2 SYNOPSIS

Name of Sponsor/Company: IPSEN Group	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: 125 U vial versus 500 U vial		
Name of Active Ingredient(s): BoNT-A-hemagglutinin		

Title of study: A phase II, randomised, double blind study to compare the safety and efficacy of one treatment cycle of clostridium botulinum type A toxin (50 U) when reconstituted from either a 125 U or 500 U presentation for the treatment of glabellar lines.
Study number: Y-47-52120-128

Investigators:
Study Coordinator: Prof. Dr. B Rzany (Berlin Site)
Berlin Site: Dr Prof. Dr. B Rzany, Dr. V. Hartmann, Dr. F. Bachmann, Dr. D. Pathirana
Dresden Site: Dr. A. Stein, Dr. Lila Vitez
Homburg Site: Dr. D. Dill-Műller, Dr. H Grema
Starnberg/Percha Site: Dr. M. Dendorfer, Prof. Dr. M. Heckmann, Dr. K. Schmied
Műnchen Site: Dr. S. Boneberger, Prof. Dr. Rudolf Rupec

Study centre(s): The study was conducted at five centres in Germany.

Publication (reference): None at time of report.

Studied period (years): Date of first enrolment: 5th March 2008 Date of last subject completed: 14th August 2008	**Phase of development**: II

Objectives: The objectives of the study were to assess the relative clinical safety and efficacy of two different presentations of botulinum type A toxin (BoNT-A)-hemagglutinin complex (50 U), manufactured using the same methodology but presented in different vial sizes (125 U or 500 U), following a single treatment cycle for the treatment of glabellar lines.

Methodology: Subjects were randomised to receive 50 U of BoNT-A-hemagglutinin complex, either from a 125 U vial or from a 500 U vial. Study medication was administered at five injection sites (0.05 mL (10 U) per injection site) in the glabellar region on Day 1. All subjects remained under observation at the study centre for 30 minutes after treatment.

Number of patients (planned and analyzed): Approximately 100 treatment naive subjects were expected to enter the trial. A total of 106 subjects were screened; 105 subjects were recruited into the study. All of these subjects were randomised: 52 subjects to the 125 U vial group and 53 subjects to the 500 U vial group. All randomised subjects who received at least one injection of the treatment dose of study medication were included for the safety analyses. The intention to treat (ITT) population, which comprised of all randomised subjects who received a full treatment dose (five injections) of study medication, was the primary population for the efficacy analysis. Five randomised subjects who did not receive a full treatment dose due to a deviation in the study medication administration (two cases of under-dosing, two cases of overdosing and one case of inadequate volume) were excluded from the ITT population.

Name of Sponsor/Company: IPSEN Group	Individual Study Table Referring to Part of the Dossier Volume: Page:	*(For national authority use only)*
Name of Finished Product: 125 U vial versus 500 U vial		
Name of Active Ingredient(s): BoNT-A-hemagglutinin		

Diagnosis and criteria for inclusion:
Subjects between 18 and 65 years of age with moderate to severe vertical glabellar lines at maximum frown at baseline.

Test product, dose and mode of administration, batch number: Study medication was supplied as a white, lyophilised powder containing 125 U of BoNT-A-hemagglutinin complex, 125 µg human serum albumin, and 2.5 mg of lactose. Dysport batch IB07.018A was used. The product was reconstituted at the investigational centre with sterile physiological saline for injection without preservative. Study medication was administered at five injection sites (0.05 mL (10 U) per injection site) in the glabellar region on Day 1.

Duration of treatment: The overall duration of the study was approximately 5 months, i.e., one month recruitment phase and 4 months follow-up. Each subject's participation in the study was considered to have ended at the last follow-up visit, (i.e., Day 113 (±3) days) after treatment with study medication.

Reference therapy, dose and mode of administration, batch number: Study medication was supplied as a white, lyophilised powder containing 500 U of BoNT-A-hemagglutinin complex, 125 µg human serum albumin, and 2.5 mg of lactose. Dysport batch IB07.026A was used. The product was reconstituted at the investigational centre with sterile physiological saline for injection without preservative. Study medication was administered at five injection sites (0.05 mL (10 U) per injection site) in the glabellar region on Day 1.

Criteria for evaluation:

Safety:
The assessment of the relative clinical safety of the two different presentations by comparison of the incidence and severity of AEs, changes in vital signs and concomitant medications.

Efficacy:
The assessment of the relative clinical efficacy of the two different presentations in terms of the proportion of responders showing a reduction of glabellar lines, based on investigator and subject assessments performed at maximum frown, and investigator assessments performed at rest.
For each of these assessments, responders were defined as subjects who had a severity grade of none (0) or mild (1) on the visit day and a severity grade of moderate (2) or severe (3) at maximum frown at baseline (Day 1, pre treatment).

Statistical methods: Safety assessments were based on the safety population and efficacy assessments on the ITT population.

Name of Sponsor/Company: IPSEN Group	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: 125 U vial versus 500 U vial		
Name of Active Ingredient(s): BoNT-A-hemagglutinin	Volume: Page:	

Summary - conclusions:

Efficacy results:

Subjects treated with the 125 U vial or 500 U vial for glabellar lines showed a good level of response at maximum frown, with more than 60% of subjects in each treatment group considered responders on Day 29. The proportion of responders measured by the subject's self assessment at maximum frown was 64.6% (31 subjects) in the 125 U vial group and 76.6% (36 subjects) in the 500 U vial group. The proportion of responders measured by the investigator's live assessment at maximum frown was 62.5% (30 subjects) in the 125 U vial group and 70.2% (33 subjects) in the 500 U vial group. The 95% confidence intervals for the difference in the proportion of responders in the 125 U and 500 U vial groups showed the differences were not statistically significant. The proportion of responders at the other follow-up visits (Day 8, 15, 57, 85 and 113) in each treatment group remained consistent for the subject's and investigator's assessment at all visits.

Overall, the proportion of responders at rest in both treatment groups was lower that the proportion of responders at maximum frown, which is consistent with the known efficacy profile of BoNT-A in this indication. In the 125 U vial group, approximately 20-25% of the subjects were responders across the follow-up visits. The proportion of responders at rest in the 500 U vial group was comparable, with approximately 25-30% of the subjects showing response across the visits. There was no statistically significant difference between the two treatment groups.

No statistically significant differences were observed in the proportion of responders at Day 29 who maintained their response at Day 113, in both treatment groups.

The efficacy analyses by gender showed no statistically significant differences in the proportion of responders between the 125 U vial and 500 U vial treatment groups.

Safety results:

The observed TEAEs in both treatment groups were consistent with the known safety profile of BoNT-A.

The observed incidence of TEAEs was higher in the 500 U vial group compared with the 125 U vial group. Thirty-three TEAEs were experienced by 18 subjects (34.6%) in the 125 U vial group and 61 TEAEs were experienced by 26 subjects (49.1%) in the 500 U vial group. Most of the TEAEs in both treatment groups were mild or moderate in intensity.

The most common treatment related TEAEs were headache (three subjects (5.8%) in the 125 U vial group and four subjects (7.5%) in the 500 U vial group), facial paresis (no subjects reported facial paresis in the 125 U vial group and four subjects (7.5%) in the 500 U vial group), injection site swelling (one subject (1.9%) in 125 U vial group and two subjects (3.8%) in 500 U vial group) and accidental overdose (no subjects in the 125 U vial group and two subjects (3.8%) in the 500 U vial group).

Name of Sponsor/Company: IPSEN Group	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: 125 U vial versus 500 U vial		
Name of Active Ingredient(s): BoNT-A-hemagglutinin	Volume: Page:	

No TEAEs represented remote distribution of the toxin. All events of facial paresis and extraocular muscle paresis occurred in muscles contiguous from the injection site.

There were three SAEs reported during the study; one subject in the 125 U vial group and two subjects in the 500 U vial group. The SAEs were renal artery stenosis, colitis and upper limb fracture. None were considered as related to treatment. No deaths were reported.

There were no clinically meaningful changes in mean vital signs, nor clinically significant individual vital sign findings reported by the investigators.

Conclusion: There was no significant difference in efficacy of the 125 vial when compared with 500 U vial for the treatment of glabellar lines..

In this study, the overall safety and efficacy of a dose of 50 U BoNT-A in reducing the appearance of glabellar lines when reconstituted from either a 125 U vial or a 500 U vial was confirmed. This study did not raise any new safety concerns and no remote effects were noted.

Date of report: 17 December 2008