



## Clinical trial results:

### A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE II TRIAL TO EVALUATE THE IMMUNOMODULATORY EFFECT OF RUTI® IN INDIVIDUALS WITH HIGH-RISK NON-MUSCLE-INVASIVE BLADDER CANCER (NMIBC) TREATED WITH INTRAVESICAL BACILLUS CALMETTE-GUÉRIN (BCG)

#### Summary

EudraCT number	2016-004311-12
Trial protocol	ES
Global end of trial date	22 December 2022

#### Results information

Result version number	v1 (current)
This version publication date	12 February 2026
First version publication date	12 February 2026

#### Trial information

##### Trial identification

Sponsor protocol code	RUTIVAC-1
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03191578
WHO universal trial number (UTN)	-

Notes:

#### Sponsors

Sponsor organisation name	ARCHIVEL FARMA, S.L.
Sponsor organisation address	Fogars de Tordera, 61 , Badalona, Spain, 08916
Public contact	CEO ARCHIVEL FARMA, S.L., ARCHIVEL FARMA, S.L., +34 93 497 24 56, orue@archivelfarma.com
Scientific contact	CEO ARCHIVEL FARMA, S.L., ARCHIVEL FARMA, S.L., +34 93 497 24 56, orue@archivelfarma.com

Notes:

#### Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	04 March 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 December 2022
Global end of trial reached?	Yes
Global end of trial date	22 December 2022
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To evaluate the systemic and mucosal immunological response of RUTI® administration prior to intravesical BCG therapy in individuals with high-risk NMIBC.

Immunological changes will be evaluated after completion of intravesical BCG therapy.

Protection of trial subjects:

The study was performed in accordance with the current version of the declaration of Helsinki, Fortaleza, Brazil, October 2013 and following the Spanish regulations, which required acceptance of the protocol by the sponsor and the coordinating investigator, protocol approval by the Ethics Committee.

The trial was conducted in agreement with the International Council on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP).

All subjects were guaranteed continued medical and nursing supervision throughout the duration of the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	16 June 2017
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	5 Years
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	12
From 65 to 84 years	28
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

Patients who attend their regular medical visits, confirming compliance criteria and obtaining written Informed Consent Form (ICF) . Four patients declined to participate after randomization due to personal reasons. Forty patients were randomized to receive two doses of either placebo (n=20) or RUTI® (n=20) vaccine.

### Pre-assignment

Screening details:

Four patients declined to participate before randomization due to personal reasons. Forty patients were randomized to receive two doses of either placebo (n=20) or RUTI® (n=20) vaccine

### Period 1

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

Blinding implementation details:

Clinical investigators, study nurses, and patients were blinded to the treatment allocation. Only pharmacy staff preparing the syringes for administration were not blinded to treatment allocation. Neither the laboratory nor the statistician carrying out the randomization had direct contact with patients.

At the end of the Interventional Phase the blind was opened, except for the study physicians who remained blind during the follow-up.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	RUTI

Arm description:

The investigational treatment tested in the trial is RUTI®. It is composed of detoxified, pasteurized and liposomal cellular wall fragments of Mtb (FCMtb).

Arm type	Experimental
Investigational medicinal product name	RUTI®
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose: 25 µg FCMtb

Interval: Day 0 (RUTI1) and Day 10 (RUTI2).

Method of administration: Two subcutaneous shots of 25 µg RUTI® (subcutaneously into deltoid region of the arm.) After vaccination, individuals will receive the standard induction course of intravesical Bacillus Calmette–Guerin (BCG) therapy (weekly BCG for six weeks).

<b>Arm title</b>	Placebo
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Arm description:

Commercially sterile saline solution (Sodium Chloride 0.9%)

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Dose: 0.3mL of 0.9% sterile normal saline solution

Interval: Day 0 (RUTI1) and Day 10 (RUTI2).

Method of administration: subcutaneously into deltoid region of the arm. After vaccination, individuals will receive the standard induction course of intravesical Bacillus Calmette–Guerin (BCG) therapy (weekly BCG for six weeks). 4 to 8 weeks after the last intravesical BCG administration (BCG6)

<b>Number of subjects in period 1</b>	RUTI	Placebo
Started	20	20
Induction course	20	20
Completed	18	16
Not completed	2	4
Exitus	1	2
Lost to follow-up	1	2

## Baseline characteristics

### Reporting groups

Reporting group title	RUTI
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Reporting group description:

The investigational treatment tested in the trial is RUTI®. It is composed of detoxified, pasteurized and liposomal cellular wall fragments of Mtb (FCMtb).

Reporting group title	Placebo
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Reporting group description:

Commercially sterile saline solution (Sodium Chloride 0.9%)

Reporting group values	RUTI	Placebo	Total
Number of subjects	20	20	40
Age categorical			
Age (years), Median (IQR) 70 (62-75): There were no significant differences in age, gender, or BMI between groups.			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	4	8	12
From 65-84 years	16	12	28
85 years and over	0	0	0
Age continuous			
Units: years			
median	71	67	
inter-quartile range (Q1-Q3)	62 to 77	59 to 74	-
Gender categorical			
Gender (male) Total population: 36 (90%)			
Units: Subjects			
Female	3	1	4
Male	17	19	36

## End points

### End points reporting groups

Reporting group title	RUTI
Reporting group description: The investigational treatment tested in the trial is RUTI®. It is composed of detoxified, pasteurized and liposomal cellular wall fragments of Mtb (FCMtb).	
Reporting group title	Placebo
Reporting group description: Commercially sterile saline solution (Sodium Chloride 0.9%)	

### Primary: Changes BL Vs w2: CD4 + CD25+

End point title	Changes BL Vs w2: CD4 + CD25+
End point description: For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (* p < 0.05; ** p < 0.01; and *** p < 0.001).	
End point type	Primary
End point timeframe: Baseline Vs W2	

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: differences (median)				
number (not applicable)	1.075	0.9955		

### Statistical analyses

Statistical analysis title	Mann-Whitney U test
Statistical analysis description: For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (* p < 0.05; ** p < 0.01; and *** p < 0.001).	
Comparison groups	Placebo v RUTI

Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	other <sup>[1]</sup>
P-value	< 0.05 <sup>[2]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - standard nonparametric comparative analysis, not a specific non-inferiority, equivalence, or superiority design.

[2] - For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\* p < 0.05; \*\* p < 0.01; and \*\*\* p < 0.001).

### Primary: Changes BL Vs w2: CD4 + CD69+

End point title	Changes BL Vs w2: CD4 + CD69+
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End point description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\* p < 0.05; \*\* p < 0.01; and \*\*\* p < 0.001).

End point type	Primary
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End point timeframe:

Baseline (RUTI1) Vs Week2 (BCG1)

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Differences (Median)				
number (not applicable)	1.229	0.9367		

### Statistical analyses

Statistical analysis title	Mann-Whitney U test
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Statistical analysis description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\* p < 0.05; \*\* p < 0.01; and \*\*\* p < 0.001).

Comparison groups	RUTI v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	other <sup>[3]</sup>
P-value	< 0.05 <sup>[4]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - standard nonparametric comparative analysis, not a specific non-inferiority, equivalence, or superiority design.

[4] - For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\* p < 0.05; \*\* p < 0.01; and \*\*\* p < 0.001).



**Primary: Changes BL Vs w2: CD4+CD137+**

End point title	Changes BL Vs w2: CD4+CD137+
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End point description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

End point type	Primary
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End point timeframe:

Baseline (RUTI1) Vs Week 2

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Differences (median)				
number (not applicable)	1.122	0.92		

**Statistical analyses**

Statistical analysis title	Mann-Whitney U test
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Statistical analysis description:

Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

Comparison groups	RUTI v Placebo
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Number of subjects included in analysis	40
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Analysis specification	Post-hoc
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Analysis type	other <sup>[5]</sup>
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P-value	< 0.05 <sup>[6]</sup>
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Method	Wilcoxon (Mann-Whitney)
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Notes:

[5] - standard nonparametric comparative analysis, not a specific non-inferiority, equivalence, or superiority design.

[6] - For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

**Primary: Changes BL Vs w2: CD4 +OX40+**

End point title	Changes BL Vs w2: CD4 +OX40+
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End point description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

End point type	Primary
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End point timeframe:

Baseline (RUTI1) Vs Week2 (BCG1)

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Differences (Median)				
number (not applicable)	1.248	1.051		

## Statistical analyses

Statistical analysis title	Mann-Whitney U test
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Statistical analysis description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

Comparison groups	RUTI v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	other <sup>[7]</sup>
P-value	< 0.05 <sup>[8]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - standard nonparametric comparative analysis, not a specific non-inferiority, equivalence, or superiority design.

[8] - Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*

## Primary: Changes BL Vs W6: CD4+CD25+CD27

End point title	Changes BL Vs W6: CD4+CD25+CD27
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End point description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

End point type	Primary
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End point timeframe:

Baseline (RUTI1) Vs W6

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Differences (Median)				
number (not applicable)	0.9971	1.232		

## Statistical analyses

Statistical analysis title	Mann-Whitney U test
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Statistical analysis description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

Comparison groups	RUTI v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	other <sup>[9]</sup>
P-value	< 0.05 <sup>[10]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - standard nonparametric comparative analysis, not a specific non-inferiority, equivalence, or superiority design.

[10] - For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

## Primary: Changes BL Vs W16: CD4+CD25+CD27

End point title	Changes BL Vs W16: CD4+CD25+CD27
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End point description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

End point type	Primary
End point timeframe:	
Baseline Vs W16	

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Differences (Median)				
number (not applicable)	1.002	1.118		

## Statistical analyses

<b>Statistical analysis title</b>	Mann-Whitney U test
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Statistical analysis description:

For the immunological response analysis, individual-level differences (paired samples) were assessed using Wilcoxon's matched-pair signed-rank test. Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

Comparison groups	RUTI v Placebo
Number of subjects included in analysis	40
Analysis specification	Post-hoc
Analysis type	other <sup>[11]</sup>
P-value	< 0.05 <sup>[12]</sup>
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Differences between the placebo and RUTI groups (unpaired samples) were evaluated using the Mann-Whitney U test. For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

[12] - . For fold-change analyses (compared with a baseline value of 1), the Wilcoxon signed-rank test was applied (\*  $p < 0.05$ ; \*\*  $p < 0.01$ ; and \*\*\*  $p < 0.001$ ).

## Secondary: The recurrence-free survival (RFS)

End point title	The recurrence-free survival (RFS)
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End point description:

Recurrence (high-grade recurrence) was defined according to the 2024 European Association of Urology (EAU) guidelines as any histology-proven high-grade disease within the bladder occurring during or after BCG therapy. Low-grade recurrence during or after BCG treatment is not considered BCG failure

End point type	Secondary
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End point timeframe:

at 5 years of follow up

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: patients				
number (not applicable)	2	5		

## Statistical analyses

No statistical analyses for this end point

## Secondary: Disease worsening: events that included diagnosis of T2 or greater

End point title	Disease worsening: events that included diagnosis of T2 or greater
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End point description:

Progression to muscle-invasive disease (T2 or greater) occurred in 4 patients (10.8%) in the total

population, all of whom were in the placebo group. This resulted in a significant difference in progression-free survival (PFS) between the groups, with rates of 77.7% for placebo and 100% for RUTI (p=0.032).

End point type	Secondary
End point timeframe:	
At three years of follow up	

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Patients				
number (not applicable)	0	4		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Cancer specific deaths

End point title	Cancer specific deaths
End point description:	
End point type	Secondary
End point timeframe:	
At 5 years of follow up	

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: patients				
number (not applicable)	0	2		

## Statistical analyses

No statistical analyses for this end point

### Secondary: Cancer specific free survival

End point title	Cancer specific free survival
End point description:	
No cancer-associated deaths were observed in the RUTI group during the 5-year follow-up, leading to a higher CSS rate in the RUTIs group (100% vs. 83.3% for placebo; p=0.067).	
End point type	Secondary

End point timeframe:  
at five years of follow up

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: Percent Patients				
number (not applicable)	89.5	50		

### Statistical analyses

No statistical analyses for this end point

**Secondary: Safety of RUTI® will be determined by analysis of local and systemic reactogenicity. The data will be expressed as: o Proportion of patients who develop a Grade 3 or 4 local reactions.**

End point title	Safety of RUTI® will be determined by analysis of local and systemic reactogenicity. The data will be expressed as: o Proportion of patients who develop a Grade 3 or 4 local reactions.
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End point description:

End point type	Secondary
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End point timeframe:

At five years of follow up

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: number of AEs				
number (not applicable)	0	0		

### Statistical analyses

No statistical analyses for this end point

**Secondary: Safety of RUTI® will be determined by analysis of local and systemic reactogenicity. The data will be expressed as: Proportion of patients who develop a Grade 3 or 4 systemic reactions**

End point title	Safety of RUTI® will be determined by analysis of local and systemic reactogenicity. The data will be expressed as: Proportion of patients who develop a Grade 3 or 4 systemic reactions
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End point description:

End point type	Secondary
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End point timeframe:

At 5 years of follow up

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: number of AEs				
number (not applicable)	0	0		

### Statistical analyses

No statistical analyses for this end point

### Secondary: Safety of RUTI® will be determined by analysis of local and systemic reactogenicity. SAEs

End point title	Safety of RUTI® will be determined by analysis of local and systemic reactogenicity. SAEs
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End point description:

End point type	Secondary
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End point timeframe:

At five years of follow up

End point values	RUTI	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	20		
Units: number of SAEs				
number (not applicable)	0	0		

### Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Overall Period

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	10
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### Reporting groups

Reporting group title	RUTI ARM
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Reporting group description: -

Reporting group title	Placebo arm
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Reporting group description: -

Serious adverse events	RUTI ARM	Placebo arm	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 20 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	RUTI ARM	Placebo arm	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	2 / 20 (10.00%)	8 / 20 (40.00%)	
General disorders and administration site conditions			
Malaise			
subjects affected / exposed	0 / 20 (0.00%)	3 / 20 (15.00%)	
occurrences (all)	0	3	
Fatigue			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Pain			
subjects affected / exposed	1 / 20 (5.00%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Asthenia			



subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	
Blood and lymphatic system disorders Anemia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1	0 / 20 (0.00%) 0	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)  Hypogastric pain subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1  0 / 20 (0.00%) 0  0 / 20 (0.00%) 0	2 / 20 (10.00%) 2  1 / 20 (5.00%) 1  1 / 20 (5.00%) 1	
Respiratory, thoracic and mediastinal disorders Influenza subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	
Skin and subcutaneous tissue disorders Injection site induration subjects affected / exposed occurrences (all)  Injection site erythema subjects affected / exposed occurrences (all)  Injection site swelling subjects affected / exposed occurrences (all)  Injection site pruritus subjects affected / exposed occurrences (all)  Edema hands and ankles subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1  1 / 20 (5.00%) 1  1 / 20 (5.00%) 1  1 / 20 (5.00%) 1  0 / 20 (0.00%) 0	1 / 20 (5.00%) 1  0 / 20 (0.00%) 0  0 / 20 (0.00%) 0  0 / 20 (0.00%) 0  1 / 20 (5.00%) 1	

Renal and urinary disorders Hematuria subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	
Musculoskeletal and connective tissue disorders Knee meniscopathy R subjects affected / exposed occurrences (all)  Arthralgia subjects affected / exposed occurrences (all)	1 / 20 (5.00%) 1  1 / 20 (5.00%) 1	0 / 20 (0.00%) 0  0 / 20 (0.00%) 0	
Infections and infestations Thoracic Herpes Zoster subjects affected / exposed occurrences (all)	0 / 20 (0.00%) 0	1 / 20 (5.00%) 1	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 June 2018	<p>Modification of exclusion criteria numbers 6 and 10, to allow the inclusion of patients receiving antiplatelet and/or anticoagulant treatment and patients with a clinical history of tuberculosis.</p> <p>Modification in the production process of the investigational product, RUTI®. The investigational medicinal product (IMP), RUTI®, has been manufactured at a dose of 25 µg FCMtb (33.3 µg/vial), incorporating improvements in the manufacturing processes of the active ingredient and the IMP.</p> <p>The collection of biopsy samples and performance of cystoscopy at week 16 will only be carried out if clinically indicated.</p> <p>The European General Data Protection Regulation (GDPR) is incorporated both in the protocol and in the patient information sheet.</p>
05 February 2019	<p>The principal investigator of the study is changed.</p> <p>The study design is modified to specify that the immunomodulatory effect will be evaluated only after the induction course of intravesical BCG.</p> <p>The intervention period will end at VISIT 1 (4–8 weeks after the last dose of the induction cycle [the 6th dose of intravesical BCG]).</p>

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.

Sample size: The study was powered for large effect sizes only; moderate or small effects may not be detected.

BCG supply shortage: Some patients did not receive maintenance BCG, which may affect long-term efficacy comparisons.

Notes:

### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/41084757>