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1) Name and Address of Sponsor/Company Merz Pharmaceuticals GmbH Eckenheimer Landstrasse 100 60318 Frankfurt/M, Germany	**AMG §42b Synopsis** (26-JAN-2015) of Clinical Study Report MRZ 60201-0617/1
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 101, Clostridium botulinum neurotoxin type A free of complexing proteins	

SYNOPSIS

Study identifier MRZ 60201-0617/1, EudraCT-Number: 2006-005396-17

5) Title of study

A prospective, randomized, double-blind international multicenter trial to investigate the efficacy and safety of NT 201 in comparison to placebo and to compare two different application schemes of NT 201 in the treatment of lateral periorbital wrinkles

- 2nd protocol amendment, date: 30-Jan-2008
- 1st protocol amendment, substantial, final amended Protocol Version 3.0, date: 06-Jun-2007
- Protocol: version 2.0, date: 24-Apr-2007

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

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8) Publication (reference)

NA

9) Study period	First subject enrolled:	03-Sep-2007	**10) Phase:** III
	Last subject completed:	12-May-2008	

Study on hold: NA

Early Termination: NA

11) Objectives

To investigate the efficacy and safety of NT 201 in comparison to placebo in the treatment of moderate to severe lateral periorbital wrinkles at maximum smile, and to assess and compare two different application schemes of NT 201 in a bilateral, intraindividual comparison. Each subject was treated on both the right and left eye area, using the same dose but different application schemes, namely 3 or 4 injections. The application scheme was randomly assigned to the side of the eye.

12) Methodology

- 4-point scale for assessment of lateral periorbital wrinkles: An independent rater blind to visit numbers and subject's treatment group assessed the severity of lateral periorbital wrinkles at maximum smile on either side according to a 4-point scale from standardized digital photographs taken at each visit.
- 4-point scale for assessment of lateral periorbital wrinkles by the investigator.
- 9-point Likert scale for the subject's global assessment of improvement of lateral periorbital wrinkles.
- Time to onset of treatment effect assessed by the subject.
- Time to fading of treatment effect assessed by the subject.

13) Number of subjects (planned and analyzed)

It was planned to randomize 108 subjects. 157 subjects were screened. Of these, 46 subjects were screening failures, and 111 were randomized and treated with study medication (NT 201: 83 subjects; placebo: 28 subjects). A total of three subjects

prematurely withdrew from the study, so 108 subjects (NT 201: 80 subjects; placebo: 28 subjects) completed the study. All 111 subjects were included in the Full Analysis Set [FAS] and the Safety Evaluation Set [SES]. Of these, 91 subjects (82%) were included in the Per-Protocol Set [PPS].

14) Diagnosis and main criteria for in- and exclusion

- Male and female subjects between 18 and 60 years of age (inclusive).
- Symmetrical lateral periorbital wrinkles on both sides of the face at maximum smile.
- Subjects with moderate (grade 2) to severe (grade 3) symmetrical lateral periorbital wrinkles determined by the investigator by use of the 4-point scale at maximum smile.
- Stable medical condition.
- Total score of the evaluated questionnaire on quality of life, skin and cosmetics [FLQA-c] had to be below the pre-defined cut-off value of 0. (Criterion was not applicable with the introduction of Protocol Amendment 2).

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

Dose and mode of administration: A single, total dose of 12 units NT 201 in 0.24 mL saline solution per side (right/left eye area) by intramuscular [i.m.] injection in three or four equal volume injections in each eye area, as randomly assigned for each subject.

Batch Number: 60506

16) Duration of treatment

The investigational medicinal product was injected only at baseline, with a study phase of 12 weeks followed by an eight-week follow-up phase.

17) Reference therapy

Dose and Mode of Administration: Placebo, with no active ingredient but identical in appearance to the active product, 0.24 mL saline solution per side (right/left eye area) by i.m. injection in three or four equal volume injections in each eye area, as randomly assigned for each subject.

Batch Number: 60201

18) Criteria for evaluation

Efficacy

Primary efficacy variable:

- Treatment response rate where treatment response was defined as an improvement of at least 1 point on the 4-point scale for lateral periorbital wrinkles (in short: wrinkle scale) assessed by an independent rater using standardized digital photographs taken at maximum smile at visit 4 (week 4) for either eye area compared to baseline.

Secondary efficacy variables:

- Treatment response rate at visits 3, 4, 6, and 7 (weeks 2, 4, 12, and 20) based on the investigator assessment on the wrinkle scale for either eye area at maximum smile compared to baseline.
- Treatment response rate where treatment response was defined as an at least moderate improvement (at least 2 points) on the 9-point scale for the subject's global assessment of improvement of lateral periorbital wrinkles at visits 3, 4, 6, and 7 (weeks 2, 4, 12, and 20).

Tertiary efficacy variables:

- Treatment response rate at visits 3, 6, and 7 (weeks 2, 12, and 20) based on the independent rater assessment on the wrinkle scale for either eye area at maximum smile compared to baseline.
- Treatment response rate at visits 3, 4, 6, and 7 (weeks 2, 4, 12, and 20) based on the independent rater assessment on the wrinkle scale for either eye area at rest compared to baseline.
- Treatment response rate at visits 3, 4, 6, and 7 (weeks 2, 4, 12, and 20) based on the investigator assessment on the wrinkle scale for either eye area at rest compared to baseline
- Time to onset of treatment effect for either eye area assessed by the subject at visits 3 and 4 (weeks 2 and 4).
- Time to fading of treatment effect for either eye area assessed by the subject at visits 5 and 6 (weeks 8 and 12).

Safety

Safety parameters:

- Incidence of adverse events [AEs] over 22 weeks (overall period).
- Standard clinical biochemistry and hematology at screening and visit 7 (week 20).
- Botulinum neurotoxin type A antibody tests (fluorescence immunoassay [FIA-AB], and, if positive, hemidiaphragm assay [HDA] at screening and visit 7 (week 20).
- Vital signs (pulse rate, blood pressure) at all visits except at visit 5 (week 8).
- Physical examination at screening and visit 7 (week 20).
- Previous and concomitant medication at all visits.
- Previous and concomitant treatments at all visits.

19) Statistical methods

A hierarchical testing procedure was applied to show the superiority of NT 201 treatment over placebo for both application schemes (3-injection regimen as first and 4-injection regimen as second level of the procedure) and to provide evidence that both application schemes are equally effective (third level) with respect to the primary efficacy parameter.

The confirmatory analysis of both superiority tests was based on the FAS. Two-group continuity corrected Chi-square tests were applied.

For showing equivalence of the different NT 201 regimens, a two-sided 90% confidence interval [CI] for the response rates difference was calculated.

Equivalence of the different treatment regimens was only concluded if the pertinent equivalence test showed significant results in the analysis based on the PPS and in the analysis based on the FAS with an equivalence interval of (-15%, 15%).

20) Summary – Conclusions

Efficacy results

The primary efficacy parameter of this study was the proportion of subjects in the FAS showing a treatment response at week 4.

The difference in proportion of responders having at least a 1-point reduction in independent rater assessment score for periorbital wrinkles at maximum smile from baseline to week 4 between the NT 201 group and placebo group was 48.45% ($p<0.0001$) for the 3-injection scheme and 54.39% ($p<0.0001$) for the 4-injection scheme, demonstrating the superiority of NT 201 over placebo. The difference in proportion of responders between the 3-injection and 4-injection regimen groups was -1.20% in the FAS and 0% in the PPS with tight CI (-11.93%, 9.56%) and (-11.97%, 11.97%), demonstrating equivalence of the 3-injection and the 4-injection regimens.

In the FAS population, the 3-injection scheme also showed a significant difference in proportions in response rates at maximum smile over time by independent rater, indicating superiority of NT 201 over placebo at week 2 but not at week 12 or follow-up due to the expected fading of treatment effect. In the 4-injection scheme, the difference in proportions showing superiority of NT 201 over placebo was also significant at week 2 and week 12 but not at follow-up.

For the investigator assessment at maximum smile and for both injection schemes, the difference between NT 201 and placebo was statistically significant at week 2, week 4, and at week 12. This indicates the superiority of NT 201 over placebo at weeks 2, 4 and 12. Tight confidence intervals [CIs] of the differences of proportions for the FAS and PPS indicate the equivalence of both injection schemes.

Assessment of at least a +2 change in subject global assessment score for periorbital wrinkles in the 3-injection and 4-injection schemes showed a statistically significant difference between the NT 201 and the placebo groups at week 2, week 4, and at week 12. This indicates for both injection regimens the superiority of NT 201 over placebo at weeks 2, 4 and 12. For differences of proportions in treatment response between the two injection schemes, the confidence intervals are completely covered by (- 15%, 15%) at weeks 2, 4, 12 and follow-up for the FAS and PPS, indicating the equivalence of both injection schemes.

With regard to the treatment response rates at rest over time by independent rater assessment in the FAS population, the 3-injection scheme showed a significant difference in proportions, indicating superiority of the NT 201 group compared to placebo at week 2 and week 4 but this difference was not statistically significant at week 12 or follow-up. In the 4-injection scheme the difference in proportions of NT 201 showing superiority over placebo was not statistically significant at any time point. Similar results were seen in the PPS populations.

For treatment response rate at rest over time by investigator assessment in the FAS population, the 3-injection scheme showed a significant difference in proportions and

superiority of NT 201 over placebo at week 2, week 4 and week 12 but not at follow-up. In the 4-injection scheme the difference in proportions was also significant, indicating superiority of NT 201 over placebo at week 2, week 4 and week 12 but not at follow-up. Similar results were seen in the PPS population, with the exception of the superiority of NT 201 over placebo not being statistically significant in either the 3-injection or 4-injection schemes at week 12. No differences were noted in the proportions between both schemes in the FAS and PPS populations at all time points.

In both NT 201 injection schemes, the majority of subjects recorded the onset of treatment within 0-6 days, and within 7 to 13 days, setting the estimated median time to onset at 6 days for NT 201. Only 5 subjects (17.9%) in the placebo group had a recorded onset.

The majority of the subjects in the NT 201 treatment group in both injection schemes who had recorded a fading of treatment effect, observed the fading at or after week 9.

Safety results

There were no deaths and no withdrawals from the study due to AEs. Few AEs occurred, with 13 subjects (15.7%) in the NT 201 group and four subjects (14.3%) in the placebo group experiencing events. Of these, six subjects in the NT 201 group had AEs considered as related to study medication. Five eye disorders occurred in the NT 201 group, but none were of severe intensity. One subject in the NT 201 group experienced dry eyes, an AE of special interest. The event was related to study medication but was of mild intensity. Three serious adverse events [SAEs], one event of depression and two events of hypertensive crisis, which occurred in two subjects in the NT 201 group, were unrelated to study medication. There were no notable differences between the two treatment groups with regard to results of laboratory investigations and vital sign measurements.

Conclusions

- NT 201 3-injection and 4-injection schemes are superior to placebo at week 2 and week 4 by independent rater assessment at maximum smile.
- NT 201 3-injection and 4-injection schemes are superior to placebo at weeks 2, 4 and 12 by investigator assessment and subject global assessment.
- NT 201 3-injection and 4-injection schemes demonstrated equivalence with both being equally effective in the majority of independent rater, investigator and subject global assessments.

- Results were achieved using the lowest common dose of botulinum toxin according to published recommended doses for the treatment of crow's feet.
- Using the application schemes in this study, NT 201 can be considered a safe and well tolerated treatment for periorbital wrinkles. The incidence of related AEs was low and mostly localized to the injection site. No new safety concerns were identified.

21) Date of Report

AMG §42b Synopsis Version 1.0 (26-JAN-2015), based on Clinical Study Report Version 1.0 (22-Jan-2009)