



Clinical trial results: BOTOX® in the Treatment of Urinary Incontinence Due to Neurogenic Detrusor Overactivity in Patients 5 to 17 Years of Age Summary

EudraCT number	2012-004877-26
Trial protocol	BE CZ AT IT DE PL FR
Global end of trial date	11 October 2018

Results information

Result version number	v1 (current)
This version publication date	27 April 2019
First version publication date	27 April 2019

Trial information

Trial identification

Sponsor protocol code	191622-120
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01852045
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Allergan
Sponsor organisation address	1st Floor, Marlow International, The Parkway, Marlow, Buckinghamshire, United Kingdom, SL7 1YL
Public contact	Clinical Trials Registry Team, Allergan plc, 001 8772778566, IR-CTRegistration@allergan.com
Scientific contact	Therapeutic Area, Head, Allergan plc, 001 862-261-7000, IR- CTRegistration@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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	11 October 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	11 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to evaluate 3 doses of onabotulinumtoxinA (botulinum toxin Type 2) for the treatment of urinary incontinence due to neurogenic detrusor overactivity in pediatric participants between the ages of 5 to 17 years to determine if 1 or more doses were safe and effective.

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	02 July 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: 17
Country: Number of subjects enrolled	Czech Republic: 5
Country: Number of subjects enrolled	France: 14
Country: Number of subjects enrolled	Italy: 6
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Canada: 3
Country: Number of subjects enrolled	Turkey: 2
Country: Number of subjects enrolled	United States: 44
Worldwide total number of subjects	114
EEA total number of subjects	65

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)	59
Adolescents (12-17 years)	55
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

114 patients were enrolled and randomised into the study; 113 received study 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	Subject, Investigator, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	OnabotulinumtoxinA 50 U

Arm description:

OnabotulinumtoxinA (botulinum toxin Type A) 50 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.

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

Dosage and administration details:

OnabotulinumtoxinA 50 U injected into the detrusor wall on Day 1. Participants were eligible for retreatment in study 191622-121 (2012-004898-30) if qualified.

Arm title	OnabotulinumtoxinA 100 U
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Arm description:

OnabotulinumtoxinA 100 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.

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

Dosage and administration details:

OnabotulinumtoxinA 100 U injected into the detrusor wall on Day 1. Participants were eligible for retreatment in study 191622-121 (2012-004898-30) if qualified.

Arm title	OnabotulinumtoxinA 200 U
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Arm description:

OnabotulinumtoxinA 200 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.

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

Dosage and administration details:

OnabotulinumtoxinA 200 U injected into the detrusor wall on Day 1. Participants were eligible for retreatment in study 191622-121 (2012-004898-30) if qualified.

Number of subjects in period 1	OnabotulinumtoxinA 50 U	OnabotulinumtoxinA 100 U	OnabotulinumtoxinA 200 U
Started	39	45	30
mITT Population	38	45	30
Safety Population: Received treatment	38	45	30
Completed	33	41	26
Not completed	6	4	4
Adverse Event	1	-	-
Withdrawal by Subject	1	-	1
Other Miscellaneous Reasons	1	3	2
Lost to follow-up	-	1	1
Lack of efficacy	3	-	-

Baseline characteristics

Reporting groups

Reporting group title	OnabotulinumtoxinA 50 U
Reporting group description: OnabotulinumtoxinA (botulinum toxin Type A) 50 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.	
Reporting group title	OnabotulinumtoxinA 100 U
Reporting group description: OnabotulinumtoxinA 100 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.	
Reporting group title	OnabotulinumtoxinA 200 U
Reporting group description: OnabotulinumtoxinA 200 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.	

Reporting group values	OnabotulinumtoxinA 50 U	OnabotulinumtoxinA 100 U	OnabotulinumtoxinA 200 U
Number of subjects	39	45	30
Age categorical Units: Subjects			
5-11 years	21	26	12
12-17 years	18	19	18
Age Continuous Units: years			
arithmetic mean	11.4	10.8	11.9
standard deviation	± 3.45	± 3.26	± 3.13
Sex: Female, Male Units: Subjects			
Female	19	15	15
Male	20	30	15
Race/Ethnicity, Customized Units: Subjects			
White	29	34	22
Black or African American	6	3	2
Asian	1	2	1
Hispanic	1	3	3
Other	2	3	2
Daily Daytime Average Frequency of Urinary Incontinence Episodes			
Urinary incontinence was defined as involuntary loss of urine as recorded by the participant in a bladder diary during the 2 consecutive days (normalised to a 12-hour daytime period) prior to the study visit. Daytime was defined as the time between waking up to start the day and first morning catheterisation and going to bed to sleep for the night. The number of incontinence episodes were averaged daily during this period.			
Units: urinary incontinence episodes per day			
arithmetic mean	2.81	2.99	3.68
full range (min-max)	0.8 to 6.7	1.3 to 6.1	0.5 to 29.5

Reporting group values	Total		
Number of subjects	114		

Age categorical			
Units: Subjects			
5-11 years	59		
12-17 years	55		
Age Continuous			
Units: years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male			
Units: Subjects			
Female	49		
Male	65		
Race/Ethnicity, Customized			
Units: Subjects			
White	85		
Black or African American	11		
Asian	4		
Hispanic	7		
Other	7		
Daily Daytime Average Frequency of Urinary Incontinence Episodes			
Urinary incontinence was defined as involuntary loss of urine as recorded by the participant in a bladder diary during the 2 consecutive days (normalised to a 12-hour daytime period) prior to the study visit. Daytime was defined as the time between waking up to start the day and first morning catheterisation and going to bed to sleep for the night. The number of incontinence episodes were averaged daily during this period.			
Units: urinary incontinence episodes per day			
arithmetic mean			
full range (min-max)	-		

End points

End points reporting groups

Reporting group title	OnabotulinumtoxinA 50 U
Reporting group description: OnabotulinumtoxinA (botulinum toxin Type A) 50 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.	
Reporting group title	OnabotulinumtoxinA 100 U
Reporting group description: OnabotulinumtoxinA 100 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.	
Reporting group title	OnabotulinumtoxinA 200 U
Reporting group description: OnabotulinumtoxinA 200 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.	

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

End point title	Change from Baseline in Daily Average Frequency of Daytime Urinary Incontinence Episodes
End point description: Urinary incontinence was defined as involuntary loss of urine as recorded by the participant in a bladder diary during the 2 consecutive days (normalised to a 12-hour daytime period) prior to the study visit. Daytime was defined as the time between waking up to start the day and first morning catheterisation and going to bed to sleep for the night. The number of incontinence episodes were averaged daily during this period. A negative change from Baseline indicates improvement. Least squares estimates were based on an Analysis of Covariance (ANCOVA) model. mITT population included participants who received study drug on Day 1, analysed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Missing data are imputed up to Week 6 using Last Observation Carried Forward (LOCF) method.	
End point type	Primary
End point timeframe: Baseline (Day -28 to Day -1) to 2 consecutive days prior to Week 6	

End point values	OnabotulinumtoxinA 50 U	OnabotulinumtoxinA 100 U	OnabotulinumtoxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	45	30	
Units: urinary incontinence episodes per day				
least squares mean (standard error)	-1.30 ($\pm$ 0.205)	-1.30 ($\pm$ 0.189)	-1.34 ($\pm$ 0.245)	

Statistical analyses

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 100U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 100 U

Number of subjects included in analysis	83
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.9949
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.549
upper limit	0.545
Variability estimate	Standard error of the mean
Dispersion value	0.276

Notes:

[1] - Least squares estimates and contrast t-test were based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 200U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 200 U
Number of subjects included in analysis	68
Analysis specification	Pre-specified
Analysis type	superiority ^[2]
P-value	= 0.9123
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.673
upper limit	0.602
Variability estimate	Standard error of the mean
Dispersion value	0.321

Notes:

[2] - Least squares estimates and contrast t-test were based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Secondary: Number of Participants with Treatment Emergent Adverse Events (TEAE)

End point title	Number of Participants with Treatment Emergent Adverse Events (TEAE)
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End point description:

An adverse event is any untoward medical occurrence in a patient or clinical investigation participant administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. Safety population included participants who underwent treatment procedure and received study drug on randomisation/Day 1, except those who received less dose due to 6 U/kg weight cap, were allocated to nearest dose group based on the actual dose received.

End point type	Secondary
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End point timeframe:

First study treatment to 12 weeks after last treatment (Up to 48 weeks after first study injection)

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	45	30	
Units: participants	27	33	23	

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Average Urine Volume at First Morning Catheterisation

End point title	Change from Baseline in Average Urine Volume at First Morning Catheterisation
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End point description:

The change in urine volume at first morning catheterisation was recorded by the participant in a bladder diary in the 2 consecutive days during the week prior to the study visit. A positive change from Baseline indicates improvement. Least squares estimates were based on an ANCOVA model. mITT population included participants who received study drug on Day 1, analyzed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.

End point type	Secondary
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End point timeframe:

Baseline (Day -28 to Day -1) to 2 consecutive days prior to Week 6

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	36	43	27	
Units: milliliters (mL)				
least squares mean (standard error)	21.93 (± 14.676)	34.90 (± 13.580)	87.49 (± 17.808)	

Statistical analyses

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 100U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 100 U

Number of subjects included in analysis	79
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.5117
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	12.97
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.12
upper limit	52.064
Variability estimate	Standard error of the mean
Dispersion value	19.694

Notes:

[3] - Least squares estimates and contrast t-test are based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 200U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 200 U
Number of subjects included in analysis	63
Analysis specification	Pre-specified
Analysis type	superiority ^[4]
P-value	= 0.0055
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	65.57
Confidence interval	
level	95 %
sides	2-sided
lower limit	19.711
upper limit	111.421
Variability estimate	Standard error of the mean
Dispersion value	23.101

Notes:

[4] - Least squares estimates and contrast t-test are based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Secondary: Percentage of Participants with Night Time Urinary Incontinence

End point title	Percentage of Participants with Night Time Urinary Incontinence
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End point description:

Urinary incontinence was defined as involuntary loss of urine and the presence or absence of night time urinary incontinence was recorded by the participant in a bladder diary in the 2 consecutive days (normalised to a 12-hour daytime period) during the week prior to the study visit. Night time was defined as the time between going to bed to sleep for the night and waking up to start the day. Percentage of participants with night time urinary incontinence were assessed and represented as categories (0, 1, 2 nights). mITT population included participants who received study drug on Day 1, analysed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.

End point type	Secondary
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End point timeframe:

Baseline (Day -28 to Day -1), Week 6

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	38	45	28	
Units: percentage of participants				
number (not applicable)				
Baseline (BL): 0 nights of incontinence	0.0	13.3	3.6	
BL: 1 night of incontinence	13.2	2.2	14.3	
BL: 2 nights of incontinence	86.8	84.4	82.1	
Week 6: 0 nights of incontinence	30.6	32.6	28.6	
Week 6: 1 night of incontinence	16.7	16.3	28.6	
Week 6: 2 nights of incontinence	52.8	51.2	42.9	

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)
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End point description:

The MCC was defined by urodynamics, as the volume infused before the participants felt they could no longer delay micturition (has a strong desire to void), had a leakage, or 500 mL was instilled. A positive change from Baseline indicates improvement (increase) in the maximum volume of urine the bladder holds. Least squares estimates were based on an ANCOVA model. mITT population included participants who received study drug on Day 1, analysed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.

End point type	Secondary
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End point timeframe:

Baseline (Day -28 to Day -1) to Week 6

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	38	28	
Units: mL				
least squares mean (standard error)	62.06 (± 14.339)	48.57 (± 13.549)	63.55 (± 17.363)	

Statistical analyses

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 100U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 100 U
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	= 0.4948
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-13.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-52.605
upper limit	25.626
Variability estimate	Standard error of the mean
Dispersion value	19.673

Notes:

[5] - Least squares estimates and contrast t-test are based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 200U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 200 U
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority ^[6]
P-value	= 0.9471
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	1.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-43.012
upper limit	45.991
Variability estimate	Standard error of the mean
Dispersion value	22.382

Notes:

[6] - Least squares estimates and contrast t-test are based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Secondary: Percentage of Participants with Involuntary Detrusor Contractions (IDC)

End point title	Percentage of Participants with Involuntary Detrusor Contractions (IDC)
End point description:	mITT population included participants who received study drug on Day 1, analysed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.
End point type	Secondary
End point timeframe:	
Week 6	

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	38	28	
Units: percentage of participants				
number (confidence interval 95%)	61.8 (43.56 to 77.83)	44.7 (28.62 to 61.70)	46.4 (27.51 to 66.13)	

Statistical analyses

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 100U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 100 U
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2027 ^[7]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.45
upper limit	1.14

Notes:

[7] - P-values for pairwise comparisons are obtained from 2-sided CMH test, stratified by age (<12 years or ≥12 years), baseline daytime urinary incontinence episodes (≤6 or >6) and anticholinergic therapy (yes/no).

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 200U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 200 U
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1564 ^[8]
Method	Cochran-Mantel-Haenszel
Parameter estimate	Relative Risk
Point estimate	0.8
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	1.21

Notes:

[8] - P-values for pairwise comparisons are obtained from a 2-sided CMH test, stratified by age (< 12 years or ≥ 12 years), baseline daytime urinary incontinence episodes (≤ 6 or > 6) and anticholinergic therapy (yes/no).

Secondary: Change from Baseline in Maximum Detrusor Pressure During the First IDC (PdetMax1stIDC) in Participants with IDC

End point title	Change from Baseline in Maximum Detrusor Pressure During the First IDC (PdetMax1stIDC) in Participants with IDC
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End point description:

Urodynamic tests were performed by site personnel qualified for performing pressure/flow cystometry. The results were verified by an independent central reviewer. Cystometry was used to measure the pressure inside of the bladder to see how well the bladder was working. A negative change from Baseline indicates improvement. Least squares estimates were based on an ANCOVA model. mITT population included participants who received study drug on Day 1, analysed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.

End point type	Secondary
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End point timeframe:

Baseline (Day-28 to Day-1) to Week 6

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	21	17	12	
Units: centimeters of water (cm H2O)				
least squares mean (standard error)	-7.64 ($\pm$ 5.301)	-12.13 ($\pm$ 5.573)	-5.46 ($\pm$ 8.267)	

Statistical analyses

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 100U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 100 U
Number of subjects included in analysis	38
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.5524
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-4.49
Confidence interval	
level	95 %
sides	2-sided
lower limit	-19.648
upper limit	10.669
Variability estimate	Standard error of the mean
Dispersion value	7.488

Notes:

[9] - Least squares estimates and contrast t-test are based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 200U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 200 U

Number of subjects included in analysis	33
Analysis specification	Pre-specified
Analysis type	superiority ^[10]
P-value	= 0.8313
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	2.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-18.427
upper limit	22.795
Variability estimate	Standard error of the mean
Dispersion value	10.181

Notes:

[10] - Least squares estimates and contrast t-test are based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Secondary: Change from Baseline in Maximum Detrusor Pressure (PdetMax) During the Storage Phase

End point title	Change from Baseline in Maximum Detrusor Pressure (PdetMax) During the Storage Phase
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End point description:

Urodynamic tests were performed by site personnel qualified for performing pressure/flow cystometry. The results were verified by an independent central reviewer. Cystometry was used to measure the pressure inside of the bladder to see how well the bladder was working. A negative change from Baseline indicates improvement. Least squares estimates were based on an ANCOVA model. mITT population included participants who received study drug on Day 1, analysed on an as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.

End point type	Secondary
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End point timeframe:

Baseline (Day 1) to Week 6

End point values	OnabotulinumtoxinA 50 U	OnabotulinumtoxinA 100 U	OnabotulinumtoxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	34	38	28	
Units: cm H ₂ O				
least squares mean (standard error)	-12.88 (± 3.793)	-20.09 (± 3.632)	-27.31 (± 4.557)	

Statistical analyses

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 100U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 100 U

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.1737
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-7.21
Confidence interval	
level	95 %
sides	2-sided
lower limit	-17.653
upper limit	3.238
Variability estimate	Standard error of the mean
Dispersion value	5.253

Notes:

[11] - Least squares estimates and contrast t-test are based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Statistical analysis title	OnabotulinumtoxinA 50U vs OnabotulinumtoxinA 200U
Comparison groups	OnabotulinumtoxinA 50 U v OnabotulinumtoxinA 200 U
Number of subjects included in analysis	62
Analysis specification	Pre-specified
Analysis type	superiority ^[12]
P-value	= 0.0157
Method	ANCOVA
Parameter estimate	Least Squares Mean Difference
Point estimate	-14.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	-26.061
upper limit	-2.793
Variability estimate	Standard error of the mean
Dispersion value	5.85

Notes:

[12] - Least squares estimates and contrast t-test are based on ANCOVA model with baseline value as covariate and treatment group, age, baseline daytime urinary incontinence episodes, anticholinergic therapy at baseline as factors.

Secondary: Change from Baseline in Detrusor Leak Point Pressure (DLPP) During the Storage Phase

End point title	Change from Baseline in Detrusor Leak Point Pressure (DLPP) During the Storage Phase
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End point description:

DLPP was defined as the lowest detrusor pressure at which urine leakage occurs in the absence of either a detrusor contraction or increased intra-abdominal pressure. Urodynamic tests were performed by site personnel qualified for performing pressure/flow cystometry. The results were verified by an independent central reviewer. Cystometry was used to measure the pressure inside of the bladder to see how well the bladder was working. A negative change from Baseline indicates improvement. Least squares estimates are based on an ANCOVA model. mITT population included participants who received study drug on Day 1, analysed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.

End point type	Secondary
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End point timeframe:

Baseline (Day -28 to -1) to Week 6

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	2	1	1	
Units: cm H2O				
arithmetic mean (standard deviation)	9.50 ($\pm$ 2.121)	-39.00 ($\pm$ 0.000)	12.00 ($\pm$ 0.000)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Participant Request for Retreatment

End point title	Time to Participant Request for Retreatment
End point description: Time from treatment on Day 1 to request for retreatment was estimated. For those participants who did not request retreatment, their data was censored using the date of their last study visit. mITT population included participants who received study drug on Day 1, analysed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.	
End point type	Secondary
End point timeframe: 48 weeks	

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	35	23	
Units: weeks				
median (confidence interval 95%)	30.6 (23.10 to 39.10)	24.1 (18.10 to 27.60)	29.6 (16.30 to 37.30)	

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Participant Qualification for Retreatment

End point title	Time to Participant Qualification for Retreatment
End point description: In order to qualify for retreatment, the criteria listed below must be fulfilled at the qualification for	

retreatment visit: Participant/parent/caregiver requests retreatment, participant has a total of at least 2 daytime urinary incontinence episodes over the 2-day bladder diary collection period, at least 12 weeks has elapsed since treatment 1 and participant has not experienced a serious treatment-related adverse event at any time. mITT population included participants who received study drug on Day 1, analysed on as-randomised basis, except those who received less than their randomised dose due to weight and dose limit of 6 U/kg, allocated to nearest dose group based on dose received. Number analysed is number of participants with non-missing values at the specified Visit.

End point type	Secondary
End point timeframe:	
48 weeks	

End point values	Onabotulinumt oxinA 50 U	Onabotulinumt oxinA 100 U	Onabotulinumt oxinA 200 U	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	27	35	23	
Units: weeks				
median (confidence interval 95%)	35.0 (23.10 to 39.10)	25.0 (20.00 to 32.10)	29.6 (16.30 to 38.00)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

First study treatment to 12 weeks after last treatment (Up to 48 weeks after first study injection)

Adverse event reporting additional description:

Safety population included participants who underwent treatment procedure and received study drug on randomisation/Day 1, except those who received less dose due to 6 U/kg weight cap, were allocated to nearest dose group based on the actual dose received.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	OnabotulinumtoxinA 50 U
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Reporting group description:

OnabotulinumtoxinA 50 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.

Reporting group title	OnabotulinumtoxinA 200 U
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Reporting group description:

OnabotulinumtoxinA 200 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.

Reporting group title	OnabotulinumtoxinA 100 U
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Reporting group description:

OnabotulinumtoxinA 100 U (not to exceed 6U/kg) injected into the detrusor wall on Day 1.

Serious adverse events	OnabotulinumtoxinA 50 U	OnabotulinumtoxinA 200 U	OnabotulinumtoxinA 100 U
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 38 (10.53%)	2 / 30 (6.67%)	3 / 45 (6.67%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Injury, poisoning and procedural complications			
Arteriovenous fistula thrombosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 45 (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
Vascular disorders			
Hypertension			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	0 / 45 (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
Nervous system disorders			

Hydrocephalus			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	2 / 38 (5.26%)	0 / 30 (0.00%)	2 / 45 (4.44%)
occurrences causally related to treatment / all	0 / 3	0 / 0	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cystitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 45 (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
Postoperative wound infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	0 / 45 (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
Encephalitis viral			
subjects affected / exposed	0 / 38 (0.00%)	0 / 30 (0.00%)	1 / 45 (2.22%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epididymitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	0 / 45 (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
Orchitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	0 / 45 (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

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

Non-serious adverse events	OnabotulinumtoxinA 50 U	OnabotulinumtoxinA 200 U	OnabotulinumtoxinA 100 U
Total subjects affected by non-serious adverse events			
subjects affected / exposed	27 / 38 (71.05%)	23 / 30 (76.67%)	33 / 45 (73.33%)
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	0 / 38 (0.00%)	2 / 30 (6.67%)	1 / 45 (2.22%)
occurrences (all)	0	2	1
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 38 (2.63%)	2 / 30 (6.67%)	7 / 45 (15.56%)
occurrences (all)	1	4	14
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 30 (0.00%)	4 / 45 (8.89%)
occurrences (all)	2	0	10
Suprapubic pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 30 (3.33%)	0 / 45 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	1 / 38 (2.63%)	2 / 30 (6.67%)	3 / 45 (6.67%)
occurrences (all)	2	2	8
Abdominal pain			
subjects affected / exposed	2 / 38 (5.26%)	1 / 30 (3.33%)	1 / 45 (2.22%)
occurrences (all)	2	2	1
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)	0 / 30 (0.00%)	3 / 45 (6.67%)
occurrences (all)	3	0	3
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 38 (5.26%)	0 / 30 (0.00%)	1 / 45 (2.22%)
occurrences (all)	3	0	1
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	2 / 38 (5.26%)	1 / 30 (3.33%)	1 / 45 (2.22%)
occurrences (all)	2	1	1

Renal and urinary disorders			
Leukocyturia			
subjects affected / exposed	1 / 38 (2.63%)	4 / 30 (13.33%)	3 / 45 (6.67%)
occurrences (all)	2	5	3
Hydronephrosis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 30 (0.00%)	1 / 45 (2.22%)
occurrences (all)	2	0	1
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	9 / 38 (23.68%)	7 / 30 (23.33%)	13 / 45 (28.89%)
occurrences (all)	11	9	21
Bacteriuria			
subjects affected / exposed	6 / 38 (15.79%)	6 / 30 (20.00%)	7 / 45 (15.56%)
occurrences (all)	11	11	12
Pharyngitis			
subjects affected / exposed	3 / 38 (7.89%)	0 / 30 (0.00%)	3 / 45 (6.67%)
occurrences (all)	3	0	3
Gastroenteritis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 30 (3.33%)	3 / 45 (6.67%)
occurrences (all)	3	1	3
Nasopharyngitis			
subjects affected / exposed	0 / 38 (0.00%)	4 / 30 (13.33%)	1 / 45 (2.22%)
occurrences (all)	0	4	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 30 (3.33%)	3 / 45 (6.67%)
occurrences (all)	0	1	4
Sinusitis			
subjects affected / exposed	2 / 38 (5.26%)	1 / 30 (3.33%)	0 / 45 (0.00%)
occurrences (all)	2	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 October 2013	The following changes were implemented with Amendment 1: Provided clarifications and guidance to investigators regarding entry criteria, study procedures and concomitant medications/procedures. In addition, the following procedures were added to the protocol: Collection of an immunogenicity sample at week 12, measurement of bladder wall thickness by ultrasound at the screening visit, an addition of renal function assessment (eGFR) volume at first IDC to be measured and recorded during urodynamics.
14 April 2016	The following changes were implemented with Amendment 2: Changed the minimum age to 5 years old from 8 years old and to include dosing information for a younger participant population. The FDA requested that, Allergan document the 'opinion of the investigator' that was used to justify treatment of UTI by each investigator. In addition, the investigator was required to describe the criteria used for qualifying 'leukocyturia' as an AE.
27 September 2017	The following changes were implemented with Amendment 3: The proposed sample size was reduced from N=132 to N=102 due to enrollment challenges.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported