Clinical trial results:
BOTOX® for the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients With Multiple Sclerosis

Summary

EudraCT number	2012-000957-30
Trial protocol	BE CZ PT GB
Global end of trial date	27 March 2015

Results information

Result version number	v1 (current)
This version publication date	27 April 2016
First version publication date	27 April 2016

Trial information

Trial identification

Sponsor protocol code	191622-117

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01600716
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Allergan Limited Marlow International The Parkway, Marlow, Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com
Scientific contact	Therapeutic Area Head,, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@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	27 March 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 March 2015
Global end of trial reached?	Yes
Global end of trial date	27 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the safety and efficacy of 100 U BOTOX compared to placebo injected into the detrusor for the treatment of urinary incontinence due to Neurogenic Detrusor Overactivity (NDO) resulting from Multiple Sclerosis (MS), in patients who are not catheterizing at baseline, and whose symptoms have not been adequately managed
with anticholinergic therapy.

Protection of trial subjects:

Patients were required to read and sign an Informed Consent Form prior to any study procedures.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	19 July 2012
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	Belgium: 5
Country: Number of subjects enrolled	Canada: 21
Country: Number of subjects enrolled	Czech Republic: 15
Country: Number of subjects enrolled	France: 3
Country: Number of subjects enrolled	Poland: 19
Country: Number of subjects enrolled	Portugal: 1
Country: Number of subjects enrolled	United States: 80
Worldwide total number of subjects	144
EEA total number of subjects	43

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)	133
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were screened up to 28 days prior to randomization on Day 1.

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	Subject, Investigator, Monitor, Carer, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	OnabotulinumtoxinA

Arm description:

OnabotulinumtoxinA 100 U is administered into the detrusor at Day 1. After a minimum of 12 weeks, patients could request/qualify for a second onabotulinumtoxinA injection.

Arm type	Experimental
Investigational medicinal product name	OnabotulinumtoxinA
Investigational medicinal product code	
Other name	BOTOX
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

OnabotulinumtoxinA 100 U is administered into the detrusor at Day 1. After a minimum of 12 weeks, patients could request/qualify for a second onabotulinumtoxinA injection.

Arm title	Placebo (Normal Saline)

Arm description:

Placebo (normal saline) is administered into the detrusor at Day 1. After a minimum of 12 weeks, patients could request/qualify for an onabotulinumtoxinA injection.

Arm type	Placebo
Investigational medicinal product name	Placebo (Normal Saline)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Placebo (normal saline) is administered into the detrusor at Day 1. After a minimum of 12 weeks, patients could request/qualify for an onabotulinumtoxinA injection.

Number of subjects in period 1	OnabotulinumtoxinA	Placebo (Normal Saline)
Started	66	78
Completed	59	71
Not completed	7	7
Other Reasons	3	1
Adverse event, non-fatal	1	1
Pregnancy	1	-
Personal Reasons	-	2
Lost to follow-up	-	2
Lack of efficacy	2	1

Baseline characteristics

Reporting groups	
Reporting group title	OnabotulinumtoxinA
Reporting group description:	
OnabotulinumtoxinA 100 U is administered into the detrusor at Day 1. After a minimum of 12 weeks, patients could request/qualify for a second onabotulinumtoxinA injection.	
Reporting group title	Placebo (Normal Saline)
Reporting group description:	
Placebo (normal saline) is administered into the detrusor at Day 1. After a minimum of 12 weeks, patients could request/qualify for an onabotulinumtoxinA injection.	

Reporting group values	OnabotulinumtoxinA	Placebo (Normal Saline)	Total
Number of subjects	66	78	144
Age categorical Units: Subjects			
Adults (18-64 years)	62	71	133
From 65-84 years	4	7	11
Age continuous Units: years			
arithmetic mean	51.5	51.7	
standard deviation	± 10.36	± 10.28	-
Gender, Male/Female Units: Participants			
Female	57	70	127
Male	9	8	17

End points

End points reporting groups

Reporting group title	OnabotulinumtoxinA
Reporting group description:	
OnabotulinumtoxinA 100 U is administered into the detrusor at Day 1. After a minimum of 12 weeks, patients could request/qualify for a second onabotulinumtoxinA injection.	
Reporting group title	Placebo (Normal Saline)
Reporting group description:	
Placebo (normal saline) is administered into the detrusor at Day 1. After a minimum of 12 weeks, patients could request/qualify for an onabotulinumtoxinA injection.	

