Clinical trial results:
A multicentre, prospective, randomized, double-blind, parallel-group placebo-controlled clinical study for the assessment of the immunomodulatory efficacy, safety and clinical impact after three and six months treatment with a sublingual polyvalent bacterial vaccine (in oral mucosa) in women with recurrent urinary tract infections (rUTIs).

Summary

EudraCT number	2013-001838-17
Trial protocol	ES GB
Global end of trial date	04 November 2020

Results information

Result version number	v1 (current)
This version publication date	11 October 2022
First version publication date	11 October 2022
Summary attachment (see zip file)	Synopsis MV140-SLG-003 (Synopsis CSR Uromune MV140-SLG-003.pdf)

Trial information

Trial identification

Sponsor protocol code	MV140-SLG-003

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02543827
WHO universal trial number (UTN)	-
Other trial identifiers	UROMUNE: MV140

Notes:

Sponsors

Sponsor organisation name	INMUNOTEK
Sponsor organisation address	PUNTO MOBI, 5, ALCALA DE HENARES, Spain, 28805
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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	03 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	04 November 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this study was to determine if immunization with the bacterial vaccine MV140 would reduce the risk of and/or prevent urinary tract infections (UTI) compared to placebo in women with recurrent UTIs.

Protection of trial subjects:

All subjects received the first dose at the hospital in order to teach them the proper administration of the drug, and to observe the patient's first in touch with the immunotherapy.
All adverse events that occured during the course of the study were recorded and assessed. These were thoroughly explored, both during a scheduled control and controls at any time when a subject reported an abnormal occurrence.
Protection of Personal Data and guarantee of digital rights. Regulation (Eu) 2016/679 of the European Parliament and of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation).
To ensure the rights of the subjects, the Main Researcher or collaborating researchers, through the information sheet, the objectives and requirements of the Study, the nature of the study drug and its possible side effects, will be explained to the subject in understandable language for the Subject. The information to be provided includes: a description of the endpoints of the study, the methodology used, the type of treatment, the benefits that the subject may obtain from the treatment as well as the risks they may have and the right to withdraw from study if desired.

Background therapy:

Currently, antibiotics remain the main strategy for the treatment of UTIs. However, there is high incidence of adverse reactions associated with the use of antibiotics. Moreover, multi-resistance of the bacteria to antibiotics is widely increasing, leading that more than 40% of the bacterial strains are resistant to available antibiotics in some regions of the world.
Altogether, it is reasonable to consider other preventive strategies than antibiotics such as those that reinforce the natural mechanisms of pathogen defense, such as immunostimulation or vaccination. A number of studies have shown that the oral administration of bacterial immune stimulants ameliorates RUTIs in adults and children by reducing the number, duration and severity of infectious clinical episodes. Thus, these clinical studies using a bacterial extract, which contains immunostimulatory components extracted from 18 uropathogenic Escherichia coli strains, have been shown to reduce the incidence of recurrent infections of the lower urinary tract in both children and adults.
The sublingual route for administration of bacterial preparations is very safe and effective for stimulating, in a strong and long-lasting way, the antigen-specific mucosa and the systemic humoral and cellular immunity. Stimulation of the oral mucosa may produce effects in distant mucosa, by activating effector mechanisms of innate and acquired immunity through the mucosal associated lymphoid tissue (MALT). The oral cavity (inductive site) contains a high density of antigen-presenting cells, mainly the Langerhans cells, with a high stimulating activity. These cells subsequently migrate to the lymph nodes, where they interact with T and B lymphocytes to induce their differentiation to effector cells. After their activation, the lymphocytes re-circulate through the different compartments of the mucosa-associated lymphoid tissue (MALT), and access different mucous membranes, including the genitourinary tract (effector site). T

Evidence for comparator: -

Actual start date of recruitment	29 September 2015
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	Spain: 200
Country: Number of subjects enrolled	United Kingdom: 40
Worldwide total number of subjects	240
EEA total number of subjects	200

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)	186
From 65 to 84 years	54
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The time of recruitment was between October 2015 (first patient enrolled) and April 2018 (last patient enrolled).

Pre-assignment

Screening details:

This study included subjects (female) with rUTI, classified as non-complicated UTIs. The number os subjects screened were 240. The number of subjects who received treatment (excluded screening failures) were 230. Efficacy evaluable population (Intention-to-treat) were 215 and those who finished were 195.

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, Data analyst

Blinding implementation details:

Neither the investigator nor the subject knew about the treatment provided. The members of the investigator team, the monitoring team and the people responsible for analysing the data did not have access to blinded data either. The Researcher/Pharmacist had a way to break the code due to an emergency.
The code break would only have been carried out in emergencies, in the case the researcher needed to know in order to provide appropriate medical treatment or to ensure the safety of the subjects

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I active treatment for 6 months

Arm description:

Sublingual MV140 treatment at a dose of 300 FTU/mL.
Subjects in Group I received active treatment consisting of a bacterial vaccine sublingually for 6 months (i.e. MV140 6M).

Arm type	Experimental
Investigational medicinal product name	UROMUNE
Investigational medicinal product code	MV140
Other name	
Pharmaceutical forms	Sublingual spray
Routes of administration	Sublingual use

Dosage and administration details:

Sublingual MV140 treatment at a dose of 300 FTU/mL, administered to 80 subjects with recurrent urinary tract infections, daily for 6 months.
The active trial medication was a polyvalent bacterial vaccine; the pharmaceutical form was a glycerinated suspension containing a mixture of four inactivated non-lysated bacterial concentrates (V121 Escherichia coli 25%, V113 Klebsiella pneumoniae 25%, V125 Enterococcus faecalis 25%, V127 Proteus vulgaris 25%) as active substance, at a final concentration of 300 Formazin Turbidity Units (FTU)/mL (equivalent to 10^9 bacteria/mL). As excipients, it contains 0.63 g of glycerol, pineapple artificial flavouring (0.01 mL), sodium chloride (9 mg/mL) and water (q.s. for 1 mL). The trial medication was administered through the sublingual route, applying two sprays daily.

Arm title	Group II placebo for 6 months

Arm description:

Subjects in Group II received placebo sublingually for 6 months

Arm type	Placebo

Investigational medicinal product name	Placebo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Sublingual spray
Routes of administration	Sublingual use

Dosage and administration details:

It contained an identical solution to the test product but no active substance (without the inactivated non-lysate bacterial concentrates), and was administrated through the sublingual route, applying two sprays daily.
The composition was glycerol 0.63 g, pineapple artificial flavouring 0.01 mL, sodium chloride 9 mg/mL and water q.s. for 1 mL.

Arm title	Group III active treatment 3 months + 3 months of placebo

Arm description:

Subjects in Group III received 3 months of active treatment and then 3 months of placebo sublingually (i.e. MV140 3M).

Arm type	Experimental
Investigational medicinal product name	UROMUNE+ Placebo
Investigational medicinal product code	MV140
Other name	Uromune+Placebo
Pharmaceutical forms	Sublingual spray
Routes of administration	Sublingual use

Dosage and administration details:

Active treatment (MV140) daily for 3 months, followed by 3 months of placebo.
The active trial medication was a polyvalent bacterial vaccine; the pharmaceutical form was a glycerinated suspension containing a mixture of four inactivated non-lysated bacterial concentrates (V121 Escherichia coli 25%, V113 Klebsiella pneumoniae 25%, V125 Enterococcus faecalis 25%, V127 Proteus vulgaris 25%) as active substance, at a final concentration of 300 Formazin Turbidity Units (FTU)/mL (equivalent to 10^9 bacteria/mL). As excipients, it contains 0.63 g of glycerol, pineapple artificial flavouring (0.01 mL), sodium chloride (9 mg/mL) and water (q.s. for 1 mL). The trial medication was administered through the sublingual route, applying two sprays daily.

Number of subjects in period 1[1]	Group I active treatment for 6 months	Group II placebo for 6 months	Group III active treatment 3 months + 3 months of placebo
Started	75	78	77
Completed	61	65	67
Not completed	14	13	10
Screening failure	4	1	-
Consent withdrawn by subject	6	5	2
Adverse event, non-fatal	2	1	3
Pregnancy	-	3	2
Other reasons	-	-	1
Lost to follow-up	2	2	-
Adverse reaction	-	1	2

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The number of subjects in the baseline period are considered to be 230, the ones that were finally enrolled in the trial. The worldwide number of subjects enrolled were 240, without screening failures.

Baseline characteristics

Reporting groups	
Reporting group title	Group I active treatment for 6 months
Reporting group description:	
Sublingual MV140 treatment at a dose of 300 FTU/mL. Subjects in Group I received active treatment consisting of a bacterial vaccine sublingually for 6 months (i.e. MV140 6M).	
Reporting group title	Group II placebo for 6 months
Reporting group description:	
Subjects in Group II received placebo sublingually for 6 months	
Reporting group title	Group III active treatment 3 months + 3 months of placebo
Reporting group description:	
Subjects in Group III received 3 months of active treatment and then 3 months of placebo sublingually (i.e. MV140 3M).	

Reporting group values	Group I active treatment for 6 months	Group II placebo for 6 months	Group III active treatment 3 months + 3 months of placebo
Number of subjects	75	78	77
Age categorical			
Individuals aged 18-75 years were enrolled. The median age was 48.0 [interquartile range, IQR, 34.0-61.5], 54.5 [IQR, 38.0-66.0] and 47.0 [34.0-58.0] years for groups receiving placebo and MV140 for 3 or 6 months.			
Units: Subjects			
Adults (18-64 years)	63	60	49
From 65-84 years	12	18	28
Gender categorical			
Women with recurrent urinary infections (rUTIs)			
Units: Subjects			
Female	75	78	77

Reporting group values	Total		
Number of subjects	230		
Age categorical			
Individuals aged 18-75 years were enrolled. The median age was 48.0 [interquartile range, IQR, 34.0-61.5], 54.5 [IQR, 38.0-66.0] and 47.0 [34.0-58.0] years for groups receiving placebo and MV140 for 3 or 6 months.			
Units: Subjects			
Adults (18-64 years)	172		
From 65-84 years	58		
Gender categorical			
Women with recurrent urinary infections (rUTIs)			
Units: Subjects			
Female	230		

Subject analysis sets	
Subject analysis set title	Efficacy Per-protocol population analysis
Subject analysis set type	Per protocol

Subject analysis set description:

Evaluable per-protocol population included randomized subjects who completed the efficacy period of 12 months and adequately complied with the protocol

Subject analysis set title	Efficacy Intention-to-treat population analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The evaluable intention-to-treat population included all randomized subjects who completed week 12 according to the treatment assignment at randomisation.

Reporting group values	Efficacy Per-protocol population analysis	Efficacy Intention-to-treat population analysis	
Number of subjects	193	215	
Age categorical			
Individuals aged 18-75 years were enrolled. The median age was 48.0 [interquartile range, IQR, 34.0-61.5], 54.5 [IQR, 38.0-66.0] and 47.0 [34.0-58.0] years for groups receiving placebo and MV140 for 3 or 6 months.			
Units: Subjects			
Adults (18-64 years)	145	164	
From 65-84 years	48	51	
Gender categorical			
Women with recurrent urinary infections (rUTIs)			
Units: Subjects			
Female	193	215	

End points

End points reporting groups

Reporting group title	Group I active treatment for 6 months
Reporting group description:	
Sublingual MV140 treatment at a dose of 300 FTU/mL. Subjects in Group I received active treatment consisting of a bacterial vaccine sublingually for 6 months (i.e. MV140 6M).	
Reporting group title	Group II placebo for 6 months
Reporting group description:	
Subjects in Group II received placebo sublingually for 6 months	
Reporting group title	Group III active treatment 3 months + 3 months of placebo
Reporting group description:	
Subjects in Group III received 3 months of active treatment and then 3 months of placebo sublingually (i.e. MV140 3M).	
Subject analysis set title	Efficacy Per-protocol population analysis
Subject analysis set type	Per protocol
Subject analysis set description:	
Evaluable per-protocol population included randomized subjects who completed the efficacy period of 12 months and adequately complied with the protocol	
Subject analysis set title	Efficacy Intention-to-treat population analysis
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The evaluable intention-to-treat population included all randomized subjects who completed week 12 according to the treatment assignment at randomisation.	

Primary: Comparison of the number of episodes of UTIs in the 3 study groups in the 9 months study period following 3 months of intervention (placebo or immunization)

End point title	Comparison of the number of episodes of UTIs in the 3 study groups in the 9 months study period following 3 months of intervention (placebo or immunization)
End point description:	
Primary efficacy analysis will be based on the comparison of the average number of episodes of UTIs in the three study groups in the 9 months study period following 3 months of intervention (placebo or immunization).	
End point type	Primary
End point timeframe:	
9 months	

End point values	Group I active treatment for 6 months	Group II placebo for 6 months	Group III active treatment 3 months + 3 months of placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	76	70	
Units: episodes				
median (inter-quartile range (Q1-Q3))				
UTI episodes	0 (0.0 to 1.0)	3 (0.5 to 6.0)	0 (0.0 to 1.0)	

Statistical analyses

Statistical analysis title	Median number of UTI episodes

Statistical analysis description:

According to the normal distribution analyzed, UTI episodes were analyzed by chi-square and Kruskal-Wallis nonparametric tests, respectively, comparing the two treatment groups to the placebo group. Post hoc tests with Bonferroni adjustments were subsequently conducted to evaluate pairwise differences.

Comparison groups	Group I active treatment for 6 months v Group II placebo for 6 months v Group III active treatment 3 months + 3 months of placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Kruskal-wallis
Confidence interval	
level	95 %
sides	2-sided

Secondary: Comparison of the proportion of subjects who remain infection free (no UTIs) in the three study groups in the 9-month study period following 3 months of intervention (placebo or immunization)

End point title	Comparison of the proportion of subjects who remain infection free (no UTIs) in the three study groups in the 9-month study period following 3 months of intervention (placebo or immunization)

End point description:

End point type	Secondary

End point timeframe:

9 months study period following 3 months of intervention (placebo or immunization)

End point values	Group I active treatment for 6 months	Group II placebo for 6 months	Group III active treatment 3 months + 3 months of placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	69	76	70	
Units: subjects				
number (not applicable)				
UTI-free participants	40	19	46	

Statistical analyses

Statistical analysis title	Proportion of UTI-free subjects

Statistical analysis description:

According to the normal distribution analyzed, UTI episodes and UTI-free rates were analyzed by chi-square and Kruskal-Wallis nonparametric tests, respectively, comparing the two treatment groups to the placebo group. Post hoc tests with Bonferroni adjustments were subsequently conducted to evaluate pairwise differences.

Comparison groups	Group I active treatment for 6 months v Group II placebo for 6 months v Group III active treatment 3 months + 3 months of placebo
Number of subjects included in analysis	215
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Kruskal-wallis
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
12 months	
Adverse event reporting additional description:	
Safety was evaluated throughout the study by recording all adverse events and all adverse reactions.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups	
Reporting group title	Group I active treatment for 6 months
Reporting group description:	
Sublingual MV140 treatment at a dose of 300 FTU/mL. Subjects in Group I received active treatment consisting of a bacterial vaccine sublingually for 6 months.	
Reporting group title	Group II placebo for 6 months
Reporting group description:	
Subjects in Group II received placebo sublingually for 6 months	
Reporting group title	Group III active treatment 3 months + 3 months of placebo
Reporting group description:	
Subjects in Group III received 3 months of active treatment and then 3 months of placebo sublingually (i.e. MV140 3M).	

Serious adverse events	Group I active treatment for 6 months	Group II placebo for 6 months	Group III active treatment 3 months + 3 months of placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	4 / 77 (5.19%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Surgical and medical procedures			
Oesophagogastric fundoplasty	Additional description: Surgery for reflux		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric operation			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cytodistension			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastric bleeding			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Hysterectomy			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Kidney infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Group I active treatment for 6 months	Group II placebo for 6 months	Group III active treatment 3 months + 3 months of placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	28 / 75 (37.33%)	39 / 78 (50.00%)	34 / 77 (44.16%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Leiomyoma			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Lipoma	Additional description: Lipoma on the left arm		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Vascular disorders			
Haematoma	Additional description: Haematoma on the left arm		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Surgical and medical procedures			
Metabolic surgery	Additional description: Bariatric surgery		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Cholecystectomy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Foot operation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Parathyroid gland operation	Additional description: Parathyroid adenoma surgery		
alternative assessment type: Systematic			

subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Skin neoplasm excision	Additional description: Removed carcinoma of the left cheek		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Asthenia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	3 / 78 (3.85%)	0 / 77 (0.00%)
occurrences (all)	1	3	0
Pyrexia	Additional description: 1 sobject affected by Febrile syndrome and 1 subject affected by Fever		
alternative assessment type: Systematic			
subjects affected / exposed	2 / 75 (2.67%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Malaise	Additional description: General malaise		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	2 / 77 (2.60%)
occurrences (all)	0	1	2
Swelling	Additional description: Neck lump		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Oedema peripheral	Additional description: Oedema in the lower limbs		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Peripheral swelling	Additional description: Group II: 1 subject affected by swollen foot Group III: 1 subject affected by swollen legs		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
Pain	Additional description: Unknown pain		
alternative assessment type: Systematic			

subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Immune system disorders			
Hypersensitivity	Additional description: Allergic reaction to antibiotic		
subjects affected / exposed	1 / 75 (1.33%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences (all)	1	1	1
Food allergy	Additional description: Food allergic reaction		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Reproductive system and breast disorders			
Atrophic vulvovaginitis	Additional description: Atrophic vagina		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Respiratory, thoracic and mediastinal disorders			
Aphonia			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Cough			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Dyspnoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Lung disorder	Additional description: Pulmonary disease		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Increased viscosity of upper respiratory secretion	Additional description: Thick mucus		
alternative assessment type: Systematic			

subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Psychiatric disorders			
Depression			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
Stress			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Depression suicidal			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Drug abuse			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Investigations			
Barium swallow			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Colonoscopy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Endoscopy			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Weight increased			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Injury, poisoning and procedural complications			

Fibula fracture	Additional description: Broken fibula		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Contusion	Additional description: Contusion in right hip		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Road traffic accident	Additional description: Traffic accident whiplash syndrome		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Injury	Additional description: Trauma from a fall		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Cardiac disorders			
Atrial fibrillation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Palpitations			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Nervous system disorders			
Dizziness			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	3 / 77 (3.90%)
occurrences (all)	0	0	3
Facial paralysis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Headache			

alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Migraine	Additional description: Migraine headaches		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Hypoaesthesia	Additional description: Numbness in neck		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Syncope			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Blood and lymphatic system disorders			
Anaemia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	2 / 78 (2.56%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Neutropenia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Ear and labyrinth disorders			
Tympanic membrane perforation	Additional description: Perforated eardrum		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Vertigo			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Eye disorders			

Eye pruritus	Additional description: Itchy eyes		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Abdominal pain			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 75 (2.67%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences (all)	2	2	1
Constipation			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Diarrhoea			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences (all)	0	1	1
Diverticulum			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Dysphagia			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Abdominal discomfort	Additional description: Gastric discomfort		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Gastrooesophageal reflux disease	Additional description: Group I: 1 subject affected by Gastroesophageal reflux (1 occurrence) Group III: 1 subject affected by Worsening of Gastro-oesophageal reflux/GOR (1 occurrence)		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1

Enterocolitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Haemorrhoids	Additional description: Internal hemorrhoids		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Gastrointestinal pain	Additional description: Intestinal spasm		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Paraesthesia oral	Additional description: Oral paresthesia		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Oral pain			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Toothache			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Vomiting			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	3
Hepatobiliary disorders			
Biliary colic			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	2	0	0
Skin and subcutaneous tissue disorders			

Blister	Additional description: Group III: - 1 subject affected by blister on ears - 1 subject affected by blister on shoulders		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	2 / 77 (2.60%)
occurrences (all)	0	0	2
Acne	Additional description: Chin spots		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Pruritus	Additional description: Itchy mouth and Generalized itching. Group I: 0 subjects affected Group II: 2 subjects affected by itchy mouth (2 occurrences) Group III: 2 subjects affected by itchy mouth (4 occurrences) and 1 by generalized itching (1 occurrence).		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	2 / 78 (2.56%)	3 / 77 (3.90%)
occurrences (all)	0	2	5
Lichen sclerosus			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Skin reaction			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Urticaria			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Renal and urinary disorders			
Hypertonic bladder	Additional description: Overactive bladder		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Renal colic			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	3	0

Trigonitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Endocrine disorders			
Adrenal mass	Additional description: Left kidney nodule		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Thyroid disorder	Additional description: Thyroid		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal and connective tissue disorders			
Back pain			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Intervertebral disc protrusion	Additional description: Cervical hernia		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Flank pain	Additional description: Flank pain		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Arthralgia	Additional description: Gonalgia		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Osteoporosis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Pain in extremity	Additional description: Pain in lower limbs		

alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Mobility decreased	Additional description: Reduced mobility		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Musculoskeletal pain	Additional description: Right shoulder pain		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Candida infection	Additional description: Candidiasis		
subjects affected / exposed	1 / 75 (1.33%)	3 / 78 (3.85%)	4 / 77 (5.19%)
occurrences (all)	1	4	7
Vaginal infection	Additional description: Vaginitis		
subjects affected / exposed	2 / 75 (2.67%)	4 / 78 (5.13%)	3 / 77 (3.90%)
occurrences (all)	2	5	4
Lower respiratory tract infection	Additional description: Chest infection		
subjects affected / exposed	3 / 75 (4.00%)	3 / 78 (3.85%)	2 / 77 (2.60%)
occurrences (all)	3	7	3
Appendicitis	Additional description: Acute appendicitis		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Nasopharyngitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences (all)	0	1	2
Tooth abscess			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Tooth infection	Additional description: Dental root canal infection		
alternative assessment type: Systematic			

subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Gastroenteritis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Gingivitis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	1	1	0
Papilloma viral infection			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Postoperative wound infection	Additional description: Infection surgery points		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Oral infection			
alternative assessment type: Systematic			
subjects affected / exposed	2 / 75 (2.67%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences (all)	3	1	1
Ear infection	Additional description: Otitis		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	1	0	1
Pharyngitis	Additional description: Group I: 1 subject affected by throat infection (1 occurrence) The rest of subjects were affected by pharyngitis		
alternative assessment type: Systematic			
subjects affected / exposed	2 / 75 (2.67%)	3 / 78 (3.85%)	2 / 77 (2.60%)
occurrences (all)	2	3	2
Pneumonia			
alternative assessment type: Systematic			

subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Pyelonephritis			
alternative assessment type: Systematic			
subjects affected / exposed	3 / 75 (4.00%)	1 / 78 (1.28%)	1 / 77 (1.30%)
occurrences (all)	3	3	1
Sinusitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	2 / 78 (2.56%)	0 / 77 (0.00%)
occurrences (all)	0	2	0
Tonsillitis			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	0 / 78 (0.00%)	1 / 77 (1.30%)
occurrences (all)	0	0	1
Urethritis			
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Viral rash	Additional description: Viral exanthem		
alternative assessment type: Systematic			
subjects affected / exposed	1 / 75 (1.33%)	0 / 78 (0.00%)	0 / 77 (0.00%)
occurrences (all)	1	0	0
Pharyngeal abscess			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Groin pain	Additional description: Suprainguinal pain		
alternative assessment type: Systematic			
subjects affected / exposed	0 / 75 (0.00%)	1 / 78 (1.28%)	0 / 77 (0.00%)
occurrences (all)	0	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 January 2014	Three centres were included to complete subject recruitment established in the protocol. The centres would refer subjects to the University Hospital of Salamanca.
01 October 2014	Modification of the study design based on consultation to the Spanish Agency of Medicines and Medical Devices: -Inclusion of a Stage II (12 additional months of follow-up) and associated modifications -Addition of inclusion and exclusion criteria
01 December 2015	Incorporating changes resulting from including Royal Berkshire Hospital, Reading UK in the study.
01 March 2016	Incorporating changes resulting from the application to MHRA.
01 August 2018	Cancellation of Stage II (12 additional months of follow-up) due to loss of follow-up and high dropout rate
02 December 2019	-Inclusion of Bioclever S.L. for support in the statistical content of the study. -Protocol modification and rewording in the following sections, based on their review: • Objectives • Efficacy outcomes and evaluation • Statistics

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported