## 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

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| **Study Title** | Prospective, open-label, single-arm, single-center trial to investigate the tolerability of NT 201 and quality of life of subjects in the treatment of blepharospasm with shortened injection intervals |
| **Name of Finished Product** | Xeomin® |
| **Name of Active Ingredient** | Botulinum neurotoxin Type A free of complexing proteins |
| **Investigator(s)** | [redacted] Bonn<br>Telephone: [redacted]<br>Telefax:<br>Email: |
| **Total number of study center(s)** | One site in Germany (single-center study) |
| **Publication (reference)** | None |
| **Study period** | Date of first enrolment: 13 SEP 2007<br>Date of last subject last visit: 28 FEB 2008 |
| **Phase of development** | II |
| **Objective(s)** | To achieve a stable quality of life and to investigate the tolerability of NT 201 in subjects with blepharospasm [BEB] treated with shortened injection intervals |
| **Methodology** | Prospective, single-arm, single-center study with an open-label treatment period and a final follow-up visit. Subjects with blepharospasm were to receive 8 injections of NT 201 in intervals of at least 6 weeks, based on their individual need, resulting in a treatment period of at least 42 weeks. The follow-up visit was to be performed at the latest 20 weeks after last injection or when the subject returned for a new injection with Botulinum Neurotoxin |

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| **Methodology (continued)** | (no study medication), which ever was sooner but not earlier than 6 weeks after last injection.<br>The treatment was to be administered as intramuscular injection of solution in the affected muscles using individually adapted doses and dilutions, but maximum 50 U per eye per injection visit. Telephone contacts were to be scheduled three weeks after each visit for assessment of primary and secondary efficacy variables as well as reporting of adverse events, occurred since last injection or follow-up of already present adverse events at last injection. The last follow-up visit performed was defined as end of the study. | |
| **Number of subjects (planned and analyzed)** | Planned: N=58 (total number of subjects to be treated)<br>N=40 (expected number of subjects evaluable)<br>Analyzed: N=8 | |
| **Diagnosis and main criteria for inclusion** | Male and female pre-treated subjects ≥ 18 and ≤ 80 years of age with bilateral BEB and need of shortened injection intervals (<12 weeks) who received at least 3 consecutive injections of Botulinum Neurotoxin Type A (Botox® or Xeomin®) directly before study entry. Blepharospasm Disability Index [BSDI] at baseline visit before injection was to be ≥ 1.6. | |
| **Investigational Product** | NT 201 powder for solution for injection in sterile saline (NaCl 0,9%) (active ingredient: Botulinum neurotoxin Type A free of complexing proteins, excipients: human serum albumin, sucrose). | |
| | Dose: | Dependent on subject need but maximum 50 U/eye per injection visit |
| | Mode of administration: | Intramuscular injection in affected muscles |
| | Batch number: | 70201336 |

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| **Duration of treatment** | Approximately 56 weeks treatment period (8 injection visits with intervals of at least 6 weeks in-between, calculated with average of 8 week intervals) followed by a follow-up period of up to 20 weeks. |
| **Criteria for evaluation** | |
| **Efficacy:** | Primary efficacy variable:<br>• Blepharospasm Disability Index<br><br>Secondary efficacy variables:<br>• Jankovic Rating Scale [JRS] sum score (severity and frequency)<br>• Subject Evaluation of Global Response [PEGR] |
| **Safety:** | • Adverse events [AEs]<br>• AEs of special interest [AESIs]: ptosis, abnormal vision, xerophthalmia, diplopia, lacrimation, corneal ulceration, dry mouth, and all other signs and symptoms, which the investigator considers to indicate toxin spread.<br>• Standard clinical chemistry and hematology<br>• Vital signs<br>• Assessment of tolerability of NT 201 by investigator<br>• Antibodies against Botulinum Neurotoxin Type A<br>• Concomitant medication<br>• Pregnancy test |

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| **Statistical methods** | All subjects who received study medication at least once were to be included in the Safety Evaluation Set [SES]. All subjects from the SES with a baseline BSDI measurement at Visit V1 and who did not meet the withdrawal criterion at telephone contact 1 [T1] were to be included into the Full Analysis Set [FAS]. The Per-Protocol Set [PPS] should consist of all subjects of the FAS for whom no major protocol violations were reported. The primary efficacy endpoint was the proportion of responders showing an improved and stable quality of life level over the course of the study. A two-sided confidence interval at the 95 % confidence level was to be calculated for the overall responder rate. |
| **Statistical methods (continued)** | Sensitivity analyses were to be performed using the method of logistic regression to assess the impact of factors like baseline BSDI level, treatment effect size after the initial injection session described by a stratification at the first telephone contact, gender and age. Efficacy analyses were to be performed on both, the FAS and the PPS. The results were to be compared and any different outcomes or considerable deviations were to be described. |
| **Summary / Conclusions** | |
| **Efficacy Results** | No reliable efficacy conclusions can be drawn due to the lack of an appropriate amount of available efficacy data following T1 investigations. However, JRS indicated improvement for most subjects as did the Patient Evaluation of Global Response for the documented ratings. |

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| **Safety Results** | Limited safety conclusions can be drawn due to the small number of safety data following Baseline investigations. No deaths, other serious adverse events [SAEs] and AEs leading to withdrawal occurred. Two adverse drug reactions [ADRs] of mild intensity (headache and rash), and two AESIs of mild and moderate intensity were reported (increased lacrimation and xerophthalmia, respectively). ADRs and AESIs were recovered at study termination. A total of 2 subjects reported at least one AE. The most frequently reported AE was headache (2 out of 2 patients). No clinically relevant findings in laboratory results and vital signs were observed. Regarding the 4 available assessments of tolerability by the investigator, moderate and good assessments were observed. For [redacted], poor tolerability was reported by the investigator for the second treatment, however, no AE was documented. No details are available on the background of poor tolerability resulting from the second treatment. Interestingly, [redacted] experienced less efficacy in the second treatment. There was no evidence during this study of any new or unexpected pathological findings. |

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| **Conclusion** | The objective of this Phase II study was to show that pre-treated patients with BEB with the need of shortened injection intervals may achieve an improved and stable quality of life level if they receive repeated NT 201 injections at short injection intervals. In addition, the tolerability of repeated shortened NT 201 administrations was investigated. The Blepharospasm Disability Index was chosen as the primary efficacy parameter to measure quality of life during a treatment period of approximately 56 weeks followed by a follow-up period of up to 20 weeks. Response to treatment was given if during the entire study period with shortened injection intervals a stable quality of life could be documented. Only such subjects were accepted for further study participation whose quality of life was relevantly reduced after 3 weeks following the first treatment,. Clinical relevance was obtained by a reduction of >0.65. However, from 8 subjects included in the study this precondition for further study participation was reached in one subject only. For this reason and due to the lack of sufficient further subject recruitment, the sponsor decided to prematurely terminate the study on 28 FEB 2008. Hence, a statistical analysis of the sparse study data was not possible. In this abbreviated study report, available individual subject data were therefore displayed in subject listings. No reliable assessments of the study data with respect to efficacy are possible with this limited set of available data. However, no evidence of any new or unexpected pathological findings was raise for NT 201 from the safety data collected during this study. |