Clinical trial results:
A Randomized, Placebo-Controlled, Double-blinded, Mechanistic Trial to Investigate the Effects of Broncho-Vaxom® (OM-85 BV) on the Innate Immune System in Patients with COPD

Summary

EudraCT number	2013-001940-71
Trial protocol	GB
Global end of trial date	31 July 2015

Results information

Result version number	v1 (current)
This version publication date	28 August 2016
First version publication date	28 August 2016

Trial information

Trial identification

Sponsor protocol code	BV2013/5

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	OM Pharma SA
Sponsor organisation address	22 rue du Bois-du-Lan, Geneva, Switzerland, CH-1217 Meyrin 2
Public contact	Clinical Research Department, OM Pharma SA, +41 79 171 81 38, lorenz.lehr@viforpharma.com
Scientific contact	Clinical Research Department, OM Pharma SA, +41 22 783 14 59, lorenz.lehr@viforpharma.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	16 June 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 July 2015
Global end of trial reached?	Yes
Global end of trial date	31 July 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the effect of Broncho-Vaxom® (BV) on the phagocytic ability of monocyte-derived macrophages (MDMs), as a measure of the innate immune system, in subjects with Chronic Obstructive Pulmonary Disease (COPD)

Protection of trial subjects:

Prior to initiation of the study, the protocol, the patient information sheet, including the Informed Consent Form (ICF), was reviewed and approved by an Independent Ethics Committees (IEC), operating in accordance with current regulations. Any modifications to the protocol, following initial IEC approval, were submitted to the IEC for review and approval prior to implementation, also implying a new signature of the ICF from patient.
The study was conducted in accordance with the principles of the Declaration of Helsinki, including amendments in force up to and including the time the study was conducted.
The study was conducted in compliance with the International Conference on Harmonisation (ICH) E6 Guideline for Good Clinical Practice (GCP), Committee for Proprietary Medicinal Products Guideline (CPMP/ICH/135/95), and compliant with the European Union Clinical Trial Directive (Directive 2001/20/EC) and/or the Code of Federal Regulations for informed consent and protection of patient rights (21 CFR, Parts 50 and 56).
Before each subject was admitted to the study, a signed and dated informed consent was obtained from the subject (or his/her legally authorised representative) according to the regulatory and legal requirements of the participating country. This consent form was retained by the Investigator as part of the study records. A copy of the document was provided to the subject. No investigations specifically required for the study were conducted until valid consent was obtained. Subjects were informed that their participation in the study was entirely voluntary and would have no effect on clinical care otherwise available and that they could withdraw consent to participate at any time without penalty or loss of further medical treatment. Subjects were told that Competent Authorities and authorised persons could examine their records but that personal information would be treated as strictly confidential and would not be publicly available.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 August 2014
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	United Kingdom: 58
Worldwide total number of subjects	58
EEA total number of subjects	58

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)	10
From 65 to 84 years	46
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

A total of 58 subjects were screened at one site (UK) and all were included in the study. No screening visit was performed for this study and there were no screening failures.
All subjects screened (N=58) were randomised to treatment with either Broncho-Vaxom® (BV) (N=28) or placebo (N=30).

Pre-assignment

Screening details:

Potential subjects were identified and recruited after screening medical records (based on inclusion/exclusion criteria) of subjects in the existing Royal Free Hospital London COPD Exacerbation patient cohort. Subjects matching the study criteria/requirements were invited to participate by mail or during a regular visit at the site.

Period 1

Period 1 title	Treatment period
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Individual study treatment boxes were identified by randomisation number only. BV capsules and placebo capsules were identical in appearance (form, weight, colour, texture of content, etc.) to ensure subject and Investigator blinding.

Arms

Are arms mutually exclusive?	Yes
Arm title	Broncho-Vaxom® (BV)

Arm description:

The dosing regimen was 1 capsule of BV (7.0 mg) per day for 30 days.

Arm type	Experimental
Investigational medicinal product name	Broncho-Vaxom® 7 mg
Investigational medicinal product code	OM-85 BV
Other name	BV
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

Subjects were instructed to take 1 capsule per day for 30 consecutive days during the treatment phase of the study. No treatment was administered during the second phase of the study (i.e., 30-day off-treatment period). The medication was to be taken in the morning on an empty stomach with some fluid.

Arm title	Placebo

Arm description:

The dosing regimen was 1 capsule of placebo per day for 30 days.

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

Dosage and administration details:

Subjects were instructed to take 1 capsule per day for 30 consecutive days during the treatment phase of the study. No treatment was administered during the second phase of the study (i.e., 30-day off-

treatment period). The medication was to be taken in the morning on an empty stomach with some fluid.

Number of subjects in period 1	Broncho-Vaxom® (BV)	Placebo
Started	28	30
Completed	23	26
Not completed	5	4
Adverse event, non-fatal	5	4

Period 2	
Period 2 title	Off-treatment follow-up period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms	
Are arms mutually exclusive?	Yes
Arm title	Broncho-Vaxom® (BV)

Arm description:

No treatment. The study included a 30-day off treatment period between Day 30 (Visit 3) and Day 60 (Visit 4).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Arm title	Placebo

Arm description:

No treatment. The study included a 30-day off treatment period between Day 30 (Visit 3) and Day 60 (Visit 4).

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Broncho-Vaxom® (BV)	Placebo
Started	23	26
Completed	18	22
Not completed	5	4
Adverse event, non-fatal	5	4

Baseline characteristics

Reporting groups	
Reporting group title	Broncho-Vaxom® (BV)
Reporting group description:	
The dosing regimen was 1 capsule of BV (7.0 mg) per day for 30 days.	
Reporting group title	Placebo
Reporting group description:	
The dosing regimen was 1 capsule of placebo per day for 30 days.	

Reporting group values	Broncho-Vaxom® (BV)	Placebo	Total
Number of subjects	28	30	58
Age categorical			
All screened patients			
Units: Subjects			
Adults (18-64 years)	6	5	11
From 65-84 years	22	23	45
85 years and over	0	2	2
Age continuous			
All screened patients			
Units: years			
arithmetic mean	69.93	71.97	
standard deviation	± 7.21	± 8.22	-
Gender categorical			
All screened patients			
Units: Subjects			
Female	8	7	15
Male	20	23	43
Smoking status			
All screened patients			
Units: Subjects			
Smoker	10	12	22
Former smoker	18	18	36
COPD Severity			
All screened patients			
Units: Subjects			
Stage I: mild	1	5	6
Stage II: moderate	12	11	23
Stage III: severe	13	12	25
Stage IV: very severe	2	2	4
Weight			
All screened patients. There was one missing value for placebo group.			
Units: kg			
arithmetic mean	76.32	77	
standard deviation	± 20.41	± 15.17	-
Height			
All screened patients. There was one missing value in placebo group.			

Units: cm			
arithmetic mean	170.46	168.07	
standard deviation	± 9.21	± 6.59	-
Body mass index			
All screened patients. There was one missing value for placebo group.			
Units: kg/m2			
arithmetic mean	26.17	27.11	
standard deviation	± 6.48	± 3.97	-
Forced vital capacity (FVC)			
All screened patients			
Units: litres			
arithmetic mean			
standard deviation	±	±	-
Forced expiratory volume in 1 second (FEV1)			
All screened patients			
Units: litres			
arithmetic mean			
standard deviation	±	±	-
Forced expiratory volume in 1 second (FEV1) predicted			
All screened patients			
Units: % predicted			
arithmetic mean			
standard deviation	±	±	-
FEV1/FVC			
All screened patients			
Units: in %			
arithmetic mean			
standard deviation	±	±	-

Subject analysis sets	
Subject analysis set title	Safety Set (SS)
Subject analysis set type	Safety analysis
Subject analysis set description: All randomised subjects who received at least 1 dose of study medication.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description: All randomised subjects who received at least 1 dose of study drug and had at least 1 baseline and 1 post-baseline assessment of the primary efficacy parameter.	
Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description: All subjects in the Full Analysis Set (FAS) who had no major protocol deviations.	

Reporting group values	Safety Set (SS)	Full Analysis Set (FAS)	Per Protocol Set (PPS)
Number of subjects	58	54	53

Age categorical			
All screened patients			
Units: Subjects			
Adults (18-64 years)	10	9	9
From 65-84 years	46	43	42
85 years and over	2	2	2
Age continuous			
All screened patients			
Units: years			
arithmetic mean	71	70.9	71
standard deviation	± 7.7	± 7.8	± 7.9
Gender categorical			
All screened patients			
Units: Subjects			
Female	15	14	14
Male	43	40	39
Smoking status			
All screened patients			
Units: Subjects			
Smoker	22	20	20
Former smoker	36	34	33
COPD Severity			
All screened patients			
Units: Subjects			
Stage I: mild	6	5	5
Stage II: moderate	23	23	23
Stage III: severe	25	23	22
Stage IV: very severe	4	3	3
Weight			
All screened patients. There was one missing value for placebo group.			
Units: kg			
arithmetic mean	76.7	76.9	77.3
standard deviation	± 17.8	± 18	± 17.9
Height			
All screened patients. There was one missing value in placebo group.			
Units: cm			
arithmetic mean	169.2	169.4	169.6
standard deviation	± 8	± 8.2	± 8.2
Body mass index			
All screened patients. There was one missing value for placebo group.			
Units: kg/m2			
arithmetic mean	26.65	26.66	26.75
standard deviation	± 5.32	± 5.33	± 5.35
Forced vital capacity (FVC)			
All screened patients			
Units: litres			
arithmetic mean	3	3	3
standard deviation	± 0.8	± 0.9	± 0.9
Forced expiratory volume in 1 second (FEV1)			

All screened patients			
Units: litres			
arithmetic mean	1.4	1.4	1.4
standard deviation	± 0.5	± 0.5	± 0.5
Forced expiratory volume in 1 second (FEV1) predicted			
All screened patients			
Units: % predicted			
arithmetic mean	52.7	53.1	53.4
standard deviation	± 18.2	± 17.7	± 17.6
FEV1/FVC			
All screened patients			
Units: in %			
arithmetic mean	46	46.4	46.6
standard deviation	± 12.5	± 12.6	± 12.7

End points

End points reporting groups

Reporting group title	Broncho-Vaxom® (BV)
Reporting group description:	
The dosing regimen was 1 capsule of BV (7.0 mg) per day for 30 days.	
Reporting group title	Placebo
Reporting group description:	
The dosing regimen was 1 capsule of placebo per day for 30 days.	
Reporting group title	Broncho-Vaxom® (BV)
Reporting group description:	
No treatment. The study included a 30-day off treatment period between Day 30 (Visit 3) and Day 60 (Visit 4).	
Reporting group title	Placebo
Reporting group description:	
No treatment. The study included a 30-day off treatment period between Day 30 (Visit 3) and Day 60 (Visit 4).	
Subject analysis set title	Safety Set (SS)
Subject analysis set type	Safety analysis
Subject analysis set description:	
All randomised subjects who received at least 1 dose of study medication.	
Subject analysis set title	Full Analysis Set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised subjects who received at least 1 dose of study drug and had at least 1 baseline and 1 post-baseline assessment of the primary efficacy parameter.	
Subject analysis set title	Per Protocol Set (PPS)
Subject analysis set type	Per protocol
Subject analysis set description:	
All subjects in the Full Analysis Set (FAS) who had no major protocol deviations.	

Primary: Change in concentration of phagocytosed Haemophilus influenzae bacteria

End point title	Change in concentration of phagocytosed Haemophilus influenzae bacteria
End point description:	
Change in phagocytic ability of Monocyte derived macrophages (MDMs) from Baseline (Visit 1, Day -1) to Day 30 (Visit 3), using LOCF (i.e., Day 30 Endpoint), as measured by change in concentration of phagocytosed bacteria following challenge with fluorescently labelled dead bacteria. The change is represented by the standard error of the least squares mean in a mixed analysis model (see subset analysis set). The MDM phagocytosis assay (with H influenzae) was performed on MDMs derived from blood samples collected at Baseline, Day 10, Day 30, and Day 60 (or early termination). The assays were performed at the central laboratory.	
End point type	Primary
End point timeframe:	
From Baseline to Day 30 Endpoint. For the primary analysis, last observation carried forward (LOCF) imputation was used for missing values at Day 30 (i.e., defined as Day 30 Endpoint).	

End point values	Broncho-Vaxom® (BV)	Placebo	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	27	54	
Units: SI units (Relative Fluorescence Units)				
arithmetic mean (standard deviation)	-265 (± 983.7)	-405.1 (± 985.6)	-335.1 (± 977.8)	

Statistical analyses

Statistical analysis title	Bacteria concentration change H influenzae

Statistical analysis description:

Change in phagocytic ability of MDMs from Baseline to Day 30 Endpoint (end of treatment), comparing both treatments. Phagocytic ability was measured as the change in concentration of phagocytosed bacteria. The effect of BV treatment (relative to placebo) was tested on the FAS using a mixed model with treatment, baseline bacteria concentration, gender, and COPD disease stage (IV versus I to III) as fixed effects.

Comparison groups	Broncho-Vaxom® (BV) v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	< 0.001 [2]
Method	t-test, 2-sided
Parameter estimate	least squares mean (LSM)
Point estimate	169.771
Confidence interval	
level	95 %
sides	2-sided
lower limit	-289.204
upper limit	628.746
Variability estimate	Standard error of the mean
Dispersion value	228.3938

Notes:

[1] - Interactions were tested using the primary model, including treatment by gender and treatment by stage of disease interactions (none of these interaction terms were significant at 0.1 and were excluded from the final model).
For the primary analysis, imputation of the last post-baseline result (following LOCF principles) was used for missing values at Day 30 (i.e., defined as Day 30 Endpoint).
[2] - MIXED MODEL:
p value for treatment: 0.4608
p value for baseline bacteria concentration: <0.0001
p value for gende: 0.3357
p value for COPD disease stage: 0.5528

Primary: Change in concentration of phagocytosed Streptococcus pneumoniae bacteria

End point title	Change in concentration of phagocytosed Streptococcus pneumoniae bacteria

End point description:

Change in phagocytic ability of Monocyte derived macrophages (MDMs) from Baseline (Visit 1, Day -1) to Day 30 (Visit 3), using LOCF (i.e., Day 30 Endpoint), as measured by change in concentration of phagocytosed bacteria following challenge with fluorescently labelled dead bacteria. The change is represented by the standard error of the least squares mean in a mixed analysis model (see subset analysis set).
The MDM phagocytosis assay (with S pneumoniae) was performed on MDMs derived from blood samples

collected at Baseline, Day 10, Day 30, and Day 60 (or early termination). The assays were performed at the central laboratory.

End point type	Primary

End point timeframe:

From Baseline to Day 30 Endpoint.
For the primary analysis, last observation carried forward (LOCF) imputation was used for missing values at Day 30 (i.e., defined as Day 30 Endpoint).

End point values	Broncho-Vaxom® (BV)	Placebo	Full Analysis Set (FAS)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	27	27	54	
Units: SI units (Relative Fluorescence Units)				
arithmetic mean (standard deviation)	-564 (± 1266)	-416.7 (± 971.5)	-490.4 (± 1120.2)	

Statistical analyses

Statistical analysis title	Bacteria concentration change S pneumoniae

Statistical analysis description:

Change in phagocytic ability of MDMs from Baseline to Day 30 Endpoint (end of treatment), comparing both treatments. Phagocytic ability was measured as the change in concentration of phagocytosed bacteria. The effect of BV treatment (relative to placebo) was tested on the FAS using a mixed model with treatment, baseline bacteria concentration, gender, and COPD disease stage (IV versus I to III) as fixed effects.

Comparison groups	Broncho-Vaxom® (BV) v Placebo
Number of subjects included in analysis	54
Analysis specification	Pre-specified
Analysis type	superiority[3]
P-value	< 0.001 [4]
Method	t-test, 2-sided
Parameter estimate	least squares mean (LSM)
Point estimate	15.363
Confidence interval	
level	95 %
sides	2-sided
lower limit	-430.024
upper limit	460.749
Variability estimate	Standard error of the mean
Dispersion value	221.632

Notes:

[3] - Interactions were tested using the primary model, including treatment by gender and treatment by stage of disease interactions (none of these interaction terms were significant at 0.1 and were excluded from the final model).
For the primary analysis, imputation of the last post-baseline result (following LOCF principles) was used for missing values at Day 30 (i.e., defined as Day 30 Endpoint).
[4] - MIXED MODEL:
p value for treatment: 0.9450
p value for baseline bacteria concentration: < 0.0001
p value for gende: 0.2445

p value for COPD disease stage: 0.8543

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from the signature of the ICF and until the last study visit (Visit 4/early termination, Day 60).Adverse events persisting at study completion were followed until resolution/stabilisation/lost to follow-up/stop of contact.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo

Reporting group description:

Subjects randomized to placebo treatment arm who received a single 30-day cycle of placebo treatment administered orally, once a day for 30 days.

Reporting group title	Broncho-Vaxom

Reporting group description:

Subjects randomized to Broncho-Vaxom (BV) treatment arm who received a single 30-day cycle of BV (7.0 mg) treatment administered orally, once a day for 30 days.

Serious adverse events	Placebo	Broncho-Vaxom	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 30 (6.67%)	1 / 28 (3.57%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Laceration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rib fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal			

disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal failure acute	Additional description: Acute		
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 28 (3.57%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Placebo	Broncho-Vaxom	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 30 (60.00%)	16 / 28 (57.14%)	
Investigations			
Blood immunoglobulin E increased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Blood glucose increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Cardiac murmur			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Haemoglobin decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			

Fall			
subjects affected / exposed	3 / 30 (10.00%)	0 / 28 (0.00%)	
occurrences (all)	4	0	
Contusion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Laceration			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Skin abrasion			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Tooth fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Haematoma			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Blood and lymphatic system disorders			
Anaemia macrocytic			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Device occlusion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Gastrointestinal disorders			

Diarrhoea			
subjects affected / exposed	1 / 30 (3.33%)	1 / 28 (3.57%)	
occurrences (all)	1	1	
Dyspepsia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	11 / 30 (36.67%)	10 / 28 (35.71%)	
occurrences (all)	11	10	
Cough			
subjects affected / exposed	2 / 30 (6.67%)	1 / 28 (3.57%)	
occurrences (all)	2	1	
Dyspnoea			
subjects affected / exposed	3 / 30 (10.00%)	0 / 28 (0.00%)	
occurrences (all)	3	0	
Wheezing			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Bursitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Joint range of motion decreased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 28 (0.00%)	
occurrences (all)	1	0	
Muscle spasms			
subjects affected / exposed	0 / 30 (0.00%)	1 / 28 (3.57%)	
occurrences (all)	0	1	
Infections and infestations			
Gastroenteritis			

subjects affected / exposed occurrences (all)	0 / 30 (0.00%) 0	1 / 28 (3.57%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
28 October 2013	New safety information available and the protocol was updated accordingly based on the revised Investigator's Brochure (Version 6.0). OM Pharma pharmacovigilance contact details (fax and email) had changed. Corrections of style errors.
03 April 2014	New safety information available and the protocol was updated accordingly based on the revised Investigator's Brochure (Version 6.0). OM Pharma pharmacovigilance contact details (fax and email) had changed. New contact details of co-ordinating investigator. Corrections of style errors.
14 July 2014	Change of the name and clarification of the study periods. Addition of the procedure for the qualitative bacterial culture and removal of blood sampling for use for opsonisation assay. Corrections of typos and clarifications of text.
20 October 2014	Clarification of the blood sampling procedure for the determination of biomarkers. Alignment of wording regarding biomarkers
21 January 2015	Change in the total number of patients to be recruited. Administrative change.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported