Clinical trial results:
Alternative Treatments of Adult female Urinary Tract Infection: a double blind, placebo controlled,factorial randomised trial of Uva ursi and open pragmatic trial of ibuprofen.

Summary

EudraCT number	2013-003327-11
Trial protocol	GB
Global end of trial date	21 January 2017

Results information

Result version number	v1 (current)
This version publication date	03 February 2018
First version publication date	03 February 2018

Trial information

Trial identification

Sponsor protocol code	3623

Additional study identifiers

ISRCTN number	ISRCTN43397016
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Southampton
Sponsor organisation address	University Road, Southampton, United Kingdom, SO17 1BJ
Public contact	Catherine Simpson, University of Southampton, 0044 2381205154, ctu@soton.ac.uk
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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	31 May 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	21 January 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate whether Uva ursi compared to placebo or the advice to take ibuprofen compared to no advice provide relief from urinary symptoms in adult women with suspected UTI.

Protection of trial subjects:

Women prepared to accept a delayed antibiotic prescription for their symptoms and who meet the eligibility criteria will be consented for randomisation. All participants will be issued a prescription for delayed antibiotics. This prescription will be used if symptoms worsen or after three to five days if symptoms are not improving (most symptoms should have settled by this time).

EXCLUSION CRITERIA
Known or suspected pregnancy or breast feeding. In women of child bearing age a urine pregnancy test will usually be performed unless not indicated (for instance prior hysterectomy)
Known immunodeficiency state, long term corticosteroids therapy or chemotherapy
Diabetes
Has any of the following (A – F) known contra-indications or cautions to ibuprofen and any as listed in the current SmPC detailed in Appendix 3:
A. Asthmatics sensitive to NSAIDS/ ibuprofen or aspirin
B. Severe heart failure and uncontrolled hypertension
C. Active gastro-intestinal ulceration or bleeding
D. Crohn’s disease or ulcerative colitis
E. Documented poor renal function
F. Chronic kidney disease (Grade 3 – 5)
Currently or within 7 days taken antibiotics
Using a NSAID or Uva ursi preparation and unwilling or unable to discontinue for the study period
Suspected upper urinary tract infection (back pain, fever>38C, systemic illness)
Women for whom immediate antibiotics are otherwise indicated - frequent recurrent infection: >3 UTI episodes in past 12 months
Defect of the blood clotting system
Bladder surgery including cystoscopy in the last four weeks.
Currently taking warfarin
Recruited to another interventional trial in the previous 6 weeks

Background therapy:

None

Evidence for comparator:

to be added

Actual start date of recruitment	03 August 2015
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 382
Worldwide total number of subjects	382
EEA total number of subjects	382

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)	337
From 65 to 84 years	45
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult women (18-70) presenting to primary care, with suspected lower urinary tract infection (suspected by GP or nurse practitioner). Subjects were recruited between August 2015 and November 2016 in GP surgeries in England.

Pre-assignment

Screening details:

Adult women with suspected lower urinary infection will be recruited in primary care, GP surgeries, walk-in centres and Out of Hours, by general practitioners or experienced practice nurses. Women prepared to accept a delayed antibiotic prescription for their symptoms and who meet the eligibility criteria will be consented for randomisation.

Pre-assignment period milestones

Number of subjects started	627[1]
Number of subjects completed	382

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Declined to participate: 43
Reason: Number of subjects	Ineligible: 137
Reason: Number of subjects	Not enough time: 36
Reason: Number of subjects	Other reasons: 29

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: 627 subjects were actively screened and for the reasons presented in the table below, 245 did not complete the pre-assignment period.

Period 1

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

Blinding implementation details:

In order to maintain blinding the placebo was approximately matched in colour and flavouring.

Arms

Are arms mutually exclusive?	Yes
Arm title	Group 1

Arm description:

Herb Uva ursi 1200mg three times a day and advice to take ibuprofen 400mg three times a day.

Arm type	Experimental
Investigational medicinal product name	Uva ursi
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Herb Uva ursi 1200mg three times a day and advice to take ibuprofen 400mg three times a day.

Arm title	Group 2

Arm description:	
Herb Uva ursi placebo three times a day and advice to take ibuprofen 400mg three times a day.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Group 3
Arm description:	
Herb Uva ursi 1200mg three times a day and no advice to take ibuprofen.	
Arm type	Experimental
Investigational medicinal product name	Uva ursi
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details:	
Herb Uva ursi 1200mg three times a day and no advice to take ibuprofen.	
Arm title	Group 4
Arm description:	
Herb Uva ursi placebo three times a day and no advice to take ibuprofen.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Number of subjects in period 1	Group 1	Group 2	Group 3
Started	102	86	97
Completed	98	80	95
Not completed	4	6	2
Subject left the UK	-	-	1
Consent withdrawn by subject	3	4	1
Lost to follow-up	1	-	-
Protocol deviation	-	2	-

Number of subjects in period 1	Group 4
Started	97
Completed	96
Not completed	1
Subject left the UK	-
Consent withdrawn by subject	1
Lost to follow-up	-
Protocol deviation	-

Baseline characteristics

Reporting groups	
Reporting group title	Group 1
Reporting group description:	
Herb Uva ursi 1200mg three times a day and advice to take ibuprofen 400mg three times a day.	
Reporting group title	Group 2
Reporting group description:	
Herb Uva ursi placebo three times a day and advice to take ibuprofen 400mg three times a day.	
Reporting group title	Group 3
Reporting group description:	
Herb Uva ursi 1200mg three times a day and no advice to take ibuprofen.	
Reporting group title	Group 4
Reporting group description:	
Herb Uva ursi placebo three times a day and no advice to take ibuprofen.	

Reporting group values	Group 1	Group 2	Group 3
Number of subjects	102	86	97
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Calculated using the date of consent and the month and year of birth (assuming 1st day of the month).			
Units: years arithmetic mean standard deviation	 45.5 ± 15.16	 39.9 ± 15.48	 44.6 ± 16.10
Gender categorical Units: Subjects			
Female Male	102 0	86 0	97 0
Midstream specimen of urine (MSU) result			
Midstream specimen of urine (MSU) result at baseline.			
Units: Subjects			
Infection No infection Missing	19 60 23	26 43 17	23 44 30
Indicator of any ‘moderately bad’ or worse symptoms			
Indicator of any ‘moderately bad’ or worse symptoms (score of 3 or higher in any of the symptoms) at			

baseline .			
Units: Subjects			
Yes	84	76	84
No	18	10	13
Temperature			
Patients's temperature at baseline.			
Units: celsius temperature			
arithmetic mean	36.7	36.7	36.7
standard deviation	± 0.45	± 0.50	± 0.42
Mean frequency symptom severity score			
This is defined as the mean severity score at baseline for all of the frequency symptoms (burning, urgency, day time frequency and night time frequency).			
Units: 0-6			
arithmetic mean	2.5	2.6	2.4
standard deviation	± 1.23	± 1.14	± 1.13

Reporting group values	Group 4	Total	
Number of subjects	97	382	
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			
Calculated using the date of consent and the month and year of birth (assuming 1st day of the month).			
Units: years			
arithmetic mean	44.8		
standard deviation	± 14.29	-	
Gender categorical			
Units: Subjects			
Female	97	382	
Male	0	0	
Midstream specimen of urine (MSU) result			
Midstream specimen of urine (MSU) result at baseline.			
Units: Subjects			
Infection	24	92	
No infection	50	197	
Missing	23	93	
Indicator of any ‘moderately bad’ or worse symptoms			
Indicator of any ‘moderately bad’ or worse symptoms (score of 3 or higher in any of the symptoms) at baseline .			
Units: Subjects			
Yes	80	324	

No	17	58	

Temperature			
Patients's temperature at baseline.			
Units: celsius temperature			
arithmetic mean	36.8		
standard deviation	± 0.41	-	
Mean frequency symptom severity score			
This is defined as the mean severity score at baseline for all of the frequency symptoms (burning, urgency, day time frequency and night time frequency).			
Units: 0-6			
arithmetic mean	2.4		
standard deviation	± 1.11	-	

End points

End points reporting groups

Reporting group title	Group 1

Reporting group description:

Herb Uva ursi 1200mg three times a day and advice to take ibuprofen 400mg three times a day.

Reporting group title	Group 2

Reporting group description:

Herb Uva ursi placebo three times a day and advice to take ibuprofen 400mg three times a day.

Reporting group title	Group 3

Reporting group description:

Herb Uva ursi 1200mg three times a day and no advice to take ibuprofen.

Reporting group title	Group 4

Reporting group description:

Herb Uva ursi placebo three times a day and no advice to take ibuprofen.

Subject analysis set title	ITT frequency imputed population B (Uva ursi group)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were randomised regardless of treatment received, took Uva Ursi (Group 1+3), and their mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4 was imputed using multiple imputation, if missing.

Subject analysis set title	ITT frequency imputed population B (Uva ursi placebo group)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were randomised regardless of treatment received, took Uva Ursi placebo (Group 2+4), and their mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4 was imputed using multiple imputation, if missing.

Subject analysis set title	ITT frequency imputed population B (Ibuprofen group)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were randomised regardless of treatment received, were advised to take ibuprofen (Group 1+2), and their mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4 was imputed using multiple imputation, if missing.

Subject analysis set title	ITT frequency imputed population B (No ibuprofen group)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were randomised regardless of treatment received, were not advised to take ibuprofen (Group 3+4), and their mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4 was imputed using multiple imputation, if missing.

Subject analysis set title	Per-Protocol population E (Uva ursi group)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol population E is formed of the Intention To Treat (ITT) population (all patients that were randomised regardless of treatment received), but excluding the following patients:
Patients who were randomised in treatment groups 1 or 2 and were not recorded as having at least ‘3’ doses of ibuprofen on days 1, 2 and 3, or patients who were randomised in treatment groups 3 or 4 and were recorded as having any use of ibuprofen.

This subject analysis set includes patients who took Uva ursi (Group 1+3) and belong to the per-protocol population E.

Subject analysis set title	Per-Protocol population E (Uva ursi placebo group)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol population E is formed of the Intention To Treat (ITT) population (all patients that were

randomised regardless of treatment received), but excluding the following patients:
Patients who were randomised in treatment groups 1 or 2 and were not recorded as having at least '3' doses of ibuprofen on days 1, 2 and 3, or patients who were randomised in treatment groups 3 or 4 and were recorded as having any use of ibuprofen.

This subject analysis set includes patients who took Uva ursi placebo (Group 2+4) and belong to the per-protocol population E.

Subject analysis set title	Per-Protocol population E (Ibuprofen group)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol population E is formed of the Intention To Treat (ITT) population (all patients that were randomised regardless of treatment received), but excluding the following patients:
Patients who were randomised in treatment groups 1 or 2 and were not recorded as having at least '3' doses of ibuprofen on days 1, 2 and 3, or patients who were randomised in treatment groups 3 or 4 and were recorded as having any use of ibuprofen.

This subject analysis set includes patients who were advised to take ibuprofen (Group 1+2) and belong to the per-protocol population E.

Subject analysis set title	Per-Protocol population E (No ibuprofen group)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol population E is formed of the Intention To Treat (ITT) population (all patients that were randomised regardless of treatment received), but excluding the following patients:
Patients who were randomised in treatment groups 1 or 2 and were not recorded as having at least '3' doses of ibuprofen on days 1, 2 and 3, or patients who were randomised in treatment groups 3 or 4 and were recorded as having any use of ibuprofen.

This subject analysis set includes patients who were not advised to take ibuprofen (Group 3+4) and belong to the per-protocol population E.

Subject analysis set title	Per-Protocol population F (Uva ursi group)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol population F is formed of the Intention To Treat (ITT) population (all patients that were randomised regardless of treatment received), but excluding the following patients:
Patients who were not recorded as having at least '3' doses of Uva ursi on days 1, 2 and 3.

This subject analysis set includes patients who took Uva ursi (Group 1+3) and belong to the per-protocol population F.

Subject analysis set title	Per-Protocol population F (Uva ursi placebo group)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol population F is formed of the Intention To Treat (ITT) population (all patients that were randomised regardless of treatment received), but excluding the following patients:
Patients who were not recorded as having at least '3' doses of Uva ursi on days 1, 2 and 3.

This subject analysis set includes patients who took Uva ursi placebo (Group 2+4) and belong to the per-protocol population F.

Subject analysis set title	Per-Protocol population F (Ibuprofen group)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol population F is formed of the Intention To Treat (ITT) population (all patients that were randomised regardless of treatment received), but excluding the following patients:
Patients who were not recorded as having at least '3' doses of Uva ursi on days 1, 2 and 3.

This subject analysis set includes patients who were advised to take ibuprofen (Group 1+2) and belong to the per-protocol population F.

Subject analysis set title	Per-Protocol population F (No ibuprofen group)
Subject analysis set type	Per protocol

Subject analysis set description:

Per-Protocol population F is formed of the Intention To Treat (ITT) population (all patients that were randomised regardless of treatment received), but excluding the following patients:
Patients who were not recorded as having at least '3' doses of Uva ursi on days 1, 2 and 3.

This subject analysis set includes patients who were not advised to take ibuprofen (Group 3+4) and belong to the per-protocol population F.

Subject analysis set title	ITT population A (Uva ursi group)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were randomised regardless of treatment received and took Uva Ursi (Group 1+3).

Subject analysis set title	ITT population A (Uva ursi placebo group)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were randomised regardless of treatment received and took Uva Ursi placebo (Group 2+4).

Subject analysis set title	ITT population A (Ibuprofen group)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were randomised regardless of treatment received and were advised to take Ibuprofen (Group 1+2).

Subject analysis set title	ITT population A (No ibuprofen group)
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who were randomised regardless of treatment received and were not advised to take Ibuprofen (Group 3+4).

Primary: Frequency symptom severity on days 2-4 (ITT frequency imputed population B - Uva ursi comparison)

End point title	Frequency symptom severity on days 2-4 (ITT frequency imputed population B - Uva ursi comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the intention to treat population with imputed frequency symptom severity scores on days 2-4 using multiple imputation.

Main comparison: Uva ursi versus Uva ursi placebo.

End point type	Primary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	ITT frequency imputed population B (Uva ursi group)	ITT frequency imputed population B (Uva ursi placebo group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	183		
Units: 0-6				
number (not applicable)	199	183		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age.

Comparison groups	ITT frequency imputed population B (Uva ursi group) v ITT frequency imputed population B (Uva ursi placebo group)
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.661
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	-0.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.21

Primary: Frequency symptom severity on days 2-4 (ITT frequency imputed population B - Ibuprofen comparison)

End point title	Frequency symptom severity on days 2-4 (ITT frequency imputed population B - Ibuprofen comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the intention to treat population with imputed frequency symptom severity scores on days 2-4 using multiple imputation.

Main comparison: Advice to take ibuprofen versus no advice to take ibuprofen.

End point type	Primary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	ITT frequency imputed population B (Ibuprofen group)	ITT frequency imputed population B (No ibuprofen group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	188	194		
Units: 0-6				
number (not applicable)	188	194		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age.

Comparison groups	ITT frequency imputed population B (Ibuprofen group) v ITT frequency imputed population B (No ibuprofen group)
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.951
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	-0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.26

Secondary: Frequency symptom severity on days 2-4 (Per-Protocol population E - Uva ursi comparison)

End point title	Frequency symptom severity on days 2-4 (Per-Protocol population E - Uva ursi comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the per-protocol ibuprofen related population E.

Main comparison: Uva ursi versus Uva ursi placebo.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	Per-Protocol population E (Uva ursi group)	Per-Protocol population E (Uva ursi placebo group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	91	80		
Units: 0-6				
arithmetic mean (standard deviation)	1.8 (± 1.20)	1.8 (± 1.14)		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age.

Comparison groups	Per-Protocol population E (Uva ursi group) v Per-Protocol

	population E (Uva ursi placebo group)
Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.805
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.36

Secondary: Frequency symptom severity on days 2-4 (Per-Protocol population E - Ibuprofen comparison)

End point title	Frequency symptom severity on days 2-4 (Per-Protocol population E - Ibuprofen comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the per-protocol ibuprofen related population E.

Main comparison: Advice to take ibuprofen versus no advice to take ibuprofen.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	Per-Protocol population E (Ibuprofen group)	Per-Protocol population E (No ibuprofen group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	115		
Units: 0-6				
arithmetic mean (standard deviation)	1.8 (± 1.24)	1.8 (± 1.14)		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age.

Comparison groups	Per-Protocol population E (Ibuprofen group) v Per-Protocol population E (No ibuprofen group)

Number of subjects included in analysis	171
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.69
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	0.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.27
upper limit	0.41

Secondary: Frequency symptom severity on days 2-4 (Per-Protocol population F - Uva ursi comparison)

End point title	Frequency symptom severity on days 2-4 (Per-Protocol population F - Uva ursi comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the per-protocol uva ursi related population F.

Main comparison: Uva ursi versus uva ursi placebo.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	Per-Protocol population F (Uva ursi group)	Per-Protocol population F (Uva ursi placebo group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	100		
Units: 0-6				
arithmetic mean (standard deviation)	1.7 (± 1.05)	1.8 (± 1.17)		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age.

Comparison groups	Per-Protocol population F (Uva ursi group) v Per-Protocol population F (Uva ursi placebo group)

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.407
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	-0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.4
upper limit	0.16

Secondary: Frequency symptom severity on days 2-4 (Per-Protocol population F - Ibuprofen comparison)

End point title	Frequency symptom severity on days 2-4 (Per-Protocol population F - Ibuprofen comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the per-protocol uva ursi related population F.

Main comparison: Advice to take ibuprofen versus no advice to take ibuprofen.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	Per-Protocol population F (Ibuprofen group)	Per-Protocol population F (No ibuprofen group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	98	111		
Units: 0-6				
arithmetic mean (standard deviation)	1.7 (± 1.17)	1.7 (± 1.06)		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age.

Comparison groups	Per-Protocol population F (Ibuprofen group) v Per-Protocol population F (No ibuprofen group)

Number of subjects included in analysis	209
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.73
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	-0.05
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.34
upper limit	0.24

Secondary: Antibiotic use during week 1 and week 2 (ITT population A - Uva ursi comparison)

End point title	Antibiotic use during week 1 and week 2 (ITT population A - Uva ursi comparison)

End point description:

Indicator of use of antibiotics as recorded in the symptom diary during weeks 1-2.

End point type	Secondary

End point timeframe:

Across days 1-14 after the start of the treatment (day 1 represents the start of the treatment).

End point values	ITT population A (Uva ursi group)	ITT population A (Uva ursi placebo group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	143	133		
Units: 0/1	143	133		

Statistical analyses

Statistical analysis title	Logistic regression

Statistical analysis description:

Logistic regression model on the antibiotic use during week 1 and week 2 adjusting for age (Uva ursi comparison).

Comparison groups	ITT population A (Uva ursi group) v ITT population A (Uva ursi placebo group)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.293
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.59

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.22
upper limit	1.58

Secondary: Antibiotic use during week 1 and week 2 (ITT population A - Ibuprofen comparison)

End point title	Antibiotic use during week 1 and week 2 (ITT population A - Ibuprofen comparison)

End point description:

Indicator of use of antibiotics as recorded in the symptom diary during weeks 1-2.

End point type	Secondary

End point timeframe:

Across days 1-14 after the start of treatment (day 1 represents the start of the treatment).

End point values	ITT population A (Ibuprofen group)	ITT population A (No ibuprofen group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	129	147		
Units: 0/1	129	147		

Statistical analyses

Statistical analysis title	Logistic regression

Statistical analysis description:

Logistic regression model on the antibiotic use during week 1 and week 2 adjusting for age (Ibuprofen comparison).

Comparison groups	ITT population A (Ibuprofen group) v ITT population A (No ibuprofen group)
Number of subjects included in analysis	276
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.009
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.27
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.1
upper limit	0.72

Secondary: Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (ITT frequency imputed population B - Uva ursi comparison)

End point title	Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (ITT frequency imputed population B - Uva ursi comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the intention to treat population with imputed frequency symptom severity scores on days 2-4 using multiple imputation, adjusting for antibiotic use up to day 4 after the start of the treatment.

Main comparison: Uva ursi versus Uva ursi placebo.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	ITT frequency imputed population B (Uva ursi group)	ITT frequency imputed population B (Uva ursi placebo group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	199	183		
Units: 0-6				
number (not applicable)	199	183		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age + indicator of use of antibiotics up to day 4 after the start of the treatment (day 1 represents the start of the treatment).

Comparison groups	ITT frequency imputed population B (Uva ursi placebo group) v ITT frequency imputed population B (Uva ursi group)
Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.704
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	-0.05

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.32
upper limit	0.21

Secondary: Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (ITT frequency imputed population B - Ibuprofen comparison)

End point title	Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (ITT frequency imputed population B - Ibuprofen comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the intention to treat population with imputed frequency symptom severity scores on days 2-4 using multiple imputation, adjusting for antibiotic use up to day 4 after the start of the treatment.

Main comparison: Advice to take ibuprofen versus No advice to take ibuprofen.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	ITT frequency imputed population B (Ibuprofen group)	ITT frequency imputed population B (No ibuprofen group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	188	194		
Units: 0-6				
number (not applicable)	188	194		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age + indicator of use of antibiotics up to day 4 after the start of the treatment (day 1 represents the start of the treatment).

Comparison groups	ITT frequency imputed population B (Ibuprofen group) v ITT frequency imputed population B (No ibuprofen group)

Number of subjects included in analysis	382
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.791
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.24
upper limit	0.31

Secondary: Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (Per-Protocol population E - Uva ursi comparison)

End point title	Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (Per-Protocol population E - Uva ursi comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the per-protocol ibuprofen related population E, adjusting for antibiotic use up to day 4 after the start of the treatment.

Main comparison: Uva ursi versus Uva ursi placebo.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	Per-Protocol population E (Uva ursi group)	Per-Protocol population E (Uva ursi placebo group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	86	75		
Units: 0-6				
number (not applicable)	86	75		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age + indicator of use of antibiotics up to day 4 after the start of the treatment (day 1 represents the start of the treatment).

Comparison groups	Per-Protocol population E (Uva ursi group) v Per-Protocol population E (Uva ursi placebo group)

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.819
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	0.04
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.28
upper limit	0.36

Secondary: Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (Per-Protocol population E - Ibuprofen comparison)

End point title	Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (Per-Protocol population E - Ibuprofen comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the per-protocol ibuprofen related population E, adjusting for antibiotic use up to day 4 after the start of the treatment.

Main comparison: Advice to take ibuprofen versus No advice to take ibuprofen.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	Per-Protocol population E (Ibuprofen group)	Per-Protocol population E (No ibuprofen group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	56	105		
Units: 0-6				
number (not applicable)	56	105		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age + indicator of use of antibiotics up to day 4 after the start of the treatment (day 1 represents the start of the treatment).

Comparison groups	Per-Protocol population E (Ibuprofen group) v Per-Protocol population E (No ibuprofen group)

Number of subjects included in analysis	161
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.486
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	0.12
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.22
upper limit	0.47

Secondary: Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (Per-Protocol population F - Uva ursi comparison)

End point title	Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (Per-Protocol population F - Uva ursi comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the per-protocol uva ursi related population F, adjusting for antibiotic use up to day 4 after the start of the treatment.

Main comparison: Uva ursi versus uva ursi placebo.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	Per-Protocol population F (Uva ursi group)	Per-Protocol population F (Uva ursi placebo group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	105	97		
Units: 0-6				
number (not applicable)	105	97		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age + indicator of use of antibiotics up to day 4 after the start of the treatment (day 1 represents the start of the treatment).

Comparison groups	Per-Protocol population F (Uva ursi group) v Per-Protocol population F (Uva ursi placebo group)

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.559
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	-0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.36
upper limit	0.2

Secondary: Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (Per-Protocol population F - Ibuprofen comparison)

End point title	Frequency symptom severity on days 2-4 adjusting for antibiotic use up to day 4 (Per-Protocol population F - Ibuprofen comparison)

End point description:

Mean frequency symptom (burning, urgency, day time frequency and night time frequency) severity score on days 2-4, for the per-protocol uva ursi related population F, adjusting for antibiotic use up to day 4 after the start of the treatment.

Main comparison: Advice to take ibuprofen versus No advice to take ibuprofen.

End point type	Secondary

End point timeframe:

Across days 2-4 after the start of the treatment (day 1 represents the start of the treatment).

End point values	Per-Protocol population F (Ibuprofen group)	Per-Protocol population F (No ibuprofen group)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	97	105		
Units: 0-6				
number (not applicable)	97	105		

Statistical analyses

Statistical analysis title	Analysis of covariance

Statistical analysis description:

ANCOVA model: Mean frequency symptom severity score on days 2-4 = intercept + uva ursi treatment group + ibuprofen treatment group + mean frequency symptom severity score at baseline + age + indicator of use of antibiotics up to day 4 after the start of the treatment (day 1 represents the start of the treatment).

Comparison groups	Per-Protocol population F (No ibuprofen group) v Per-Protocol population F (Ibuprofen group)

Number of subjects included in analysis	202
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.878
Method	ANCOVA
Parameter estimate	Least squares means difference
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.31

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All adverse events, for patients randomised into the trial, should be reported from the time the patient signs the informed consent form until four weeks after randomisation.

Adverse event reporting additional description:

Adverse events presenting to the participants GP will be notified by the practitioner.
In addition participants will carry a study card which highlights the need to notify their own doctor regarding adverse events. As a final check all participants will be asked to consent to a medical notes review which will take place three months after study re

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Group 1: Uva ursi + Advice to take ibuprofen
Reporting group description: -	
Reporting group title	Group 2: Uva ursi placebo + Advice to take ibuprofen
Reporting group description: -	
Reporting group title	Group 3: Uva ursi + No advice to take ibuprofen
Reporting group description: -	
Reporting group title	Group 4: Uva ursi placebo + No advice to take ibuprofen

Reporting group description: -

Serious adverse events	Group 1: Uva ursi + Advice to take ibuprofen	Group 2: Uva ursi placebo + Advice to take ibuprofen	Group 3: Uva ursi + No advice to take ibuprofen
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	1 / 97 (1.03%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Right iliac fossa pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	0 / 97 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	1 / 97 (1.03%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Group 4: Uva ursi placebo + No advice to take ibuprofen		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 97 (1.03%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events			
General disorders and administration site conditions			
Right iliac fossa pain			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences causally related to treatment / all	0 / 0		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Group 1: Uva ursi + Advice to take ibuprofen	Group 2: Uva ursi placebo + Advice to take ibuprofen	Group 3: Uva ursi + No advice to take ibuprofen
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 102 (0.98%)	1 / 86 (1.16%)	2 / 97 (2.06%)
General disorders and administration site conditions			
Right iliac fossa pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			
Abdominal pains and epigastric pains			
subjects affected / exposed	1 / 102 (0.98%)	0 / 86 (0.00%)	0 / 97 (0.00%)
occurrences (all)	1	0	0
Skin and subcutaneous tissue disorders			
Dry, cracked skin on both hands			
subjects affected / exposed	0 / 102 (0.00%)	1 / 86 (1.16%)	0 / 97 (0.00%)
occurrences (all)	0	1	0
Rash			

subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Itchy rash to torso and limbs			
subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Pelvic pain			
subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	1 / 97 (1.03%)
occurrences (all)	0	0	1
Thrush			
subjects affected / exposed	0 / 102 (0.00%)	0 / 86 (0.00%)	0 / 97 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	Group 4: Uva ursi placebo + No advice to take ibuprofen		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 97 (3.09%)		
General disorders and administration site conditions			
Right iliac fossa pain			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal pains and epigastric pains			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences (all)	0		
Skin and subcutaneous tissue disorders			
Dry, cracked skin on both hands			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences (all)	0		
Rash			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences (all)	0		
Itchy rash to torso and limbs			

subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Pelvic pain			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		
Infections and infestations			
Abdominal wall abscess			
subjects affected / exposed	0 / 97 (0.00%)		
occurrences (all)	0		
Thrush			
subjects affected / exposed	1 / 97 (1.03%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2015	Protocol updated (v2) - Informed Consent Forms for the Main Trial amended to include consent to have a pregnancy test if required and to provide a urine sample for microbial culture. - Patient Information Sheets for the Main Trial amended to clarify how participant contact details will be securely stored. - Trial Participant Treatment Card amended to include telephone number for the Southampton Clinical Trials Unit. - Qualitative Research GP Invitation Letter – this is a new document. - Symptom Diary by Recall – this is a new document. - Symptom Diary by Recall Guidelines – this is a new document.
24 April 2015	Protocol updated (v3) - Modified trial design replacing ibuprofen/placebo with 'advice to take ibuprofen/no advice'. This resulted in changes to the trial titles (full and simplified); primary and secondary objectives; the method of statistical analysis and sample size. - Patient Pack Instruction Cards have been designed to be included in the patient packs to instruct the clinician to advise the participant to take ibuprofen or to give no recommendation. - The IMP labels have been amended in line with the new trial design. - The Investigator Brochure for Uva ursi has been changed to remove all reference to ibuprofen and NuPharm laboratories and to document that Essential Nutrition will be responsible for packaging, labelling and distribution of the Patient Packs. - The IMPDs for Uva ursi and placebo have been updated to include the 6 and 9 month stability data and the proposed shelf life for Uva ursi capsules is 21 months based on the 9 month real-time stability data. - The protocol and study documents have been amended in line with the new trial design and all references to ibuprofen have been removed from patient facing documents. Amended study documents include: ICFs (4), PISs (4), GP notification letter, Trial Participant Treatment Card, Clinic Poster, Qualitative Research Invitation Letters (2), Participant Diary. - The participant focus group discussions have been removed. - The recording of AR/AEs restricted to those judged to be possibly related to the study - medical areas/symptoms specified. - Participant Urine Collection Instruction Sheet - this is a new document. - Some minor changes to the text of the protocol and trial documents for clarification purposes or to correct typographical and grammatical errors. New logos for SCTU and the trial added where appropriate. - Changes to the DMEC membership.

24 March 2016	Protocol updated (v4) - Version 3 of the protocol stated incorrectly in the Trial Synopsis that Uva ursi should be taken 4 times a day instead of 3 times a day. In the main body of the protocol the dosage regimen is specified correctly. This was a typographical error but as the Trial Synopsis is the first point of reference to the IMP in the protocol it was considered a significant error. - Patient Information Sheet for the Main Trial amended to a) clarify why a pregnancy test is being carried out. b) include that if participant falls pregnant whilst taking the IMP they will need to be followed up by their GP until the outcome of their pregnancy is known c) correct grammatical error - Uva Ursi changed to Uva ursi through out - Patient Information Sheet for the Main Trial + Day 4 Urine Collection amended as above for PIS for the Main Trial. - Participant Diary amended by merging the treatment tables on p7 & p9 to collect information more accurately as to when participants took any other treatments. The same data is being collected but in a different format. Some minor changes have been made to the text and order of the diary to correct typographical and grammatical errors or for clarification purposes. - Addition of 5 new sites: NHS West Sussex PCT; NHS Surrey PCT; NHS East Sussex Downs & Welad PCT; NHS Brighton and Hove City PCT; NHS Hastings and Rother PCT - Approval of letters to participants following a serious protocol and GCP breach where formal written consent, as detailed in Section 7.2.1 of the protocol, has not been taken from 18 participants taking part in the Qualitative Interviews.
19 May 2016	Protocol updated (v5) [REJECTED BY MHRA - SEE V6 RESUBMISSION] - IMPDs updated with 18 month stability data to give shelf life of 30 months. - Increased sample size from 328 to 376 and extended recruitment period to 30/09/16. - Protocol amended to clarify that GPs and nurse prescribers (NP) can be interviewed as part of the qualitative research study; to clarify that these interviews can take place over the phone; to specify the number of GP/NPs that will be interviewed and to clarify the consent process for both patient and GP/NP interviews. - PIS updated to include explanation why participants should consult their GP immediately if they develop symptoms of a kidney infection and to clarify that they will be contacted by the research team if after 3 weeks they have not returned their diary or there is key information missing. - Participant Diary amended to explain that participants will receive a £5 voucher when they have returned a fully completed diary. - The list of staff conducting specified research procedures has been extended to include HCAs and CTAs.
28 July 2016	Protocol updated (v6) Resubmission of v5 of the protocol with the following change as requested by the MHRA: - Exclusion criterion "Recruited to another interventional randomised control trial in previous 4 weeks" amended to " Recruited to another interventional trial in previous 6 weeks".

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

None.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28886751