



Clinical trial results:

NGR019: Randomized double-blind phase II study of NGR-hTNF versus placebo as maintenance treatment in advanced malignant pleural mesothelioma (MPM)

Summary

EudraCT number	2010-023614-31
Trial protocol	IT DE
Global end of trial date	02 October 2018

Results information

Result version number	v1 (current)
This version publication date	01 January 2020
First version publication date	01 January 2020

Trial information

Trial identification

Sponsor protocol code	NGR019
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	MolMed S.p.A.
Sponsor organisation address	Via Olgettina, 58, Milan, Italy, 20132
Public contact	Clinical Operations, MolMed S.p.A., 0039 02212771, clinical.operations@molmed.com
Scientific contact	Clinical Operations, MolMed S.p.A., 0039 02212771, clinical.operations@molmed.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	31 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 October 2018
Global end of trial reached?	Yes
Global end of trial date	02 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare progression-free survival (PFS) in patients randomized to NGR-hTNF versus patients randomized to placebo

Protection of trial subjects:

The study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki. The study was performed in compliance with Good Clinical Practice (CPMP/ICH/135/95), and the essential documents are archived as required by the applicable regulatory requirements. The study and any amendments were reviewed by an Independent Ethics Committees or Institutional Review Boards.

Background therapy:

Where applicable and as appropriate according to the Institutional clinical practice and literature guidelines, patients in both arms should receive Best Supportive Care (BSC). All concomitant medication(s) must be reported in the Case Report Form (CRF).

- BSC includes antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.
- BSC excludes surgery, immunotherapy, anticancer therapy, and radiotherapy (except palliative).

Evidence for comparator: -

Actual start date of recruitment	18 May 2011
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	Italy: 135
Country: Number of subjects enrolled	Russian Federation: 2
Worldwide total number of subjects	137
EEA total number of subjects	135

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	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	27
From 65 to 84 years	110
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was performed in a total of 12 investigational study sites in total (11 in Italy and 1 in Russia). Other sites were opened in Italy (1 site) and in Germany (2 sites), but no patients were enrolled in these sites.

Department of Medical Oncology and Haematology, Istituto Clinico Humanitas, Rozzano (Milan), Italy, was the Coordinator Centre

Pre-assignment

Screening details:

137 patients were enrolled: 69 in arm A, and 68 in arm B.

3 patients in arm A were not treated due to progression of disease (n=1), informed consent withdrawal (n=1) and physician decision (n=1).

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A (experimental group = NGR-hTNF + BSC)

Arm description:

- NGR-hTNF: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs.
- Best Supportive Care (BSC): where applicable and as appropriate according to Institutional clinical practice and literature guidelines. It included antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.

All concomitant medication(s) had to be reported in the Case Report Form (CRF).

Arm type	Experimental
Investigational medicinal product name	NGR-hTNF
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The patients will receive NGR-hTNF/placebo administration every week by 60-minute intravenous infusion at 0.8 µg/m² until progressive disease.

Acetaminophen/paracetamol 1000 mg p.o. or i.v. is recommended as prophylaxis 30 to 60 minutes prior starting each infusion of NGR-hTNF/placebo.

No concomitant hydration is allowed during the NGR-hTNF/placebo infusion period.

No corticosteroid therapy is allowed during NGR-hTNF infusion and for two subsequent hours.

Arm title	Arm B (control group = Placebo + BSC)
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Arm description:

- Placebo: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs.
- Best Supportive Care: where applicable and as appropriate according to Institutional clinical practice and literature guidelines. It included antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.

All concomitant medication(s) had to be reported in the Case Report Form (CRF).

Arm type	Placebo
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Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.8 µg/m² as 60-minute iv infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurred.

Number of subjects in period 1^[1]	Arm A (experimental group = NGR-hTNF + BSC)	Arm B (control group = Placebo + BSC)
Started	66	68
Completed	53	59
Not completed	13	9
Adverse event, serious fatal	1	-
Physician decision	6	4
Consent withdrawn by subject	-	2
Adverse event, non-fatal	4	-
Other	1	3
Lost to follow-up	1	-

Notes:

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

Justification: The analysis were performed on treated patients.

Baseline characteristics

Reporting groups

Reporting group title	Arm A (experimental group = NGR-hTNF + BSC)
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Reporting group description:

- NGR-hTNF: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs.
- Best Supportive Care (BSC): where applicable and as appropriate according to Institutional clinical practice and literature guidelines. It included antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.

All concomitant medication(s) had to be reported in the Case Report Form (CRF).

Reporting group title	Arm B (control group = Placebo + BSC)
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Reporting group description:

- Placebo: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs.
- Best Supportive Care: where applicable and as appropriate according to Institutional clinical practice and literature guidelines. It included antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.

All concomitant medication(s) had to be reported in the Case Report Form (CRF).

Reporting group values	Arm A (experimental group = NGR-hTNF + BSC)	Arm B (control group = Placebo + BSC)	Total
Number of subjects	66	68	134
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	9	26
From 65-84 years	49	59	108
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	69.4	70.3	
standard deviation	± 8.48	± 7.89	-
Gender categorical Units: Subjects			
Female	18	17	35
Male	48	51	99

End points

End points reporting groups

Reporting group title	Arm A (experimental group = NGR-hTNF + BSC)
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Reporting group description:

- NGR-hTNF: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs.
- Best Supportive Care (BSC): where applicable and as appropriate according to Institutional clinical practice and literature guidelines. It included antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.

All concomitant medication(s) had to be reported in the Case Report Form (CRF).

Reporting group title	Arm B (control group = Placebo + BSC)
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Reporting group description:

- Placebo: 0.8 µg/m² as 60-minute intravenous infusion every week until confirmed evidence of disease progression or unacceptable toxicity occurs.
- Best Supportive Care: where applicable and as appropriate according to Institutional clinical practice and literature guidelines. It included antibiotics, analgesics, antiemetics, thoracentesis, pleurodesis, blood transfusions, nutritional support, and focal external-beam radiation for control of pain, cough, dyspnea, or hemoptysis.

All concomitant medication(s) had to be reported in the Case Report Form (CRF).

Primary: Progression-free survival (PFS), defined as the time from the date of randomization until disease progression, or death due to any cause.

End point title	Progression-free survival (PFS), defined as the time from the date of randomization until disease progression, or death due to any cause.
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End point description:

Defined as the time from the date of randomization until disease progression, or death due to any cause.

Progression is defined using Response Evaluation Criteria In Solid Tumors (RECIST), as a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to relative increase of 20% the sum must also demonstrate an absolute increase of at least 5 mm. In addition the appearance of one or more new lesions was also considered progression.

End point type	Primary
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End point timeframe:

Assessed every 6 weeks, up to the last treatment cycle.

End point values	Arm A (experimental group = NGR- hTNF + BSC)	Arm B (control group = Placebo + BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: months				
median (confidence interval 95%)	3.3 (2.7 to 4.2)	4.0 (2.8 to 5.3)		

Statistical analyses

Statistical analysis title	Progression-free survival (PFS)
Statistical analysis description: The median PFS was 3.3 months (95% CI: 2.7-4.2 months) in arm A and 4.0 months (95% CI: 2.8-5.3 months) in arm B. Two (3.0%) patients in arm A and 5 (7.4%) in arm B were censored, while events (i.e. failures) were reported in 64 (97%) patients in arm A and in 63 (92.6%) in arm B. The comparison between arms in the log rank model did not show statistically significant differences ($p = 0.505$).	
Comparison groups	Arm A (experimental group = NGR-hTNF + BSC) v Arm B (control group = Placebo + BSC)
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.505
Method	Logrank

Secondary: Overall Survival (OS)

End point title	Overall Survival (OS)
End point description: OS was defined as the time from the date of randomization until death due to any cause, or the last date the patient was known to be alive. End point related data are reported as median (95% CI).	
End point type	Secondary
End point timeframe: Assessed every 6 weeks, up to the completion of the last treatment cycle or in case of discontinuation of the treatment before disease progression. OS was assessed every 12 weeks after the last treatment cycle up to study completion.	

End point values	Arm A (experimental group = NGR- hTNF + BSC)	Arm B (control group = Placebo + BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: months				
median (confidence interval 95%)	14.0 (10.2 to 17.2)	17.4 (12.4 to 23.6)		

Statistical analyses

Statistical analysis title	Overall survival
Statistical analysis description: The median OS was 14.0 months (95% CI: 10.2-17.2 months) in arm A and 17.4 months (95% CI: 12.4-23.6 months) in arm B. Ten (15.2%) patients in arm A and 15 (22.1%) in arm B were censored, while events (i.e. deaths) were reported in 56 (84.8%) patients in arm A and in 53 (77.9%) in arm B. The comparison between arms in the log rank model did not show statistically significant differences ($p = 0.082$).	
Comparison groups	Arm A (experimental group = NGR-hTNF + BSC) v Arm B (control group = Placebo + BSC)

Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.082
Method	Logrank

Secondary: Response rate (RR)

End point title	Response rate (RR)
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End point description:

RR was defined as the percentage of patients who had a best-response rating of complete (CR) or partial response (PR). The tumor thickness perpendicular to the chest wall or mediastinum was assessed according to modified RECIST criteria for MPM. All other measurable lesions were unidimensionally measured as per the standard RECIST criteria.

End point type	Secondary
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End point timeframe:

Assessed every 6 weeks, up to the last treatment cycle or after treatment discontinuation before disease progression.

End point values	Arm A (experimental group = NGR- hTNF + BSC)	Arm B (control group = Placebo + BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: patients	0	5		

Statistical analyses

No statistical analyses for this end point

Secondary: Quality of life (QoL)

End point title	Quality of life (QoL)
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End point description:

QoL was assessed using the modified version for Mesothelioma of Lung Cancer Symptom Scale (LCSS) questionnaire (LCSS-Meso), which consists of eight 100-mm visual analogue scales (VAS), with scores reported from 0 to 100 (0 representing the best score). The 8 individual items of the LCSS questionnaire evaluated were: loss of appetite, fatigue, cough, dyspnoea, pain, symptoms of lung cancer, influence of illness on daily activities and overall quality of life.

Symptomatic progression was defined as a worsening in the average symptom burden index by 25% from baseline.

End point type	Secondary
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End point timeframe:

Assessed at the baseline, prior to randomization, and then every 6 weeks up to the last treatment cycle.

End point values	Arm A (experimental group = NGR- hTNF + BSC)	Arm B (control group = Placebo + BSC)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	66	68		
Units: subjects	24	26		

Statistical analyses

Statistical analysis title	Time to symptomatic progression
Statistical analysis description:	
Symptomatic progression (months) was calculated as: [(Date of symptomatic progression or censoring - Date of randomization) + 1] / 30.4	
The median time to symptomatic progression was 24.4 months (95% CI: 2.4-24.4 months) in arm A and 6.4 months (95% CI: 3.0-14.1 months) in arm B.	
42 (63.6%) patients in arm A and 42 (61.8%) in arm B were censored, while events (i.e. symptomatic progression) were reported in 24 (36.4%) patients in arm A and in 26 (38.2%) in arm B.	
Comparison groups	Arm B (control group = Placebo + BSC) v Arm A (experimental group = NGR-hTNF + BSC)
Number of subjects included in analysis	134
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.774
Method	Logrank

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Assessed every 3 weeks, up to the completion of the last treatment cycle. After that, unrelated events were registered for the following 28 days; whereas, related serious adverse events were followed indefinitely until resolution or stabilization.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.1
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Reporting groups

Reporting group title	Arm A (experimental group = NGR-hTNF + BSC)
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Reporting group description: -	
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Reporting group title	Arm B (control group = Placebo + BSC)
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Reporting group description: -	
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Serious adverse events	Arm A (experimental group = NGR-hTNF + BSC)	Arm B (control group = Placebo + BSC)	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 66 (7.58%)	6 / 68 (8.82%)	
number of deaths (all causes)	56	53	
number of deaths resulting from adverse events	2	0	
Injury, poisoning and procedural complications			
Lower limb fracture			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic fracture			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Jugular vein thrombosis			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Aortic aneurysm			

subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Pain			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Condition aggravated			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (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			
Pulmonary embolism			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspnoea			

subjects affected / exposed	1 / 66 (1.52%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	1 / 1	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	1 / 66 (1.52%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Sepsis			
subjects affected / exposed	0 / 66 (0.00%)	1 / 68 (1.47%)	
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: 5 %

Non-serious adverse events	Arm A (experimental group = NGR-hTNF + BSC)	Arm B (control group = Placebo + BSC)	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	60 / 66 (90.91%)	56 / 68 (82.35%)	
Investigations			
Blood urea increased			
subjects affected / exposed	0 / 66 (0.00%)	5 / 68 (7.35%)	
occurrences (all)	0	10	
Vascular disorders			
Hypertension			
subjects affected / exposed	11 / 66 (16.67%)	7 / 68 (10.29%)	
occurrences (all)	16	16	
Hypotension			
subjects affected / exposed	4 / 66 (6.06%)	0 / 68 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	4 / 66 (6.06%)	2 / 68 (2.94%)	
occurrences (all)	6	3	
General disorders and administration site conditions			

Chills			
subjects affected / exposed	27 / 66 (40.91%)	7 / 68 (10.29%)	
occurrences (all)	87	10	
Fatigue			
subjects affected / exposed	13 / 66 (19.70%)	13 / 68 (19.12%)	
occurrences (all)	20	36	
Pyrexia			
subjects affected / exposed	13 / 66 (19.70%)	9 / 68 (13.24%)	
occurrences (all)	19	16	
Asthenia			
subjects affected / exposed	8 / 66 (12.12%)	10 / 68 (14.71%)	
occurrences (all)	9	13	
Chest pain			
subjects affected / exposed	7 / 66 (10.61%)	15 / 68 (22.06%)	
occurrences (all)	12	27	
Influenza like illness			
subjects affected / exposed	5 / 66 (7.58%)	3 / 68 (4.41%)	
occurrences (all)	5	7	
Oedema peripheral			
subjects affected / exposed	5 / 66 (7.58%)	2 / 68 (2.94%)	
occurrences (all)	6	4	
Pain			
subjects affected / exposed	5 / 66 (7.58%)	5 / 68 (7.35%)	
occurrences (all)	5	5	
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 66 (9.09%)	6 / 68 (8.82%)	
occurrences (all)	9	14	
Diarrhoea			
subjects affected / exposed	6 / 66 (9.09%)	6 / 68 (8.82%)	
occurrences (all)	9	10	
Nausea			
subjects affected / exposed	6 / 66 (9.09%)	5 / 68 (7.35%)	
occurrences (all)	9	7	
Vomiting			

subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 9	6 / 68 (8.82%) 7	
Abdominal pain upper subjects affected / exposed occurrences (all)	3 / 66 (4.55%) 5	4 / 68 (5.88%) 4	
Dyspepsia subjects affected / exposed occurrences (all)	2 / 66 (3.03%) 2	4 / 68 (5.88%) 8	
Gastrooesophageal reflux disease subjects affected / exposed occurrences (all)	0 / 66 (0.00%) 0	4 / 68 (5.88%) 5	
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	11 / 66 (16.67%) 16	12 / 68 (17.65%) 23	
Dyspnoea subjects affected / exposed occurrences (all)	8 / 66 (12.12%) 11	6 / 68 (8.82%) 14	
Musculoskeletal and connective tissue disorders Musculoskeletal pain subjects affected / exposed occurrences (all)	6 / 66 (9.09%) 7	3 / 68 (4.41%) 4	
Back pain subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 7	4 / 68 (5.88%) 4	
Arthralgia subjects affected / exposed occurrences (all)	4 / 66 (6.06%) 6	8 / 68 (11.76%) 16	
Metabolism and nutrition disorders Decreased appetite subjects affected / exposed occurrences (all)	5 / 66 (7.58%) 8	6 / 68 (8.82%) 7	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported