Clinical trial results:
A Study Evaluating the Efficacy and Safety of BOTOX® and Solifenacin in Patients with Overactive Bladder and Urinary Incontinence

Summary

EudraCT number	2012-003255-11
Trial protocol	GB DE CZ BE PL
Global end of trial date	27 March 2015

Results information

Result version number	v1 (current)
This version publication date	01 June 2016
First version publication date	01 June 2016

Trial information

Trial identification

Sponsor protocol code	191622-125

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01767519
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan Limited
Sponsor organisation address	Allergan Limited Marlow International The Parkway, Marlow, United Kingdom, SL7 1YL
Public contact	Allergan Limited EU Regulatory Dept, Allergan Limited, 44 1628 494444, ml-eu_reg_affairs@allergan.com
Scientific contact	Allergan Limited EU Regulatory Dept, 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	25 September 2015
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 September 2014
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 primary objective of this study was to evaluate the efficacy and safety of intradetrusor BOTOX 100 U compared to placebo in patients with overactive bladder (OAB) and urinary incontinence whose symptoms had not been adequately managed with anticholinergic therapy and were solifenacin-naïve.

Protection of trial subjects:

All study participants were required to read and sign an Informed Consent Form.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	25 March 2013
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: 2
Country: Number of subjects enrolled	Canada: 13
Country: Number of subjects enrolled	Czech Republic: 49
Country: Number of subjects enrolled	United Kingdom: 5
Country: Number of subjects enrolled	Germany: 25
Country: Number of subjects enrolled	Poland: 96
Country: Number of subjects enrolled	United States: 166
Worldwide total number of subjects	356
EEA total number of subjects	177

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)	190
From 65 to 84 years	160
85 years and over	6

Subject disposition

Recruitment

Recruitment details:

Participant Flow is for Treatment cycle 1, which is the double-blind portion of the study and includes the primary timepoint.

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BOTOX®

Arm description:

Treatment Cycle 1: BOTOX injected at Day 1 with one solifenacin placebo capsule taken orally once daily for up to 24 weeks. After a minimum of 12 weeks, patients could request/qualify for a second BOTOX injection.

Arm type	Experimental
Investigational medicinal product name	BOTOX®
Investigational medicinal product code	
Other name	onabotulinumtoxinA, botulinum toxin Type A
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Treatment Cycle 1: BOTOX injected at Day 1 with one solifenacin placebo capsule taken orally once daily for up to 24 weeks. After a minimum of 12 weeks, patients could request/qualify for a second BOTOX injection.

Arm title	solifenacin

Arm description:

Treatment Cycle 1: Oral solifenacin taken once daily starting at Day 1 for up to 24 weeks with intradetrusor injection of BOTOX placebo on Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.

Arm type	Active comparator
Investigational medicinal product name	solifenacin
Investigational medicinal product code	
Other name	Vesicare
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Treatment Cycle 1: Oral solifenacin taken once daily starting at Day 1 for up to 24 weeks with intradetrusor injection of BOTOX placebo on Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.

Arm title	placebo

Arm description:

Treatment Cycle 1: One solifenacin placebo capsule taken orally once daily starting at Day 1 for up to 24 weeks with an intradetrusor injection of BOTOX placebo at Day 1. After a minimum of 12 weeks,

patients could request/qualify for a BOTOX injection.

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intramuscular use

Dosage and administration details:

Treatment Cycle 1: One solifenacin placebo capsule taken orally once daily starting at Day 1 for up to 24 weeks with an intradetrusor injection of BOTOX placebo at Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.

Number of subjects in period 1	BOTOX®	solifenacin	placebo
Started	145	151	60
Completed	131	138	55
Not completed	14	13	5
Other Reasons	4	4	2
Adverse event, non-fatal	5	5	1
Personal Reasons	1	-	-
Lost to follow-up	3	1	2
Lack of efficacy	1	-	-
Protocol deviation	-	3	-

Baseline characteristics

Reporting groups	
Reporting group title	BOTOX®
Reporting group description:	
Treatment Cycle 1: BOTOX injected at Day 1 with one solifenacin placebo capsule taken orally once daily for up to 24 weeks. After a minimum of 12 weeks, patients could request/qualify for a second BOTOX injection.	
Reporting group title	solifenacin
Reporting group description:	
Treatment Cycle 1: Oral solifenacin taken once daily starting at Day 1 for up to 24 weeks with intradetrusor injection of BOTOX placebo on Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.	
Reporting group title	placebo
Reporting group description:	
Treatment Cycle 1: One solifenacin placebo capsule taken orally once daily starting at Day 1 for up to 24 weeks with an intradetrusor injection of BOTOX placebo at Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.	

Reporting group values	BOTOX®	solifenacin	placebo
Number of subjects	145	151	60
Age categorical Units: Subjects			
Adults (18-64 years)	77	79	34
From 65-84 years	67	69	24
85 years and over	1	3	2
Age continuous Units: years			
arithmetic mean	61.4	62.9	61.2
standard deviation	± 12.82	± 11.79	± 12.19
Gender, Male/Female Units: Participants			
Male	22	17	9
Female	123	134	51
Age, Customized Units: Subjects			
<65 years	77	79	34
≥65 years	68	72	26

Reporting group values	Total		
Number of subjects	356		
Age categorical Units: Subjects			
Adults (18-64 years)	190		
From 65-84 years	160		
85 years and over	6		
Age continuous Units: years			
arithmetic mean			
standard deviation	-		

Gender, Male/Female Units: Participants			
Male	48		
Female	308		
Age, Customized Units: Subjects			
<65 years	190		
≥65 years	166		

End points

End points reporting groups

Reporting group title	BOTOX®

Reporting group description:

Treatment Cycle 1: BOTOX injected at Day 1 with one solifenacin placebo capsule taken orally once daily for up to 24 weeks. After a minimum of 12 weeks, patients could request/qualify for a second BOTOX injection.

Reporting group title	solifenacin

Reporting group description:

Treatment Cycle 1: Oral solifenacin taken once daily starting at Day 1 for up to 24 weeks with intradetrusor injection of BOTOX placebo on Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.

Reporting group title	placebo

Reporting group description:

Treatment Cycle 1: One solifenacin placebo capsule taken orally once daily starting at Day 1 for up to 24 weeks with an intradetrusor injection of BOTOX placebo at Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.

Primary: Change from Study Baseline in Number of Episodes of Urinary Incontinence in Treatment Cycle 1

End point title	Change from Study Baseline in Number of Episodes of Urinary Incontinence in Treatment Cycle 1[1]

End point description:

Urinary incontinence is defined as involuntary loss of urine as recorded in a patient bladder diary in the 3 consecutive days prior to the study visit in Treatment Cycle 1. The number of incontinence episodes are averaged daily during this period. A negative number change from baseline indicates an improvement and a positive number change from baseline indicates a worsening.

End point type	Primary

End point timeframe:

Study Baseline, Week 12

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	BOTOX®	solifenacin	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	151	60	
Units: Incontinence Episodes				
arithmetic mean (standard deviation)				
Study Baseline	4.86 (± 3.206)	5.23 (± 3.333)	4.38 (± 2.485)	
Change from Study Baseline at Week 12	-3.1 (± 2.799)	-2.66 (± 3.059)	-0.98 (± 2.417)	

Statistical analyses

No statistical analyses for this end point

Primary: Percentage of Patients with 100% Reduction in Incontinence Episodes in Treatment Cycle 1

End point title	Percentage of Patients with 100% Reduction in Incontinence Episodes in Treatment Cycle 1[2]

End point description:

Urinary incontinence is defined as involuntary loss of urine as recorded in a patient bladder diary in the 3 consecutive days prior to the study visit in Treatment Cycle 1. The number of incontinence episodes are averaged daily during this period and compared to baseline to determine 100% reduction in episodes.

End point type	Primary

End point timeframe:

Study Baseline, Week 12

Notes:

[2] - 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	BOTOX®	solifenacin	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	151	60	
Units: Percentage of Patients				
number (not applicable)	33.8	24.5	11.7	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Patients with a Positive Response on the Single-Item Treatment Benefit Scale During Treatment Cycle 1

End point title	Percentage of Patients with a Positive Response on the Single-Item Treatment Benefit Scale During Treatment Cycle 1

End point description:

A positive treatment response on the Treatment Benefit Scale is a score of either 1 or 2, representing ‘greatly improved’ or ‘improved.’

End point type	Secondary

End point timeframe:

Week 12

End point values	BOTOX®	solifenacin	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	151	60	
Units: Percentage of Patients				
number (confidence interval)	71.3 (62.9 to 78.7)	74 (66.1 to 80.9)	44.8 (31.7 to 58.5)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Study Baseline in the Number of Micturition Episodes in Treatment Cycle 1

End point title	Change from Study Baseline in the Number of Micturition Episodes in Treatment Cycle 1

End point description:

The number of micturition episodes (the number of times a patient urinates into the toilet) in Treatment Cycle 1 was recorded by the patient in a bladder diary during 3 consecutive days in the week prior to the visit. A negative number change from baseline indicates an improvement and a positive number change from baseline indicates a worsening.

End point type	Secondary

End point timeframe:

Study Baseline, Week 12

End point values	BOTOX®	solifenacin	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	151	60	
Units: Micturition Episodes				
arithmetic mean (standard deviation)				
Study Baseline	10.74 (± 2.52)	10.4 (± 2.665)	10.18 (± 2.491)	
Change from Study Baseline at Wk 12 (N=135,144,57)	-2.4 (± 2.827)	-2.03 (± 2.833)	-0.87 (± 2.413)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Study Baseline in the Number of Nocturia Episodes in Treatment Cycle 1

End point title	Change from Study Baseline in the Number of Nocturia Episodes in Treatment Cycle 1

End point description:

Nocturia episodes are measured over a 3 day diary prior to each visit in Treatment Cycle 1. A nocturia episode is a void (urinating into the toilet) that interrupts one's sleep. A negative number change from baseline indicates an improvement and a positive number change from baseline indicates a worsening.

End point type	Secondary

End point timeframe:

Study Baseline, Week 12

End point values	BOTOX®	solifenacin	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	151	60	
Units: Nocturia Episodes				
arithmetic mean (standard deviation)				
Study Baseline	2.03 (± 1.159)	2.04 (± 1.083)	1.98 (± 0.937)	
Change from Study Baseline at Wk 12 (N=135,144,57)	-0.54 (± 1.195)	-0.49 (± 1.133)	-0.23 (± 1.091)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Study Baseline in the Role Limitations Domain on the King's Health Questionnaire in Treatment Cycle 1

End point title	Change from Study Baseline in the Role Limitations Domain on the King's Health Questionnaire in Treatment Cycle 1

End point description:

The King's Health Questionnaire is a disease-specific questionnaire that measures the quality of life of patients with urinary incontinence. The questionnaire consists of 7 domains, including the role limitations domain. Domain scores range from 0 to 100, with a lower score indicating a preferable health status. A negative number change from baseline indicates an improvement and a positive number change from baseline indicates a worsening.

End point type	Secondary

End point timeframe:

Study Baseline, Week 12

End point values	BOTOX®	solifenacin	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	150	59	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Study Baseline	76.09 (± 24.281)	72.11 (± 26.581)	81.36 (± 20.781)	
Change from Study Baseline at Wk 12 (N=135,145,57)	-30 (± 33.259)	-23.79 (± 31.899)	-17.25 (± 29.033)	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Study Baseline in the Social Limitations Domain on the King's Health Questionnaire in Treatment Cycle 1

End point title	Change from Study Baseline in the Social Limitations Domain on the King's Health Questionnaire in Treatment Cycle 1

End point description:

The King's Health Questionnaire is a disease-specific questionnaire that measures the quality of life of patients with urinary incontinence. The questionnaire consists of 7 domains, including the social limitations domain. Domain scores range from 0 to 100, with a lower score indicating a preferable health status. A negative number change from baseline indicates an improvement and a positive number change from baseline indicates a worsening.

End point type	Secondary

End point timeframe:

Study Baseline, Week 12

End point values	BOTOX®	solifenacin	placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	145	150	59	
Units: Scores on a Scale				
arithmetic mean (standard deviation)				
Study Baseline	59.66 (± 21.442)	56.22 (± 22.708)	62.57 (± 22.551)	
Change from Study Baseline at Wk 12 (N=135,145,57)	-13.46 (± 21.906)	-12.7 (± 21.361)	-7.6 (± 21.667)	

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:

The safety population includes all patients who received at least 1 dose of study medication. The safety population is used to assess adverse events and serious adverse events. Adverse events and serious adverse events are displayed for the placebo-controlled treatment Cycle 1.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	18.0

Reporting groups

Reporting group title	BOTOX®

Reporting group description:

Treatment Cycle 1: BOTOX injected at Day 1 with one solifenacin placebo capsule taken orally once daily for up to 24 weeks. After a minimum of 12 weeks, patients could request/qualify for a second BOTOX injection.

Reporting group title	placebo

Reporting group description:

Treatment Cycle 1: One solifenacin placebo capsule taken orally once daily starting at Day 1 for up to 24 weeks with an intradetrusor injection of BOTOX placebo at Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.

Reporting group title	solifenacin

Reporting group description:

Treatment Cycle 1: Oral solifenacin taken once daily starting at Day 1 for up to 24 weeks with intradetrusor injection of BOTOX placebo on Day 1. After a minimum of 12 weeks, patients could request/qualify for a BOTOX injection.

Serious adverse events	BOTOX®	placebo	solifenacin
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 145 (4.14%)	2 / 60 (3.33%)	6 / 147 (4.08%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Breast cancer			
subjects affected / exposed	1 / 145 (0.69%)	0 / 60 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Limb traumatic amputation			

subjects affected / exposed	1 / 145 (0.69%)	0 / 60 (0.00%)	0 / 147 (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
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	1 / 145 (0.69%)	0 / 60 (0.00%)	0 / 147 (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
Bradycardia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 60 (0.00%)	0 / 147 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 145 (0.69%)	0 / 60 (0.00%)	0 / 147 (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			
Migraine			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 145 (0.69%)	0 / 60 (0.00%)	0 / 147 (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	0 / 145 (0.00%)	1 / 60 (1.67%)	0 / 147 (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
Reproductive system and breast disorders			
Endometrial hyperplasia	Additional description: FEMALE ONLY		
subjects affected / exposed	0 / 145 (0.00%)	0 / 60 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			

Cholelithiasis			
subjects affected / exposed	0 / 145 (0.00%)	0 / 60 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Anxiety			
alternative assessment type: Non-systematic			
subjects affected / exposed	1 / 145 (0.69%)	0 / 60 (0.00%)	0 / 147 (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
Polysubstance dependence			
subjects affected / exposed	0 / 145 (0.00%)	0 / 60 (0.00%)	1 / 147 (0.68%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	0 / 145 (0.00%)	1 / 60 (1.67%)	0 / 147 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Osteoarthritis			
alternative assessment type: Non-systematic			
subjects affected / exposed	0 / 145 (0.00%)	0 / 60 (0.00%)	2 / 147 (1.36%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
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	BOTOX®	placebo	solifenacin
Total subjects affected by non-serious adverse events			
subjects affected / exposed	95 / 145 (65.52%)	27 / 60 (45.00%)	78 / 147 (53.06%)
Investigations			
Residual urine volume			
subjects affected / exposed	10 / 145 (6.90%)	1 / 60 (1.67%)	0 / 147 (0.00%)
occurrences (all)	10	1	0

Gastrointestinal disorders			
Dry mouth			
alternative assessment type: Non-systematic			
subjects affected / exposed	4 / 145 (2.76%)	0 / 60 (0.00%)	12 / 147 (8.16%)
occurrences (all)	4	0	12
Renal and urinary disorders			
Urinary retention			
subjects affected / exposed	10 / 145 (6.90%)	0 / 60 (0.00%)	1 / 147 (0.68%)
occurrences (all)	12	0	2
Dysuria			
alternative assessment type: Non-systematic			
subjects affected / exposed	6 / 145 (4.14%)	2 / 60 (3.33%)	8 / 147 (5.44%)
occurrences (all)	6	2	11
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	37 / 145 (25.52%)	6 / 60 (10.00%)	15 / 147 (10.20%)
occurrences (all)	53	7	19
Bacteriuria			
subjects affected / exposed	11 / 145 (7.59%)	3 / 60 (5.00%)	14 / 147 (9.52%)
occurrences (all)	15	3	15
Nasopharyngitis			
alternative assessment type: Non-systematic			
subjects affected / exposed	2 / 145 (1.38%)	3 / 60 (5.00%)	2 / 147 (1.36%)
occurrences (all)	2	3	2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported