2 SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
IPSEN Group</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier

Volume:
Page:</td><td rowspan="3">(For national authority use only)</td></tr>
<tr><td>Name of Finished Product:
Dysport®</td></tr>
<tr><td>Name of Active Ingredient:
Clostridium botulinum toxin type A-haemagglutinin complex</td></tr>
<tr><td colspan="3">Title of study: Post marketing surveillance (non-interventional study) for evaluating the efficacy and safety of Dysport Czech patients suffering from post-stroke arm spasticity
Study number: A-38-52120-113</td></tr>
<tr><td colspan="3">Coordinating investigator: Ass. Prof. MUDr. Edvard EHLER, Head of Neurological Department, Krajská Nemocnice Pardubice, Kyjevská 44, 532 03 Pardubice, Czech Republic</td></tr>
<tr><td colspan="3">Study centres: 9 centres in Czech Republic</td></tr>
<tr><td colspan="3">Publication (reference): None</td></tr>
<tr><td colspan="2">Studied period (years):
Date of first enrolment: 10 December 2008
Date of last completed: 21 March 2012</td><td>Phase of development: IV (non-interventional post-authorisation safety study (PASS))</td></tr>
<tr><td colspan="3">Objectives:
<u>Primary objective:</u>
To provide a further assessment of the benefit-risk of Dysport as a marketed product
<u>Secondary objectives:</u>
• To provide quality of life (QoL) assessment
• To gather exploratory data on the interval between treatment injections</td></tr>
<tr><td colspan="3">Methodology:
This was a national, multicentre, open, non-randomised, non-interventional, PASS conducted in 9 investigational sites in Czech Republic.
As this was a non-interventional study, the decision to prescribe Dysport was to be taken prior to, and independently from the decision to enrol the subject. Centres were to prescribe Dysport according to their usual practice and within the summary of product characteristics (SmPC).
Study visits included a baseline visit (Visit 1) and a follow-up visit (Visit 2) approximately 4 weeks later. After disappearance of its effect, Dysport was injected again during Visit 3 and Visit 4, according to the investigator's decision. Visit 5, the end of study visit, was performed by telephone contact approximately 3 to 5 weeks after Visit 4.</td></tr>
</table>

Name of Sponsor/Company: IPSEN Group	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Dysport®		
Name of Active Ingredient: Clostridium botulinum toxin type A-haemagglutinin complex	Volume: Page:	

Number of subjects (planned and analysed):

A total of 200 subjects were planned to be enrolled in the study. However, only 48 subjects were enrolled during the 18-month recruitment period.

Diagnosis and criteria for inclusion:

Subjects were eligible for participation in the study if they met the following criteria:

(1) Subjects with stroke of either haemorrhagic or ischemic origin scheduled to receive Dysport, with stroke onset at least 3 months prior to study entry

(2) Adults over the age of 18 years

(3) Arm spasticity with Modified Ashworth Scale (MAS) ≥2 at least in one part

Subjects were excluded from entering the trial for the following reasons:

(1) Subject has hypersensitivity to Dysport (any of its components) or drugs with a similar chemical structure

(2) Subject is pregnant. Absence of pregnancy should be confirmed prior injecting the product

(3) Subject has been previously treated with any botulinum toxin

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

The decision to prescribe Dysport was to be made prior to and independently from the decision to enrol the subject in this non-interventional study. The choice of Dysport was at the Investigator's discretion. The drug was administered by intramuscular injection. The particular muscles/sites, number of injection sites and the dose were to be determined by the investigator in accordance with clinical practice at the hospital and with SmPC.

Dysport is a white, lyophilised powder containing 500 units of Clostridium botulinum toxin type A-haemagglutinin complex, 125 µg human serum albumin, and 2.5 mg of lactose. The product was to be reconstituted at the investigational sites with sterile physiologic saline solution for injection without preservative.

Commercially available Dysport was prescribed on a real-life basis to study subjects. Therefore, various batch numbers were recorded into the case report form (CRF).

Duration of treatment: Approximately 1 year

Reference therapy, dose and mode of administration, batch number: None

Name of Sponsor/Company: IPSEN Group	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Dysport®		
Name of Active Ingredient: Clostridium botulinum toxin type A-haemagglutinin complex	Volume: Page:	

Criteria for evaluation:

Effectiveness:

Primary endpoint and evaluation:

Global assessment of spasticity by MAS

Secondary endpoints and evaluations:

- Subject's QoL evaluation using standard Disability Assessment Scale (DAS)
- Interval between separate administration sessions

Safety:

Collection of treatment related adverse events (AEs)

Statistical methods:

In this study, a sample size of 200 subjects was chosen on the basis of practical constraints and not on statistical considerations. Therefore, it was not intended to serve as the basis for definitive conclusions about safety or effectiveness.

Statistical analyses to be performed were agreed during a meeting on 11 October 2013 between NEOX (the clinical research organisation (CRO)) and the sponsor according to Section 11 of the protocol. The statistical analysis of effectiveness and safety was only descriptive; McNemar's and Wilcoxon signed-rank tests were performed. Summary statistics like counts, mean, standard deviation (SD), median, minima, maxima or frequencies/percentages, as appropriate, were performed.

Summary - conclusions:

Study subjects:

A total of 200 subjects suffering with post-stroke arm spasticity requiring treatment with Dysport were expected to be recruited in 10-30 centres. However, only 48 subjects were enrolled in 9 centres during the 18-month recruitment period due to poor recruitment subsequent to other competing studies. The study was prematurely interrupted; the recruitment of new subjects was not performed.

Of the 48 subjects who were treated with at least 1 dose of Dysport (and included in the intent to treat (ITT)/safety population), 36 subjects (75.0%) completed the study. Among the 12 subjects (25.0%) who discontinued the study, 2 subjects (4.2%) were lost to follow-up. For 10 subjects (20.8%), the discontinuation was due to another reason: 3 subjects (6.3%) didn't want to continue the study treatment, 3 subjects (6.3%) had small effect on spasticity, 1 subject (2.1%) didn't want to continue due to weakness in the hand (Dysport-injected limb), 1 subject (2.1%) had planned tendon surgery, 1 subject (2.1%) had

Name of Sponsor/Company: IPSEN Group	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Dysport®		
Name of Active Ingredient: Clostridium botulinum toxin type A-haemagglutinin complex	Volume: Page:	

recurrent stroke and 1 subject (2.1%) had substantial and persistent decrease of spasticity.

There were more male (66.7%) than female subjects included in the study. All the subjects were Caucasian. The mean (±SD) age at inclusion was 59.2 (±14.3) years. The mean (±SD) height was 173.3 (±7.1) cm. The mean (±SD) weight was 81.3 (±14.4) kg.

The strokes experienced by the subjects at least 3 months prior to the study entry were of ischemic origin for 39 subjects (81.3%) and of haemorrhagic origin for 9 subjects (18.8%). Most of the subjects (42 (87.5%)) experienced other significant medical or surgical conditions.

At baseline, the mean (±SD) MAS score for each extensor muscle evaluated ranged from 2.23 (±0.78) (thumb flexors) to 2.57 (±0.83) (forearm pronators). Most of the subjects had a MAS score for thumb flexors of 2 or 3 (23 and 19 subjects, respectively). The mean (±SD) DAS score for each area evaluated ranged from 1.12 (±0.89) (pain) to 2.23 (±0.59) (dressing). Most of the subjects had a DAS score for dressing of 2 or 3 (29 and 15 subjects, respectively) at baseline.

Effectiveness results:

Primary analysis

- For each specific location analysed, a decrease in the mean MAS score was observed after each Dysport injection, i.e. after Visit 1, Visit 3 and Visit 4. At Visit 5, the mean (±SD) MAS score ranged from 1.8 (±0.82) (wrist flexors and thumb flexors) to 2.3 (±0.74) (forearm pronators).
- The difference in mean MAS score compared to Visit 1 was the biggest between Visit 2 and Visit 1 (i.e. 4 weeks after the first injection of Dysport) for forearm pronators (-0.31), finger flexors (-0.61) and thumb flexors (-0.43) and between Visit 5 and Visit 1 (i.e. after 3 injections of Dysport) for elbow flexors (-0.39) and wrist flexors (-0.53).
- The difference in mean MAS score compared to Visit 1 was significant for each visit for wrist flexors and thumb flexors.
- The largest decrease in the mean MAS score occurred between Visit 1 and Visit 2 for each specific location, with a difference in the mean MAS score ranging from -0.31 (forearm pronators) to -0.61 (finger flexors). The mean MAS score increased between Visit 2 and Visit 3 for each specific location: the difference (V3-V2) in mean MAS score ranged from 0.17 (elbow flexors) to 0.43 (finger flexors). This increase could be explained by the fact that there is no injection of Dysport at Visit 2 as this visit corresponds to the peak effect of the first injection of Dysport,

Name of Sponsor/Company: IPSEN Group	Individual Study Table Referring to Part of the Dossier	*(For national authority use only)*
Name of Finished Product: Dysport®		
Name of Active Ingredient: Clostridium botulinum toxin type A-haemagglutinin complex	Volume: Page:	

performed at Visit 1.

Secondary analysis

- For each specific area analysed, a decrease in the mean DAS score was observed after most of the Dysport injections, i.e. after Visit 1, Visit 3 and Visit 4. At Visit 5, the mean (±SD) DAS score ranged from 0.8 (±0.68) (pain) to 1.8 (±0.89) (limb position and hygiene).
- The difference in mean DAS score compared to Visit 1 was the biggest between Visit 2 and Visit 1 (i.e. 4 weeks after the first injection of Dysport) for hygiene (-0.38), dressing (-0.58) and pain (-0.54) and between Visit 5 and Visit 1 (i.e. after 3 injections of Dysport) for limb position (-0.33).
- The difference in mean DAS score compared to Visit 1 was significant for each visit for dressing and pain.
- Similarly to MAS, the largest decrease in the mean DAS score occurred between Visit 1 and Visit 2 for each specific area, with a difference in the mean DAS score ranging from -0.25 (limb position) to -0.58 (dressing). The mean DAS score increased between Visit 2 and Visit 3 for each specific area, with a difference (V3-V2) in the mean DAS score ranging from 0.02 (hygiene) to 0.28 (dressing).
- The interval of days between Visit 3/Visit 1 Dysport injections (mean 121.2 days, minimum 68 days, maximum 259 days) was longer than between Visit 4/Visit 3 (mean 99.7 days, minimum 56 days, maximum 175 days).
- For most of the subjects (81.0% and 72.7%, respectively), the intervals between Dysport injections at Visit 1 and Visit 3 and at Visit 3 and Visit 4 were greater than 84 days.

Safety results:

There was no related AE reported to the safety department during the study. No new safety issues arose from this study.

Conclusion:

Due to the low number of subjects enrolled into the study, no conclusion regarding the safety of Dysport in subjects with post-stroke upper limb spasticity can be drawn. The findings of this study tend to confirm the known extensive evidence of botulinum neurotoxin type A effectiveness in subjects with post-stroke upper limb spasticity in real-life settings.

Overall, the findings of this study do not change the favourable benefit-risk profile of

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: Dysport®		
Name of Active Ingredient: Clostridium botulinum toxin type A-haemagglutinin complex		
Dysport in adults with post-stroke upper limb spasticity. Date of report: 29 July 2016		