



Clinical trial results:

Randomized double-blind placebo-controlled prospective, parallel, multicentre clinical trial of bacterial vaccine (BACTEK®) sublingual (oral mucosa) in patients with repeat bronchospasm for the immunomodulatory efficacy evaluation, security and clinical impact.

Summary

EudraCT number	2012-002450-24
Trial protocol	ES
Global end of trial date	24 May 2017

Results information

Result version number	v1
This version publication date	20 November 2021
First version publication date	20 November 2021
Summary attachment (see zip file)	Summary (MV130-SLG-002 Resumen Eng.pdf)

Trial information

Trial identification

Sponsor protocol code	MV130-SLG-002
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01734811
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inmunotek S.L.
Sponsor organisation address	C/ PUNTO MOBI, 5, Alcalá de Henares/ Madrid, Spain, 28805
Public contact	Miguel Casanovas; Medical Director, Inmunotek S.L., 34 916510010, mcasanovas@inmunotek.com
Scientific contact	Miguel Casanovas; Medical Director, Inmunotek S.L., 34 916510010, mcasanovas@inmunotek.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	27 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 September 2016
Global end of trial reached?	Yes
Global end of trial date	24 May 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the efficacy of a bacterial vaccine administered sublingually to prevent episodes of bronchospasm in patients with bronchospasm episodes induced by recurrent respiratory tract infections, compared with a placebo group

Protection of trial subjects:

The subjects were not subjected to any technique that could cause them pain or be considered harmful to them

Background therapy:

N/A

Evidence for comparator:

N/A

Actual start date of recruitment	03 September 2012
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: 121
Worldwide total number of subjects	121
EEA total number of subjects	121

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)	59
Children (2-11 years)	62
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0

85 years and over	0
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Subject disposition

Recruitment

Recruitment details:

The number of patients that were included in the study was 120 and those who finished were 115.

Pre-assignment

Screening details:

- Subjects whose parents /legal representative have given written informed consent.
- Both gender
- Subject up to 36 months of age.
- Subjects with recurrent bronchospasms ; 3 or more exacerbations in the last 12 months

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	Investigator, Monitor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	Active group

Arm description:

The subjects will receive daily biological vaccines pray (2 puff of 100 µL) of for 6 months, followed by other 6 months of observation

Arm type	Active comparator
Investigational medicinal product name	Bactek
Investigational medicinal product code	MV130
Other name	
Pharmaceutical forms	Sublingual spray, solution
Routes of administration	Sublingual use

Dosage and administration details:

2 daily spray (200 microlitres per day)

Arm title	Placebo
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Arm description:

The subjects will receive daily placebo spray (2 puff of 100 µL) of for 6 months, followed by other 6 months of observation

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

Dosage and administration details:

2 daily placebo spray (200 microlitres per day)

Number of subjects in period 1	Active group	Placebo
Started	62	59
Completed	59	54
Not completed	3	5
Consent withdrawn by subject	-	1
Adverse event, non-fatal	-	2
Lost to follow-up	3	2

Baseline characteristics

Reporting groups

Reporting group title	overall trial
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Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	121	121	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	59	59	
Children (2-11 years)	62	62	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: months			
arithmetic mean	23.1		
standard deviation	± 7.7	-	
Gender categorical			
Units: Subjects			
Female	51	51	
Male	70	70	

End points

End points reporting groups

Reporting group title	Active group
Reporting group description: The subjects will receive daily biological vaccines pray (2 puff of 100 µL) of for 6 months, followed by other 6 months of observation	
Reporting group title	Placebo
Reporting group description: The subjects will receive daily placebo spray (2 puff of 100 µL) of for 6 months, followed by other 6 months of observation	

Primary: Wheezing attacks (WA)

End point title	Wheezing attacks (WA)
End point description: Recurrent bronchospasm (wheezing attacks) during a period of 12 months after the initiation of the treatment. The number of bronchospasm (wheezing attacks) episodes between control and placebo groups were compared.	
End point type	Primary
End point timeframe: One year per subject	

End point values	Active group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	59		
Units: Percentage				
number (confidence interval 95%)	2.8 (2.4 to 3.3)	5.3 (4.5 to 6.2)		

Attachments (see zip file)	End Point/EFFICACY EVALUATION end point.pdf
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Statistical analyses

Statistical analysis title	EPISODES OF WA BEFORE THE INITIATION OF TREATMENT
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[1]
P-value	= 0.102 ^[2]
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - Active group: The mean was 9.3 (8.2-10.4) and the median 8.0 (7.0-10.0).
Placebo group: The mean was 10.3 (8.9-11.6) and the median 9.0 (7.0-11.3).
Hodges-Lehman estimator was -1.0 (-2.0, 0.0)

[2] - The differences between both groups of treatment were not significant.

Statistical analysis title	PREVIOUS MONTHLY WA
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[3]
P-value	= 0.053 ^[4]
Method	Wilcoxon (Mann-Whitney)

Notes:

[3] - Active group: The mean was 0.8 (0.7-0.9) and the median 0.7 (0.6-0.8)

Placebo group: The mean was 0.9 (0.8-1.1) and the median 0.8 (0.6-1.0).

Hodges-Lehman estimator was -0.1 (-0.2, 0.0)

[4] - The differences between both groups of treatment were not significant.

Statistical analysis title	EPISODES OF WA FROM MONTH 1 TO 12
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[5]
P-value	< 0.001 ^[6]
Method	Wilcoxon (Mann-Whitney)

Notes:

[5] - Active group: The mean was 2.8 (2.4-3.3) and the median 3.0 (2.0-4.0).

Placebo group: The mean was 5.3 (4.5-6.2) and the median 5.0 (3.0-7.0)

Hodges-Lehmann estimator was -2.0 (-3.0, -1.0)

[6] - The active group had an improvement of 40% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	EPISODES OF WA DURING THE FIRST MONTH TREATMENT
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[7]
P-value	= 0.054 ^[8]
Method	Wilcoxon (Mann-Whitney)

Notes:

[7] - Active group: The mean was 0.5 (0.3-0.7) and the median 0.0 (0.0-1.0).

Placebo group: The mean was 0.8 (0.6-1.1) and the median 1.0 (0.0-1.0).

The active group had an improvement of 100% over placebo.

Hodges-Lehmann estimator was 0.0 (0.0, 0.0)

[8] - The differences between both groups of treatment were not significant

Statistical analysis title	EPISODES OF WA DURING THE 2ND MONTH TREATMENT
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[9]
P-value	= 0.063 ^[10]
Method	Wilcoxon (Mann-Whitney)

Notes:

[9] - Active group: The mean was 0.4 (0.2-0.5) and the median 0.0 (0.0-1.0)

Placebo group: The mean was 0.6 (0.4-0.7) and the median 0.5 (0.0-1.0)

Hodges-Lehmann estimator was 0.0 (0.0, 0.0)

[10] - The differences between both groups of treatment were not significant.

Statistical analysis title	ACCUMULATED WA DURING THE FIRST 2MONTHS TREATMENT
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[11]
P-value	= 0.007 ^[12]
Method	Wilcoxon (Mann-Whitney)

Notes:

[11] - Active group: The mean was 0.9 (0.6-1.1) and the median 1.0 (0.0-1.0).

Placebo group: The mean was 1.4 (1.1-1.7) and the median 1.0 (1.0-2.0).

Hodges-Lehmann estimator was 0.0 (-1.0, 0.0)

[12] - The differences between both groups of treatment were significant.

Statistical analysis title	EPISODES OF WA IN THE THIRD MONTH OF THE TREATMENT
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[13]
P-value	= 0.022 ^[14]
Method	Wilcoxon (Mann-Whitney)

Notes:

[13] - Active group: The mean was 0.3 (0.2-0.5) and the median 0.0 (0.0-1.0)

Placebo group: The mean was 0.6 (0.4-0.8) and the median 0.5 (0.0-1.0)

Hodges-Lehmann estimator was 0.0 (0.0, 0.0)

[14] - The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	ACCUMULATED EPISODES WA DURING THE FIRST 3 MONTHS
Statistical analysis description: ACCUMULATED EPISODES OF WA DURING THE FIRST 3 MONTHS OF TREATMENT	
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[15]
P-value	= 0.002 ^[16]
Method	Wilcoxon (Mann-Whitney)

Notes:

[15] - Active group: The mean was 1.2 (0.9-1.4) and the median 1.0 (0.0-2.0).

Placebo group: The mean was 2.0 (1.6-2.4) and the median 2.0 (1.0-3.0).

Hodges-Lehmann estimator was -1.0 (-1.0, 0.0)

[16] - The active group had an improvement of 50% over placebo.
The differences between both groups of treatment were significant.

Statistical analysis title	EPISODES OF WA IN THE 4-5-6-MONTHS OF TREATMENT
Comparison groups	Placebo v Active group

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[17]
P-value	= 0.018 ^[18]
Method	Wilcoxon (Mann-Whitney)

Notes:

[17] - Active group: The mean was 0.6 (0.4-0.8) and the median 0.0 (0.0-1.0).

Placebo group: The mean was 1.1 (0.8-1.3) and the median 1.0 (0.0-2.0).

Hodges-Lehmann estimator was 0.0 (-1.0, 0.0)

[18] - The active group had an improvement of 100% over placebo.

The differences between both groups of treatment were significant.

Statistical analysis title	ACCUMULATED EPISODES OF WA IN THE FIRST 6 MONTHS
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Statistical analysis description:

Accumulated episodes of WA in the first 6 months (period of treatment) of the clinical trial.v

Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[19]
P-value	< 0.001 ^[20]
Method	Wilcoxon (Mann-Whitney)

Notes:

[19] - Active group: The mean was 1.8 (1.5-2.1) and the median 2.0 (1.0-3.0).

Placebo group: The mean was 3.1 (2.6-3.5) and the median 3.0 (2.0-4.0).

[20] - The active group had an improvement of 33% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	EPISODES OF WA END OF 6 MONTHS -END OF THE TRIAL
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Statistical analysis description:

Episodes of WA from the end of the sixth month (end of the treatment) to the end of the trial.

Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[21]
P-value	< 0.001 ^[22]
Method	Wilcoxon (Mann-Whitney)

Notes:

[21] - Active group: The mean was 1.0 (0.7-1.4) and the median 1.0 (0.0-2.0).

Placebo group: The mean was 2.3 (1.8-2.8) and the median 2.0 (1.0-3.0).

Hodges-Lehmann estimator was -1.0 (-2.0, -1.0)

[22] - The active group had an improvement of 50% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS W/WA AFTER THE INITIATION TO END TRIAL
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Statistical analysis description:

DAYS WITH WA AFTER THE INITIATION OF THE TREATMENT TO THE END OF THE TRIAL

Comparison groups	Active group v Placebo
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Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[23]
P-value	< 0.001 ^[24]
Method	Wilcoxon (Mann-Whitney)

Notes:

[23] - Active group: The mean was 22.9 (18.0-27.8) and the median 19.0 (8.5-35.5).

Placebo group: The mean was 46.1 (37.6-54.5) and the median 42.0 (21.5-59.8).

Hodges-Lehmann estimator was -20.0 (-30.0, -11.0).

[24] - The active group had an improvement of 55% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITH WA IN THE FIRST MONTH OF TREATMENT
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[25]
P-value	= 0.122 ^[26]
Method	Wilcoxon (Mann-Whitney)

Notes:

[25] - Active group: The mean was 4.4 (2.7-6.1) and the median 0.0 (0.0-7.8)

Placebo group: The mean was 6.9 (4.4-9.4) and the median 3.5 (0.0-11.0).

Hodges-Lehmann estimator was 0.0 (-2.0, 0.0)

[26] - The active group had an improvement of 100% over placebo. However, the differences between both groups of treatment were not significant.

Statistical analysis title	DAYS WITH WA IN THE SECOND MONTH OF TREATMENT
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[27]
P-value	= 0.031 ^[28]
Method	Wilcoxon (Mann-Whitney)

Notes:

[27] - Active group: The mean was 3.0 (1.7-4.4) and the median 0.0 (0.0-4.0).

Placebo group: The mean was 5.9 (3.8-7.9) and the median 2.0 (0.0-10.0).

Hodges-Lehmann estimator was 0.0 (-2.0, 0.0)

[28] - The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITH WA IN THE THIRD MONTH OF TREATMENT
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[29]
P-value	= 0.019 ^[30]
Method	Wilcoxon (Mann-Whitney)

Notes:

[29] - Active group: The mean was 2.3 (1.3-3.4) and the median 0.0 (0.0-3.0).

Placebo group: The mean was 4.9 (3.3-6.6) and the median 1.5 (0.0-7.3).

Hodges-Lehmann estimator was 0.0 (-3.0, 0.0)

[30] - The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITH WA IN THE 4-5-6 MONTHS OF TREATMENT
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[31]
P-value	= 0.034 ^[32]
Method	Wilcoxon (Mann-Whitney)

Notes:

[31] - Active group: The mean was 4.5 (2.7-6.3) and the median 0.0 (0.0-6.8).

Placebo group: The mean was 7.9 (5.4-10.5) and the median 5.5 (0.0-12.0).

Hodges-Lehmann estimator was 0.0 (-5.0, 0.0)

[32] - The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS W/WA FROM END TREATMENT TO END TRIAL
Statistical analysis description: DAYS WITH WA FROM THE END OF TREATMENT TO THE END OF THE TRIAL	
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[33]
P-value	< 0.001 ^[34]
Method	Wilcoxon (Mann-Whitney)

Notes:

[33] - Active group: The mean was 8.6 (5.5-11.8) and the median 4.0 (0.0-11.8).

Placebo group: The mean was 20.4 (15.2-25.5) and the median 19.0 (5.8-30.3).

Hodges-Lehmann estimator was -10.0 (-15.0, -5.0)

[34] - The active group had an improvement of 79% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	AVERAGE OF DAYS OF DURATION OF EACH WA
Statistical analysis description: AFTER THE INITIATION OF THE TREATMENT TO THE END OF THE TRIAL	
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[35]
P-value	= 0.005 ^[36]
Method	Wilcoxon (Mann-Whitney)

Notes:

[35] - Active group: The mean was 7.1 (5.8-8.5) and the median 6.0 (4.0-9.5).

Placebo group: The mean was 8.9 (7.9-9.8) and the median 7.9 (6.2-11.0).

Hodges-Lehmann estimator was -2.0 (-3.3, -0.6)

[36] - The active group had an improvement of 24% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS FREE WA UNTIL 1ST EPISODE WA AFTER INITIATION
Statistical analysis description: AFTER THE INITIATION OF THE TREATMENT	
Comparison groups	Placebo v Active group

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[37]
P-value	< 0.001 ^[38]
Method	Wilcoxon (Mann-Whitney)

Notes:

[37] - Active group: The mean was 83.2 (56.1-110.2) and the median 41.0 (15.0-94.5).

Placebo group: The mean was 22.5 (11.7-33.3) and the median 5.0 (2.0-29.8)

Hodges-Lehmann estimator was 27.0 (14.0, 43.0)

The Kaplan-Meier analysis showed that difference between both groups was significant

[38] - Active group had an improvement of 88% over placebo.

The differences between both groups of treatment were significant.

Statistical analysis title	DAYS FREE WA UNTIL 1ST EPISODE WA AFTER 1 MONTH
Statistical analysis description: AFTER 1 MONTH OF THE TREATMENT	
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[39]
P-value	= 0.004 ^[40]
Method	Wilcoxon (Mann-Whitney)

Notes:

[39] - Active group: The mean was 95.9 (68.1-123.6) and the median 56.5 (21.3-106.3)

Placebo group: The mean was 48.3 (31.9-64.7) and the median 30.0 (11.8-54.3).

Hodges-Lehmann estimator was 20.0 (6.0, 40.0)

The Kaplan-Meier analysis showed that difference between both groups was significant

[40] - Active group had an improvement of 47% over placebo.

The differences between both groups of treatment were significant.

Statistical analysis title	DAYS FREE WA UNTIL 1ST EPISODE WA AFTER 2 MONTHS
Statistical analysis description: DAYS FREE OF WA UNTIL THE FIRST EPISODE OF WA AFTER 2 MONTHS OF THE TREATMENT	
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[41]
P-value	= 0.011 ^[42]
Method	Wilcoxon (Mann-Whitney)

Notes:

[41] - It was considered 305 days as the maximum possible value.

Active group: The mean was 105.5 (77.2-133.7) and the median 60.5 (25.0- 120.0).

Placebo group: The mean was 65.8 (42.3-89.3) and the median 27.0 (11.8-83.3).

Hodges-Lehmann estimator was 19.0 (3.0, 42.0)

The Kaplan-Meier analysis showed that the difference between both groups was significant

[42] - Active group had an improvement of 55% over placebo.

The differences between both groups of treatment were significant.

Statistical analysis title	DAYS FREE WA UNTIL 1ST EPISODE WA AFTER 3 MONTHS
Statistical analysis description: DAYS FREE OF WA UNTIL THE FIRST EPISODE OF WA AFTER 3 MONTHS OF THE TREATMENT	
Comparison groups	Active group v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[43]
P-value	= 0.087 ^[44]
Method	Wilcoxon (Mann-Whitney)

Notes:

[43] - It was considered 275 days as the maximum possible value.

Active group: The mean was 108.1 (80.2-136.1) and the median 57.0 (18.0-275.0).

Placebo group: The mean was 74.3 (50.8-97.8) and the median 30.5 (13.5-112.0).

Hodges-Lehmann estimator was 14.0 (0.0, 40.0)

The Kaplan-Meier analysis showed that difference between both groups was not significant.

[44] - Active group had an improvement of 46% over placebo.

The differences between both groups of treatment were significant.

Statistical analysis title	DAYS FREE WA UNTIL 1ST EPISODE WA AFTER 6 MONTHS
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Statistical analysis description:

DAYS FREE OF WA UNTIL THE FIRST EPISODE OF WA AFTER THE END (6 MONTHS) OF THE TREATMENT

Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[45]
P-value	< 0.001 ^[46]
Method	Wilcoxon (Mann-Whitney)

Notes:

[45] - It was considered 180 (half year) as the maximum possible value.

Active group: The mean was 120.8 (103.3-138.2) and the median 180.0 (48.5-180.0).

Placebo group: The mean was 76.9 (59.3-94.6) and the median 44.5 (20.0-121.5).

Hodges-Lehmann estimator was 41.0 (6.0, 66.0)

The Kaplan-Meier analysis showed that the difference between both groups was significant

[46] - Active group had an improvement of 75% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL DAYS FREE OF WA
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Statistical analysis description:

TOTAL DAYS FREE OF WA

Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[47]
P-value	< 0.001 ^[48]
Method	Wilcoxon (Mann-Whitney)

Notes:

[47] - Active group: The mean was 337.1 (332.2-342.0) and the median 341.0 (324.5-351.5).

Placebo group: The mean was 313.9 (305.5-322.4) and the median 318.0 (300.3-338.5).

Hodges-Lehmann estimator was 20.0 (11.0, 30.0)

[48] - Active group had an improvement of 7% over placebo.

The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITHOUT WA IN THE FIRST MONTH
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[49]
P-value	= 0.122 ^[50]
Method	Wilcoxon (Mann-Whitney)

Notes:

[49] - Active group: The mean was 25.6 (24.0-27.3) and the median 30.0 (30.0-22.3).
Placebo group: The mean was 23.2 (20.7-25.6) and the median 26.5 (19.0-30.0).
Hodges-Lehmann estimator was 0.0 (0.0, 3.0)

[50] - Active group had an improvement of 12% over placebo.
The differences between both groups of treatment were not significant.

Statistical analysis title	DAYS WITHOUT WA IN THE FIRST TWO MONTHS
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[51]
P-value	= 0.013 ^[52]
Method	Wilcoxon (Mann-Whitney)

Notes:

[51] - Active group: The mean was 52.6 (50.5-54.7) and the median 56.0 (47.3-60.0).
Placebo group: The mean was 47.2 (43.8-50.6) and the median 50.0 (40.0-58.0).
Hodges-Lehmann estimator was 4.0 (0.0, 8.0)

[52] - Active group had an improvement of 11% over placebo.
The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITHOUT WA IN THE FIRST THREE MONTH
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[53]
P-value	= 0.002 ^[54]
Method	Wilcoxon (Mann-Whitney)

Notes:

[53] - Active group: The mean was 80.3 (77.8-82.8) and the median 82.5 (74.0-90.0).
Placebo group: The mean was 72.3 (68.2-76.3) and the median 74.5 (65.0-82.3)
Hodges-Lehmann estimator was 7.0 (2.0, 10.0)

[54] - Active group had an improvement of 10% over placebo.
The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITHOUT WA IN THE FIRST SIX MONTH
Statistical analysis description: DAYS WITHOUT WA IN THE FIRST SIX MONTH	
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[55]
P-value	< 0.001 ^[56]
Method	Wilcoxon (Mann-Whitney)

Notes:

[55] - Active group: The mean was 165.7 (162.6-168.9) and the median 168.5 (157.8-176.0).
Placebo group: The mean was 154.3 (149.2-159.4) and the median 159.0 (142.8-168.3).
Hodges-Lehmann estimator was 10.0 (5.0, 14.0)

[56] - Active group had an improvement of 6% over placebo.
The differences between both groups of treatment were significant.

Secondary: Symptom (SS) and medication (MS)

End point title	Symptom (SS) and medication (MS)
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End point description:	
Symptom (SS) and medication (MS) scores and the combination of both (SMS) during the WA. Review of medication consumed from the beginning to the end of the wheezing attacks per subject	
End point type	Secondary
End point timeframe:	
One year	

End point values	Active group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	59		
Units: percentage				
number (confidence interval 95%)	1088.3 (922.1 to 1254.4)	1760.9 (1505.9 to 2016.0)		

Statistical analyses

Statistical analysis title	DAYS WITH NASAL MUCUS SECRETION
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[57]
P-value	= 0.005 ^[58]
Method	Wilcoxon (Mann-Whitney)

Notes:

[57] - Active group: The mean was 76.7 (61.7-91.6) and the median 71.0 (32.0-101.3).

Placebo group: The mean was 108.0 (90.6-125.4) and the median 100.5 (61.8-146.8).

Hodges-Lehman estimator was -33.0 (-55.0, -10.0).

[58] - The active group had an improvement of 29% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITH FEVER
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[59]
P-value	= 0.068 ^[60]
Method	Wilcoxon (Mann-Whitney)

Notes:

[59] - Active group: The mean was 10.2 (8.4-12.0) and the median 9.5 (5.0-14.0).

Placebo group: The mean was 15.8 (12.2-19.5) and the median 11.5 (7.0-20.5).

Hodges-Lehman estimator was -3.0 (-7.0, -0.0).

[60] - The active group had an improvement of 17% over placebo. The differences between both groups of treatment were not significant.

Statistical analysis title	DAYS WITH BRONCHIAL MUCUS SECRETION
Comparison groups	Placebo v Active group

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[61]
P-value	= 0.008 ^[62]
Method	Wilcoxon (Mann-Whitney)

Notes:

[61] - Active group: The mean was 30.0 (22.4-37.7) and the median 21.0 (8.0-42.5).

Placebo group: The mean was 53.2 (39.1-67.3) and the median 41.0 (14.8-73.0).

Hodges-Lehman estimator was -14.0 (-28.0, -4.0)

[62] - The active group had an improvement of 49% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITH COUGH
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[63]
P-value	= 0.013 ^[64]
Method	Wilcoxon (Mann-Whitney)

Notes:

[63] - Active group: The mean was 69.5 (54.2-84.8) and the median 54.5 (26.0-87.0).

Placebo group: The mean was 85.7 (72.3-99.1) and the median 78.5 (53.0-113.0).

Hodges-Lehman estimator was -22.0 (-37.0, -4.0)

[64] - The active group had an improvement of 31% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITH DYSPNOEA
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[65]
P-value	= 0.003 ^[66]
Method	Wilcoxon (Mann-Whitney)

Notes:

[65] - Active group: The mean was 14.7 (9.9-19.5) and the median 8.5 (1.3-18.0).

Placebo group: The mean was 32.7 (20.7-44.8) and the median 19.5 (6.8-43.3).

Hodges-Lehman estimator was -8.0 (-16.0, -2.0)

[66] - The active group had an improvement of 56% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITH WHEEZING
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[67]
P-value	< 0.001 ^[68]
Method	Wilcoxon (Mann-Whitney)

Notes:

[67] - The mean was 11.5 (7.2-15.8) and the median 5.0 (0.0-14.0)

The mean was 32.2 (20.4-44.1) and the median 19.0 (7.0-44.0).

Hodges-Lehman estimator was -11.0 (-18.0, -6.0)

[68] - The active group had an improvement of 74% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	DAYS WITH DISCOMFORT
Comparison groups	Placebo v Active group

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[69]
P-value	= 0.01 ^[70]
Method	Wilcoxon (Mann-Whitney)

Notes:

[69] - Active group: The mean was 20.7 (13.8-27.7) and the median 11.0 (3.3-32.3).

Placebo group: The mean was 33.6 (24.4-42.9) and the median 20.0 (13.8-42.3).

Hodges-Lehman estimator was -10.0 (-16.0, -2.0).

[70] - The active group had an improvement of 45% over placebo. The differences between both groups of treatment were significant.

Secondary: Symptom (SS) and medication scores (MS) and the combination of both (SMS)

End point title	Symptom (SS) and medication scores (MS) and the combination of both (SMS)
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End point description:

Symptom (SS) and medication scores (MS) and the combination of both (SMS) during all the study

End point type	Secondary
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End point timeframe:

One year

End point values	Active group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	59		
Units: Percentage				
number (confidence interval 95%)	330.8 (252.8 to 408.7)	796.4 (611.6 to 981.2)		

Statistical analyses

Statistical analysis title	TOTAL SYMPTOM SCORE DURING THE WA
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Statistical analysis description:

It includes the score of all the symptoms during the WA (fever, nasal mucus, bronchial mucus, cough, dyspnoea, wheezing and discomfort). The maximum possible daily value was 19.

Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[71]
P-value	< 0.001 ^[72]
Method	Wilcoxon (Mann-Whitney)

Notes:

[71] - Active group: The mean was 106.1 (78.9-133.2) and the median 80.0 (19.5-154.5).

Placebo group: The mean was 230.8 (164.7-296.8) and the median 168.0 (91.8-253.3).

Hodges-Lehmann estimator was -75.0 (-113.0, -40.0)

[72] - The active group had an improvement of 52% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL NORMALIZED MEDICATION SCORE DURING THE WA
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Statistical analysis description:

The maximum value of symptom scores during the WA was 19 and the corresponding medication scores was 24. Therefore, for the combination of both scores, medication score was adjusted to have the same weight as symptom by a factor of 0.79 (the ratio between 19 and 24).

Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[73]
P-value	< 0.001 ^[74]
Method	Wilcoxon (Mann-Whitney)

Notes:

[73] - Active group: The mean was 224.7 (167.1-282.3) and the median 164.0 (43.5-311.5).
 Placebo group: The mean was 565.6 (426.3-704.9) and the median 456.0 (205.5-765.8).
 Hodges-Lehmann estimator was -240.5 (-386.0, -143.0).

[74] - The active group had an improvement of 64% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL COMBINATION OF SS AND MS DURING THE WA
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[75]
P-value	< 0.001 ^[76]
Method	Wilcoxon (Mann-Whitney)

Notes:

[75] - Active group: The mean was 330.8 (252.8-408.7) and the median 277.5 (60.8-514.5).
 Placebo group: The mean was 796.4 (611.6-981.2) and the median 600.0 (282.5-1095.3).
 Hodges-Lehmann estimator was -329.5 (-511.0, -188.0)

[76] - The active group had an improvement of 54% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	OVERALL SYMPTOM SCORE
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Statistical analysis description:

As descriptive statistics, the results were expressed as the mean (with the 95% confidence interval) and the median (with first and third quartile: IQ range).

Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[77]
P-value	= 0.001 ^[78]
Method	Wilcoxon (Mann-Whitney)

Notes:

[77] - Active group: The mean was 319.9 (258.2-381.7) and the median 276.5 (151.0-426.0).
 Placebo group: The mean was 522.3 (410.1-634.5) and the median 421.0 (303.0-673.0).
 Hodges-Lehman estimator was -147.0 (-248.0, -63.0)

[78] - The active group had an improvement of 34% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SYMPTOM SCORE IN THE FIRST THREE MONTHS
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Statistical analysis description:

As descriptive statistics, the results were expressed as the mean (with the 95% confidence interval) and the median (with first and third quartile: IQ range).

Comparison groups	Active group v Placebo
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Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[79]
P-value	= 0.031 ^[80]
Method	Wilcoxon (Mann-Whitney)

Notes:

[79] - Active group: The mean was 150.0 (120.1-181.5) and the median 121.5 (57.8-215.8).

Placebo group: The mean was 217.3 (165.3-269.3) and the median 165.5 (100.0-273.3).

Hodges-Lehman estimator was -44.0 (-87.0, -4.0)

[80] - The active group had an improvement of 27% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SYMPTOM SCORE IN THE FIRST SIX MONTHS
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Statistical analysis description:

As descriptive statistics, the results were expressed as the mean (with the 95% confidence interval) and the median (with first and third quartile: IQ range).

Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[81]
P-value	= 0.017 ^[82]
Method	Wilcoxon (Mann-Whitney)

Notes:

[81] - Active group: The mean was 237.8 (190.8-284.9) and the median 215.0 (112.0-320.5).

Placebo group: The mean was 357.3 (271.2-443.4) and the median 290.5 (163.5-452.8)

Hodges-Lehman estimator was -75.5 (-146.0, -15.0)

[82] - The active group had an improvement of 26% over placebo.

The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SYMPTOM SCORE FROM SIX TO TWELVE MONTHS
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Statistical analysis description:

As descriptive statistics, the results were expressed as the mean (with the 95% confidence interval) and the median (with first and third quartile: IQ range).

Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[83]
P-value	= 0.001 ^[84]
Method	Wilcoxon (Mann-Whitney)

Notes:

[83] - Active group: The mean was 75.6 (52.2-98.9) and the median 42.0 (17.0-102.5).

Placebo group: The mean was 154.7 (111.6-197.7) and the median 110.0 (53.8-187.5).

Hodges-Lehman estimator was -50.0 (-81.0, -21.0).

[84] - The active group had an improvement of 62% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF RESPIRATORY SYMPTOMS
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Statistical analysis description:

Respiratory symptoms are cough, dyspnoea and wheezing

Comparison groups	Active group v Placebo
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Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[85]
P-value	= 0.002 ^[86]
Method	Wilcoxon (Mann-Whitney)

Notes:

[85] - Active group: The mean was 133.9 (107.0-160.8) and the median 115.0 (53.8-165.5).

Placebo group: The mean was 222.6 (166.8-278.3) and the median 157.0 (110.0-295.3).

Hodges-Lehman estimator was -53.0 (-97.0, -21.0)

[86] - The active group had an improvement of 27% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF OTHER SYMPTOMS
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[87]
P-value	= 0.001 ^[88]
Method	Wilcoxon (Mann-Whitney)

Notes:

[87] - Active group: The mean was 186.0 (148.0-224.0) and the median 152.0 (73.3-262.0).

Placebo group: The mean was 299.7 (239.6-359.8) and the median 253.5 (175.3-353.8).

Hodges-Lehman estimator was -84.0 (-151.0, -38.0).

[88] - The active group had an improvement of 40% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF NASAL MUCUS SECRETION
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[89]
P-value	= 0.004 ^[90]
Method	Wilcoxon (Mann-Whitney)

Notes:

[89] - Active group: The mean was 103.1 (81.4-124.9) and the median 82.0 (42.0-147.8).

Placebo group: The mean was 152.4 (123.7-181.2) and the median 123.0 (83.8-199.5).

Hodges-Lehman estimator was -44.0 (-75.0, -12.0).

[90] - The active group had an improvement of 33% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF BRONCHIAL MUCUS SECRETION
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[91]
P-value	= 0.005 ^[92]
Method	Wilcoxon (Mann-Whitney)

Notes:

[91] - Active group: The mean was 42.7 (30.9-54.5) and the median 29.0 (11.0-59.0).

Placebo group: The mean was 80.3 (57.5-103.1) and the median 58.5 (24.0-102.5)

Hodges-Lehman estimator was -21.0 (-41.0, -6.0).

[92] - The active group had an improvement of 50% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF COUGH
Comparison groups	Active group v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[93]
P-value	= 0.02 ^[94]
Method	Wilcoxon (Mann-Whitney)

Notes:

[93] - Active group: The mean was 97.7 (76.2-119.2) and the median 83.0 (35.5-119.5).

Placebo group: The mean was 126.4 (103.0-149.8) and the median 104.5 (72.0-153.5).

Hodges-Lehman estimator was -30.0 (-54.0, -5.0)

[94] - The active group had an improvement of 21% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF DYSPNOEA
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[95]
P-value	= 0.004 ^[96]
Method	Wilcoxon (Mann-Whitney)

Notes:

[95] - Active group: The mean was 20.7 (14.1-27.3) and the median 11.0 (2.0-26.5).

Placebo group: The mean was 49.4 (29.6-69.3) and the median 25.5 (10.0-62.8).

Hodges-Lehman estimator was -11.0 (-21.0, -3.0)

[96] - The active group had an improvement of 57% over placebo. The differences between both groups of treatment were significant

Statistical analysis title	TOTAL SCORE OF WHEEZING
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[97]
P-value	< 0.001 ^[98]
Method	Wilcoxon (Mann-Whitney)

Notes:

[97] - Active group: The mean was 15.5 (9.9-21.2) and the median 6.5 (0.0-20.8).

Placebo group: The mean was 46.7 (28.2-65.2) and the median 25.5 (8.5-61.5).

Hodges-Lehman estimator was -15.0 (-24.0, -6.0)

[98] - The active group had an improvement of 75% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF DISCOMFORT
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[99]
P-value	= 0.01 ^[100]
Method	Wilcoxon (Mann-Whitney)

Notes:

[99] - Active group: The mean was 30.0 (20.3-39.7) and the median 14.5 (4.0-47.5).

Placebo group: The mean was 51.1 (36.2-66.0) and the median 31.0 (18.8-59.5).

Hodges-Lehman estimator was -14.0 (-23.0, -3.0)

[100] - The active group had an improvement of 53% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL MEDICATION SCORE
Comparison groups	Active group v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[101]
P-value	< 0.001 ^[102]
Method	Wilcoxon (Mann-Whitney)

Notes:

[101] - Active group: The mean was 768.4 (636.1-900.6) and the median 681.5 (318.3-1033.5).
 Placebo group: The mean was 1238.6 (1035.4-1441.8) and the median 1043.5 (669.5-1696.0).
 Hodges-Lehman estimator was -403.5 (-647.0, -191.0).

[102] - The active group had an improvement of 35% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL MEDICATION SCORE IN THE FIRST THREE MONTHS
Statistical analysis description:	
As descriptive statistics, the results were expressed as the mean (with the 95% confidence interval) and the median (with first and third quartile: IQ range)	
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[103]
P-value	= 0.003 ^[104]
Method	Wilcoxon (Mann-Whitney)

Notes:

[103] - Active group: The mean was 319.9 (268.4-371.3) and the median 311.0 (133.8-487.8).
 Placebo group: The mean was 486.1 (404.6-567.6) and the median 406.5 (260.3-715.5).
 Hodges-Lehman estimator was -142.5 (-236.0, -49.0)

[104] - The active group had an improvement of 23% over placebo. The differences between both groups of treatment were significant

Statistical analysis title	TOTAL MEDICATION SCORE IN THE FIRST SIX MONTHS
Statistical analysis description:	
As descriptive statistics, the results were expressed as the mean (with the 95% confidence interval) and the median (with first and third quartile: IQ range).	
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[105]
P-value	= 0.002 ^[106]
Method	Wilcoxon (Mann-Whitney)

Notes:

[105] - Active group: The mean was 562.4 (468.7-656.0) and the median 509.5 (265.3-773.5).
 Placebo group: The mean was 846.7 (713.6-979.9) and the median 776.0 (470.5-1191.5).
 Hodges-Lehman estimator was -249.0 (-217.0, -100.0)

[106] - The active group had an improvement of 34% over placebo. The differences between both groups of treatment were significant

Statistical analysis title	TOTAL MEDICATION SCORE FROM SIX TO TWELVE MONTHS
Statistical analysis description:	
As descriptive statistics, the results were expressed as the mean (with the 95% confidence interval) and the median (with first and third quartile: IQ range).	
Comparison groups	Active group v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[107]
P-value	< 0.001 ^[108]
Method	Wilcoxon (Mann-Whitney)

Notes:

[107] - Active group: The mean was 220.6 (165.1-276.0) and the median 187.0 (53.0-312.5).

Placebo group: The mean was 406.4 (305.9-507.0) and the median 302.5 (103.8-488.3).

Hodges-Lehman estimator was -136.0 (-204.0, -64.0)

[108] - The active group had an improvement of 38% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF ANTIBIOTICS
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[109]
P-value	= 0.013 ^[110]
Method	Wilcoxon (Mann-Whitney)

Notes:

[109] - Active group: The mean was 32.8 (23.0-42.7) and the median 22.5 (6.0-44.5).

Placebo group: The mean was 54.8 (39.8-69.8) and the median 41.5 (18.8-77.3).

Hodges-Lehman estimator was -16.0 (-28.0, -2.0).

[110] - The active group had an improvement of 46% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF ANTIPYRETIC/ANTI-INFLAMMATORY
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[111]
P-value	= 0.064 ^[112]
Method	Wilcoxon (Mann-Whitney)

Notes:

[111] - Active group: The mean was 40.1 (30.3-50.0) and the median 31.0 (18.0-50.5).

Placebo group: The mean was 72.9 (51.1-94.8) and the median 38.5 (19.5-98.3).

Hodges-Lehman estimator was -12.0 (-29.0, 0.0)

[112] - The active group had an improvement of 19% over placebo. The differences between both groups of treatment were not significant.

Statistical analysis title	TOTAL SCORE BETA2-AGONISTS,INHL CORTICOS,MONTELUKA
Statistical analysis description:	
TOTAL SCORE OF BETA2-AGONISTS, INHALED CORTICOSTEROIDS AND MONTELUKAST	
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[113]
P-value	< 0.001 ^[114]
Method	Wilcoxon (Mann-Whitney)

Notes:

[113] - Active group: The mean was 521.8 (422.6-621.0) and the median 435.5 (221.5-696.3).

Placebo group: The mean was 919.2 (745.9-1092.5) and the median 818.5 (486.8-1275.0).

Hodges-Lehman estimator was -323.0 (-487.0, -168.0).

[114] - The active group had an improvement of 47% over placebo. The differences between both

groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF SALBUTAMOL
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[115]
P-value	< 0.001 ^[116]
Method	Wilcoxon (Mann-Whitney)

Notes:

[115] - Active group: The mean was 147.3 (111.0-183.6) and the median 92.0 (40.3-224.0). (Figure 69 and Table 4)

Placebo group: The mean was 328.9 (242.4-415.3) and the median 252.5 (120.0-387.0).

Hodges-Lehman estimator was -130.0 (-193.0, -65.0)

[116] - The active group had an improvement of 64% over placebo. The differences between both groups of were significant.

Statistical analysis title	TOTAL SCORE OF INHALED BUDESONIDE
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[117]
P-value	< 0.001 ^[118]
Method	Wilcoxon (Mann-Whitney)

Notes:

[117] - Active group: The mean was 179.3 (115.9-242.6) and the median 38.0 (0.0-272.0).

Placebo group: The mean was 392.5 (296.0-489.1) and the median 323.0 (80.0-539.0).

Hodges-Lehman estimator was -185.0 (-282.0, -62.0).

[118] - The active group had an improvement of 88% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF PREDNISOLONE DROPS
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[119]
P-value	= 0.002 ^[120]
Method	Wilcoxon (Mann-Whitney)

Notes:

[119] - Active group: The mean was 5.3 (3.0-7.7) and the median 0.0 (0.0-8.0).

Placebo group: The mean was 12.4 (7.3-17.4) and the median 7.5 (0.0-18.0).

Hodges-Lehman estimator was -3.0 (-7.0, 0.0).

[120] - The active group had an improvement of 100% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	TOTAL SCORE OF MONTELUKAST 4 mg
Comparison groups	Active group v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[121]
P-value	= 0.957 ^[122]
Method	Wilcoxon (Mann-Whitney)

Notes:

[121] - Active group: The mean was 189.9 (164.7-215.1) and the median 212.5 (129.8-254.0).

Placebo group: The mean was 185.4 (157.3-213.6) and the median 206.0 (141.5-257.0).

Hodges-Lehman estimator was 0.0 (-30.0, 34.0).

[122] - The differences between both groups of treatment were not significant.

Statistical analysis title	TOTAL SCORE OF OTHER MEDICATION
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[123]
P-value	= 0.333 ^[124]
Method	Wilcoxon (Mann-Whitney)

Notes:

[123] - Active group: The mean was 173.6 (100.5-246.8) and the median 58.0 (9.8-213.0).

Placebo group: The mean was 191.7 (122.3-261.1) and the median 103.0 (19.0-194.5).

Hodges-Lehman estimator was -11.0 (-58.0, 14.0)

[124] - The active group had an improvement of 44% over placebo. The differences between both groups of treatment were not significant

Statistical analysis title	TOTAL COMBINATION OF SYMPTOM AND MEDICATION SCORES
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[125]
P-value	< 0.001 ^[126]
Method	Wilcoxon (Mann-Whitney)

Notes:

[125] - Active group: The mean was 1088.3 (922.1-1254.4) and the median 925.0 (584.3-1504.0).

Placebo group: The mean was 1760.9 (1505.9-2016.0) and the median 1702.0 (1043.3-2316.3).

Hodges-Lehman estimator was -594.0 (-884.0, -308.0).

[126] - The active group had an improvement of 46% over placebo. The differences between both groups of treatment were significant.

Secondary: Health resource consumption

End point title	Health resource consumption
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End point description:

The unscheduled visits to health centre, emergency service visits, days of hospitalization and cost thereof, complementary tests, phone calls to the doctor or paediatrician were counted per patient.

End point type	Secondary
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End point timeframe:

One year

End point values	Active group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	59		
Units: Percentage				
number (confidence interval 95%)	13.5 (11.2 to 15.9)	17.9 (14.7 to 21.1)		

Statistical analyses

Statistical analysis title	TOTAL HEALTH RESOURCES
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[127]
P-value	= 0.055 ^[128]
Method	Wilcoxon (Mann-Whitney)

Notes:

[127] - Active group: The mean was 13.5 (11.2-15.9) and the median 11.0 (7.0-19.0).

Placebo group: The mean was 17.9 (14.7-21.1) and the median 14.5 (10.0-23.0).

Hodges-Lehman estimator was -3.0 (-9.0, 0.0)

[128] - The active group had an improvement of 24% over placebo. The differences between both groups of treatment were not significant.

Statistical analysis title	DAYS IN THE INTENSIVE CARE UNIT
Comparison groups	Placebo v Active group
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[129]
P-value	= 0.0293 ^[130]
Method	Wilcoxon (Mann-Whitney)

Notes:

[129] - Active group: The mean was 0.0 (0.0-0.0) and the median 0.0 (0.0-0.0).

Placebo group: The mean was 0.1 (-0.1-0.2) and the median 0.0 (0.0-0.0).

Hodges-Lehman estimator was -0.0 (-0.0, 0.0)

[130] - The active group had no improvement over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	NON-PROGRAMMED VISITS TO PAEDIATRICIAN
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[131]
P-value	= 0.151 ^[132]
Method	Wilcoxon (Mann-Whitney)

Notes:

[131] - Active group: The mean was 8.6 (6.8-10.5) and the median 6.5 (3.3-13.8).

Placebo group: The mean was 10.5 (8.5-12.5) and the median 9.5 (4.0-15.0).

Hodges-Lehman estimator was -2.0 (-4.0, 1.0)

[132] - The active group had an improvement of 32% over placebo. The differences between both groups of treatment were not significant.

Statistical analysis title	NON-PROGRAMMED VISITS TO SPECIALIST
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Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[133]
P-value	= 0.15 ^[134]
Method	Wilcoxon (Mann-Whitney)

Notes:

[133] - Active group: The mean was 0.5 (0.2-0.7) and the median 0.0 (0.0-0.8).

Placebo group: The mean was 0.8 (0.4-1.2) and the median 0.0 (0.0-1.0).

Hodges-Lehman estimator was 0.0 (0.0, 0.0)

[134] - The active group had no improvement over placebo. The differences between both groups of treatment were not significant

Statistical analysis title	VISITS TO URGENCIES
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[135]
P-value	= 0.081 ^[136]
Method	Wilcoxon (Mann-Whitney)

Notes:

[135] - Active group: The mean was 2.6 (2.0-3.2) and the median 2.0 (1.0-4.0).

Placebo group: The mean was 3.9 (3.0-4.9) and the median 3.0 (1.0-5.3).

Hodges-Lehman estimator was -1.0 (-2.0, 0.0).

[136] - The active group had an improvement of 33% over placebo. The differences between both groups of treatment were not significant.

Statistical analysis title	DAYS OF HOSPITALIZATION
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[137]
P-value	= 0.916 ^[138]
Method	Wilcoxon (Mann-Whitney)

Notes:

[137] - Active group: The mean was 0.7 (0.2-1.3) and the median 0.0 (0.0-0.0).

Placebo group: The mean was 0.9 (0.2-1.5) and the median 0.0 (0.0-0.0).

Hodges-Lehman estimator was 0.0 (0.0, 0.0)

[138] - The active group had no improvement over placebo. The differences between both groups of treatment were not significant

Statistical analysis title	COMPLEMENTARY TESTS
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[139]
P-value	= 0.61 ^[140]
Method	Wilcoxon (Mann-Whitney)

Notes:

[139] - Active group: The mean was 0.7 (0.4-1.0) and the median 0.0 (0.0-1.0).

Placebo group: The mean was 0.6 (0.3-0.9) and the median 0.0 (0.0-1.0).

[140] - The active group had no improvement over placebo. The differences between both groups of treatment were not significant.

Statistical analysis title	TELEPHONE CALLS TO PEDIATRITIAN
Comparison groups	Active group v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[141]
P-value	= 0.025 ^[142]
Method	Wilcoxon (Mann-Whitney)

Notes:

[141] - Active group: The mean was 0.4 (0.2-0.6) and the median 0.0 (0.0-0.8).

Placebo group: The mean was 1.1 (0.6-1.6) and the median 0.0 (0.0-1.0).

Hodges-Lehman estimator was 0.0 (0.0, 0.0).

[142] - The active group had no improvement over placebo. The differences between both groups of treatment were significant.

Secondary: Social resources

End point title	Social resources
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End point description:

Number of the absenteeism days from nursery, caregivers to the child at home and during hospital admissions per patient.

End point type	Secondary
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End point timeframe:

One year

End point values	Active group	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	62	59		
Units: Percentage				
number (confidence interval 95%)	23 (5.4 to 40.5)	24.7 (11.9 to 37.5)		

Statistical analyses

Statistical analysis title	DAYS OF SCHOOL/KINDERGARTEN ABSENTEEISM
Comparison groups	Active group v Placebo
Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[143]
P-value	= 0.031 ^[144]
Method	Wilcoxon (Mann-Whitney)

Notes:

[143] - Active group: The mean was 15.4 (6.4-24.3) and the median 4.0 (0.0-17.3).

Placebo group: The mean was 19.4 (11.8-27.0) and the median 11.0 (2.0-25.0).

Hodges-Lehman estimator was -3.0 (-9.0, 0.0)

[144] - The active group had an improvement of 64% over placebo. The differences between both groups of treatment were significant.

Statistical analysis title	CAREGIVERS
Comparison groups	Active group v Placebo

Number of subjects included in analysis	121
Analysis specification	Pre-specified
Analysis type	superiority ^[145]
P-value	= 0.04 ^[146]
Method	Wilcoxon (Mann-Whitney)

Notes:

[145] - Active group: The mean was 23.0 (5.4-40.5) and the median 5.5 (0.0-19.0).

Placebo group: The mean was 24.7 (11.9-37.5) and the median 13.0 (2.0-27.0)

Hodges-Lehman estimator was -2.0 (-10.0, 0.0)

[146] - The active group had an improvement of 58% over placebo. The differences between both groups of treatment were significant.

Adverse events

Adverse events information

Timeframe for reporting adverse events:

One year

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	24.0
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Reporting groups

Reporting group title	Active
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Active	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 61 (0.00%)	1 / 59 (1.69%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Epileptic seizure			
subjects affected / exposed	0 / 61 (0.00%)	1 / 59 (1.69%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Active	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	36 / 61 (59.02%)	42 / 59 (71.19%)	
Vascular disorders			
Epistaxis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	
occurrences (all)	2	0	
Surgical and medical procedures			
Adenotonsillectomy			

subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 59 (0.00%) 0	
General disorders and administration site conditions			
General malaise			
subjects affected / exposed	1 / 61 (1.64%)	2 / 59 (3.39%)	
occurrences (all)	3	2	
Fatigue			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Heart murmur			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Aphthas			
subjects affected / exposed	0 / 61 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Immune system disorders			
Hypoglycemia			
subjects affected / exposed	0 / 61 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Atopic Eczema			
subjects affected / exposed	1 / 61 (1.64%)	2 / 59 (3.39%)	
occurrences (all)	2	2	
Urticaria			
subjects affected / exposed	2 / 61 (3.28%)	3 / 59 (5.08%)	
occurrences (all)	2	3	
Anaphylaxis			
subjects affected / exposed	0 / 61 (0.00%)	1 / 59 (1.69%)	
occurrences (all)	0	1	
Social circumstances			
Stomatitis			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	
occurrences (all)	1	0	
Psychiatric disorders			
Apnoea			
subjects affected / exposed	1 / 61 (1.64%)	0 / 59 (0.00%)	
occurrences (all)	1	0	

Investigations Kidney stones subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 59 (0.00%) 0	
Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) Head injury subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1 0 / 61 (0.00%) 0	2 / 59 (3.39%) 2 4 / 59 (6.78%) 4	
Blood and lymphatic system disorders Iron-deficiency anaemia subjects affected / exposed occurrences (all) Adenitis subjects affected / exposed occurrences (all) Neutropenia subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2 1 / 61 (1.64%) 1 1 / 61 (1.64%) 1	3 / 59 (5.08%) 3 0 / 59 (0.00%) 0 0 / 59 (0.00%) 0	
Eye disorders Corneal ulcer subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	1 / 59 (1.69%) 1	
Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) Gastroenteritis subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all) Constipation	5 / 61 (8.20%) 6 5 / 61 (8.20%) 5 2 / 61 (3.28%) 2	9 / 59 (15.25%) 11 13 / 59 (22.03%) 16 2 / 59 (3.39%) 3	

subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2	0 / 59 (0.00%) 0	
Abdominal pain subjects affected / exposed occurrences (all)	2 / 61 (3.28%) 2	0 / 59 (0.00%) 0	
Oral candidiasis subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	0 / 59 (0.00%) 0	
Hepatobiliary disorders Herpetic Gingivoestomatitis subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	1 / 59 (1.69%) 1	
Skin and subcutaneous tissue disorders Dermatitis subjects affected / exposed occurrences (all)	4 / 61 (6.56%) 6	9 / 59 (15.25%) 11	
Hand-foot-and-mouth disease subjects affected / exposed occurrences (all)	5 / 61 (8.20%) 5	1 / 59 (1.69%) 1	
Scarlet fever subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	2 / 59 (3.39%) 3	
Renal and urinary disorders Nephrocalcinosis subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 59 (0.00%) 0	
Pyelonephritis subjects affected / exposed occurrences (all)	1 / 61 (1.64%) 1	0 / 59 (0.00%) 0	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 61 (0.00%) 0	2 / 59 (3.39%) 2	
Musculoskeletal and connective tissue disorders Synovitis subjects affected / exposed occurrences (all)	3 / 61 (4.92%) 3	1 / 59 (1.69%) 1	

<p>Infections and infestations</p> <p>Abscess</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 61 (1.64%)</p> <p>1</p>	<p>1 / 59 (1.69%)</p> <p>1</p>	
<p>Cellulitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 61 (1.64%)</p> <p>1</p>	<p>1 / 59 (1.69%)</p> <p>1</p>	
<p>Chickenpox</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>4 / 61 (6.56%)</p> <p>4</p>	<p>1 / 59 (1.69%)</p> <p>1</p>	
<p>Conjunctivitis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>10 / 61 (16.39%)</p> <p>14</p>	<p>4 / 59 (6.78%)</p> <p>6</p>	
<p>Herpes Labialis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 61 (0.00%)</p> <p>0</p>	<p>1 / 59 (1.69%)</p> <p>1</p>	
<p>Facial herpes</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 61 (1.64%)</p> <p>1</p>	<p>0 / 59 (0.00%)</p> <p>0</p>	
<p>Mononucleosis</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>1 / 61 (1.64%)</p> <p>1</p>	<p>0 / 59 (0.00%)</p> <p>0</p>	
<p>Metabolism and nutrition disorders</p> <p>Coeliac disease</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 61 (0.00%)</p> <p>0</p>	<p>1 / 59 (1.69%)</p> <p>1</p>	
<p>Mouth Bleeding</p> <p>subjects affected / exposed</p> <p>occurrences (all)</p>	<p>0 / 61 (0.00%)</p> <p>0</p>	<p>1 / 59 (1.69%)</p> <p>2</p>	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 June 2013	<p>Se incluye un centro nuevo para conseguir el tamaño de la muestra establecido en el protocolo y no tener que solicitar una ampliación del periodo de reclutamiento.</p> <p>Este estudio podría revelar que la mejora de inmunidad frente a estos virus se debe a un mecanismo de reconocimiento cruzado: Es concebible que la mejora de la respuesta frente a estos virus en individuos tratados con el producto se traduzca en cambios en la identidad y número (breadth) de epítomos específicos de los virus que son reconocidos. Por ello, en este objetivo sintetizaremos epitopos solapantes correspondiente a las proteínas de la capsida de una cepa de estos virus y mediante ensayos de producción de citocinas por ELISPOT determinaremos el número e identidad de los péptidos que son reconocidos en los individuos antes y a lo largo de las inmunizaciones. Los péptidos que sean objeto de reconocimiento se compararán con los proteomas de las bacterias incluidas en el producto.</p>
02 January 2015	<p>El Dr. Rafael Calderón deja de prestar sus servicios en el Hospital de Manises, y por tanto como Investigador Principal del ensayo. El nuevo Investigador Principal será la Dra. M^a José Palao Ortuño. Actualmente la Dra. Palao es Investigador Colaborador de este ensayo y desempeña las mismas funciones que el Investigador Principal.</p> <p>Se amplía el periodo de reclutamiento a 3 años, debido a la imposibilidad de reclutar el nº de sujetos establecidos en el protocolo (120), en el periodo establecido de 2 años. Por ello también se amplía la duración del ensayo un año más.</p>

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported