Clinical trial results:
BOTOX® Efficacy and Safety in the Treatment of Knee Osteoarthritis

Summary

EudraCT number	2014-001076-58
Trial protocol	CZ DK
Global end of trial date	07 March 2016

Results information

Result version number	v1 (current)
This version publication date	01 April 2017
First version publication date	01 April 2017

Trial information

Trial identification

Sponsor protocol code	191622-145

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02230956
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan, Inc
Sponsor organisation address	2525 Dupont Drive, Irvine, United States, 92612
Public contact	Therapeutic Area Head,, Allergan, Inc, +1 7142464500, clinicaltrials@allergan.com
Scientific contact	Therapeutic Area Head,, Allergan, Inc, +1 7142464500, clinicaltrials@allergan.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	07 March 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	07 March 2016
Global end of trial reached?	Yes
Global end of trial date	07 March 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This study evaluated the efficacy and safety of a single intra-articular injection of 2 doses of BOTOX® (onabotulinumtoxinA) compared with placebo as treatment for knee osteoarthritis symptoms.

Protection of trial subjects:

All participants were required to read and sign an informed consent form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 October 2014
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	Czech Republic: 49
Country: Number of subjects enrolled	Denmark: 54
Country: Number of subjects enrolled	United States: 73
Worldwide total number of subjects	176
EEA total number of subjects	103

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)	108
From 65 to 84 years	68
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Participants with knee osteoarthritis were randomized in a 1:1:2 ratio to receive BOTOX 400 U, BOTOX 200 U, or placebo treatment.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Carer, Data analyst, Assessor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	OnabotulinumtoxinA 400 U

Arm description:

OnabotulinumtoxinA 400 U injection into the intra-articular space of the study knee on Day 1.

Arm type	Experimental
Investigational medicinal product name	botulinum toxin Type A
Investigational medicinal product code	
Other name	BOTOX® onabotulinumtoxinA
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Injection into the intra-articular space of the knee.

Arm title	OnabotulinumtoxinA 200 U

Arm description:

OnabotulinumtoxinA 200 U injection into the intra-articular space of the study knee on Day 1.

Arm type	Experimental
Investigational medicinal product name	botulinum toxin Type A
Investigational medicinal product code	
Other name	BOTOX® onabotulinumtoxinA
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:

Injection into the intra-articular space of the knee.

Arm title	Placebo

Arm description:

Placebo (Normal Saline) injection into the intra-articular space of the study knee on Day 1.

Arm type	Placebo
Investigational medicinal product name	Normal Saline
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraarticular use

Dosage and administration details:
Injection into the intra-articular space of the knee.

Number of subjects in period 1	OnabotulinumtoxinA 400 U	OnabotulinumtoxinA 200 U	Placebo
Started	44	43	89
Completed	39	37	82
Not completed	5	6	7
Adverse event, non-fatal	1	1	-
Personal Reasons	2	1	1
Lost to follow-up	1	1	2
Other Miscellaneous Reason	-	1	2
Lack of efficacy	1	1	1
Protocol deviation	-	1	1

Baseline characteristics

Reporting groups	
Reporting group title	OnabotulinumtoxinA 400 U
Reporting group description:	
OnabotulinumtoxinA 400 U injection into the intra-articular space of the study knee on Day 1.	
Reporting group title	OnabotulinumtoxinA 200 U
Reporting group description:	
OnabotulinumtoxinA 200 U injection into the intra-articular space of the study knee on Day 1.	
Reporting group title	Placebo
Reporting group description:	
Placebo (Normal Saline) injection into the intra-articular space of the study knee on Day 1.	

Reporting group values	OnabotulinumtoxinA 400 U	OnabotulinumtoxinA 200 U	Placebo
Number of subjects	44	43	89
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	30	26	52
From 65-84 years	14	17	37
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	60.7	60.2	61.1
standard deviation	± 8.25	± 8.41	± 7.79
Gender, Male/Female Units: Subjects			
Female	30	26	51
Male	14	17	38

Reporting group values	Total		
Number of subjects	176		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	108		

From 65-84 years	68		
85 years and over	0		

Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Gender, Male/Female			
Units: Subjects			
Female	107		
Male	69		

End points

End points reporting groups

Reporting group title	OnabotulinumtoxinA 400 U
Reporting group description:	
OnabotulinumtoxinA 400 U injection into the intra-articular space of the study knee on Day 1.	
Reporting group title	OnabotulinumtoxinA 200 U
Reporting group description:	
OnabotulinumtoxinA 200 U injection into the intra-articular space of the study knee on Day 1.	
Reporting group title	Placebo
Reporting group description:	
Placebo (Normal Saline) injection into the intra-articular space of the study knee on Day 1.	

Primary: Change from Baseline in the 7-Day Average Daily Pain Score Using an 11-Point Scale

End point title	Change from Baseline in the 7-Day Average Daily Pain Score Using an 11-Point Scale[1]
End point description:	
Participants recorded the pain in their knee during the previous 24 hours in a daily diary where: 0=no pain to 10= worst pain possible. The daily pain scores over 7-days were averaged. A negative change from Baseline indicates improvement.	
End point type	Primary
End point timeframe:	
Baseline, Week 8	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analysis is reported for this outcome measure

End point values	OnabotulinumtoxinA 400 U	OnabotulinumtoxinA 200 U	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	43	89	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	5.92 (± 1.222)	6.09 (± 1.313)	6 (± 1.15)	
Change from Baseline at Week 8	-1.68 (± 1.641)	-2.07 (± 1.602)	-1.98 (± 1.793)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC™) Pain Score Using an 11-Point Scale

End point title	Change from Baseline in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC™) Pain Score Using an 11-Point Scale

End point description:

The WOMAC Pain Score consisted of 5 questions about pain completed by the participant where: 0=no pain to 10=extreme pain for a total possible Pain Score of 0 (best) to 50 (worst). A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 4, 8, 12, 16, 20 and 24

End point values	Onabotulinumtoxin A 400 U	Onabotulinumtoxin A 200 U	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	43	89	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	5.84 (± 1.629)	5.41 (± 1.806)	5.34 (± 1.548)	
Change from Baseline at Week 1 (n = 44, 43, 88)	-1.75 (± 1.567)	-1.61 (± 1.666)	-1.62 (± 1.805)	
Change from Baseline at Week 4 (n = 43, 43, 86)	-1.82 (± 1.893)	-1.67 (± 1.763)	-1.81 (± 1.848)	
Change from Baseline at Week 8 (n = 40, 39, 84)	-2.02 (± 1.899)	-1.52 (± 1.907)	-1.76 (± 1.976)	
Change from Baseline at Week 12 (n = 39, 39, 84)	-1.81 (± 1.975)	-1.82 (± 1.87)	-1.75 (± 2.014)	
Change from Baseline at Week 16 (n = 40, 38, 80)	-1.67 (± 1.841)	-1.64 (± 2.174)	-1.62 (± 1.901)	
Change from Baseline at Week 20 (n = 39, 38, 80)	-1.79 (± 1.937)	-1.68 (± 2.066)	-1.78 (± 2.037)	
Change from Baseline at Week 24 (n = 39, 37, 82)	-1.93 (± 2.289)	-1.81 (± 2.181)	-1.69 (± 2.008)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the WOMAC™ Physical Function Score Using an 11-Point Scale

End point title	Change from Baseline in the WOMAC™ Physical Function Score Using an 11-Point Scale

End point description:

The WOMAC Physical Function Score consisted of 17 questions about the difficulty of daily activities completed by the participant where: 0=no difficulty to 10=extreme difficulty for a total possible Physical Function Score of 0 (best) to 170 (worst). A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Weeks 1, 4, 8, 12, 16, 20 and 24

End point values	Onabotulinumtoxin A 400 U	Onabotulinumtoxin A 200 U	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	43	89	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	5.56 (± 1.804)	5.35 (± 1.995)	4.99 (± 1.854)	
Change from Baseline at Week 1 (n = 44, 43, 88)	-1.33 (± 1.424)	-1.64 (± 1.87)	-1.44 (± 1.933)	
Change from Baseline at Week 4 (n = 43, 43, 86)	-1.26 (± 1.672)	-1.66 (± 1.908)	-1.35 (± 2.069)	
Change from Baseline at Week 8 (n = 40, 39, 84)	-1.54 (± 1.819)	-1.5 (± 2.043)	-1.27 (± 2.07)	
Change from Baseline at Week 12 (n = 39, 39, 84)	-1.3 (± 1.648)	-1.68 (± 1.781)	-1.4 (± 2.17)	
Change from Baseline at Week 16 (n = 40, 38, 80)	-1.29 (± 1.558)	-1.59 (± 2.127)	-1.09 (± 1.991)	
Change from Baseline at Week 20 (n = 39, 38, 80)	-1.34 (± 1.651)	-1.44 (± 2.172)	-1.18 (± 2.087)	
Change from Baseline at Week 24 (n = 39, 37, 82)	-1.48 (± 2.029)	-1.56 (± 2.232)	-1.12 (± 1.998)	

Statistical analyses

No statistical analyses for this end point

Secondary: Patient Global Impression of Change (GIC) Using a 7-Point Scale

End point title	Patient Global Impression of Change (GIC) Using a 7-Point Scale

End point description:

The participant rated the change in their health status since enrollment using a 7-point scale where: +3=very much improved, +2=much improved, +1=minimally improved, 0=no change, -1=minimally worse, -2=much worse and -3=very much worse. Negative scores indicate worsening and positive scores indicate improvement.

End point type	Secondary

End point timeframe:

Weeks 1, 4, 8, 12, 16, 20 and 24

End point values	Onabotulinumtoxin A 400 U	Onabotulinumtoxin A 200 U	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	43	89	
Units: score on a scale				
arithmetic mean (standard deviation)				
Week 1 (n = 44, 43, 87)	0.9 (± 1)	1.2 (± 0.97)	1.1 (± 1.09)	
Week 4 (n = 43, 43, 86)	0.9 (± 1.24)	1.2 (± 1.23)	1.2 (± 1.1)	
Week 8 (n = 40, 39, 84)	1.1 (± 1.09)	0.9 (± 1.35)	1 (± 1)	
Week 12 (n = 39, 39, 84)	1.1 (± 1.35)	1.2 (± 1.3)	1 (± 1.14)	
Week 16 (n = 40, 38, 80)	1.1 (± 1.31)	1.1 (± 1.36)	1 (± 1.1)	
Week 20 (n = 39, 38, 80)	1.1 (± 1.24)	1 (± 1.42)	1 (± 1.2)	

Week 24 (n = 39, 37, 82)	0.8 (± 1.34)	1 (± 1.41)	0.9 (± 1.28)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in the 7-Day Average Daily Worst Pain Score Using an 11-Point Scale

End point title	Change from Baseline in the 7-Day Average Daily Worst Pain Score Using an 11-Point Scale

End point description:

Participants recorded the pain in their knee during the previous 24 hours in a daily diary where: 0=no pain to10= worst pain possible. The daily worst pain scores over 7-days were averaged. A negative change from Baseline indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	Onabotulinumtoxin A 400 U	Onabotulinumtoxin A 200 U	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	44	43	89	
Units: score on a scale				
arithmetic mean (standard deviation)				
Baseline	6.5 (± 1.243)	6.84 (± 1.342)	6.63 (± 1.157)	
Week 24	-1.48 (± 1.894)	-2.07 (± 2.126)	-1.8 (± 1.896)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Up to Day 172	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	18.1

Reporting groups	
Reporting group title	OnabotulinumtoxinA 400 U
Reporting group description: OnabotulinumtoxinA 400 U injection into the intra-articular space of the study knee on Day 1.	
Reporting group title	OnabotulinumtoxinA 200 U
Reporting group description: OnabotulinumtoxinA 200 U injection into the intra-articular space of the study knee on Day 1.	
Reporting group title	Placebo
Reporting group description: Placebo (Normal Saline) injection into the intra-articular space of the study knee on Day 1.	

Serious adverse events	OnabotulinumtoxinA 400 U	OnabotulinumtoxinA 200 U	Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 44 (13.64%)	4 / 43 (9.30%)	6 / 89 (6.74%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Muscle strain			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Meniscus injury			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Bradycardia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebrovascular accident			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dizziness			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Basal ganglia infarction			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal detachment			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Constipation			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Vomiting			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 44 (0.00%)	1 / 43 (2.33%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	2 / 89 (2.25%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Incision site infection			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	1 / 44 (2.27%)	0 / 43 (0.00%)	0 / 89 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 44 (0.00%)	0 / 43 (0.00%)	1 / 89 (1.12%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	OnabotulinumtoxinA 400 U	OnabotulinumtoxinA 200 U	Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	9 / 44 (20.45%)	15 / 43 (34.88%)	26 / 89 (29.21%)
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 44 (2.27%)	5 / 43 (11.63%)	2 / 89 (2.25%)
occurrences (all)	1	5	2
Musculoskeletal and connective tissue disorders			
Joint swelling			
subjects affected / exposed	0 / 44 (0.00%)	4 / 43 (9.30%)	4 / 89 (4.49%)
occurrences (all)	0	5	5
Osteoarthritis			
subjects affected / exposed	1 / 44 (2.27%)	2 / 43 (4.65%)	5 / 89 (5.62%)
occurrences (all)	1	2	6
Arthralgia			
subjects affected / exposed	4 / 44 (9.09%)	9 / 43 (20.93%)	9 / 89 (10.11%)
occurrences (all)	5	11	12
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	3 / 44 (6.82%)	2 / 43 (4.65%)	8 / 89 (8.99%)
occurrences (all)	3	2	8

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 September 2014	Amendment 1 added an assessment of the skin at the site of injection on day 1, at all follow-up visits, and at the exit visit. This amendment also added stopping criteria for the study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported