2 SYNOPSIS

Name of Sponsor/Company: IPSEN Pharma GmbH	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Dysport®		
Name of Active Ingredient(s): Botulinum Neurotoxin A	Volume: Page:	
Title of study: A national, multicenter, non-interventional, prospective, longitudinal study for treatment with botulinum toxin A injections in naïve and pre-treated patients suffering from cervical dystonia (Dysport®) Study number: A-94-52120-165		
Investigator: [redacted]		
Study centre(s): 41 investigational sites in Germany and Austria		
Publication (reference): none		
Studied period (years): Date of first enrolment: 05 July 2012 Date of last completed: 19 January 2016	Phase of development: Phase IV, Non-Interventional Study	
Objectives: *Primary Objective* Evaluation of the treatment effect of Dysport® in cervical dystonia (CD) after two injection cycles in naïve and pre-treated subjects *Secondary Objectives* • Evaluation of the treatment effect of Dysport® in CD after one injection cycle in naïve and pre-treated subjects • Evaluation of the treatment effect of Dysport® in CD after three injection cycles in naïve and pre-treated subjects • Evaluation of the treatment effect of Dysport® in CD after four injection cycles in naïve and pre-treated subjects • Evaluation of dose modifications in the course of four injection cycles in naïve and pre-treated subjects • Evaluation of the quality of life (CD questionnaire CDQ-24) in naïve and pre-treated subjects • Evaluation of the treatment effect of Dysport® and the quality of life in the subtypes torticollis, torticaput, laterocollis and laterocaput • Group comparison between two subject populations (naïve vs. pre-treated subjects)		
Methodology: multicentre, non-interventional, prospective, longitudinal study conducted at 41 centres in Germany and Austria		
Number of patients (planned and analysed):		

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Planned:	360 subjects
Enrolled:	361 subjects
Treated:	360 subjects
Evaluated:	273 subjects
Main analysis population:	273 subjects
Modified main analysis population:	233 subjects
Complete analysis population:	236 subjects

Diagnosis and criteria for inclusion:

Diagnosis: CD

Criteria for inclusion:

- Written informed consent
- Males and females aged 18 years or older with capacity to consent
- Suffering from CD with rotational torticollis/-caput or laterocollis/-caput as the primary component
- With the intention to be treated with Dysport®
- Naïve to botulinum neurotoxin type A (BoNT-A)
  or
  pre-treated with BoNT-A
  - on a regular basis for at least 2 years prior to inclusion and
  - last injection with Dysport® and
  - last injection between 3 and 6 months prior to inclusion

Test product, dose and mode of administration, batch number:

Treatment with Dysport® was to follow the recommendations of the Summary of Product Characteristics

Duration of treatment: range from 134 to 764 days

Reference therapy, dose and mode of administration, batch number: Not Applicable

Criteria for evaluation:

Efficacy:

Primary Effectiveness Variable

Difference of the total TSUI score between V1 and V3 (value at V3 minus value at V1)

Secondary Effectiveness Variables

- Difference of total TSUI score between V1 and V2 (value at V2 minus value at V1)
- Difference of total TSUI score between V1 and V4 (value at V4 minus value at V1)

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- Difference of total TSUI score between V1 and V5 (value at V5 minus value at V1)
- Difference of total TSUI score between V1 and the individual last visit (value at last visit minus value at V1)
- Dose modification (yes, no) in the course of 4 injection cycles
- Difference of CDQ-24 total score between V1 and V3 (value at V3 minus value at V1)
- Difference of CDQ-24 total score between V1 and V5 (value at V5 minus value at V1)
- Difference of CDQ-24 total score between V1 and the individual last visit (value at last visit minus value at V1)

Safety:

As this was a non-interventional study in which Dysport® was administered and managed within routine medical care, investigators were requested to report only related serious and non-serious adverse events (AE) or serious AEs (SAEs). With the amendment no. 2 the AE reporting procedure was changed, so that also not-related serious adverse events were to be reported.

Statistical methods:

Summary statistics were provided for the primary effectiveness variable and secondary effectiveness variables overall and stratified by primary component of CD and BoNT-A pre-treatment status.

Exploratory analyses of covariance (ANCOVA) were applied for changes of the total TSUI score from baseline (V1) to V2, V3, V4, V5 and the individual last visit.

Summary - conclusions:

A total of 361 subjects were enrolled in this study; of these 273 subjects were analysed. The mean (± standard deviation) age was 56.8 (± 12.7) years. There were 168 (61.5%) females and 105 (38.5%) males.

Effectiveness results:

- Starting from a mean TSUI score of 6.4 points at baseline (V1), the mean change to V3 (primary effectiveness variable) was -1.2 points (SD: 3.4 points). There were no differences between primary components of CD.
- Improvement in the TSUI score was more pronounced in treatment-naïve compared to pre-treated subjects. This effect was mainly caused by subjects with a more severe condition of their disease at baseline. At low baseline TSUI score levels, advantage of treatment-naïve over pre-treated subjects was only marginal.
- This trend also applies for changes of the total TSUI score from V1 to V2, V4, V5 and the individual last visit.
- In analogy with the TSUI score results, quality of life (CDQ-24) clearly improved

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during the course of the observation period for treatment-naïve subjects, while pre-treated subjects showed only a minimal improvement, remaining basically at the level of the baseline visit. Again, there were no differences between primary components of CD.

- Dose modifications in the course of the study were performed in 65.6% of subjects. There were no marked differences between primary components of CD. However, dose modifications were less frequently necessary for pre-treated subjects (53.9%) compared to treatment-naïve subjects (86.8%).

Safety results:

There were no safety analyses planned in this study; however the investigators were requested to report related AEs (non-serious and serious) and following Amendment No. 2 also not related SAEs to the safety department of the drug manufacturer using the usual process for such reactions. A safety data listing was generated from the Ipsen global safety database.

In total, 31 AEs were reported in 15 subjects during the study following Dysport® treatment and were entered in the Global Drug Safety Database. Eleven of these AEs were reported as serious (7 subjects); thereof 5 SAEs (2 dysphasia, 2 muscular weakness and one dyspnea) were considered as related to the study medication and 6 SAEs (one concussion, one chest injury, one fall, one muscular weakness and one septic shock and one asphyxia both leading to death) as not related by the reporter. Of the 20 non-serious AEs (11 subjects), 13 were considered as related and one as not related to the administration of Dysport® by the reporter. Causal relationship of 6 AEs was not assessed by the reporter. The most frequently reported reactions are listed for the indication of CD (dysphagia (7 subjects) and muscular weakness (5 subjects; all local muscle weakness)). An additional death occurred during this study and was assessed by the Investigator as not related to Dysport. At that time, the protocol did not require for non-related SAEs to be reported to Ipsen pharmacovigilance department and it was therefore not included in Ipsen Global Drug Safety Database.

Conclusion:

- The results from this study are in line with the known efficacy profile of Dysport®. They show that both, pre-treated and treatment-naïve subjects benefit from treatment with Dysport®.
- A difference was found for pre-treated versus treatment-naïve subjects.
  - Treatment-naïve subjects improved over the course of the study in both, functional aspects (measured by TSUI) and quality of life (measured by CDQ-24)

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- Pre-treated subjects started with better scores in TSUI and CDQ-24; these were maintained within moderate ranges over the course of the study, demonstrating that a stable level of functional aspects and of quality of life aspects could be maintained during the observation period.
- Treatment-naïve subjects with a more severe baseline condition, reflected by a higher TSUI score, showed the largest improvement during the study.

- No difference in treatment effect could be detected for the head and neck subtypes of CD.
- No new safety findings emerged from this study.

Date of report:
16 January 2017