Clinical trial results:
Randomized double-blind placebo-controlled prospective, parallel, multicentre clinical trial of bacterial polyvalent vaccine (BACTEK ®) administered by sublingual mucosa in subjects with chronic obstructive pulmonary disease (COPD) for efficacy evaluation, safety, and immunomodulatory response.

Summary

EudraCT number	2012-003253-28
Trial protocol	ES
Global end of trial date	23 April 2023

Results information

Result version number	v1 (current)
This version publication date	09 May 2024
First version publication date	09 May 2024
Summary attachment (see zip file)	MV130-SLG-001 Synopsis_23Apr24 (MV130-SLG-001 Synopsis_23Apr24.pdf)

Trial information

Trial identification

Sponsor protocol code	MV130-SLG-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01842360
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Inmunotek S.L.
Sponsor organisation address	calle Punto Mobi 5, Alcalá de Henares, Spain, 28805
Public contact	Miguel Casanovas; Medical Director, Inmunotek S.L., 34 912908942, mcasanovas@inmunotek.com
Scientific contact	Miguel Casanovas; Medical Director, Inmunotek S.L., 34 912908942, 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	23 April 2024
Is this the analysis of the primary completion data?	Yes
Primary completion date	23 April 2023
Global end of trial reached?	Yes
Global end of trial date	23 April 2023
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, compared with placebo, in subjects with moderate and severe COPD based on the number of exacerbations of COPD .

Protection of trial subjects:

All subjects received the first dose at the hospital and were trained in the proper administration of the drug. The subsequent doses were administered at subjects's home. All adverse events that occurred during the course of the study were recorded and assessed. Protection of Personal Data and guarantee of digital rights. Regulation (Eu) 2016/679 of the European Parliament and of The Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and repealing Directive 95/46/EC (General Data Protection Regulation). To ensure the rights of the subjects, the principal investigator or collaborating researchers, through the information sheet explained, the objectives and requirements of the study, the nature of the study drug, and its possible side effects, to the subject. The information to be provided includes: a description of the study endpoints, the methodology used, the type of treatment, the benefits that the subject may obtain from the treatment as well as the risks they may have and the right to withdraw from study if desired.

Background therapy:

Currently, antibiotics remain the main strategy for the treatment of recurrent respiratory tract infections. However, these present with a number of limitations. In fact, we are currently in an antibiotic crisis due to the rapidly increasing antimicrobial resistance worldwide. In this sense, novel preventive strategies are urgently needed. A number of studies have demonstrated sublingual administration of Bactek (MV130) is able to significantly reduce the number of respiratory infectious clinical episodes in children and adults. The sublingual route for administration of bacterial preparations is very safe and effective for stimulating, in a strong and long-lasting way, the antigen-specific mucosa and the systemic humoral and cellular immunity. Stimulation of the oral mucosa may produce effects in the distant mucosa, by activating effector mechanisms of innate and acquired immunity through the mucosal associated lymphoid tissue (MALT). The oral cavity (inductive site) contains a high density of antigen-presenting cells with a high stimulating activity. These cells subsequently migrate to the lymph nodes, where they interact with T and B lymphocytes to induce their differentiation to effector cells. After their activation, the lymphocytes re-circulate through the different compartments of the mucosa-associated lymphoid tissue (MALT), and access different mucous membranes, including the respiratory tract (effector site).

Evidence for comparator: -

Actual start date of recruitment	16 April 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Spain: 198
Worldwide total number of subjects	198
EEA total number of subjects	198

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)	61
From 65 to 84 years	137
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The time of recruitment was between May 2013 (first patient enrolled) and July 2019 (last patient enrolled).

Pre-assignment

Screening details:

This study included adult subjects diagnosed of moderate or severe COPD (3 or more moderate or severe exaerbations in the previous year). Subjects screened were 198. Number of subjects who received treatment (excluded screening failures) were 142. Efficacy evaluable population (Intention-to-treat) were 198. The immunological study were 60.

Period 1

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

Blinding implementation details:

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Group I Active treatment for 12 months + 6 months follow-up

Arm description:

Sublingual MV130 treatment at a dose of 300 FTU. Subjects in Group I received active treatment consisting of a whole-cell inactivated bacterial vaccine sublingually for 12 months (i.e. MV130 12M).

Arm type	Experimental
Investigational medicinal product name	Bactek
Investigational medicinal product code	MV130
Other name	
Pharmaceutical forms	Sublingual spray
Routes of administration	Sublingual use

Dosage and administration details:

Sublingual MV130 treatment at a dose of 300 FTU, administered to 97 subjects with recurrent moderate or severe COPD exacerbations, daily for 12 months. The active trial medication was a polyvalent bacterial vaccine; the pharmaceutical form was a glycerinated suspension containing a mixture of four inactivated non-lysate bacterial concentrates (V101 Staphylococcus epidermidis 15%, V102 Staphylococcus aureus 15%, V104 Streptococcus pneumoniae 60%, V113 Klebsiella pneumoniae 4%, V103 Haemophilus influenzae 3%, Moraxella catarrhalis 3%) as active substance, at a final concentration of 300 Formazin Turbidity Units (FTU). As excipients, it contains 0.63 g of glycerol, artificial pineapple flavouring (0.01 mL), sodium chloride (9 mg) and water (q.s. for 1 mL) per mL. The trial medication was administered through the sublingual route, applying two sprays daily.

Arm title	Group II placebo for 12 months + 6 months follow-up

Arm description:

Subjects in Group II received placebo sublingually for 12 months.

Arm type	Placebo

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

Dosage and administration details:

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

Number of subjects in period 1	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up
Started	97	101
Completed	63	79
Not completed	34	22
Consent withdrawn by subject	24	9
Adverse event, non-fatal	3	5
Non compliance	2	1
Discontinued intervention	2	1
Lost to follow-up	3	6

Baseline characteristics

Reporting groups

Reporting group title	Group I Active treatment for 12 months + 6 months follow-up
Reporting group description:	
Sublingual MV130 treatment at a dose of 300 FTU. Subjects in Group I received active treatment consisting of a whole-cell inactivated bacterial vaccine sublingually for 12 months (i.e. MV130 12M).	
Reporting group title	Group II placebo for 12 months + 6 months follow-up
Reporting group description:	
Subjects in Group II received placebo sublingually for 12 months.	

Reporting group values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Total
Number of subjects	97	101	198
Age categorical			
Individuals aged 44–84 years were enrolled. The median age was 72.0 [interquartile range, IQR, 65.0–77.0] and 68 [IQR, 61.0–76.0] years for groups receiving placebo and MV130 respectively.			
Units: Subjects			
Adults (18-64 years)	30	31	61
From 65-84 years	67	70	137
Age continuous			
Units: years			
median	68.0	72.0	
inter-quartile range (Q1-Q3)	61.0 to 76.0	65.0 to 77.0	-
Gender categorical			
Adult subjects with a definite diagnosis of moderate or severe COPD (3 or more moderate or severe COPD exacerbations in the previous 12 months).			
Units: Subjects			
Female	19	25	44
Male	78	76	154

Subject analysis sets

Subject analysis set title	Efficacy ITT evaluable population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
As stated in the protocol, efficacy analyses were carried out by intention-to-treat (ITT). Evaluable ITT population included all randomized subjects. The background and demographic data was described in the ITT population according to the treatment assignment at randomization.	
Subject analysis set title	Efficacy PP evaluable population
Subject analysis set type	Per protocol
Subject analysis set description:	
Evaluable per-protocol population included randomized subjects who completed the efficacy period and adequately complied with the protocol.	
Subject analysis set title	Immunological study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The planned number of subjects included in the trial but also in the immunological sub-study was 60.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety analysis included all randomized subjects, i.e. 198 individuals: 101 placebo (P) and 97 MV130.

Reporting group values	Efficacy ITT evaluable population	Efficacy PP evaluable population	Immunological study
Number of subjects	198	142	60
Age categorical			
Individuals aged 44–84 years were enrolled. The median age was 72.0 [interquartile range, IQR, 65.0–77.0] and 68 [IQR, 61.0–76.0] years for groups receiving placebo and MV130 respectively.			
Units: Subjects			
Adults (18-64 years)	61	63	
From 65-84 years	137	79	
Age continuous			
Units: years			
median	69.0	68.8	
inter-quartile range (Q1-Q3)	63 to 76	63 to 75	
Gender categorical			
Adult subjects with a definite diagnosis of moderate or severe COPD (3 or more moderate or severe COPD exacerbations in the previous 12 months).			
Units: Subjects			
Female	44	35	
Male	154	107	

Reporting group values	Safety		
Number of subjects	198		
Age categorical			
Individuals aged 44–84 years were enrolled. The median age was 72.0 [interquartile range, IQR, 65.0–77.0] and 68 [IQR, 61.0–76.0] years for groups receiving placebo and MV130 respectively.			
Units: Subjects			
Adults (18-64 years)	61		
From 65-84 years	137		
Age continuous			
Units: years			
median	69.0		
inter-quartile range (Q1-Q3)	63 to 76		
Gender categorical			
Adult subjects with a definite diagnosis of moderate or severe COPD (3 or more moderate or severe COPD exacerbations in the previous 12 months).			
Units: Subjects			
Female	44		
Male	154		

End points

End points reporting groups

Reporting group title	Group I Active treatment for 12 months + 6 months follow-up
Reporting group description:	
Sublingual MV130 treatment at a dose of 300 FTU. Subjects in Group I received active treatment consisting of a whole-cell inactivated bacterial vaccine sublingually for 12 months (i.e. MV130 12M).	
Reporting group title	Group II placebo for 12 months + 6 months follow-up
Reporting group description:	
Subjects in Group II received placebo sublingually for 12 months.	
Subject analysis set title	Efficacy ITT evaluable population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
As stated in the protocol, efficacy analyses were carried out by intention-to-treat (ITT). Evaluable ITT population included all randomized subjects. The background and demographic data was described in the ITT population according to the treatment assignment at randomization.	
Subject analysis set title	Efficacy PP evaluable population
Subject analysis set type	Per protocol
Subject analysis set description:	
Evaluable per-protocol population included randomized subjects who completed the efficacy period and adequately complied with the protocol.	
Subject analysis set title	Immunological study
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The planned number of subjects included in the trial but also in the immunological sub-study was 60.	
Subject analysis set title	Safety
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety analysis included all randomized subjects, i.e. 198 individuals: 101 placebo (P) and 97 MV130.	

Primary: Number of COPD exacerbations due to infectious episodes.

End point title	Number of COPD exacerbations due to infectious episodes.
End point description:	
End point type	Primary
End point timeframe:	
Comparison in the number of COPD episodes in the two study groups in the 18-month study period.	

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	Efficacy PP evaluable population
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	97	101	198	142
Units: episodes				
median (inter-quartile range (Q1-Q3))	2.0 (1.0 to 3.0)	3.0 (1.0 to 5.0)	2.0 (1.0 to 4.0)	2.0 (1.0 to 4.8)

Statistical analyses

Statistical analysis title	Median number of COPD exacerbations.
Comparison groups	Group I Active treatment for 12 months + 6 months follow-up v Group II placebo for 12 months + 6 months follow-up
Number of subjects included in analysis	198
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.01
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Decrease in the rate of COPD exacerbations per study group at 12 months (end of the trial treatment) and 6 months after the trial's termination (follow-up).

End point title	Decrease in the rate of COPD exacerbations per study group at 12 months (end of the trial treatment) and 6 months after the trial's termination (follow-up).

End point description:

Incidence is the number of new events per total subjects in the sample population. Incidence frequency is the number of events in a period, usually one year.

End point type	Secondary

End point timeframe:

The 18 months duration of the study by person-years incidence rates and incidence-risk ratio.

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: rate				
number (not applicable)	1.86	2.67	2.30	

Statistical analyses

Statistical analysis title	Incidence-rate comparison

Statistical analysis description:

Incidence is the number of new events per total subjects in the sample. Incidence frequency is the number of events in a period, usually one year. Thus, we see that the incidence of exacerbations in one year per treatment group of MV130/Placebo treatment group is 1.87/2.68 (≈1.9/2.7) new exacerbations which is a difference of 0.81 (0.44-1.18) exacerbations between the two groups and a P<0.001. This is called incidence rate.

Comparison groups	Group I Active treatment for 12 months + 6 months follow-up v Group II placebo for 12 months + 6 months follow-up v Efficacy ITT evaluable population
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Poisson
Confidence interval	
level	95 %
sides	2-sided

Secondary: Decrease in severity of COPD exacerbations.

End point title	Decrease in severity of COPD exacerbations.

End point description:

The severity of exacerbations was to be measured by the consumption of health care resources: ED/Hospitalisation/ICU/Consultations visits, as follows:

ICU hospitalisation 4 points
Hospitalisation 3 points
Emergency room visit 2 points
Consultation resulting in change in usual treatment 1 point

End point type	Secondary

End point timeframe:

18 months.

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: points				
median (inter-quartile range (Q1-Q3))	1 (0 to 5)	3 (1 to 23)	2 (0 to 9)	

Statistical analyses

Statistical analysis title	Decrease in COPD exacerbation severity

Statistical analysis description:

The mean of health care consumption was 17.5±34.7 points in the placebo group versus 9.2±27.9 points in the MV130 group.

Comparison groups	Group II placebo for 12 months + 6 months follow-up v Group I Active treatment for 12 months + 6 months follow-up v Efficacy ITT evaluable population
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0094
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Time elapsed between the start of the treatment and the first COPD exacerbation.

End point title	Time elapsed between the start of the treatment and the first COPD exacerbation.

End point description:

For reference, median survival or event-free times are reported with the 95% CI of the median.

End point type	Secondary

End point timeframe:

18 months.

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: time				
median (confidence interval 95%)	6.35 (4.41 to 9.00)	4.42 (3.38 to 6.61)	5.52 (4.06 to 6.61)	

Statistical analyses

Statistical analysis title	Time free of events

Statistical analysis description:

The median time to first event in the placebo group is 4.4 months and in the treatment group is 6.4 months.

Comparison groups	Group I Active treatment for 12 months + 6 months follow-up

	v Group II placebo for 12 months + 6 months follow-up v Efficacy ITT evaluable population
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3917
Method	Logrank
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard error of the mean

Secondary: Use of drugs (antibiotics, corticosteroids, etc).

End point title	Use of drugs (antibiotics, corticosteroids, etc).

End point description:

The use of drugs will be calculated using the following index:
- antibiotics: 1 point
- inhaled corticosteroids: 2 points
- sistemic corticosteroids: 3 points
- use of oxyygen: 4 points
- use of mechanical ventilation: 5 points

End point type	Secondary

End point timeframe:

18 months.

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: points				
median (inter-quartile range (Q1-Q3))	24 (0 to 71)	40 (9 to 112)	30 (3 to 84)	

Statistical analyses

Statistical analysis title	Total use of drugs

Statistical analysis description:

The use of oxygen and mechanical ventilation is not available. The other three index are used. As for the previous index the number of days with any of these drugs is used.

Comparison groups	Group I Active treatment for 12 months + 6 months follow-up v Group II placebo for 12 months + 6 months follow-up v Efficacy ITT evaluable population

Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0232
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Number of hospitalizations due to COPD exacerbations.

End point title	Number of hospitalizations due to COPD exacerbations.

End point description:

There were 26 hospitalizations in 16 patients in the MV130 group versus 51 hospitalizations in 29 patients in the placebo group (Fisher's exact test of the number of patients, P=0.044).
The same patient could have more than one hospitalizations.

End point type	Secondary

End point timeframe:

18 months.

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: number				
median (inter-quartile range (Q1-Q3))	0.0 (0.0 to 0.0)	0.0 (0.0 to 1.0)	0.0 (0.0 to 0.0)	

Statistical analyses

Statistical analysis title	Number of hospitalizations per patient.

Statistical analysis description:

The mean number of hospitalizations in the MV130 group was 0.27±0.91 and in the placebo group 0.5±1.05 hospitalizations (exact MW, P=0.042).In relation to ICU stay, there were only 3 ICU stays: 1 in the MV130 group (6 days duration) and 2 in the placebo group (6 and 13 days duration).

Comparison groups	Group II placebo for 12 months + 6 months follow-up v Group I Active treatment for 12 months + 6 months follow-up v Efficacy ITT evaluable population

Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0319
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Days of hospitalization due to COPD exacerbations.

End point title	Days of hospitalization due to COPD exacerbations.
End point description:	
End point type	Secondary
End point timeframe:	
18 months.	

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: days				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 6)	0 (0 to 0)	

Statistical analyses

Statistical analysis title	Hospitalisation days
Statistical analysis description:	
The mean number of days of hospitalization in the MV130 group is 2.1 and in the placebo group 4.1 days. Significant differences (P=0.0264) can be observed.	
Comparison groups	Group I Active treatment for 12 months + 6 months follow-up v Group II placebo for 12 months + 6 months follow-up v Efficacy ITT evaluable population
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0264
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)

Confidence interval	
level	95 %
sides	2-sided

Secondary: Number of visits to the Emergency Room.

End point title	Number of visits to the Emergency Room.
End point description:	
End point type	Secondary
End point timeframe:	
18 months.	

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: number				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 1)	0 (0 to 1)	

Statistical analyses

Statistical analysis title	Mean number of emergency room visits
Statistical analysis description:	
The mean number of emergency room visits was 0.37 (±1.15) for the MV130 group and 0.87 (±1.61) for the placebo group.	
Comparison groups	Group II placebo for 12 months + 6 months follow-up v Group I Active treatment for 12 months + 6 months follow-up v Efficacy ITT evaluable population
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0037
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Number of unscheduled medical consultations due to COPD

exacerbations.

End point title	Number of unscheduled medical consultations due to COPD exacerbations.

End point description:

End point type	Secondary

End point timeframe:

18 months.

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: number				
median (inter-quartile range (Q1-Q3))	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	

Statistical analyses

Statistical analysis title	median number of unshcedueled medical visits

Statistical analysis description:

The mean number of emergency room visits was 0.08 (±0.31) for the MV130 group and 0.31 (±0.88) for the placebo group.

Comparison groups	Group I Active treatment for 12 months + 6 months follow-up v Group II placebo for 12 months + 6 months follow-up v Efficacy ITT evaluable population
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1008
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Health-related quality of life, as determined by an adapted version of the specific CAT test.

End point title	Health-related quality of life, as determined by an adapted version of the specific CAT test.

End point description:

End point type	Secondary

End point timeframe:

18 months.

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Efficacy ITT evaluable population	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: Points				
median (inter-quartile range (Q1-Q3))	-1.5 (-7.0 to 1.5)	-1.0 (-5.0 to 3.0)	-1.0 (-6.0 to 2.0)	

Statistical analyses

Statistical analysis title	Mean differences in CAT score

Statistical analysis description:

Statistical analysis of differences at 12 months is shown as it is the treatment time period. The difference between study groups is 2.2 (CI 95% -4.3, -0.14). At 18 months the difference is of 1.5 points (CI 95% -3.8, 0.7).

Comparison groups	Group I Active treatment for 12 months + 6 months follow-up v Group II placebo for 12 months + 6 months follow-up v Efficacy ITT evaluable population
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0367
Method	t-test, 2-sided
Parameter estimate	Median difference (final values)
Confidence interval	
level	95 %
sides	2-sided
Variability estimate	Standard deviation

Secondary: Healthcare expenditure resulting from resource consumption during episodes of COPD exacerbations occurring during the trial period.

End point title	Healthcare expenditure resulting from resource consumption during episodes of COPD exacerbations occurring during the trial period.

End point description:

Healthcare expenditure was assessed as the sum of:
- Complementary tests
- Programmed visits to the specialist
- Total number of visits to the specialist
- Non-programmed visits to the specialist
- ICU hospitalization days
- Vists to the emergency room
- Days hospitalized

- Sum of antibiotics
- Number of visits to GP
- Sum of oral corticosteroids
- Number of telephone calls to the GP
- Sum of inhalers
- Home visits
- Sum of antipyretics

The total consumption of medical resources was addedd for the placebo and MV130 groups. Differences in total score were evaluated and related to healthcare expenditure. A sum of the total resource consumption showed a total score of 8231 in the placebo group compared with 5202 in the MV130 group, showing a 36.8% resource consumption reduction and thus a direct association with a reduction in healthcare expenditure.

End point type	Secondary
End point timeframe:	
18 months.	

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	97	101		
Units: sum	5202	8231		

Statistical analyses

No statistical analyses for this end point

Secondary: Adverse events and overall tolerability (adverse reactions).

End point title	Adverse events and overall tolerability (adverse reactions).
End point description:	
Total number of adverse events in Active (MV130) and Placebo groups were compared.	
End point type	Secondary
End point timeframe:	
18 months.	

End point values	Group I Active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	Safety	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	97	101	198	
Units: Number	116	113	229	

Statistical analyses

Statistical analysis title	Differences in total number of adverse events.

Statistical analysis description:

The total number of adverse events were 229, from them 113 (49.6%) were from the placebo group and 116 (50.4%) were from the active group. These 229 events were experienced in 103 subjects, 49 (48.5%) from the placebo group, while 54 (55.6%) belonging to group receiving MV130. No significant differences between treatment groups were found (Fisher's exact test, P=0.3234).

Comparison groups	Group I Active treatment for 12 months + 6 months follow-up v Group II placebo for 12 months + 6 months follow-up v Safety
Number of subjects included in analysis	396
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3234
Method	Fisher exact
Confidence interval	
level	95 %
sides	2-sided

Adverse events

Adverse events information

Timeframe for reporting adverse events:

18 months.

Adverse event reporting additional description:

Safety was evaluated throughout the study by recording all adverse events and all adverse reactions.

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	25.0

Reporting groups

Reporting group title	Group I active treatment for 12 months + 6 months follow-up
Reporting group description: -	
Reporting group title	Group II placebo for 12 months + 6 months follow-up

Reporting group description: -

Serious adverse events	Group I active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 97 (8.25%)	12 / 101 (11.88%)	
number of deaths (all causes)	1	2	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Metastases to central nervous system			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Brain neoplasm			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma of colon			

subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Adenocarcinoma pancreas			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Unstable angina			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Surgical and medical procedures			
Surgery			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Petit mal epilepsy			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Cerebrovascular accident			
subjects affected / exposed	0 / 97 (0.00%)	2 / 101 (1.98%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemorrhage intracranial			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Apendicitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Pulmonary embolism			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemoptysis			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary aspergillosis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Mycobacterium avium complex infection			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cytomegalovirus infection			

subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Group I active treatment for 12 months + 6 months follow-up	Group II placebo for 12 months + 6 months follow-up	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 97 (46.39%)	36 / 101 (35.64%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Prostatic adenoma			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Thyroid adenoma			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Phlebitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Intermittent claudication			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Surgical and medical procedures			
Cholecystectomy			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Circumcision			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Dental implantation			

subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Hernia repair			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Pterygium operation			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Surgery	Additional description: Surgery due to inversion of left eye lid.		
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	1 / 97 (1.03%)	3 / 101 (2.97%)	
occurrences (all)	1	4	
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 97 (0.00%)	3 / 101 (2.97%)	
occurrences (all)	0	3	
Oedema peripheral			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Temperature regulation disorder			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Pyrexia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Seasonal allergy			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Prostatitis			
subjects affected / exposed	2 / 97 (2.06%)	2 / 101 (1.98%)	
occurrences (all)	2	2	
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Respiratory, thoracic and mediastinal disorders			
Acute sinusitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Catarrh			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Dysphonia			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Epistaxis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Laryngeal oedema			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 97 (2.06%)	0 / 101 (0.00%)	
occurrences (all)	2	0	
Pharyngitis			
subjects affected / exposed	3 / 97 (3.09%)	0 / 101 (0.00%)	
occurrences (all)	5	0	
Pharyngotonsillitis			
subjects affected / exposed	2 / 97 (2.06%)	1 / 101 (0.99%)	
occurrences (all)	2	1	
Rhinitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Rhinorrhoea			

subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Tonsillitis			
subjects affected / exposed	2 / 97 (2.06%)	1 / 101 (0.99%)	
occurrences (all)	2	1	
Upper respiratory tract infection			
subjects affected / exposed	5 / 97 (5.15%)	8 / 101 (7.92%)	
occurrences (all)	5	9	
Investigations			
Lumbar puncture			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Postoperative wound infection			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Epicondylitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Foot fracture			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Fall			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
anemia postoperative			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Upper limb fracture			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Animal bite			

subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	2 / 97 (2.06%)	0 / 101 (0.00%)	
occurrences (all)	3	0	
Cardiac failure congestive			
subjects affected / exposed	0 / 97 (0.00%)	2 / 101 (1.98%)	
occurrences (all)	0	3	
Atrial fibrillation			
subjects affected / exposed	1 / 97 (1.03%)	3 / 101 (2.97%)	
occurrences (all)	1	3	
Tachycardia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Syncope			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Sciatica			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Paraesthesia			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Dizziness			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Ear and labyrinth disorders			

Tinnitus			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Eye disorders			
Blepharitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Conjunctival haemorrhage			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Eye disorder			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Uveitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	1 / 97 (1.03%)	2 / 101 (1.98%)	
occurrences (all)	1	2	
Colitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Constipation			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	4 / 97 (4.12%)	1 / 101 (0.99%)	
occurrences (all)	4	1	
Gastroenteritis			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Gastrointestinal haemorrhage			

subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	2	
Haemorrhoids			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Inguinal hernia			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Large intestine polyp			
subjects affected / exposed	2 / 97 (2.06%)	0 / 101 (0.00%)	
occurrences (all)	2	0	
Odynophagia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Rectal haemorrhage			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Tooth disorder			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis allergic			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Purpura senile			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Dermatitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Urticaria			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	

Renal and urinary disorders			
Renal colic			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Urinary incontinence			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Urinary retention			
subjects affected / exposed	2 / 97 (2.06%)	1 / 101 (0.99%)	
occurrences (all)	2	1	
Urinary tract infection			
subjects affected / exposed	8 / 97 (8.25%)	3 / 101 (2.97%)	
occurrences (all)	13	3	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	6 / 97 (6.19%)	1 / 101 (0.99%)	
occurrences (all)	7	1	
Back pain			
subjects affected / exposed	7 / 97 (7.22%)	1 / 101 (0.99%)	
occurrences (all)	7	2	
Gout			
subjects affected / exposed	0 / 97 (0.00%)	2 / 101 (1.98%)	
occurrences (all)	0	2	
Gouty arthritis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
invertebral disc protusion			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Muscle contracture			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Myopathy			

subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Synovial cyst			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Infections and infestations			
Abcess			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Ear lobe infection			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Gingivitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
helocibacter infection			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Herpes zoster			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Oral candidiasis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Oral herpes			
subjects affected / exposed	0 / 97 (0.00%)	2 / 101 (1.98%)	
occurrences (all)	0	2	
Otitis media acute			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	

Parotitis			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Periodontitis			
subjects affected / exposed	3 / 97 (3.09%)	1 / 101 (0.99%)	
occurrences (all)	4	1	
Postoperative wound infection			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Skin infection			
subjects affected / exposed	1 / 97 (1.03%)	1 / 101 (0.99%)	
occurrences (all)	1	1	
Tooth abscess			
subjects affected / exposed	1 / 97 (1.03%)	2 / 101 (1.98%)	
occurrences (all)	1	2	
Tooth infection			
subjects affected / exposed	1 / 97 (1.03%)	3 / 101 (2.97%)	
occurrences (all)	1	3	
Viral infection			
subjects affected / exposed	1 / 97 (1.03%)	0 / 101 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hypoglycaemia			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	
Diabetes mellitus			
subjects affected / exposed	0 / 97 (0.00%)	1 / 101 (0.99%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 September 2012	- Added details on IMP, administration schedule, study population, permitted medication. - Added clarification on identical formula for all patients. - Study objective and variables homogenized. - Parameters from pharmacogenetic study included. - Justification for 30% reduction in the number of exacerbations included compared to placebo. - Minor typographical corrections.
21 June 2013	-Two new investigators were included, and one was removed. -Added details on administration instructions. - Added subjects suffering severe COPD. - Clarification about when the visits were performed. - Changes on exclusion/inclusion criteria.
12 February 2014	A new study site was included: Hospital Universitario Torrejón de Ardoz.
10 March 2014	A new study site was included: Hospital 12 de Octubre.
29 October 2014	An inclusion criterion was modified (induced sputum instead of bronchoalveolar lavage).
26 October 2015	A new study site was included: Hospital Universitario La Paz.
21 June 2016	Minor typographical corrections.
09 January 2017	A new study site was included: Hospital Universitario de Vic.
21 June 2017	Minor typographical corrections.
29 December 2017	Minor typographical corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported