of glabellar frown lines was clearly and consistently demonstrated
- The treatment effect was evident after 4 days and present at least up to 120 days post-injection
- NT 201 was safe and well tolerated
- No new safety concerns were identified

The population in this clinical study is not comparable to populations in other studies performed in this indication due to application of the FLQA-k (Freiburg Life Quality Assessment – 'Lebensqualität, Haut und Kosmetik') questionnaire as additional inclusion criterion. This was a request of the BfArM. As a consequence only subjects with a considerable psychological strain were enrolled leading to a more challenging test population.

21) Date of Report

AMG §42b Synopsis Final Version 1.0 (15-JUN-2012), based on Clinical Study Report Version 1.0 (12-SEP-2008)