Clinical trial results:
Azithromycin for acute COPD exacerbations with hospitalisation: the BACE trial

Summary

EudraCT number	2013-004420-11
Trial protocol	BE
Global end of trial date	19 January 2018

Results information

Result version number	v1 (current)
This version publication date	18 December 2019
First version publication date	18 December 2019

Trial information

Trial identification

Sponsor protocol code	s55829

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02135354
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	KU Leuven
Sponsor organisation address	Herestraat 49 Box 706, Leuven, Belgium, 3000
Public contact	Kristina Vermeersch, KU Leuven - UZ Leuven , 0032 016342284, kristina.vermeersch@kuleuven.be
Scientific contact	Prof. Dr. Wim Janssens, KU Leuven - UZ Leuven , 0032 016346812, wim.janssens@kuleuven.be

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	18 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	19 January 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To prove the effectiveness of azithromycin on top of standard therapy in the acute treatment of COPD exacerbations which require hospitalization

Protection of trial subjects:

Ethics review and approval
Informed consent
Repeated safety evaluations through:
-ECG monitoring
-sputum culture assessment
-quality of life and symptom assessment questionnaires

Background therapy:

Patients were randomized (1:1) to receive azithromycin or placebo on top of a standardized acute treatment of:
*Systemic corticosteroids:
methylprednisolone 40mg IV or 32mg PO once daily for 5 days (switch IV to PO as soon as possible)

*Antibiotics:
-amoxi-clavulanate 1g IV four times a day or 2g PO twice a day for 7 days (alternative regimen: 1g IV four times a day or 875/125mg PO three times a day for 7 days)
-or moxifloxacin 400mg IV or 400mg PO once daily for 5 days

*Short-acting bronchodilators:
via inhalation

*Respiratory support:
-oxygen
-noninvasive ventilation
-Mechanical ventilation

Evidence for comparator:

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Actual start date of recruitment	01 August 2014
Long term follow-up planned	Yes
Long term follow-up rationale	Efficacy, Safety, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 301

Worldwide total number of subjects	301
EEA total number of subjects	301

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)	131
From 65 to 84 years	166
85 years and over	4

Subject disposition

Recruitment

Recruitment details:

Consortium: patients were recruited in 6 academic and 14 nonacademic hospitals within Belgium
Recruitment period: between August2014 and April2017

Pre-assignment

Screening details:

A total of 2063 patients were screened by 15 hospitals within the Consortium
Patients were screened as per inclusion and exclusion criteria specified in the trial protocol

Period 1

Period 1 title	Overall trial: day 1 up to day 270 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Carer, Assessor

Blinding implementation details:

-Study drug identity was concealed by a format that was identical in packaging, labelling, schedule of administration and appearance
-Patients were randomly assigned in a 1:1 ratio to receive either azithromycin or placebo, with a permuted block size of 10 and sequential assignment, stratified by center
-Randomization was based on an online generated randomization schedule (http://www.randomization.com). Unique randomization codes were locally obtained through a secured

Arms

Are arms mutually exclusive?	Yes
Arm title	Azithromycin

Arm description:

From day 1 up to and including day 3: 500 mg azithromycin PO once a day
From day 4 up to and including day 90: 250 mg azithromycin PO once every 2 days

Arm type	Experimental
Investigational medicinal product name	Azithromycin monohydrate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

From day 1 up to and including day 3: 500 mg PO once a day
From day 4 up to and including day 90: 250 mg PO once every 2 days

Arm title	Placebo

Arm description:

From day 1 up to and including day 3: 500 mg placebo PO once a day
From day 4 up to and including day 90: 250 mg placebo PO once every 2 days

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

From day 1 up to and including day 3: 500 mg once a day
From day 4 up to and including day 90: 250 mg once every 2 days

Number of subjects in period 1	Azithromycin	Placebo
Started	147	154
End of intervention (day 90)	131	129
Completed	118	115
Not completed	29	39
Consent withdrawn by subject	7	11
Adverse event, non-fatal	6	12
Death	7	9
Miscellaneous	3	-
Lost to follow-up	6	2
Non-adherence	-	5

Baseline characteristics

Reporting groups	
Reporting group title	Azithromycin
Reporting group description:	
From day 1 up to and including day 3: 500 mg azithromycin PO once a day From day 4 up to and including day 90: 250 mg azithromycin PO once every 2 days	
Reporting group title	Placebo
Reporting group description:	
From day 1 up to and including day 3: 500 mg placebo PO once a day From day 4 up to and including day 90: 250 mg placebo PO once every 2 days	

Reporting group values	Azithromycin	Placebo	Total
Number of subjects	147	154	301
Age categorical			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Units: years			
arithmetic mean	66	67	
standard deviation	± 9	± 10	-
Gender categorical			
Units: Subjects			
Female	66	66	132
Male	81	88	169
GOLD stage			
GOLD= Global Initiative for Chronic Obstructive Lung Disease (guideline 2017)			
Units: Subjects			
GOLD A	0	1	1
GOLD B	26	30	56
GOLD C	1	2	3
GOLD D	120	121	241
Smoking status			
Units: Subjects			
Current smoker	63	65	128
Non smoker	84	89	173
Number of AECOPD in the previous year			
AECOPD= acute exacerbation of COPD			
Units: Subjects			
One	38	51	89

Two	41	37	78
Three	31	19	50
More than three	37	47	84
Number of AECOPD in previous year requiring hospitalization Units: Subjects			
None	64	64	128
One	55	58	113
Two	15	16	31
Three	6	6	12
More than three	7	10	17
Intervention by general practitioner before admission Units: Subjects			
Systemic corticosteroids	48	37	85
Antibiotics	50	54	104
None	49	63	112
Lower respiratory symptoms at admission - Sputum production Units: Subjects			
Sputum	97	86	183
No sputum	50	68	118
Lower respiratory symptoms at admission - Sputum purulence Units: Subjects			
Purulence	67	57	124
None	80	97	177
Lower respiratory symptoms at admission - Cough Units: Subjects			
Cough	115	108	223
None	32	46	78
Inhaled respiratory medicine - LABA			
LABA: long acting B2 agonist			
Units: Subjects			
Yes	136	145	281
No	11	9	20
Inhaled respiratory therapy - LAMA			
LAMA: long acting muscarinic antagonist			
Units: Subjects			
Yes	118	123	241
No	29	31	60
Inhaled respiratory therapy - ICS			
ICS: inhaled corticosteroids			
Units: Subjects			
Yes	118	123	241
No	29	31	60
Inhaled respiratory therapy - SAMA			
SAMA: short-acting muscarinic antagonist			
Units: Subjects			
Yes	108	109	217
No	39	45	84
Standardized acute treatment -			

Respected Units: Subjects			
Yes	134	141	275
No	13	13	26
Standardized acute treatment - Received antibiotics Units: Subjects			
Yes	145	152	297
No	2	2	4
Standardized acute treatment - Pathogen susceptible to antibiotic Units: Subjects			
Yes	136	144	280
No	11	10	21
Height Continuous Units: Meter			
arithmetic mean	1.66	1.66	
standard deviation	± 9	± 9	-
Weight Continuous Units: Kg			
arithmetic mean	67	70	
standard deviation	± 20	± 18	-
Body Mass Index Continuous Units: Kg/m²			
arithmetic mean	24.5	25.1	
standard deviation	± 5.9	± 6.5	-
Smoking history Units: Pack-years			
median	44	43	
inter-quartile range (Q1-Q3)	37 to 50	35 to 50	-
Laboratory value: C-reactive protein Units: mg/L			
median	14.2	21.6	
inter-quartile range (Q1-Q3)	3.5 to 61.4	4.5 to 59.6	-
Laboratory value: leucocytes Units: x10^9/L			
median	10.95	9.90	
inter-quartile range (Q1-Q3)	9.00 to 13.89	8.20 to 13.70	-
Laboratory value: neutrophils Units: x10^9/L			
median	8.20	7.70	
inter-quartile range (Q1-Q3)	6.00 to 11.20	5.60 to 11.20	-
Laboratory value: eosinophils Units: x10^9/L			
median	0.06	0.07	
inter-quartile range (Q1-Q3)	0.00 to 0.20	0.00 to 0.20	-
mMRC dyspnea score			
mMRC= modified Medical Research Council questionnaire Scale between 0 and 4 The higher the score, the worse the outcome			
Units: Scale between 0 and 4			
median	4	4	
inter-quartile range (Q1-Q3)	2 to 4	2 to 4	-

Pre-bronchodilator FEV1			
FEV1= forced expiratory volume in 1 second			
Units: Liter			
median	0.90	0.95	
inter-quartile range (Q1-Q3)	0.69 to 1.23	0.71 to 1.36	-

Subject analysis sets

Subject analysis set title	Intention-to-treat set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All patients who consented to participate in the study and fulfilled all inclusion/exclusion criteria.

Reporting group values	Intention-to-treat set		
Number of subjects	301		
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Units: years			
arithmetic mean	66		
standard deviation	± 10		
Gender categorical			
Units: Subjects			
Female			
Male			
GOLD stage			
GOLD= Global Initiative for Chronic Obstructive Lung Disease (guideline 2017)			
Units: Subjects			
GOLD A			
GOLD B			
GOLD C			
GOLD D			
Smoking status			
Units: Subjects			
Current smoker			
Non smoker			
Number of AECOPD in the previous year			
AECOPD= acute exacerbation of COPD			
Units: Subjects			
One			

Two Three More than three			
Number of AECOPD in previous year requiring hospitalization Units: Subjects			
None One Two Three More than three			
Intervention by general practitioner before admission Units: Subjects			
Systemic corticosteroids Antibiotics None			
Lower respiratory symptoms at admission - Sputum production Units: Subjects			
Sputum No sputum			
Lower respiratory symptoms at admission - Sputum purulence Units: Subjects			
Purulence None			
Lower respiratory symptoms at admission - Cough Units: Subjects			
Cough None			
Inhaled respiratory medicine - LABA			
LABA: long acting B2 agonist			
Units: Subjects			
Yes No			
Inhaled respiratory therapy - LAMA			
LAMA: long acting muscarinic antagonist			
Units: Subjects			
Yes No			
Inhaled respiratory therapy - ICS			
ICS: inhaled corticosteroids			
Units: Subjects			
Yes No			
Inhaled respiratory therapy - SAMA			
SAMA: short-acting muscarinic antagonist			
Units: Subjects			
Yes No			
Standardized acute treatment -			

Respected Units: Subjects			
Yes			
No			
Standardized acute treatment - Received antibiotics Units: Subjects			
Yes			
No			
Standardized acute treatment - Pathogen susceptible to antibiotic Units: Subjects			
Yes			
No			
Height Continuous Units: Meter arithmetic mean standard deviation	±		
Weight Continuous Units: Kg arithmetic mean standard deviation	±		
Body Mass Index Continuous Units: Kg/m² arithmetic mean standard deviation	±		
Smoking history Units: Pack-years median inter-quartile range (Q1-Q3)			
Laboratory value: C-reactive protein Units: mg/L median inter-quartile range (Q1-Q3)			
Laboratory value: leucocytes Units: x10^9/L median inter-quartile range (Q1-Q3)			
Laboratory value: neutrophils Units: x10^9/L median inter-quartile range (Q1-Q3)			
Laboratory value: eosinophils Units: x10^9/L median inter-quartile range (Q1-Q3)			
mMRC dyspnea score			
mMRC= modified Medical Research Council questionnaire Scale between 0 and 4 The higher the score, the worse the outcome			
Units: Scale between 0 and 4 median inter-quartile range (Q1-Q3)			

Pre-bronchodilator FEV1			
FEV1= forced expiratory volume in 1 second			
Units: Liter median inter-quartile range (Q1-Q3)			

End points

End points reporting groups

Reporting group title	Azithromycin
Reporting group description:	
From day 1 up to and including day 3: 500 mg azithromycin PO once a day From day 4 up to and including day 90: 250 mg azithromycin PO once every 2 days	
Reporting group title	Placebo
Reporting group description:	
From day 1 up to and including day 3: 500 mg placebo PO once a day From day 4 up to and including day 90: 250 mg placebo PO once every 2 days	
Subject analysis set title	Intention-to-treat set
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All patients who consented to participate in the study and fulfilled all inclusion/exclusion criteria.	

Primary: Treatment failure rate at day 90

End point title	Treatment failure rate at day 90
End point description:	
Event rate (95% CI) obtained using Kaplan-Meier methodology.	
End point type	Primary
End point timeframe:	
From date of randomization (day 1) to end of intervention (day 90)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	49.5 (41.5 to 58.1)	60.4 (52.4 to 68.5)		

Statistical analyses

Statistical analysis title	Difference in treatment failure rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0526
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.73

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.53
upper limit	1.01

Secondary: Treatment failure rate at day 270

End point title	Treatment failure rate at day 270
End point description:	
Event rate (95% CI) obtained using Kaplan-Meier methodology.	
End point type	Secondary
End point timeframe:	
From date of randomization (day 1) to end of follow-up (day 270)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	82.2 (75.2 to 88.2)	84.8 (78.3 to 90.3)		

Statistical analyses

Statistical analysis title	Difference in treatment failure rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.157
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.83
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.64
upper limit	1.08

Secondary: Number of treatment failures at day 90

End point title	Number of treatment failures at day 90

End point description: Mean Cumulative Function (MCF) (95% CI).	
End point type	Secondary
End point timeframe: From date of randomization (day 1) to end of intervention (day 90)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Events				
number (confidence interval 95%)	0.79 (0.62 to 0.95)	1.03 (0.85 to 1.20)		

Statistical analyses

Statistical analysis title	Difference in number of treatment failures
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0395
Method	Logrank
Parameter estimate	Difference in MCF
Point estimate	-0.24
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.48
upper limit	0

Secondary: Number of treatment failures at day 270	
End point title	Number of treatment failures at day 270
End point description: Mean Cumulative Function (MCF) (95% CI).	
End point type	Secondary
End point timeframe: From date of randomization (day 1) to end of follow-up (day 270)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Events				
number (confidence interval 95%)	2.41 (2.08 to 2.73)	2.54 (2.21 to 2.87)		

Statistical analyses

Statistical analysis title	Difference in number of treatment failures
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1103 [1]
Method	Logrank
Parameter estimate	Difference in MCF
Point estimate	-0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.6
upper limit	0.34

Notes:

[1] - Unadjusted

Secondary: COPD Assessment Test (CAT) score at day 90

End point title	COPD Assessment Test (CAT) score at day 90

End point description:

Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Score				
arithmetic mean (confidence interval 95%)	17.7 (16.4 to 19.0)	16.9 (15.5 to 18.3)		

Statistical analyses

Statistical analysis title	Difference in COPD Assessment Test score
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.697
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	0.35
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.43
upper limit	2.13

Secondary: COPD Assessment Test (CAT) score at day 270	
End point title	COPD Assessment Test (CAT) score at day 270
End point description:	
Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.	
End point type	Secondary
End point timeframe:	
From date of randomization (day 1) to end of follow-up (day 270)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Score				
arithmetic mean (confidence interval 95%)	18.3 (16.8 to 19.8)	18.5 (17.0 to 20.0)		

Statistical analyses

Statistical analysis title	Difference in COPD Assessment Test score
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3921
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	-0.87

Confidence interval	
level	95 %
sides	2-sided
lower limit	-2.85
upper limit	1.12

Secondary: Total days of systemic corticosteroid use at day 90

End point title	Total days of systemic corticosteroid use at day 90

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Days				
number (confidence interval 95%)	15.9 (14.9 to 16.9)	14.8 (13.9 to 15.7)		

Statistical analyses

Statistical analysis title	Difference in total days of corticosteroid use
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1217
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	1.07
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.98
upper limit	1.17

Secondary: Total days of systemic corticosteroid use at day 270

End point title	Total days of systemic corticosteroid use at day 270

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Days				
number (confidence interval 95%)	27.1 (26.1 to 28.2)	27.2 (26.2 to 28.3)		

Statistical analyses

Statistical analysis title	Difference in total days of corticosteroid use
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8817
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.94
upper limit	1.05

Secondary: Treatment intensification rate at day 90

End point title	Treatment intensification rate at day 90

End point description:

Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	47.4 (38.8 to 55.4)	59.7 (51.1 to 67.4)		

Statistical analyses

Statistical analysis title	Difference in treatment intensification rate
Comparison groups	Placebo v Azithromycin
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0272
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.96

Secondary: Treatment intensification rate at day 270

End point title	Treatment intensification rate at day 270
End point description:	
Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk.	
End point type	Secondary
End point timeframe:	
From date of randomization (day 1) to end of follow-up (day 270)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	79.2 (71.2 to 85.3)	84.1 (76.7 to 89.4)		

Statistical analyses

Statistical analysis title	Difference in treatment intensification rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0709
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.61
upper limit	1.02

Secondary: Step-up in hospital care rate at day 90

End point title	Step-up in hospital care rate at day 90
End point description:	
Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk.	
End point type	Secondary
End point timeframe:	
From date of randomization (day 1) to end of intervention (day 90)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	13.2 (8.2 to 19.5)	27.7 (20.6 to 35.3)		

Statistical analyses

Statistical analysis title	Difference in step-up in hospital care rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.003
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.43

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.25
upper limit	0.75

Secondary: Step-up in hospital care rate at day 270

End point title	Step-up in hospital care rate at day 270

End point description:

Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	36.5 (28.3 to 44.7)	45.2 (36.6 to 53.3)		

Statistical analyses

Statistical analysis title	Difference in step-up in hospital care rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0536
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.48
upper limit	1.01

Secondary: Mortality rate at day 90

End point title	Mortality rate at day 90

End point description:

Event rate (95% CI) obtained using Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	2.2 (0.7 to 6.5)	3.6 (1.5 to 8.3)		

Statistical analyses

Statistical analysis title	Difference in momrtality rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5075
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.62
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	2.59

Secondary: Mortality rate at day 270

End point title	Mortality rate at day 270

End point description:

Event rate (95% CI) obtained using Kaplan-Meier methodology.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	5.3 (2.6 to 10.8)	6.7 (3.5 to 12.5)		

Statistical analyses

Statistical analysis title	Difference in mortality rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.617
Method	Logrank
Parameter estimate	Hazard ratio (HR)
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.29
upper limit	2.09

Secondary: New exacerbation rate at day 90

End point title	New exacerbation rate at day 90
End point description:	
Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk.	
End point type	Secondary
End point timeframe:	
From date of randomization (day 1) to end of intervention (day 90)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	39.6 (31.3 to 47.7)	51.0 (42.3 to 59.0)		

Statistical analyses

Statistical analysis title	Difference in new exacerbation rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0497
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.7
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	1

Secondary: New exacerbation rate at day 270	
End point title	New exacerbation rate at day 270
End point description: Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk.	
End point type	Secondary
End point timeframe: From date of randomization (day 1) to end of follow-up (day 270)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Percentage				
number (confidence interval 95%)	75.1 (66.6 to 81.7)	79.5 (71.5 to 85.5)		

Statistical analyses

Statistical analysis title	Difference in new exacerbation rate
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1324
Method	Gray's test
Parameter estimate	Hazard ratio (HR)
Point estimate	0.81

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.62
upper limit	1.06

Secondary: Number of new exacerbations at day 90

End point title	Number of new exacerbations at day 90
End point description: Mean Cumulative Function (MCF) (95% CI).	
End point type	Secondary
End point timeframe: From date of randomization (day 1) to end of intervention (day 90)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Events				
number (confidence interval 95%)	0.57 (0.44 to 0.70)	0.75 (0.60 to 0.90)		

Statistical analyses

Statistical analysis title	Difference in number of new exacerbations
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
Method	Logrank
Parameter estimate	Difference in MCF
Point estimate	-0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.37
upper limit	0.02

Secondary: Number of new exacerbations at day 270

End point title	Number of new exacerbations at day 270
End point description: Mean Cumulative Function (MCF) (95% CI).	

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Events				
number (confidence interval 95%)	2.08 (1.80 to 2.36)	2.18 (1.92 to 2.45)		

Statistical analyses

Statistical analysis title	Difference in number of new exacerbations
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5997
Method	Logrank
Parameter estimate	Difference in MCF
Point estimate	-0.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.49
upper limit	0.28

Secondary: Total dose of systemic corticosteroid use at day 90

End point title	Total dose of systemic corticosteroid use at day 90

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Mg				
number (confidence interval 95%)	340.2 (335.4 to 345.1)	321.8 (317.6 to 326.0)		

Statistical analyses

Statistical analysis title	Difference in total dose of corticosteroid use
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	1.06
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.08

Secondary: Total dose of systemic corticosteroid use at day 270

End point title	Total dose of systemic corticosteroid use at day 270

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Mg				
number (confidence interval 95%)	603.4 (598.4 to 608.5)	603.5 (598.4 to 608.6)		

Statistical analyses

Statistical analysis title	Difference in total dose of corticosteroid use
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9903
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.99
upper limit	1.01

Secondary: Total days of non-study antibiotics at day 90	
End point title	Total days of non-study antibiotics at day 90
End point description:	
Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.	
End point type	Secondary
End point timeframe:	
From date of randomization (day 1) to end of intervention (day 90)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Days				
number (confidence interval 95%)	10.5 (9.6 to 11.5)	13.7 (12.8 to 14.7)		

Statistical analyses

Statistical analysis title	Difference in total days of non-study antibiotics
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.77

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.68
upper limit	0.86

Secondary: Total days of non-study antibiotics at day 270

End point title	Total days of non-study antibiotics at day 270

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Days				
number (confidence interval 95%)	21.1 (20.2 to 22.1)	21.6 (20.7 to 22.6)		

Statistical analyses

Statistical analysis title	Difference in total day of non-study antibiotics
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4592
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.98
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.92
upper limit	1.04

Secondary: Total hospital days at day 90

End point title	Total hospital days at day 90

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Days				
number (confidence interval 95%)	10.7 (9.3 to 12.3)	14.0 (12.3 to 16.1)		

Statistical analyses

Statistical analysis title	Difference in total hospital days
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0061
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.76
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.92

Secondary: Total hospital days at day 270

End point title	Total hospital days at day 270

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Days				
number (confidence interval 95%)	22.2 (18.3 to 27.0)	28.5 (23.8 to 34.2)		

Statistical analyses

Statistical analysis title	Difference in total hospital days
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0631
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.78
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	1.01

Secondary: Total ICU days at day 90

End point title	Total ICU days at day 90

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Days				
number (confidence interval 95%)	3.0 (1.8 to 5.1)	11.4 (9.1 to 14.3)		

Statistical analyses

Statistical analysis title	Difference in total ICU days
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.26
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.15
upper limit	0.47

Secondary: Total ICU days at day 270

End point title	Total ICU days at day 270

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Days				
number (confidence interval 95%)	5.1 (4.0 to 6.5)	11.1 (9.2 to 13.3)		

Statistical analyses

Statistical analysis title	Difference in total ICU days
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.46

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.34
upper limit	0.63

Secondary: Number of general practitionner contacts at day 90

End point title	Number of general practitionner contacts at day 90

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Events				
number (confidence interval 95%)	2.4 (2.0 to 2.7)	2.6 (2.3 to 3.0)		

Statistical analyses

Statistical analysis title	Difference in number of GP contacts
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3119
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.9
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.74
upper limit	1.1

Secondary: Number of general practitionner contacts at day 270

End point title	Number of general practitionner contacts at day 270

End point description:

Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Events				
number (confidence interval 95%)	6.1 (5.7 to 6.6)	6.6 (6.1 to 7.1)		

Statistical analyses

Statistical analysis title	Difference in number of GP contacts
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1511
Method	Poisson regression
Parameter estimate	Rate ratio
Point estimate	0.92
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.83
upper limit	1.03

Secondary: Pre-bronchodilator FEV1 at day 90

End point title	Pre-bronchodilator FEV1 at day 90

End point description:

Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Liter				
arithmetic mean (confidence interval 95%)	1.3 (0.9 to 1.7)	1.2 (1.1 to 1.3)		

Statistical analyses

Statistical analysis title	Difference in pre-bronchodilator FEV1
Comparison groups	Placebo v Azithromycin
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5008
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	0.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.26
upper limit	0.53

Secondary: Pre-bronchodilator FEV1 at day 270

End point title	Pre-bronchodilator FEV1 at day 270

End point description:

Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Liter				
arithmetic mean (confidence interval 95%)	1.1 (1.0 to 1.2)	1.2 (1.1 to 1.3)		

Statistical analyses

Statistical analysis title	Difference in pre-bronchodilator FEV1
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.1933
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	-0.09
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.23
upper limit	0.05

Secondary: mMRC questionnaire score at day 90

End point title	mMRC questionnaire score at day 90

End point description:

Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Score				
arithmetic mean (confidence interval 95%)	3.1 (3.0 to 3.3)	3.2 (3.0 to 3.4)		

Statistical analyses

Statistical analysis title	Difference in mMRC questionnaire score
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	-0.08

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.33
upper limit	0.17

Secondary: mMRC questionnaire score at day 270

End point title	mMRC questionnaire score at day 270

End point description:

Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of follow-up (day 270)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Score				
arithmetic mean (confidence interval 95%)	3.3 (3.2 to 3.5)	3.2 (3.0 to 3.4)		

Statistical analyses

Statistical analysis title	Difference in mMRC questionnaire qcore
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5886
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	0.08
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.2
upper limit	0.35

Secondary: EQ5D questionnaire score at day 90

End point title	EQ5D questionnaire score at day 90

End point description:

Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Score				
arithmetic mean (confidence interval 95%)	61.6 (58.3 to 65.0)	61.2 (57.7 to 64.6)		

Statistical analyses

Statistical analysis title	Difference in EQ5D questionnaire score
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8842
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	0.34
Confidence interval	
level	95 %
sides	2-sided
lower limit	-4.28
upper limit	4.97

Secondary: EQ5D questionnaire score at day 270

End point title	EQ5D questionnaire score at day 270

End point description:

Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Score				
arithmetic mean (confidence interval 95%)	57.3 (53.7 to 60.9)	60.2 (56.3 to 64.1)		

Statistical analyses

Statistical analysis title	Difference in EQ5D questionnaire score
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2967
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	-2.73
Confidence interval	
level	95 %
sides	2-sided
lower limit	-7.86
upper limit	2.4

Secondary: SSQ5 questionnaire score at day 90

End point title	SSQ5 questionnaire score at day 90

End point description:

Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.

End point type	Secondary

End point timeframe:

From date of randomization (day 1) to end of intervention (day 90)

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Score				
arithmetic mean (confidence interval 95%)	8.1 (7.8 to 8.4)	7.9 (7.6 to 8.2)		

Statistical analyses

Statistical analysis title	Difference in SSQ5 questionnaire score
Comparison groups	Placebo v Azithromycin
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2559
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	0.18
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.13
upper limit	0.49

Secondary: SSQ5 questionnaire score at day 270

End point title	SSQ5 questionnaire score at day 270
End point description:	
Estimated mean value (95% CI) obtained using a weighted General Estimating Equations (GEE) model with factors for group, treatment and their interaction. Baseline was included as a covariate.	
End point type	Secondary
End point timeframe:	
From date of randomization (day 1) to end of follow-up (day 270)	

End point values	Azithromycin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	147	154		
Units: Score				
arithmetic mean (confidence interval 95%)	8.2 (7.8 to 8.5)	8.0 (7.7 to 8.3)		

Statistical analyses

Statistical analysis title	Difference in SSQ5 questionnaire score
Comparison groups	Azithromycin v Placebo
Number of subjects included in analysis	301
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2
Method	Chi-squared
Parameter estimate	Difference in expected means
Point estimate	0.2

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.12
upper limit	0.52

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Timeframe: from the signature of informed consent (day 0) to the end of follow-up (day 270).

Assessment type	Systematic

Dictionary used

Dictionary name	CTCAE
Dictionary version	4

Reporting groups

Reporting group title	Azithromycin

Reporting group description:

From day 1 up to and including day 3: 500 mg azithromycin PO once a day
From day 4 up to and including day 90: 250 mg azithromycin PO once every 2 days

Reporting group title	Placebo

Reporting group description:

From day 1 up to and including day 3: 500 mg placebo PO once a day
From day 4 up to and including day 90: 250 mg placebo PO once every 2 days

Serious adverse events	Azithromycin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	58 / 147 (39.46%)	69 / 154 (44.81%)	
number of deaths (all causes)	7	9	
number of deaths resulting from adverse events			
Investigations			
Laboratory investigations			
subjects affected / exposed	2 / 147 (1.36%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasm malignant			
subjects affected / exposed	2 / 147 (1.36%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 1	0 / 1	
Cardiac disorders			
Cardiovascular disorders			
subjects affected / exposed	5 / 147 (3.40%)	7 / 154 (4.55%)	
occurrences causally related to treatment / all	0 / 5	0 / 7	
deaths causally related to treatment / all	0 / 4	0 / 2	

Nervous system disorders			
Cerebrovascular disorder			
subjects affected / exposed	2 / 147 (1.36%)	4 / 154 (2.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorder			
subjects affected / exposed	4 / 147 (2.72%)	5 / 154 (3.25%)	
occurrences causally related to treatment / all	0 / 3	0 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	50 / 147 (34.01%)	62 / 154 (40.26%)	
occurrences causally related to treatment / all	0 / 86	0 / 116	
deaths causally related to treatment / all	0 / 2	0 / 6	
Renal and urinary disorders			
Renal disorder			
subjects affected / exposed	0 / 147 (0.00%)	2 / 154 (1.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Psychological disorder			
subjects affected / exposed	2 / 147 (1.36%)	1 / 154 (0.65%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal disorder			
subjects affected / exposed	2 / 147 (1.36%)	4 / 154 (2.60%)	
occurrences causally related to treatment / all	0 / 2	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Azithromycin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 147 (4.08%)	7 / 154 (4.55%)	
Cardiac disorders			
QT prolongation	Additional description: Leading to study drug discontinuation Timeframe: from the signature of informed consent (day 0) to the end of intervention (day 90)		
subjects affected / exposed	2 / 147 (1.36%)	1 / 154 (0.65%)	
occurrences (all)	2	1	
NSTEMI	Additional description: Leading to study drug discontinuation Timeframe: from the signature of informed consent (day 0) to the end of intervention (day 90)		
subjects affected / exposed	0 / 147 (0.00%)	1 / 154 (0.65%)	
occurrences (all)	0	1	
Takotsubo cardiomyopathy	Additional description: Leading to study drug discontinuation Timeframe: from the signature of informed consent (day 0) to the end of intervention (day 90)		
subjects affected / exposed	0 / 147 (0.00%)	1 / 154 (0.65%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea	Additional description: Leading to study drug discontinuation Timeframe: from the signature of informed consent (day 0) to the end of intervention (day 90)		
subjects affected / exposed	2 / 147 (1.36%)	0 / 154 (0.00%)	
occurrences (all)	2	0	
Nausea	Additional description: Leading to study drug discontinuation Timeframe: from the signature of informed consent (day 0) to the end of intervention (day 90)		
subjects affected / exposed	1 / 147 (0.68%)	0 / 154 (0.00%)	
occurrences (all)	1	0	
Abdominal discomfort	Additional description: Leading to study drug discontinuation Timeframe: from the signature of informed consent (day 0) to the end of intervention (day 90)		
subjects affected / exposed	1 / 147 (0.68%)	1 / 154 (0.65%)	
occurrences (all)	1	1	
Pancolitis	Additional description: Leading to study drug discontinuation Timeframe: from the signature of informed consent (day 0) to the end of intervention (day 90)		
subjects affected / exposed	0 / 147 (0.00%)	1 / 154 (0.65%)	
occurrences (all)	0	1	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Target enrolment was not met due to early termination, which leaves the trial underpowered

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/27099485

http://www.ncbi.nlm.nih.gov/pubmed/31046405