Primary: Change from Baseline in Daily Average Frequency of Urinary Incontinence Episodes

End point title	Change from Baseline in Daily Average Frequency of Urinary Incontinence Episodes[1]
End point description:	
Incontinence is defined as involuntary loss of urine as recorded in a patient bladder diary. The number of episodes of urinary incontinence is recorded over a 3-day period the week of the study visit. A negative number change from baseline indicates a reduction in incontinence episodes (improvement) and a positive number change indicates an increase in incontinence episodes (worsening).	
End point type	Primary
End point timeframe:	
Baseline, Week 6	

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	Placebo (Normal Saline)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	78		
Units: Episodes				
arithmetic mean (standard deviation)				
Baseline	4.18 (± 3.167)	4.32 (± 2.422)		
Change from Baseline at Week 6	-3.34 (± 2.881)	-1.1 (± 2.083)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Maximum Cystometric Capacity (MCC)

End point title	Change from Baseline in Maximum Cystometric Capacity (MCC)
End point description:	
MCC represents the maximum volume of urine the bladder holds. A positive number change from baseline represents an improvement (increase) in the maximum volume of urine the bladder holds and a negative number change from baseline represents a worsening (decrease) in the maximum volume of	

urine the bladder holds.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	OnabotulinumtoxinA	Placebo (Normal Saline)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	65	78		
Units: Milliliters (mL)				
arithmetic mean (standard deviation)				
Baseline	246.4 (± 138.49)	245.7 (± 133.9)		
Change from Baseline at Week 6 (N=62,72)	127.2 (± 139.25)	-1.8 (± 93.23)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Maximum Detrusor Pressure During the First Involuntary Detrusor Contraction (IDC)

End point title	Change from Baseline in Maximum Detrusor Pressure During the First Involuntary Detrusor Contraction (IDC)

End point description:

Maximum detrusor pressure represents the maximum pressure (peak amplitude) in the bladder during the first involuntary contraction of the bladder muscle. A negative number change from baseline indicates an improvement in pressure and a positive number change from baseline indicates a worsening in pressure.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	OnabotulinumtoxinA	Placebo (Normal Saline)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	57	69		
Units: Centimeters of Water (cm H2O)				
arithmetic mean (standard deviation)				
Baseline	35.9 (± 34.9)	36.1 (± 37.21)		
Change from Baseline at Week 6 (N=25,51)	-19.6 (± 37.61)	3.7 (± 33.24)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Incontinence Quality of Life Instrument (I-QOL) Total Summary Score

End point title	Change from Baseline in Incontinence Quality of Life Instrument (I-QOL) Total Summary Score

End point description:

The I-QOL is a validated, disease-specific quality of life (QOL) questionnaire containing 22 questions designed to measure impact of urinary incontinence on patients' lives. Each question is answered on a 5-point scale (1 = worst QOL, and 5 = best QOL). The scores are totaled over the 22 questions and normalized to a score of 0-100 (0=worst QOL and 100=best QOL). A positive change from baseline represents an improvement and a negative change from baseline represents a worsening.

End point type	Secondary

End point timeframe:

Baseline, Week 6

End point values	OnabotulinumtoxinA	Placebo (Normal Saline)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	58	74		
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Baseline	32.43 (± 16.337)	34.24 (± 21.163)		
Change from Baseline at Week 6 (N=55,68)	40.39 (± 26.499)	9.92 (± 15.863)		

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Duration of Treatment Effect

End point title	Duration of Treatment Effect

End point description:

The duration of treatment effect is the time to patient request for retreatment.

End point type	Other pre-specified

End point timeframe:

Up to 52 Weeks

End point values	Onabotulinumtoxin A	Placebo (Normal Saline)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66[2]	78		
Units: Weeks				
median (confidence interval 95%)	51.7 (36.9 to 9999)	12.6 (12.3 to 13)		

Notes:

[2] - The upper CI limit is not estimable; too few pts requested retreatment prior to study end (9999=NA)

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events were recorded from signing the informed consent to the end of study.	
Adverse event reporting additional description:	
Adverse events and serious adverse events are analyzed by treatment cycle (cycle 1 and cycle 2).	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups	
Reporting group title	OnabotulinumtoxinA Treatment Cycle 1
Reporting group description:	
OnabotulinumtoxinA 100 U is administered into the detrusor at Day 1. Median duration of exposure is 50.7 weeks.	
Reporting group title	Placebo (Normal Saline)/OnabotulinumtoxinA
Reporting group description:	
Placebo (normal saline) is administered into the detrusor at Day 1. After a minimum of 12 weeks, an onabotulinumtoxinA injection is given. Median duration of exposure is 12.2 weeks.	
Reporting group title	OnabotulinumtoxinA/OnabotulinumtoxinA Treatment Cycle 2
Reporting group description:	
OnabotulinumtoxinA 100 U is administered into the detrusor at Day 1. After a minimum of 12 weeks, a second onabotulinumtoxinA injection is given. Median duration of exposure is 12.5 weeks.	
Reporting group title	Placebo (Normal Saline)
Reporting group description:	
Placebo (normal saline) is administered into the detrusor at Day 1. Median duration of exposure is 15.2 weeks.	

Serious adverse events	OnabotulinumtoxinA Treatment Cycle 1	Placebo (Normal Saline)/OnabotulinumtoxinA	OnabotulinumtoxinA/OnabotulinumtoxinA Treatment Cycle 2
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 66 (10.61%)	2 / 67 (2.99%)	0 / 30 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Spinal Compression Fracture			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 30 (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
Fall			
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 66 (1.52%)	1 / 67 (1.49%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 30 (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
Nervous system disorders			
Multiple Sclerosis Relapse			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 67 (1.49%)	0 / 30 (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
General disorders and administration site conditions			
Pyrexia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 30 (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
Renal and urinary disorders			
Dysuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 30 (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
Musculoskeletal and connective tissue disorders			
Muscular Weakness	Additional description: Onset date was 135 days after administration of onabotulinumtoxinA		
alternative assessment type: Non-systematic			

subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	0 / 30 (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
Infections and infestations			
Urinary Tract Infection			
subjects affected / exposed	3 / 66 (4.55%)	0 / 67 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infectious Colitis			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	0 / 30 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Placebo (Normal Saline)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 78 (3.85%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Injury, poisoning and procedural complications			
Spinal Compression Fracture			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Fall			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 78 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Acute Coronary Syndrome			
subjects affected / exposed	0 / 78 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			

Multiple Sclerosis Relapse				
alternative assessment type: Non-systematic				
subjects affected / exposed	1 / 78 (1.28%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Multiple sclerosis				
subjects affected / exposed	0 / 78 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Pyrexia				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 78 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Renal and urinary disorders				
Dysuria				
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 78 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Muscular Weakness	Additional description: Onset date was 135 days after administration of onabotulinumtoxinA			
alternative assessment type: Non-systematic				
subjects affected / exposed	0 / 78 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Urinary Tract Infection				
subjects affected / exposed	0 / 78 (0.00%)			
occurrences causally related to treatment / all	0 / 0			
deaths causally related to treatment / all	0 / 0			
Infectious Colitis				

subjects affected / exposed	1 / 78 (1.28%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	OnabotulinumtoxinA Treatment Cycle 1	Placebo (Normal Saline)/OnabotulinumtoxinA	OnabotulinumtoxinA /OnabotulinumtoxinA Treatment Cycle 2
Total subjects affected by non-serious adverse events			
subjects affected / exposed	50 / 66 (75.76%)	38 / 67 (56.72%)	21 / 30 (70.00%)
Investigations			
Residual Urine Volume			
subjects affected / exposed	11 / 66 (16.67%)	5 / 67 (7.46%)	1 / 30 (3.33%)
occurrences (all)	13	5	1
Nervous system disorders			
Multiple Sclerosis Relapse			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	1 / 30 (3.33%)
occurrences (all)	1	0	1
Renal and urinary disorders			
Urinary Retention			
alternative assessment type: Non-systematic			
subjects affected / exposed	11 / 66 (16.67%)	9 / 67 (13.43%)	6 / 30 (20.00%)
occurrences (all)	12	9	6
Dysuria			
subjects affected / exposed	5 / 66 (7.58%)	1 / 67 (1.49%)	3 / 30 (10.00%)
occurrences (all)	5	1	6
Leukocyturia			
subjects affected / exposed	4 / 66 (6.06%)	2 / 67 (2.99%)	1 / 30 (3.33%)
occurrences (all)	4	4	1
Haematuria			

subjects affected / exposed	3 / 66 (4.55%)	2 / 67 (2.99%)	0 / 30 (0.00%)
occurrences (all)	3	2	0
Renal Cyst			
subjects affected / exposed	3 / 66 (4.55%)	1 / 67 (1.49%)	3 / 30 (10.00%)
occurrences (all)	3	1	3
Micturition Urgency			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 66 (3.03%)	0 / 67 (0.00%)	2 / 30 (6.67%)
occurrences (all)	2	0	3
Pollakiuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 66 (3.03%)	0 / 67 (0.00%)	2 / 30 (6.67%)
occurrences (all)	2	0	3
Urine Abnormality			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	3
Urine Odour Abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 66 (1.52%)	0 / 67 (0.00%)	2 / 30 (6.67%)
occurrences (all)	1	0	3
Psychiatric disorders			
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 66 (0.00%)	0 / 67 (0.00%)	2 / 30 (6.67%)
occurrences (all)	0	0	2
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	26 / 66 (39.39%)	17 / 67 (25.37%)	9 / 30 (30.00%)
occurrences (all)	48	21	13
Bacteriuria			
subjects affected / exposed	12 / 66 (18.18%)	6 / 67 (8.96%)	3 / 30 (10.00%)
occurrences (all)	21	7	3
Nasopharyngitis			
alternative assessment type: Non-systematic			

subjects affected / exposed	4 / 66 (6.06%)	0 / 67 (0.00%)	0 / 30 (0.00%)
occurrences (all)	4	0	0

Non-serious adverse events	Placebo (Normal Saline)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	48 / 78 (61.54%)		
Investigations			
Residual Urine Volume			
subjects affected / exposed	2 / 78 (2.56%)		
occurrences (all)	2		
Nervous system disorders			
Multiple Sclerosis Relapse			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences (all)	2		
Gastrointestinal disorders			
Diarrhoea			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 78 (5.13%)		
occurrences (all)	5		
Renal and urinary disorders			
Urinary Retention			
alternative assessment type: Non-systematic			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	3		
Dysuria			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences (all)	1		
Leukocyturia			
subjects affected / exposed	6 / 78 (7.69%)		
occurrences (all)	6		
Haematuria			
subjects affected / exposed	6 / 78 (7.69%)		
occurrences (all)	6		
Renal Cyst			
subjects affected / exposed	3 / 78 (3.85%)		
occurrences (all)	4		
Micturition Urgency			

alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 78 (0.00%)		
occurrences (all)	0		
Pollakiuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 78 (0.00%)		
occurrences (all)	0		
Urine Abnormality			
subjects affected / exposed	0 / 78 (0.00%)		
occurrences (all)	0		
Urine Odour Abnormal			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 78 (0.00%)		
occurrences (all)	0		
Psychiatric disorders			
Insomnia			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences (all)	1		
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	9 / 78 (11.54%)		
occurrences (all)	13		
Bacteriuria			
subjects affected / exposed	6 / 78 (7.69%)		
occurrences (all)	9		
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 78 (1.28%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 December 2012	1) Immunogenicity testing (for toxin binding and toxin neutralizing antibodies) was included; and 2) A primary analysis of the data when all patients had been enrolled into the main study and had completed at least 12 weeks post-randomization (or prematurely exited prior to week 12) was included.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported