SYNOPSIS OF CLINICAL STUDY REPORT **ANNEX I ICH E3**

Name of Sponsor/Company: Hannover Medical School (HMS)	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use only)*
Name of Finished Product Vistabel	Volume:	
Name of Active Ingredient: Clostridium Botulinum Toxin Typ A	Page:	
Title of Study: Clostridium botulinum Typ A Neurotoxinkomplex zur adjuvanten Behandlung von depressiven Störungen – Eine randomisierte, kontrollierte Studie		
Investigators: Prof. Dr. Tillmann Krüger		
Study centre(s): Hannover Medical School (MHH)		
Publication (reference): 31. Wollmer MA, de Boer C, Kalak N, Beck J, Götz T, Schmidt T, Hodzic M, Bayer U, Kollmann T, Kollewe K, Sönmez D, Duntsch K, Haug MD, Schedlowski M, Hatzinger M, Dressler D, Brand S, Holsboer-Trachsler E, Kruger TH. Facing depression with botulinum toxin: A randomized controlled trial. J Psychiatr Res. 2012, 46: 574-581.		
Studied period (years): 2 (date of first enrolment) October 2009 (date of last completed) January 2011	Phase of development: IIa	
Objectives: To assess botulinum toxin injection to the glabellar region as an adjunctive treatment of major depression.		
Methodology: Randomized, cross-over, double-blind, placebo-controlled study		
Number of patients (planned and analysed): 30/30		
Diagnosis and main criteria for inclusion: Inclusion criteria were: age 25-65 years, on-going major depressive disorder (DSMIV 296.xx) diagnosed according to the Structured Clinical Interview for Axis I DSM-IV disorders (SCID I; >15 points on the Hamilton Depression Rating Scale at screening) with or without a history of dysthymic disorder (DSM-IV 300.4), and a moderate to severe vertical glabellar line during maximum voluntary frowning according to a four-point clinical severity score (Honeck et al., 2003) as well as qualitatively and quantitatively stable treatment with one or, at most, two antidepressants for at least four weeks. For ethical reasons we did not include untreated patients unless they had not responded to at least one treatment trial with an antidepressant during on-going index episode and were reluctant to undergo another one.		
Test product, dose and mode of administration, batch number: For the verum condition onabotulinumtoxinA (Vistabel, Botox Cosmetic, Allergan) was dissolved in 0.9%		

NaCl solution (B. Braun Medical) at a concentration of 100U/2.5 ml. Injections were made using insulin syringes with 30G needles at five specific points in the glabellar region (Supplemental Fig. 1).Women received 29 U of onabotulinumtoxinA in total. We injected 7 U to the procerus muscle, 6 U bilaterally to the medial part of the corrugator muscles, and 5 U bilaterally to the lateral part of the corrugator muscles. The same injection scheme was applied in the open case series (Finzi and Wasserman, 2006). To account for their higher muscle mass, men received two more units at each injection site, i.e. 39 U in total. For the placebo condition we injected identical volumes of 0.9% NaCl solution according to the described injection scheme. The intervention took place once at the end of the baseline visit.

ATC: M03AX21

Duration of treatment:

Single treatment/injection

Reference therapy, dose and mode of administration, batch number: Saline

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Name of Finished Product: Saline	Volume:	
Name of Active Ingredient: None	Page:	

Criteria for evaluation:

Efficacy: The primary end point of the trial was change in the 17-item version of the Hamilton Depression Rating Scale (HAM-D17) score at the visit after six weeks versus baseline. The clinical response measured by the HAM-D17 score was classified as nonresponse (<25% reduction), partial response (25%e49% reduction), response (50% reduction), or remission (HAM-D17 score 7).

Safety: Assessing all adverse events regularly

Statistical methods: Data were analyzed using two-way analyses of variance (ANOVA) for repeated measures with the factors group (verum vs. placebo) and time (seven time points throughout the sixteenweek follow-up period as well as two time points, baseline and six weeks after baseline, for the primary end point). In the case of deviation from sphericity, ANOVAs were performed using GreenhouseeGeisser (3) corrected degrees of freedom. Inner subject effects of time by group interactions are reported. Where appropriate, post-hoc tests with a BonferronieHolm adjustment were used, applying Student's t-tests or, in the case of variance inhomogeneity, the more robust Welch-test. These tests were also applied for continuous baseline variables. For categorical variables Fisher's exact tests were employed. All tests were two-sided. Variance is reported as standard deviation (SD) unless otherwise noted. Effect sizes are reported as partial h2, Cohen's d, or odds ratio (OR). To assess linear relationship between scales, Pearson's correlation coefficients (r) were calculated. Test results with an alpha level □0.05 are reported as significant. Statistical analyses were conducted using SPSS 19.0 for Windows.

Summary - Conclusions

Efficacy Results: Throughout the sixteen-week follow-up period there was a significant improvement in depressive symptoms in the verum group compared to the placebo group as measured by the Hamilton Depression Rating Scale ($F(6,168) = 5.76$, $p < 0.001$, $h2 = 0.17$). Six weeks after a single treatment scores of onabotulinumtoxinA recipients were reduced on average by 47.1% and by 9.2% in placebo-treated participants ($F(1,28) = 12.30$, $p = 0.002$, $h2 = 0.31$, $d = 1.28$). The effect size was even larger at the end of the study ($d = 1.80$). Treatment-dependent clinical improvement was also reflected in the Beck Depression Inventory, and in the Clinical Global Impressions Scale.

Safety Results: The study treatment was well tolerated. Apart from local irritation immediately after injection, short episodes of headache during the first weeks were the only relevant and possibly treatment-related adverse events during the trial. They occurred both in the verum and in the placebo group (40.0% vs. 26.7%, Fisher's exact, $p = 0.7$).

Conclusion: This study shows that a single treatment of the glabellar region with botulinum toxin may shortly accomplish a strong and sustained alleviation of depression in patients, who did not improve

sufficiently on previous medication. It supports the concept, that the facial musculature not only expresses, but also regulates mood states

Date of the report: 14.12.2012

ADDITIONAL REQUIREMENTS ACCORDING TO § 42B AMG

Address of Sponsor [1]: Hannover Medical School, Carl-Neuberg-Str. 1, 30625 Hannover
Name(s) of all Principal Investigator(s) and Name(s) and Address(es) of Study Centre(s)[1,2]: Prof. Dr. Tillmann Krüger, Department of Psychiatry, address see above
Information about Subsequent Substantial Amendments of Study Protocol: -
Information about Temporary Halt(s) and Premature Termination of the Trial: -

[1] if not recorded in Annex I.
[2] informed consent(s) of principal investigator(s) is/are required according to German data protection law. If a principal investigator is not consent, only the name and address of the study centre have to be recorded.