Clinical trial results:
Randomised trial of detrusor botulinum toxin injection (BOTOX®) compared to placebo in women with idiopathic detrusor overactivity

Summary

EudraCT number	2004-002981-39
Trial protocol	GB
Global end of trial date	18 February 2015

Results information

Result version number	v1 (current)
This version publication date	29 March 2019
First version publication date	29 March 2019

Trial information

Trial identification

Sponsor protocol code	v1.1aug05

Additional study identifiers

ISRCTN number	ISRCTN26091555
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University Hospitals of Leicester NHS Trust
Sponsor organisation address	Gwendolen Road, Leicester, United Kingdom, LE5 4PW
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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	06 September 2010
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 August 2010
Global end of trial reached?	Yes
Global end of trial date	18 February 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of detrusor muscle injection of purified botulinum toxin A (BOTOX®) in relieving symptoms of detrusor overactivity.

Protection of trial subjects:

Trial data were reviewed periodically by an independent data monitoring committee to ensure no excess adverse events were occurring.

Background therapy: -

Evidence for comparator:

the comparator was placebo in this study because there was no active alternative treatment for women who had failed treatment with oral medication at the time of the study

Actual start date of recruitment	22 June 2006
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 240
Worldwide total number of subjects	240
EEA total number of subjects	240

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)	154
From 65 to 84 years	86

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients with a urodynamic diagnosis of detrusor overactivity who had failed to improve after 8 weeks of any antimuscarinic drugs were eligible. Patients had to have at least 8 voids in 24 hours and at least 2 episodes of moderate or severe urgency in 24 hours.

Pre-assignment

Screening details:

Patients were screened at their first review appointment after commencing oral medication. Study information was given and patients were seen again two weeks later to complete the screening form to ensure eligibility (number of voids, number of urgency episodes

Period 1

Period 1 title	Randomisation and treatment
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Blinding implementation details:

Drug and placebo were packaged identically in opaque sealed boxes with the randomisation number on the box; boxes were used in randomisation number order. Drug and placebo were not identical so the drug was made up by the scrub nurse out of sight of the administering surgeon who was given an unlabelled syringe to administer to the patient. The drug box number was recorded in the CRF. Surgeons administering the product were not involved in data collection.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients receiving placebo injection

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravesical use

Dosage and administration details:

Placebo powder for injection, reconstituted in 20mls normal saline

Arm title	Active treatment

Arm description:

Patients receiving 200 units onabotulinum toxin (BOTOX)

Arm type	Experimental
Investigational medicinal product name	onabotulinum toxin
Investigational medicinal product code	PL 0426/0074
Other name	BOTOX
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravesical use

Dosage and administration details:

200 units of powder, reconstituted in 20mls of normal saline

Number of subjects in period 1	Placebo	Active treatment
Started	118	122
Completed	118	122

Period 2	
Period 2 title	Six week follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients receiving placebo injection

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravesical use

Dosage and administration details:

Placebo powder for injection, reconstituted in 20mls normal saline

Arm title	Active treatment

Arm description:

Patients receiving 200 units onabotulinum toxin (BOTOX)

Arm type	Experimental
Investigational medicinal product name	onabotulinum toxin
Investigational medicinal product code	PL 0426/0074
Other name	BOTOX
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravesical use

Dosage and administration details:

200 units of powder, reconstituted in 20mls of normal saline

Number of subjects in period 2	Placebo	Active treatment
Started	118	122
Completed	114	118
Not completed	4	4
missing visit	2	2
patient withdrawal (self)	2	1
Lost to follow-up	-	1

Period 3	
Period 3 title	Three month follow up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients receiving placebo injection

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravesical use

Dosage and administration details:

Placebo powder for injection, reconstituted in 20mls normal saline

Arm title	Active treatment

Arm description:

Patients receiving 200 units onabotulinum toxin (BOTOX)

Arm type	Experimental
Investigational medicinal product name	onabotulinum toxin
Investigational medicinal product code	PL 0426/0074
Other name	BOTOX
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravesical use

Dosage and administration details:

200 units of powder, reconstituted in 20mls of normal saline

Number of subjects in period 3	Placebo	Active treatment
Started	114	118
Completed	103	102
Not completed	11	16
Missed visit	9	13
Patient withdrawn (self)	1	2
Lost to follow-up	1	1

Period 4	
Period 4 title	Six month follow up (Primary outcome)
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Patients receiving placebo injection

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Powder for injection
Routes of administration	Intravesical use

Dosage and administration details:

Placebo powder for injection, reconstituted in 20mls normal saline

Arm title	Active treatment

Arm description:

Patients receiving 200 units onabotulinum toxin (BOTOX)

Arm type	Experimental
Investigational medicinal product name	onabotulinum toxin
Investigational medicinal product code	PL 0426/0074
Other name	BOTOX
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Intravesical use

Dosage and administration details:

200 units of powder, reconstituted in 20mls of normal saline

Number of subjects in period 4	Placebo	Active treatment
Started	103	102
Completed	111	116
Not completed	3	1
Patient withdrawn (self)	1	1
Lost to follow-up	2	-
Joined	11	15
Attended despite earlier missed visit	11	15

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Patients receiving placebo injection	
Reporting group title	Active treatment
Reporting group description:	
Patients receiving 200 units onabotulinum toxin (BOTOX)	

Reporting group values	Placebo	Active treatment	Total
Number of subjects	118	122	240
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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
median	58.2	60.7	
inter-quartile range (Q1-Q3)	51.5 to 69.2	50.8 to 67.8	-
Gender categorical			
All patients were female			
Units: Subjects			
Female	118	122	240
Male	0	0	0
Body Mass index >30			
Units: Subjects			
BMI >30	50	49	99
BMI<=30	68	73	141
Ethnicity			
Units: Subjects			
White British	109	118	227
Other	7	4	11
not recorded	2	0	2
Smoking			
Units: Subjects			
Yes	24	30	54
No	94	92	186
Previous continence surgery			
Units: Subjects			

Any previous surgery	46	44	90
No previous surgery	72	78	150
Continence status Units: Subjects			
Continent, no leaks	8	6	14
Has leakage	110	116	226
Baseline voiding frequency Units: Episodes			
median	10.7	10.3	
inter-quartile range (Q1-Q3)	9.3 to 13.3	9.3 to 12.7	-
Incontinence episodes per 24 hours Units: Episodes			
median	6.2	6.2	
inter-quartile range (Q1-Q3)	3.0 to 8.7	3.7 to 8.3	-
Urgency episodes Units: Episodes			
median	7.7	8.0	
inter-quartile range (Q1-Q3)	6.0 to 9.7	5.7 to 10.3	-
Urgency severity Score			
Indevus urgency severity score; a value from 0-3 with greater score indicating greater urgency			
Units: number			
median	2.1	2.1	
inter-quartile range (Q1-Q3)	1.7 to 2.3	1.7 to 2.4	-
Maximum voided urine volume			
Maximum recorded void from 3 day bladder diary			
Units: mls			
median	300	350	
inter-quartile range (Q1-Q3)	250 to 420	275 to 450	-
mean voided volume			
mean voided volume from three day bladder diary			
Units: mls			
median	164.4	165.8	
inter-quartile range (Q1-Q3)	121.8 to 198.0	122. to 203.7	-
ICIQ UI score			
International Consultation on Incontinence Short Form score; a numerical value from 0-21 with higher values indicating greater incontinence			
Units: number			
median	16.0	17.0	
inter-quartile range (Q1-Q3)	13.8 to 18.0	14.0 to 19.0	-
Incontinence-Quality of LIfe score (I-QoL)			
quality of life score, with greater scores indicating better quality of life (range 0-100)			
Units: number			
median	23.3	24.4	
inter-quartile range (Q1-Q3)	12.5 to 34.1	11.4 to 38.6	-

End points

End points reporting groups	
Reporting group title	Placebo
Reporting group description: Patients receiving placebo injection	
Reporting group title	Active treatment
Reporting group description: Patients receiving 200 units onabotulinum toxin (BOTOX)	
Reporting group title	Placebo
Reporting group description: Patients receiving placebo injection	
Reporting group title	Active treatment
Reporting group description: Patients receiving 200 units onabotulinum toxin (BOTOX)	
Reporting group title	Placebo
Reporting group description: Patients receiving placebo injection	
Reporting group title	Active treatment
Reporting group description: Patients receiving 200 units onabotulinum toxin (BOTOX)	
Reporting group title	Placebo
Reporting group description: Patients receiving placebo injection	
Reporting group title	Active treatment
Reporting group description: Patients receiving 200 units onabotulinum toxin (BOTOX)	

Primary: Urinary voiding frequency at 6 months after treatment	
End point title	Urinary voiding frequency at 6 months after treatment
End point description: Voiding frequency at six months after treatment	
End point type	Primary
End point timeframe: Six months after treatment	

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99[1]	100[2]		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	9.67 (8.37 to 11.67)	8.33 (6.83 to 10.0)		

Notes:
[1] - 99 women returned valid diary data at this time point
[2] - 100 women returned valid diary data at this time point

Statistical analyses

Statistical analysis title	Comparison of primary outcome at 6 months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Incontinence episodes per 24 hours

End point title	Incontinence episodes per 24 hours

End point description:

End point type	Secondary

End point timeframe:
Six months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	100		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	6.0 (1.33 to 8.33)	1.67 (0 to 5.33)		

Statistical analyses

Statistical analysis title	Comparison of incontinence episodes
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Urgency episodes per 24 hours at six months

End point title	Urgency episodes per 24 hours at six months

End point description:

End point type	Secondary

End point timeframe:

Six months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	100		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	6.33 (4.0 to 8.67)	3.83 (1.17 to 6.67)		

Statistical analyses

Statistical analysis title	Comparison of urgency episodes at six months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Urgency severity score (IUSS) at six months

End point title	Urgency severity score (IUSS) at six months

End point description:

End point type	Secondary

End point timeframe:

Six months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	100		
Units: Score				
median (inter-quartile range (Q1-Q3))	1.9 (1.5 to 2.3)	1.5 (1.0 to 2.0)		

Statistical analyses

Statistical analysis title	Comparison of IUSS score at six months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0006
Method	Wilcoxon (Mann-Whitney)

Secondary: Continence rate at six months

End point title	Continence rate at six months
End point description:	
End point type	Secondary
End point timeframe:	
Six months after treatment	

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	100		
Units: Number of continent patients				
number (not applicable)				
Continent-yes	12	31		
Continent-no	87	69		

Statistical analyses

Statistical analysis title	Comparison of continent rate
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.002
Method	OR and 95% CI

Secondary: ICIQ score at six months

End point title	ICIQ score at six months

End point description:

End point type	Secondary

End point timeframe:

Six months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	100		
Units: Score				
median (inter-quartile range (Q1-Q3))	15.0 (11.0 to 18.0)	10.0 (4.0 to 15.0)		

Statistical analyses

Statistical analysis title	Comparison of ICIQ score at six months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: IQoL score at six months

End point title	IQoL score at six months

End point description:

End point type	Secondary

End point timeframe:

Six months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	99	100		
Units: Score				
median (inter-quartile range (Q1-Q3))	27.27 (18.18 to 46.59)	55.11 (23.3 to 78.41)		

Statistical analyses

Statistical analysis title	Comparison of IQOL score at six months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	199
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Voiding frequency per 24 hours at six weeks

End point title	Voiding frequency per 24 hours at six weeks

End point description:

End point type	Secondary

End point timeframe:

Six weeks after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97[3]		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	9.67 (8.37 to 11.67)	8.0 (6.33 to 10.0)		

Notes:

[3] - 97patients returned valid urinary diaries for this data point

Statistical analyses

Statistical analysis title	Comparison of voiding frequency at 6 weeks
Comparison groups	Placebo v Active treatment

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Incontinence episodes per 24 hours at six weeks

End point title	Incontinence episodes per 24 hours at six weeks

End point description:

End point type	Secondary

End point timeframe:

Six weeks after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	5.33 (1.67 to 7.0)	0.33 (0 to 4.0)		

Statistical analyses

Statistical analysis title	Comparison of incontinence episodes at six weeks
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Urgency episodes per 24 hours at six weeks

End point title	Urgency episodes per 24 hours at six weeks

End point description:

End point type	Secondary

End point timeframe:

Six weeks after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	6.17 (4.0 to 9.0)	2.67 (0 to 6.33)		

Statistical analyses

Statistical analysis title	Comparison of urgency episodes at six weeks
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Urgency severity score (IUSS) at six weeks

End point title	Urgency severity score (IUSS) at six weeks

End point description:

End point type	Secondary

End point timeframe:

Six weeks after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97		
Units: Score				
median (inter-quartile range (Q1-Q3))	1.90 (1.40 to 2.20)	1.30 (0.7 to 1.90)		

Statistical analyses

Statistical analysis title	Comparison of IUSS score at six weeks
Comparison groups	Placebo v Active treatment

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Continence rate at six weeks

End point title	Continence rate at six weeks

End point description:

End point type	Secondary

End point timeframe:

Six weeks after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97		
Units: Number				
number (not applicable)				
Continent-yes	13	43		
Continent-no	85	54		

Statistical analyses

Statistical analysis title	Comparison of continence rate at six weeks
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	OR and 95% CI

Secondary: ICIQ score at six weeks

End point title	ICIQ score at six weeks

End point description:

End point type	Secondary

End point timeframe:

Six weeks after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97		
Units: Score				
median (inter-quartile range (Q1-Q3))	14.0 (1.0 to 18.0)	7.0 (1.0 to 18.0)		

Statistical analyses

Statistical analysis title	Comparison of ICIQ score at six weeks
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: IQoL score at six weeks

End point title	IQoL score at six weeks

End point description:

End point type	Secondary

End point timeframe:

Six weeks after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97		
Units: Score				
median (inter-quartile range (Q1-Q3))	30.68 (17.05 to 51.14)	55.68 (22.72 to 85.23)		

Statistical analyses

Statistical analysis title	Comparison of IQOL score at six weeks
Comparison groups	Placebo v Active treatment

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Voiding frequency per 24 hours at three months

End point title	Voiding frequency per 24 hours at three months

End point description:

End point type	Secondary

End point timeframe:

Thre months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86[4]	86[5]		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	9.67 (8.0 to 11.0)	8.0 (6.3 to 10.0)		

Notes:

[4] - 86 women returned valid urinary diaries for this period

[5] - 86 women returned valid urinary diaries for this period

Statistical analyses

Statistical analysis title	Comparison of voiding frequency at 3 months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Incontinence episodes per 24 hours at 3 months

End point title	Incontinence episodes per 24 hours at 3 months

End point description:

End point type	Secondary

End point timeframe:

Three months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	86		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	5.33 (2.0 to 8.33)	1.0 (0 to 6.0)		

Statistical analyses

Statistical analysis title	Comparison of incontinence episodes @ three months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Urgency episodes per 24 hours at three months

End point title	Urgency episodes per 24 hours at three months

End point description:

End point type	Secondary

End point timeframe:

Three months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	86		
Units: Episodes				
median (inter-quartile range (Q1-Q3))	7.0 (3.67 to 8.67)	3.0 (0.67 to 6.33)		

Statistical analyses

Statistical analysis title	Comparison of urgency episodes at three months
Comparison groups	Active treatment v Placebo

Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Urgency severity score (IUSS) at 3 months

End point title	Urgency severity score (IUSS) at 3 months

End point description:

End point type	Secondary

End point timeframe:

Three months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	86		
Units: Score				
median (inter-quartile range (Q1-Q3))	1.90 (1.40 to 2.30)	1.30 (0.80 to 2.0)		

Statistical analyses

Statistical analysis title	Comparison of IUSS score at three months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: Continence rate at 3 months

End point title	Continence rate at 3 months

End point description:

End point type	Secondary

End point timeframe:

Three months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	86		
Units: Number				
number (not applicable)				
Continent-yes	12	36		
Continent-no	74	50		

Statistical analyses

Statistical analysis title	Comparison of continent rate at 3 months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	OR and 95% CI

Secondary: ICIQ score at 3 months

End point title	ICIQ score at 3 months

End point description:

End point type	Secondary

End point timeframe:

Three months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	86		
Units: Score				
median (inter-quartile range (Q1-Q3))	15.0 (9.0 to 17.0)	8.0 (3.0 to 14.0)		

Statistical analyses

Statistical analysis title	Comparison of ICIQ score at three months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Secondary: IQOL score at 3 months

End point title	IQOL score at 3 months

End point description:

End point type	Secondary

End point timeframe:

Three months after treatment

End point values	Placebo	Active treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	86	86		
Units: Score				
median (inter-quartile range (Q1-Q3))	25.0 (14.77 to 44.32)	64.77 (27.27 to 90.91)		

Statistical analyses

Statistical analysis title	Comparison of IQOL score at three months
Comparison groups	Placebo v Active treatment
Number of subjects included in analysis	172
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse event reported was open throughout treatment and follow up phases of the study, according to ICH-GCP guidelines in force during the trial.

Adverse event reporting additional description:

Standard European Directive definitions of adverse events and adverse reactions were followed (Directive 2001/20/EC). Fatal or life threatening events were reported as soon as possible but within seven days of the event. Non-fatal or life threatening were reported as soon as possible within fifteen days.

Assessment type	Systematic

Dictionary used

Dictionary name	ICH-GCP
Dictionary version	2001

Reporting groups

Reporting group title	Placebo

Reporting group description:

Patients receiving placebo injection

Reporting group title	Active treatment

Reporting group description:

Patients receiving 200 units onabotulinum toxin (BOTOX)

Serious adverse events	Placebo	Active treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 118 (1.69%)	2 / 122 (1.64%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Respiratory, thoracic and mediastinal disorders			
Pneumonia			
subjects affected / exposed	0 / 118 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Urinary clot retention			
subjects affected / exposed	1 / 118 (0.85%)	0 / 122 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Generalised muscle weakness			

subjects affected / exposed	0 / 118 (0.00%)	1 / 122 (0.82%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Active treatment	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	39 / 118 (33.05%)	85 / 122 (69.67%)	
Renal and urinary disorders			
Urinary tract infection	Additional description: Defined in the protocol as a non-serious adverse event because it was an expected outcome; adverse event was based on patient reported symptoms and receipt of an antibiotic prescription from the GP. Numbers included are all patients 1 or more UTI		
subjects affected / exposed	12 / 118 (10.17%)	36 / 122 (29.51%)	
occurrences (all)	12	36	
Voiding difficulty	Additional description: Voiding difficulty was not classed as a serious adverse event in the trial protocol because it was expected. Patient reported outcome, not based on scan measured residual volume		
subjects affected / exposed	1 / 118 (0.85%)	10 / 122 (8.20%)	
occurrences (all)	1	10	
Need for intermittent self-catheterisation	Additional description: Classified as a non-serious amendment in the study protocol because it was expected. Defined as the need to perform ISC to assist with voiding		
subjects affected / exposed	4 / 118 (3.39%)	18 / 122 (14.75%)	
occurrences (all)	4	18	
Need for analgesia before discharge			
subjects affected / exposed	22 / 118 (18.64%)	21 / 122 (17.21%)	
occurrences (all)	22	21	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 August 2005	• New protocol version 1.1 • Reduce dosage from 300 units to 200 units. • Revised urinary retention rate of 17% • Appeal against decision not to allow CI to treat. • Request to contact not active patients directly. MREC approval granted 08/09/05 MHRA approval granted 12/12/05 R&D approval granted: 22/06/2006
18 November 2005	• New protocol version 1.2 • Primary outcome changed to change in frequency episodes from baseline to follow-up. • Sample size therefore reduced to 180. • Follow-up shortened, so primary outcome is 6 months. MREC approval granted 05/12/05 MHRA approval granted 05/01/06 R&D approval granted: 22/06/2006
19 December 2005	(Submitted electronically to MHRA after phone conversation with Mike Nicholls – effectively merged with amendment 2) • New protocol version 1.3 • Primary outcome changed to urinary frequency between groups at 6 months. • Sample size therefore increased to 240. MREC approval granted 03/02/06 MHRA approval granted 05/01/06 R&D approval granted: 22/06/2006
04 September 2006	• Addition of reminder letters to be sent to patients regarding six week and six month follow up visits. • DMEC charter MREC approval granted 24/10/06 following modification MHRA approval granted 07/09/07 R&D approval granted: 21/03/2007
13 October 2006	• Revised versions of information leaflet and consent form to allow administrator access to casenotes. MREC approval granted 31/10/06 MHRA approval granted 25/09/07 R&D approval granted: 21/03/2007

07 February 2007	• New protocol version 6.1 • Includes detailed plans for open label extension, and approval of Extension documents (Consent Form, PI Leaflet, new PI leaflet for main study, GP letter) MREC approval granted 19/03/07 following modification MHRA approval granted 07/09/07 R&D approval granted: 21/03/2007
23 March 2007	• Notification of intention to add additional centres to the trial MREC approval granted by date of each SSA approval: Wolverhampton 18/07/07 Ashford 14/08/07 Yeovil 30/08/07 MHRA approval granted 03/09/07
20 June 2007	• New protocol version 6.2 • Notification of change of personnel in trial office, and approval of advertising posters for centres and GP practices in catchment areas of recruiting hospitals. MREC approval for protocol (considered a NSA) granted 28/06/2007 MREC approval for amendment 9 granted 04/07/2007 MHRA approval granted 25/09/07 R&D approval granted: 05/10/2007
02 August 2007	• 3 month forms letter to be sent to a patient for their 3 month follow-up with a Form 5, Diary and Questionnaires MREC approval granted 05/09/07 MHRA approval granted 25/09/07 R&D approval granted: 11/10/2007
14 September 2007	• Notification of new safety data from the manufacturers, and updated SPC. • Copies of recent publications • New versions of PIL and consent (v1.9 12th September) • New investigator brochure v1.3 MREC approval granted: 11th December 2007 MHRA approval granted: 12th October 2007 R&D approval: 24th January 2008
30 July 2008	• Amendment of Form 7 (Form 7a) • Help sheet for Forms 5 and 7 • For MHRA only – send copies of SSI approvals for latest three collaborating centres MREC approval granted: 21st August 2008 MHRA approval granted: 20th August 2008 R&D approval: 14/11/2008
29 August 2008	• Updated protocol, version 6.3, dated 28th August 2008 MREC approval granted: 19th September 2008 MHRA approval granted: 15th September 2008 R&D approval: 14/11/2008

29 July 2011	RELAX Plus, qualitative sub-study; qualitative interviews with recruited patients to explore their lived experience of severe overactive bladder symptoms. Including: • Study protocol v 1.0 18th may 2011-06-20 • Interview consent form v 1.0 20th June 2011 • Patient information leaflet v 1.0 20th June 2011 • Research personnel CV & GCP • Invitation letter v 1.0 20th June 2011 • Reply slip v 1.0 20th June 2011 MREC approval granted: 26/08/2011 MHRA approval granted: 30/08/2011 R&D approval: 27/10/2011

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/22236796