



Clinical trial results:

Open, multicentre study on the equivalent efficacy and safety of Botulinum toxin A (500 Units Dysport®) in the treatment of heterogeneous forms of cervical dystonia

Summary

EudraCT number	2004-002086-20
Trial protocol	AT
Global end of trial date	04 April 2008

Results information

Result version number	v1 (current)
This version publication date	11 March 2016
First version publication date	11 March 2016

Trial information

Trial identification

Sponsor protocol code	A-94-52120-098
-----------------------	----------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	IPSEN PHARMA GmbH
Sponsor organisation address	Willy-Brandt-Straße 3, Ettlingen, Germany, D-76275
Public contact	Medical Director, Neurology, Ipsen, clinical.trials@ipsen.com
Scientific contact	Medical Director, Neurology, Ipsen, clinical.trials@ipsen.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 December 2009
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 February 2008
Global end of trial reached?	Yes
Global end of trial date	04 April 2008
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The results of a dose finding study have shown that 500 units Dysport® are the optimal starting dose for the treatment of patients with rotational torticollis. Although Dysport is an established first-line neurological treatment for cervical dystonia since its registration in Germany in 1995, there are only little data available on dose, efficacy and safety in the treatment of heterogeneous forms of cervical dystonia.

The aim of this multicentre open study is to demonstrate the equivalent efficacy and safety in the treatment of the two most frequent forms of cervical dystonia (predominantly rotational torticollis and predominantly laterocollis) with the standard initial dose of 500 units Dysport.

Protection of trial subjects:

This clinical study was designed and implemented and reported in accordance with the International Conference on Harmonization (ICH) Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), with applicable local regulations (including European Directive 2001/20/EC), and with the ethical principles laid down in the Declaration of Helsinki.

The clinical trial was performed taking into account the German Medicinal Product Act (AMG). The study was submitted to the Federal Institute for Drugs and Medical Devices (BfArM) and to the responsible regulatory authorities. The patients participating in the study were insured in accordance with the provisions of the German Drug Law (AMG, in particular §40 paragraph 3).

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2004
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 16
Country: Number of subjects enrolled	Germany: 500
Worldwide total number of subjects	516
EEA total number of subjects	516

Notes:

Subjects enrolled per age group

In utero	0
----------	---

Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	409
From 65 to 84 years	106
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

First subject enrolled on 28October2004. To conduct the study 105 German and 5 Austrian centres were selected.

Pre-assignment

Screening details:

516 Subjects were enrolled to study. Due to non-availability of safety data, one subject was excluded. The Intention-To-Treat population (ITT) consisted of 515 subjects.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Arm title	Dysport 500 units
-----------	-------------------

Arm description:

Predominantly rotatory torticollis & Laterocollis: treatment with a single dose of 500 units Dysport®

Arm type	Experimental
Investigational medicinal product name	Dysport
Investigational medicinal product code	
Other name	Clostridium botulinum Toxin Type A
Pharmaceutical forms	Powder for injection
Routes of administration	Intramuscular use

Dosage and administration details:

A single injection with 500 units Dysport®, diluted in 2.5 ml 0.9 % NaCl (= 200 units / ml), administered by intramuscular injections according to an injection protocol with optional follow-up injection at week 12.

Number of subjects in period 1 ^[1]	Dysport 500 units
Started	515
Completed	489
Not completed	26
Insufficient compliance	6
Consent withdrawn by subject	1
Unspecified	7
Lost to follow-up	9
Discontinuation of drug therapy by investigator	1
Lack of efficacy	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: Worldwide numbers reported are per all treated 516 subjects. However, baseline period is per 515 Safety population subjects (includes all patients who received the study medication and for whom any safety data were recorded). Due to non-availability of safety data one subject was excluded from safety population.

Baseline characteristics

Reporting groups

Reporting group title	Dysport 500 units
-----------------------	-------------------

Reporting group description:

Predominantly rotatory torticollis & Laterocollis: treatment with a single dose of 500 units Dysport®

Reporting group values	Dysport 500 units	Total	
Number of subjects	515	515	
Age categorical			
Units: Subjects			
< 30	24	24	
30 to < 40	60	60	
40 to < 50	147	147	
50 to < 60	126	126	
60 to < 70	112	112	
70 to < 80	43	43	
≥ 80	3	3	
Age continuous			
Units: years			
arithmetic mean	51.9		
standard deviation	± 12.7	-	
Gender categorical			
Units: Subjects			
Female	353	353	
Male	162	162	
Race			
Units: Subjects			
Caucasian	511	511	
Asian	1	1	
Oriental	3	3	
BMI			
The Safety population includes all patients who received the study medication and for whom any safety data were recorded			
n=510, Body mass index (BMI)			
Units: kg/m ²			
arithmetic mean	25.3		
standard deviation	± 4.4	-	

End points

End points reporting groups

Reporting group title	Dysport 500 units
Reporting group description: Predominantly rotatory torticollis & Laterocollis: treatment with a single dose of 500 units Dysport®	
Subject analysis set title	Treatment Group: Rotatory torticollis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Rotatory torticollis is a subset group	
Subject analysis set title	Treatment Group: Laterocollis
Subject analysis set type	Sub-group analysis
Subject analysis set description: Laterocollis is a subset group	

Primary: Change from baseline in the total score of the Tsui rating scale (patient in sitting position)

End point title	Change from baseline in the total score of the Tsui rating scale (patient in sitting position)
End point description: The Tsui rating scale measures severity and duration of head deviation, shoulder elevation and head tremor. This instrument is based on 4 subscores: <ul style="list-style-type: none">• Subscore A: amplitude of rotation, deflection (tilt) and ante- / retrocollis (range: 0–9 points)• Subscore B: duration of movement (values 1 or 2)• Subscore C: severity and duration of shoulder elevation (range: 0–3 points)• Subscore D: severity and duration of tremor (range: 0–4 points) The total score was to be calculated as follows: total score = subscores (A x B) + C + D The total score ranges between 0 and 25 points. A high (low) total score represents severe (mild) CD. The ITT population includes all patients of the Safety population with a baseline (visit 1, week 0) and a post-baseline (visit 2, week 4 or visit 3, week 12) assessment of the Tsui rating scale.	
End point type	Primary
End point timeframe: From Baseline (visit 1) to the first on-treatment visit [visit 2 (week 4)/visit 3 (week 12)]	

End point values	Dysport 500 units	Treatment Group: Rotatory torticollis	Treatment Group: Laterocollis	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	503	396	107	
Units: Score of the Tsui rating scale				
arithmetic mean (standard deviation)				
Baseline (V1)	8.4 (± 3.5)	8.4 (± 3.5)	8.3 (± 3.3)	
First on-treatment measurement (V2/V1)	4.6 (± 3.1)	4.6 (± 3.2)	4.3 (± 2.6)	
First on-treatment measurement - Baseline (V2-V1)	-3.8 (± 3.1)	-3.8 (± 3.3)	-4 (± 2.6)	

Statistical analyses

Statistical analysis title	Rotatory torticollis vs Laterocollis
Statistical analysis description:	
ANCOVA model includes the baseline total Tsui score (patient in sitting position) as covariate ($p < 0.0001$) and the main type of CD as between-group factor (due to non-significance the interaction between baseline total Tsui score and the main type of CD was removed from the model)	
Comparison groups	Treatment Group: Rotatory torticollis v Treatment Group: Laterocollis
Number of subjects included in analysis	503
Analysis specification	Pre-specified
Analysis type	other ^[1]
P-value	= 0.2552
Method	ANCOVA
Notes:	
[1] - Exploratory analysis	

Secondary: Tsui subscores (patient in sitting position)

End point title	Tsui subscores (patient in sitting position)
End point description:	
The Tsui rating scale measures severity and duration of head deviation, shoulder elevation and head tremor. This instrument is based on 4 subscores:	
<ul style="list-style-type: none"> • Subscore A: amplitude of rotation, deflection (tilt) and ante- / retrocollis (range: 0–9 points) • Subscore B: duration of movement (values 1 or 2) • Subscore C: severity and duration of shoulder elevation (range: 0–3 points) • Subscore D: severity and duration of tremor (range: 0–4 points) 	
The total score was to be calculated as follows: total score = subscores (A x B) + C + D	
The total score ranges between 0 and 25 points. A high (low) total score represents severe (mild) CD.	
The ITT population includes all patients of the Safety population with a baseline (visit 1, week 0) and a post-baseline (visit 2, week 4 or visit 3, week 12) assessment of the Tsui rating scale.	
End point type	Secondary
End point timeframe:	
At Baseline (visit 1), first on-treatment visit [visit 2 (week 4) / visit 3 (week 12)], V2 minus V1, V3 minus V1	

End point values	Dysport 500 units			
Subject group type	Reporting group			
Number of subjects analysed	503			
Units: score of the Tsui rating scale				
arithmetic mean (standard deviation)				
Subscore A: V1 (n=396)	3.5 (± 1.4)			
Subscore A: V2 (n=394)	2.2 (± 1.4)			
Subscore A: V3 (n=386)	2.7 (± 1.5)			

Subscore A:V2 minus V1 (N= 500)	-1.4 (± 1.3)			
Subscore A:V3 minus V1 (N= 490)	-0.8 (± 1.3)			
Subscore B: V1 (n=396)	1.8 (± 0.4)			
Subscore B: V2 (n=394)	1.4 (± 0.6)			
Subscore B: V3 (n=386)	1.6 (± 0.5)			
Subscore B:V2 minus V1 (N= 500)	-0.3 (± 0.6)			
Subscore B:V3 minus V1 (N= 490)	-0.2 (± 0.5)			
Subscore c: V1 (n=396)	0.9 (± 0.9)			
Subscore C: V2 (n=394)	0.6 (± 0.8)			
Subscore C: V3 (n=386)	0.7 (± 0.8)			
Subscore C:V2 minus V1 (N= 500)	-0.4 (± 0.8)			
Subscore C:V3 minus V1 (N= 490)	-0.2 (± 0.8)			
Subscore D: V1 (n= 396)	1.2 (± 1.3)			
Subscore D: V2 (n=394)	0.6 (± 0.7)			
Subscore D: V3 (n= 386)	0.8 (± 0.9)			
Subscore D:V2 minus V1 (N= 500)	-0.6 (± 1)			
Subscore D:V3 minus V1 (N= 490)	-0.4 (± 0.9)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in CDQ total score and subscores

End point title	Change from baseline in CDQ total score and subscores
-----------------	---

End point description:

The Craniocervical Dystonia Questionnaire (CDQ-24) is a disease-specific QoL instrument and was to be assessed at visits 1 to 3. It consists of 24 items investigating problems in daily living skills related to CD. This instrument is based on 5 subscales:

- Stigma (items 7, 8, 9, 10, 18, 22)
- Emotional well-being (items 11, 12, 13, 14, 15)
- Pain (items 4, 5, 21)
- Activities of daily living (ADL, items 1, 2, 3, 6, 19, 20)
- Social / family life (items 16, 17, 23, 24)

There are five possible answers to each item representing increasing severity of impairment (scores 0 to 4). In order to obtain scores of the individual subscales, the total score of each subscale (sum of the individual item scores) was transformed linearly to a 0 to 100 scale, where a score of 0 indicates the best

The ITT population includes all patients of the Safety population with a baseline (visit 1, week 0) and a post-baseline (visit 2, week 4 or visit 3, week 12) assessment of the Tsui rating scale.

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline (visit 1) to visit 2 (week 4), visit 3 (week 12).

End point values	Dysport 500 units			
Subject group type	Reporting group			
Number of subjects analysed	503			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Total score: V2 minus V1 (N=484)	-11.1 (± 16.1)			
Total score: V3 minus V1 (N=474)	-11.8 (± 14.6)			
Stigma: V2 minus V1 (N=485)	-16.8 (± 24)			
Stigma: V3 minus V1 (N=476)	-16.4 (± 22.5)			
Emotional well-being: V2 minus V1 (N=485)	-10.3 (± 19.9)			
Emotional well-being: V3 minus V1 (N=476)	-11.1 (± 18.7)			
Pain: V2 minus V1 (N=491)	-11.5 (± 27.8)			
Pain: V3 minus V1 (N=484)	-13.2 (± 25.5)			
Activities of daily living: V2 minus V1 (N=483)	-11.1 (± 19.6)			
Activities of daily living: V3 minus V1 (N=474)	-12.5 (± 18.6)			
Social / family life: V2 minus V1 (N=481)	-5.6 (± 17.9)			
Social / family life: V3 minus V1 (N=469)	-6.7 (± 17.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in the items of the patient dairy based on Day-to-day functions and activities, Pain and duration of pain.

End point title	Change from baseline in the items of the patient dairy based on Day-to-day functions and activities, Pain and duration of pain.
-----------------	---

End point description:

The ITT population includes all patients of the Safety population with a baseline (visit 1, week 0) and a post-baseline (visit 2, week 4 or visit 3, week 12) assessment of the Tsui rating scale.

The weekly recorded patient diary consists of the three items "Day-to-Day Capacities and Activities", "Pain" and "Duration of Pain". Each item was rated by the patient on an 11-point scale ranging from 0 = no problems at all to 10 = most severe problems (the actual wording is adapted to each item in question).

End point type	Secondary
----------------	-----------

End point timeframe:

From Baseline (visit 1) to visit 2 (week 4), visit 3 (week 12).

End point values	Dysport 500 units			
Subject group type	Reporting group			
Number of subjects analysed	503			
Units: Units on a scale				
arithmetic mean (standard deviation)				
Day-to-day functions & activities: W4-W0 (N=454)	-1.1 (± 3)			
Day-to-day functions & activities: W12-W0 (N=384)	-1.1 (± 2.6)			
Pain: W4-W0 (N= 452)	-0.8 (± 2.7)			
Pain: W12-W0 (N=383)	-0.9 (± 2.5)			
Duration of pain: W4-W0 (N=451)	-1.2 (± 2.9)			
Duration of pain: W12-W0 (N=382)	-1.3 (± 2.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of subjects without pain and/or with a pain reduction based on Global assessment of pain by investigator and patient

End point title	Number of subjects without pain and/or with a pain reduction based on Global assessment of pain by investigator and patient
-----------------	---

End point description:

The ITT population includes all patients of the Safety population with a baseline (visit 1, week 0) and a post-baseline (visit 2, week 4 or visit 3, week 12) assessment of the Tsui rating scale.

At visits 2 and 3 investigators and patients had to assess change of global pain according to the following response categories:

- 1 = no pain (anymore)
- 2 = less pain
- 3 = no change
- 4 = more pain

End point type	Secondary
----------------	-----------

End point timeframe:

'Visits 2 and 3 by Investigator and Visits 2 and 3 by Patient'

End point values	Dysport 500 units			
Subject group type	Reporting group			
Number of subjects analysed	503			
Units: number of patients				
Investigator: No pain V2	131			
Investigator: No pain V3	142			
Investigator: Less pain V2	205			
Investigator: Less pain V3	227			
Investigator: No change V2	94			
Investigator: No change V3	87			
Investigator: More pain V2	70			
Investigator: More pain V3	33			

Patient: No pain V2	128			
Patient: No pain V3	132			
Patient: Less pain V2	202			
Patient: Less pain V3	231			
Patient: No change V2	82			
Patient: No change V3	83			
Patient: More pain V2	88			
Patient: More pain V3	44			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to week 12

Adverse event reporting additional description:

Treatment with a single dose of 500 units Dysport®

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	9.1
--------------------	-----

Reporting groups

Reporting group title	Dysport 500 units
-----------------------	-------------------

Reporting group description:

'Treatment with a single dose of 500 units Dysport®' as suggested by study team and highlight the change.

Serious adverse events	Dysport 500 units		
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 515 (2.14%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung adenocarcinoma			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Femur fracture			

subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Bradycardia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Coronary artery disease			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Myocardial infarction			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Blindness			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Peritonitis			

subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pulmonary congestion			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Apathy			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Muscular weakness			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Non-serious adverse events	Dysport 500 units		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	206 / 515 (40.00%)		
Vascular disorders			
Circulatory collapse			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Hypertension			
subjects affected / exposed	4 / 515 (0.78%)		
occurrences (all)	4		
Orthostatic hypotension			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Thrombophlebitis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Surgical and medical procedures			
Limb operation			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	3 / 515 (0.58%)		
occurrences (all)	3		
Facial pain			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Fatigue			
subjects affected / exposed	6 / 515 (1.17%)		
occurrences (all)	6		
Gait disturbance			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
General physical health deterioration			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		

Influenza like illness			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Injection site pain			
subjects affected / exposed	7 / 515 (1.36%)		
occurrences (all)	7		
Injection site paraesthesia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Local swelling			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Oedema peripheral			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Sensation of foreign body			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Thirst			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Cough			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Dyspnoea			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Rhinitis allergic			

subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Throat irritation			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Anxiety disorder			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Conversion disorder			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Depression			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Initial insomnia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Middle insomnia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Panic attack			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Psychotic disorder			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Restlessness			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Investigations			
Blood pressure diastolic increased			

subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Blood pressure increased			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Blood pressure orthostatic abnormal			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Coronary artery disease			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Tachycardia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Nervous system disorders			
Burning sensation			
subjects affected / exposed	4 / 515 (0.78%)		
occurrences (all)	4		
Cervical root pain			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Disturbance in attention			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	12 / 515 (2.33%)		
occurrences (all)	13		
Dysarthria			
subjects affected / exposed	4 / 515 (0.78%)		
occurrences (all)	4		
Head discomfort			

subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Head titubation			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	17 / 515 (3.30%)		
occurrences (all)	21		
Hypoaesthesia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Mastication disorder			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Migraine			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Neuritis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Paraesthesia			
subjects affected / exposed	4 / 515 (0.78%)		
occurrences (all)	4		
Paralysis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Paresis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Restless legs syndrome			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Speech disorder			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Tongue paralysis			

subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Tremor			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Ear and labyrinth disorders			
Sudden hearing loss			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Tinnitus			
subjects affected / exposed	3 / 515 (0.58%)		
occurrences (all)	3		
Vertigo			
subjects affected / exposed	4 / 515 (0.78%)		
occurrences (all)	5		
Eye disorders			
Blepharitis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Dry eye			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Eyelid ptosis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Glaucoma			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Keratoconjunctivitis sicca			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Vision blurred			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Gastrointestinal disorders			

Abdominal discomfort			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	3 / 515 (0.58%)		
occurrences (all)	3		
Constipation			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Dental caries			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	4 / 515 (0.78%)		
occurrences (all)	4		
Dry mouth			
subjects affected / exposed	6 / 515 (1.17%)		
occurrences (all)	6		
Dysphagia			
subjects affected / exposed	51 / 515 (9.90%)		
occurrences (all)	51		
Gastritis			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Gastrointestinal pain			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 515 (0.58%)		
occurrences (all)	3		
Toothache			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		

Skin and subcutaneous tissue disorders			
Alopecia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Eczema			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	2		
Hyperhidrosis			
subjects affected / exposed	3 / 515 (0.58%)		
occurrences (all)	3		
Pruritus			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Pruritus generalised			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Rash			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	3		
Urticaria			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Renal and urinary disorders			
Dysuria			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Haematuria			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Nephritis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Endocrine disorders			
Goitre			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Musculoskeletal and connective tissue			

disorders			
Arthralgia			
subjects affected / exposed	5 / 515 (0.97%)		
occurrences (all)	5		
Arthritis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	8 / 515 (1.55%)		
occurrences (all)	8		
Bursitis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Joint range of motion decreased			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Joint stiffness			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Muscular weakness			
subjects affected / exposed	70 / 515 (13.59%)		
occurrences (all)	70		
Musculoskeletal discomfort			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Musculoskeletal disorder			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	12 / 515 (2.33%)		
occurrences (all)	9		
Musculoskeletal stiffness			

subjects affected / exposed	5 / 515 (0.97%)		
occurrences (all)	5		
Myalgia			
subjects affected / exposed	8 / 515 (1.55%)		
occurrences (all)	9		
Neck pain			
subjects affected / exposed	34 / 515 (6.60%)		
occurrences (all)	35		
Osteoarthritis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	2		
Pain in extremity			
subjects affected / exposed	3 / 515 (0.58%)		
occurrences (all)	4		
Pain in jaw			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Trismus			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Infections and infestations			
Acute tonsillitis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Bronchitis			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Cystitis			
subjects affected / exposed	3 / 515 (0.58%)		
occurrences (all)	3		
Device related infection			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Eye infection viral			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		

Herpes simplex			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Herpes zoster			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Hordeolum			
subjects affected / exposed	2 / 515 (0.39%)		
occurrences (all)	2		
Laryngitis			
subjects affected / exposed	3 / 515 (0.58%)		
occurrences (all)	4		
Nasopharyngitis			
subjects affected / exposed	19 / 515 (3.69%)		
occurrences (all)	20		
Otitis media			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Pneumonia bacterial			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Rhinitis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Vulvovaginal mycotic infection			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		

Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		
Hypokalaemia			
subjects affected / exposed	1 / 515 (0.19%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 March 2006	<p>Amendments to the study protocol leading to new versions of the study protocol contains :-</p> <ul style="list-style-type: none">• Duration of the study : Approx. 3.5 years.• Data Monitoring : A statistical data review will be performed after completion of the first 200 patients. In accordance with the ICH E9 Guideline, Item 4.1, a so-called "Trial Monitoring" or "Data Monitoring" is recommended to evaluate and confirm the quality of the conduct of the study. To prevent jeopardizing the power of the study and/or bias, no efficacy data will be analyzed and no analyses stratified by indication group will be performed. Only initial values, demographic data, distribution of indication groups, protocol violations, withdrawal rate etc, will be descriptively analyzed. Safety data, that is adverse events, will be encoded according to MedDRA, version 9.0, and appropriately analyzed.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported