Azithromycin during Acute Chronic Obstructive Pulmonary Disease Exacerbations Requiring Hospitalization (BACE) A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial

Peer-reviewed author version

Vermeersch, Kristina; Gabrovska, Maria; AUMANN, Joseph; Demedts, Ingel K.; Corhay, Jean-Louis; Marchand, Eric; Slabbynck, Hans; Haenebalcke, Christel; Haerens, Michiel; Hanon, Shane; Jordens, Paul; Peche, Rudi; Fremault, Antoine; Lauwerier, Tine; Delporte, Anja; Vandenberk, Bert; Willems, Rik; Everaerts, Stephanie; Belmans, Ann; BOGAERTS, Kris; Verleden, Geert M.; Troosters, Thierry; Ninane, Vincent; Brusselle, Guy G.; Janssens, Wim; Vincken, Walter; Debrock, Alix; Lamont, Jan; Tits, Geert; Delobbe, Alain & Martinot, Jean-Benoit (2019)
Azithromycin during Acute Chronic Obstructive Pulmonary Disease Exacerbations Requiring Hospitalization (BACE) A Multicenter, Randomized, Double-Blind, Placebo-controlled Trial. In: AMERICAN JOURNAL OF RESPIRATORY AND CRITICAL CARE MEDICINE, 200(7), p. 857-868.

DOI: 10.1164/rccm.201901-0094OC
Handle: http://hdl.handle.net/1942/29906

ONLINE DATA SUPPLEMENT

Supplement to:
Vermeersch K, Gabrovska M, Aumann J, et al. Azithromycin during acute COPD exacerbations requiring hospitalization.

This supplement contains the following items:

I. BACE TRIAL CONSORTIUM

1. AUTHOR'S CONTRIBUTIONS

The protocol was initiated by WJ, designed in collaboration with GGB and modified on the basis of input from the Consortium. The data were gathered by study personnel at each participating hospital, overseen by the local investigator. The statistical analysis plan was implemented by independent biostatisticians AB and KB. The cardiac safety assessment was performed by independent cardiologists BV and RW. All authors participated in interpreting the results. The first and final draft were written by KV and revised on the basis of input from the other authors and the Steering Committee. All the authors made the decision to submit the manuscript for publication and assume responsibility for the data, the accuracy of the analyses, and vouch for the fidelity of the study to the protocol.

2. LIST OF STUDY SITES IN BELGIUM

N°	Site	Address	City
1	UZ Gasthuisberg Leuven	Herestraat 49	3000, Leuven
2	UZ Gent	De Pintelaan 185	9000, Gent
3	Jessa ziekenhuis	Stadsomvaart 11, Campus Virga Jesse	3500, Hasselt
4	GZA St.-Augustinus	Oosterveldlaan 24	2610, Wilrijk
5	Imelda ziekenhuis	Imeldalaan 9	2820, Bonheiden
6	UZ Brussel	Laarbeeklaan 101	1090, Brussel
7	CHU St.-Pierre	Rue Haute 322	1000, Brussel
8	CHU-UCL Namur	Avenue Dr. Gaston Therasse 1	5530, Yvoir
9	CHU de Liège	Domaine Universitaire du Sart Tilman B35	4000, Luik
10	ZNA Middelheim	Lindendreef 1	2020, Antwerpen
11	St.-Andries ziekenhuis	Bruggestraat 84	8700, Tielt
12	AZ Delta	Wilgenstraat 2	8800, Roeselare
13	AZ St.-Jan	Ruddershove 10	8000, Brugge
14	AZ Maria Middelares	Kortrijksesteenweg 1026	9000, Gent
15	AZ Groeninge	Loofstraat 43	8500, Kortrijk
16	CHU de Charleroi	Route de Gozée 706	6110, Charleroi
17	Grand Hôpital de Charleroi	Rue de la Duchère 6, site St.-Joseph	6060, Charleroi
18	Clinique Reine Astrid	Rue devant les religieuses 2	4960, Malmedy
19	Clinique Ste.-Elisabeth	Place Louise Godin 15	5000, Namen
20	Onze-Lieve-Vrouwziekenhuis	Moorselbaan 164	9300, Aalst

3. LIST OF COLLABORATORS

UZ Gasthuisberg Leuven – W Janssens (PI), G M Verleden, P Van Bleyenbergh, L Dupont, N Lorent, P Van Den Brande (Co-Is), K Vermeersch, K Denaux, K De Bent, M Spruyt, W Dewit (Coordinators). **UZ Gent –** G G Brusselle (PI), B Demeyere, S Vermeersch, A Delporte, L Raman (Coordinators). **Jessa ziekenhuis, Campus Virga Jesse –** J Aumann (PI), G Deslypere, A Van Den Bergh, W Van Rompaey (Co-Is). **GZA St.-Augustinus –** A Debrock (PI), P Ardies (Coordinator). **Imelda ziekenhuis –** T Lauwerier (PI), A Delbaere (Coordinator). **UZ Brussel –** W Vincken (PI), S Hanon (Co-I), D Schuermans, K Van Eeckhoudt (Coordinators). **CHU St.-Pierre –** V Ninane (PI), M Gabrovska (Co-I), F De Cock, S Carlier (Coordinators). **CHU-UCL Namur –** E Marchand (PI). **CHU de Liège –** JL Corhay (PI), S Ziant, E Rubens (Coordinators). **ZNA Middelheim –** H Slabbynck (PI), J Raskin (Co-I), P Janssens (Coordinator). **St.-Andries ziekenhuis –** G Tits (PI). **AZ Delta –** I K Demedts (PI), M Masschelin, L Breyne (Coordinators). **AZ St.-Jan –** C Haenebalcke (PI), V Ringoet, R De Pauw, C Depuydt, S Muyldermans (Co-Is). **AZ Maria Middelares –** J Lamont (PI), A Casneuf (Coordinator). **AZ Groeninge –** M Haerens (PI), M Leys, H Bode, T Moerman (Co-Is), C Gheysens (Coordinator). **CHU de Charleroi –** R Peché (PI), P Oumaziz (Coordinator). **Grand Hôpital de Charleroi, site St.-Joseph –** A Fremault (PI), P Duwez (Coordinator). **Clinique Reine Astrid –** A Delobbe (PI). **Clinique Ste.-Elisabeth –** JB Martinot (PI). **Onze-Lieve-Vrouwziekenhuis Aalst –** P Jordens (PI), C Van de Kerkhove, H Nguyen (Co-Is). **Safety Committee –** R Willems, B Vandenberk. **Statistical Analysis Committee** – A Belmans, K Bogaerts. **Steering Committee –** W Janssens (Chair), G G Brusselle, G M Verleden, K Bogaerts, T Troosters, V Ninane. **Endpoint Committee –** W Janssens, K Vermeersch, L Burggraeve.

II. SUPPLEMENTARY DATA

1. Methods:

Table E1. Standardized treatment for an acute COPD exacerbation requiring hospitalization

Therapy		Specifications
Systemic corticosteroids		Methylprednisolone 40 mg IV or 32 mg PO OD for 5 days (switch IV to PO as soon as possible)
Antibiotics		
	First choice:	Amoxi-Clavulanate 1 g IV QID or 2 g PO BID for 7 days (or alternative regimen of 1 g IV QID or 875/125 mg PO TID for 7 days)
	Alternatives: In case of:	Moxifloxacin 400 mg IV or 400 mg PO OD for 5 days - Intolerance or allergy to Amoxi-Clavulanate - Clinical failure on GP-initiated Amoxi-Clavulanate treatment
	In case of:	Anti-Pseudomonas antibiotics - Bronchiectasis - History of positive cultures for Pseudomonas - High risk of Pseudomonas - Clinical failure on GP-initiated treatment
Short-acting bronchodilators		Via inhalation
Respiratory support		Oxygen Non-invasive ventilation[a] Mechanical ventilation[a]

Note: [a]Considered as exclusion criteria if needed on moment of randomization.
Abbreviations: COPD, chronic obstructive pulmonary disease; IV, intravenous; PO, per os; OD, once a day; QID, 4 times a day; BID, 2 times a day; GP, general practitioner

Table E2. Full list of exclusion criteria

	Exclusion criteria
1	Mechanical or non-invasive ventilation at the moment of randomization
2	Prolonged QT interval on ECG: QTcB >450 msec for male or >470 msec for female
3	History of life-threatening arrhythmias
4	Myocardial infarction (NSTEMI or STEMI) less than 6 weeks before randomization
5	Unstable angina pectoris or acute myocardial infarction (NSTEMI or STEMI) at admission
6	Concomitant use of a drug with high risk for QT prolongation and *Torsade de Pointes* (amiodarone, flecainide, procainamide, sotalol, droperidol, haldol, citalopram, other macrolides)
7	Documented uncorrected severe hypokalemia (K^+ <3.0 mmol/L) or hypomagnesemia (Mg^{2+} <0.5 mmol/L)
8	Chronic systemic corticosteroid use (>4 mg methylprednisolone/day for ≥2 months)
9	Use of macrolides during at least 2 weeks preceding inclusion
10	Allergy to macrolides
11	Active cancer treatment
12	Life expectancy <3 months
13	Pregnant or breast-feeding subjects. Woman of childbearing potential must have a pregnancy test performed and a negative result must be documented before starting the treatment.

Abbreviations: ECG, electrocardiogram; NSTEMI, non-ST elevation myocardial infarction; QTcB, QT interval corrected according to Bazett's formula; STEMI, ST elevation myocardial infarction

Full list of secondary endpoints

Key hierarchical secondary endpoints were the number of treatment failures (TF) at day 90, the COPD assessment test (CAT) score at day 90 and total days of systemic corticosteroid use at day 90. Other secondary endpoints were the key secondary endpoints at day 270 and endpoints assessed at day 90 and day 270 including time-to-TF, time-to-first treatment intensification (TI), time-to-first step-up in hospital care (SH), time-to-death, time-to-new exacerbation (with new exacerbation defined as the composite of TI and SH after the index event), number of new exacerbations, total dose and total days of systemic corticosteroid use, total days of non-study antibiotic use, total days of hospitalization, total days of intensive care, forced expiratory volume in 1 second (FEV1), quality of life (European Quality of Life – 5 Dimensions [EQ5D] questionnaire) and symptom assessments (CAT, modified Medical Research Council [mMRC] – breathlessness questionnaire and the Speech, Spatial and Qualities of Hearing Scale – 5-items [SSQ5] questionnaire), number of general practitioner (GP) visits and average costs of hospitalization.

Table E3. Overview of study assessments

Assessment	Visit								
	Screening	**Randomization**	**Switch to maintenance dose**	**Day of discharge**	**Control visit 1: 1 month after discharge**	**Control visit 2: End of intervention**	**Telephone call 1**	**Telephone call 2**	**Control visit 3: End of follow-up**
	(48 hours)	(D1, within 48h after hospital admission)	(D4, +max 72h*)	(DX, at investigator's discretion)	(DX+28, +14 day window)	(D90, allowed from day 86 until day 150)	(D150, ±7 day window)	(D210, ±7 day window)	(D270, +14 day window)
Chest X-ray	X								
ECG[b]	X		X		X[a]	X[a]			(X[a])
Arterial blood gas	X								
Laboratory[c]	X		X						
Spontaneous sputum sample[d]	X			X[a]		X[a]			X[a]
Pre- & post-bronchodilator spirometry				X		X			X
Eligibility + informed consent	X								
Anamnesis + medical history		X							
Current respiratory medication		X		X		X			X
Vital parameters	X	X	X	X		X			X
mMRC + CAT questionnaire		X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]	X[a]
EQ5D questionnaire		X[a]		X[a]		X[a]			X[a]
SSQ5D questionnaire		X[a]		X[a]		X[a]			X[a]
PROactive sub-study[e]				(X[a])		(X[a])			(X[a])
Study drug intake		X	X	X	X	X			
Check therapy adherence			X	X	X	X	X	X	X
Check prim./sec. endpoints			X	X	X	X	X	X	X
Record (serious) adverse events			X	X	X	X	X	X	X
Diary instruction + overview				X	X	X	X	X	X

Notes: *With exception of starting the maintenance dose; [a]Test performed in addition to clinical routine; [b]ECG only to be performed at D270 if prolonged QT interval, severe arrhythmia's or severe conductance disturbances were present on ECG of D90; [c]Screening laboratory: *hemoglobin, hematocrit, total white blood cell count and differentiation, platelets, creatinine, ureum, Na^+, K^+, Cl^-, $HCO3^-$, Mg^{2+}, AST, ALT, LDH, glucose, CRP, Ths-troponine;* D4 laboratory: *total white blood cell count and differentiation, Na^+, K^+, Cl^-, $HCO3^-$, Mg^{2+}, Ths-troponine, 25-hydroxyvitamin D, total IgE, specific Aspergillus fumigatus IgE and IgG (ImmunoCAP);* [d]If sputum sample is available, bacterial culture and antibiogram including macrolides to be performed; [e]Dynaport© to be worn for 7 days and questionnaire to be completed on day 8 only if patients consented to participation in the PROactive sub-study.

Abbreviations: ECG, electrocardiogram; mMRC, modified Medical Research Council; CAT, COPD Assessment Test; EQ5D, European Quality of Life – 5 Dimensions; SSQ5, Speech, Spatial and Qualities of hearing scale – 5 items.

II. SUPPLEMENTARY DATA

2. RESULTS

Table E4. Primary, key hierarchical and other secondary endpoints in the per-protocol population

	Visit	Azithromycin (n=147)	Placebo (n=154)	Estimator	Treatment effect (95% CI)	P-value
Primary endpoint						
Treatment failure rate †	Day 90	49.0 (40.5;58.3)	59.4 (50.8;68.2)	HR	0.73 (0.52;1.03)	0.0740
Key hierarchical secondary endpoints						
Number of treatment failures ‡	Day 90	0.78 (0.60;0.96)	0.96 (0.78;1.13)	Δ in MCF	-0.17 (-0.42;0.08)	0.0950
CAT score ¥	Day 90	17.5 (16.1;18.8)	16.7 (15.2;18.2)	Δ in means	0.63 (-1.22;2.48)	0.5033
Total days of steroid use *	Day 90	14.8 (13.8;15.9)	13.9 (13.0;14.9)	Rate ratio	1.07 (0.96;1.18)	0.2124
Other secondary endpoints						
Treatment failure rate †	Day 270	81.5 (73.9;88.0)	83.3 (76.0;89.4)	HR	0.86 (0.65;1.14)	0.2880
Number of treatment failures ‡	Day 270	2.43 (2.06;2.79)	2.41 (2.07;2.75)	Δ in MCF	0.02 (-0.48;0.51)	0.4131
CAT score ¥	Day 270	18.4 (16.8;19.9)	18.7 (17.0;20.3)	Δ in means	-0.62 (-2.74;1.50)	0.5681
Total days of steroid use *	Day 270	27.1 (26.1;28.2)	27.2 (26.2;28.3)	Rate ratio	1.00 (0.94;1.05)	0.8817
Treatment intensification rate $	Day 90	46.6 (37.4;55.2)	58.6 (49.1;66.8)	HR	0.69 (0.49;0.98)	0.0377
	Day 270	79.0 (70.2;85.4)	82.5 (74.2;88.3)	HR	0.82 (0.62;1.08)	0.1601
Step-up in hospital care rate $	Day 90	12.9 (7.5;19.6)	28.4 (20.6;36.7)	HR	0.40 (0.22;0.74)	0.0033
	Day 270	36.2 (27.4;45.1)	43.3 (34.2;52.1)	HR	0.71 (0.47;1.07)	0.0979
Mortality rate †	Day 90	1.7 (0.4;6.5)	2.5 (0.8;7.4)	HR	0.68 (0.11;4.07)	0.6704
	Day 270	4.4 (1.8;10.2)	5.2 (2.4;11.3)	HR	0.82 (0.25;2.69)	0.7441
New exacerbation rate $	Day 90	40.0 (31.1;48.8)	48.8 (39.5;57.5)	HR	0.76 (0.52;1.11)	0.1528
	Day 270	75.9 (66.7;82.8)	77.8 (68.9;84.4)	HR	0.89 (0.66;1.19)	0.4130
Number of new exacerbations ‡	Day 90	0.60 (0.45;0.75)	0.68 (0.54;0.81)	Δ in MCF	-0.08 (-0.28;0.13)	0.4669
	Day 270	2.17 (1.82;2.52)	2.05 (1.72;2.37)	Δ in MCF	0.12 (-0.35;0.60)	0.6188
Total dose of steroid use (mg) *	Day 90	340.2 (335.4;345.1)	321.8 (317.6;326.0)	Rate ratio	1.06 (1.04;1.08)	<0.0001
	Day 270	603.4 (598.4;608.5)	603.5 (598.4;608.6)	Rate ratio	1.00 (0.99;1.01)	0.9903
Total days of non-study antibiotics *	Day 90	10.5 (9.6;11.5)	13.7 (12.8;14.7)	Rate ratio	0.77 (0.68;0.86)	<0.0001
	Day 270	21.1 (20.2;22.1)	21.6 (20.7;22.6)	Rate ratio	0.98 (0.92;1.04)	0.4592
Total hospital days *	Day 90	10.6 (9.1;12.3)	13.6 (11.8;15.8)	Rate ratio	0.78 (0.63;0.96)	0.0179
	Day 270	22.7 (18.5;27.9)	26.1 (21.4;31.7)	Rate ratio	0.87 (0.66;1.15)	0.3350
Total ICU days *	Day 90	3.0 (1.8;5.1)	11.9 (9.3;15.1)	Rate ratio	0.25 (0.14;0.46)	<0.0001
	Day 270	5.1 (4.0;6.5)	10.0 (8.1;12.1)	Rate ratio	0.51 (0.37;0.70)	<0.0001
Number of GP contacts *	Day 90	2.4 (2.0;2.7)	2.6 (2.3;3.0)	Rate ratio	0.90 (0.74;1.10)	0.3119
	Day 270	6.1 (5.7;6.6)	6.6 (6.1;7.1)	Rate ratio	0.92 (0.83;1.03)	0.1511
Pre-bronchodilator FEV1 (L) ¥	Day 90	1.3 (0.9;1.7)	1.2 (1.1;1.3)	Δ in means	0.11 (-0.34;0.56)	0.6262
	Day 270	1.1 (1.0;1.2)	1.2 (1.1;1.3)	Δ in means	-0.11 (-0.24;0.03)	0.1378
mMRC score ¥	Day 90	3.1 (2.9;3.3)	3.1 (2.9;3.3)	Δ in means	-0.07 (-0.35;0.20)	0.5975
	Day 270	3.4 (3.2;3.6)	3.2 (3.0;3.4)	Δ in means	0.10 (-0.19;0.40)	0.4989
EQ5D score ¥	Day 90	61.5 (57.9;65.0)	62.0 (58.3;65.7)	Δ in means	-0.65 (-5.52;4.23)	0.7951
	Day 270	56.0 (52.3;59.8)	60.9 (56.6;65.2)	Δ in means	-4.51 (-9.93;0.91)	0.1028
SSQ5 score ¥	Day 90	8.0 (7.7;8.3)	7.9 (7.6;8.2)	Δ in means	0.12 (-0.22;0.46)	0.4819
	Day 270	8.2 (7.8;8.5)	8.0 (7.7;8.3)	Δ in means	0.19 (-0.15;0.53)	0.2794

Data are presented as follows: †Event rate (95% CI) obtained using Kaplan-Meier methodology. Groups were compared using a log-rank test. Treatment effect presented as hazard ratio (HR). ‡Mean Cumulative Function (MCF) (95% CI). Groups were compared using a log-rank test for MCFs. Treatment effect presented as difference in MCF. ¥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. Groups were compared using GEE by a Chi-squared test. Treatment effect presented as difference in expected means. *Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset. Treatment effect presented as rate ratio. $Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk. Groups were compared using Gray's test. Treatment effect presented as HR. New exacerbation is defined as the composite of TI and SH for respiratory reasons after the index event.

Abbreviations: CAT, COPD assessment test; Δ: symbol indicating difference; FEV1, forced expiratory volume in 1 second; GP, general practitioner; ICU, intensive care unit; MCF, mean cumulative function; mMRC, modified Medical Research Council questionnaire; EQ5D, European Quality of Life – 5 dimensions questionnaire; SSQ5, the Speech, Spatial and Qualities of Hearing Scale – 5 items questionnaire.

Note: day 90: end of intervention; day 270: end of follow-up.

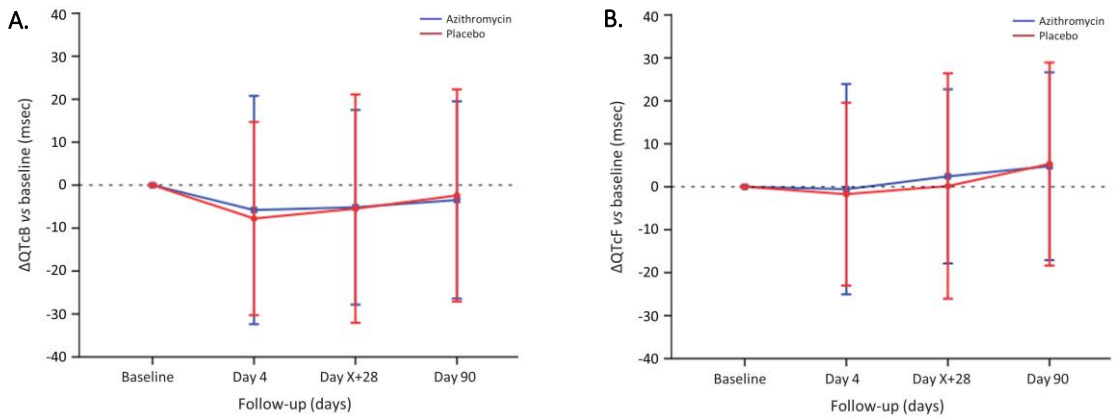


Figure E1. Effect of the 3-month intervention with low-dose azithromycin on the QT interval

Data are presented as mean QTc differences (Δ) compared to baseline with SD.

No significant QTc prolongation was observed in the azithromycin group, neither when QT correction was performed with (A) Bazett's formula (QTcB), nor with (B) Fridericia's formula (QTcF). With QTcB: Δday4= -5.8±26.6msec, ΔdayX+28= -5.2±22.7msec, Δday90= -3.5±23.0msec (p=0.154); and with QTcF: Δday4= -0.6±24.5msec, ΔdayX+28= 2.5±20.3msec, Δday90= 4.8±21.8msec (p=0.142).

Note: baseline: hospital admission; day X: day of discharge, at the investigator's discretion; day 90: end of intervention; day 270: end of follow-up.

Table E5. Overview of inhaled therapy for COPD throughout the study

		Baseline	Day X	Day 90	Day 270
	Azithromycin	n=147	n=143	n=131	n=118
	Placebo	n=154	n=150	n=129	n=115
None	Azi.	5 (3.4)	1 (0.7)	0 (0)	0 (0)
	Plac.	5 (3.2)	0 (0)	0 (0)	2 (1.7)
ICS only	Azi.	4 (2.7)	2 (1.4)	1 (0.8)	1 (0.8)
	Plac.	0 (0)	0 (0)	0 (0)	0 (0)
LAMA only	Azi.	2 (1.4)	2 (1.4)	2 (1.5)	3 (2.5)
	Plac.	3 (1.9)	5 (3.3)	6 (4.7)	3 (2.6)
LABA only	Azi.	5 (3.4)	4 (2.8)	2 (1.5)	2 (1.7)
	Plac.	5 (3.2)	4 (2.7)	3 (2.3)	4 (3.5)
ICS LABA	Azi.	15 (10.2)	7 (4.9)	3 (2.3)	7 (5.9)
	Plac.	21 (13.6)	10 (6.7)	8 (6.2)	5 (4.3)
ICS LAMA	Azi.	0 (0)	0 (0)	2 (1.5)	2 (1.7)
	Plac.	1 (0.6)	0 (0)	1 (0.8)	0 (0)
LAMA LABA	Azi.	17 (11.6)	18 (12.6)	15 (11.5)	13 (11.0)
	Plac.	18 (11.7)	23 (15.3)	19 (14.7)	15 (13.0)
ICS LAMA LABA	Azi.	99 (67.3)	109 (76.2)	106 (80.9)	90 (76.3)
	Plac.	101 (65.6)	108 (72.0)	92 (71.3)	86 (74.8)
	p-value	0.529	0.510	0.298	0.517

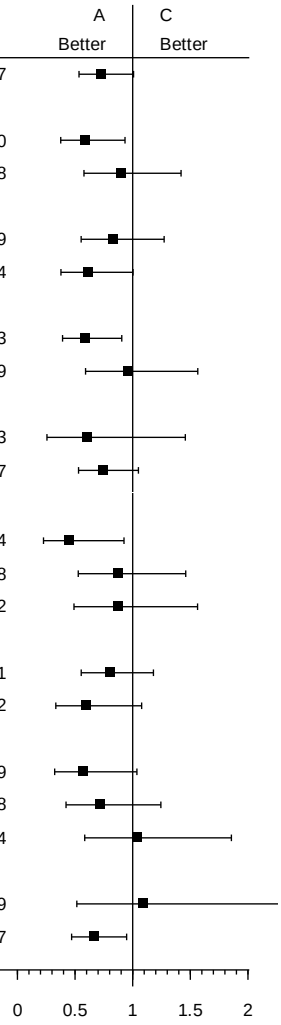
Data are presented as number of patients on inhaled therapy for COPD at the given time point (no. (%)).

Abbreviations: LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; SABA, short-acting beta-agonist

Note: baseline: hospital admission; day X: day of discharge, at the investigator's discretion; day 90: end of intervention; day 270: end of follow-up.

Table E6. Subgroup analyses of the primary endpoint, treatment failure rate within 90 days, in the intention-to-treat population

Subgroup	Azithromycin [n] Est. (95% CI)	Control [n] Est. (95% CI)	Effect of Treatment (95% CI)	P
Total Population	[147] 49.5% (41.5%; 58.1%)	[154] 60.4% (52.4%; 68.5%)	0.73 (0.53; 1.01)	0.0557
Age (Interaction: p = 0.1934)				
<= 65 years	[71] 45.1% (34.1%; 57.8%)	[86] 62.3% (51.6%; 73.0%)	0.59 (0.38; 0.93)	0.0240
> 65 years	[76] 53.5% (42.5%; 65.2%)	[68] 58.2% (46.5%; 70.4%)	0.91 (0.58; 1.42)	0.6648
Gender (Interaction: p = 0.3441)				
Male	[81] 52.8% (42.2%; 64.2%)	[88] 59.0% (48.5%; 69.8%)	0.84 (0.55; 1.27)	0.4089
Female	[66] 45.4% (33.9%; 58.6%)	[66] 62.3% (50.3%; 74.4%)	0.62 (0.38; 1.00)	0.0514
Smoking (Interaction: p = 0.1434)				
Non-Smoker	[84] 47.7% (37.4%; 59.2%)	[89] 64.7% (54.2%; 75.0%)	0.60 (0.39; 0.91)	0.0153
Smoker	[63] 51.8% (39.9%; 65.0%)	[65] 54.9% (43.1%; 67.6%)	0.96 (0.59; 1.56)	0.8749
GOLD (Interaction: p = 0.6748)				
A,B	[26] 33.0% (18.0%; 55.3%)	[31] 47.8% (31.6%; 67.2%)	0.61 (0.26; 1.46)	0.2663
C,D	[121] 53.0% (44.2%; 62.3%)	[123] 63.5% (54.7%; 72.4%)	0.75 (0.53; 1.05)	0.0927
Former GOLD (Interaction: p = 0.2812)				
I, II	[36] 33.3% (20.5%; 51.2%)	[42] 55.5% (40.9%; 71.2%)	0.46 (0.23; 0.92)	0.0294
III	[55] 51.1% (38.5%; 65.1%)	[59] 57.5% (45.1%; 70.5%)	0.88 (0.53; 1.46)	0.6158
IV	[38] 58.6% (43.6%; 74.4%)	[39] 68.2% (52.7%; 82.6%)	0.88 (0.49; 1.56)	0.6532
CRP at Screening (Interaction: p = 0.4008)				
Low CRP	[103] 50.9% (41.5%; 61.1%)	[104] 59.0% (49.4%; 68.8%)	0.81 (0.55; 1.18)	0.2701
High CRP	[44] 45.9% (32.2%; 62.3%)	[49] 62.8% (48.5%; 77.1%)	0.60 (0.33; 1.08)	0.0872
Anthonisen (Interaction: p = 0.3664)				
I	[43] 43.8% (29.9%; 60.8%)	[62] 60.2% (47.6%; 73.0%)	0.58 (0.32; 1.04)	0.0659
II	[46] 53.2% (39.6%; 68.2%)	[45] 68.5% (54.4%; 81.8%)	0.72 (0.42; 1.24)	0.2428
III	[53] 52.8% (40.0%; 66.9%)	[43] 50.2% (35.9%; 66.5%)	1.04 (0.58; 1.86)	0.8914
ICS Use (Interaction: p = 0.2423)				
No	[29] 49.4% (32.9%; 68.8%)	[31] 44.6% (28.8%; 64.1%)	1.10 (0.52; 2.33)	0.8109
Yes	[118] 49.6% (40.7%; 59.2%)	[123] 64.6% (55.7%; 73.4%)	0.67 (0.47; 0.95)	0.0237

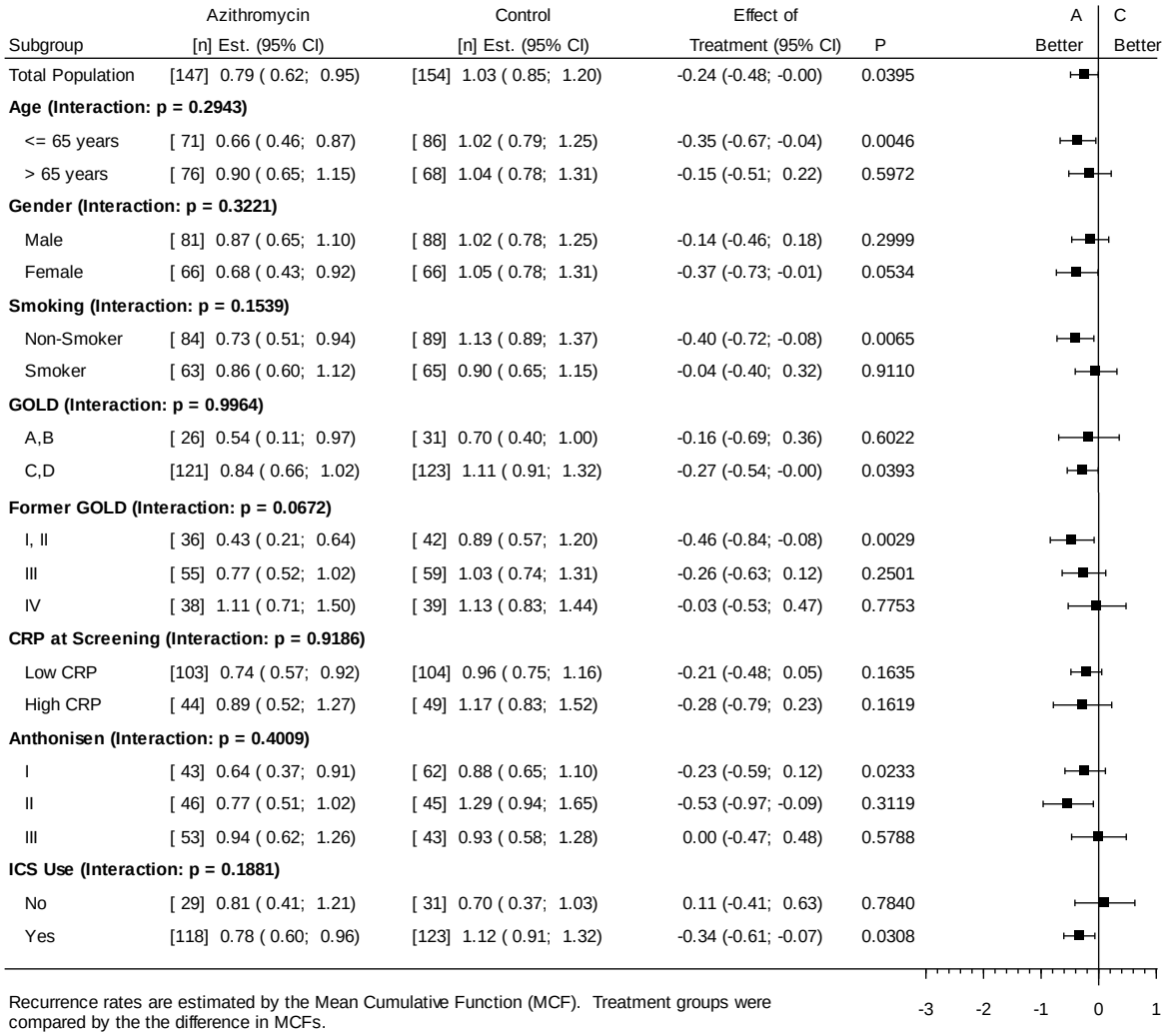


Event rates in the two groups were estimated using Kaplan-Meier methodology. Treatment Effect is a hazard ratio obtained using a Cox regression that included a factor for randomised treatment, subgroup and their interaction.

NC = Not Calculated due to an insufficient number of patients in some groups.

Table E7. Subgroup analyses of the key hierarchical secondary endpoint, number of treatment failures within 90 days, in the intention-to-treat population

Subgroup	Azithromycin [n] Est. (95% CI)	Control [n] Est. (95% CI)	Effect of Treatment (95% CI)	P
Total Population	[147] 0.79 (0.62; 0.95)	[154] 1.03 (0.85; 1.20)	-0.24 (-0.48; -0.00)	0.0395
Age (Interaction: p = 0.2943)				
<= 65 years	[71] 0.66 (0.46; 0.87)	[86] 1.02 (0.79; 1.25)	-0.35 (-0.67; -0.04)	0.0046
> 65 years	[76] 0.90 (0.65; 1.15)	[68] 1.04 (0.78; 1.31)	-0.15 (-0.51; 0.22)	0.5972
Gender (Interaction: p = 0.3221)				
Male	[81] 0.87 (0.65; 1.10)	[88] 1.02 (0.78; 1.25)	-0.14 (-0.46; 0.18)	0.2999
Female	[66] 0.68 (0.43; 0.92)	[66] 1.05 (0.78; 1.31)	-0.37 (-0.73; -0.01)	0.0534
Smoking (Interaction: p = 0.1539)				
Non-Smoker	[84] 0.73 (0.51; 0.94)	[89] 1.13 (0.89; 1.37)	-0.40 (-0.72; -0.08)	0.0065
Smoker	[63] 0.86 (0.60; 1.12)	[65] 0.90 (0.65; 1.15)	-0.04 (-0.40; 0.32)	0.9110
GOLD (Interaction: p = 0.9964)				
A,B	[26] 0.54 (0.11; 0.97)	[31] 0.70 (0.40; 1.00)	-0.16 (-0.69; 0.36)	0.6022
C,D	[121] 0.84 (0.66; 1.02)	[123] 1.11 (0.91; 1.32)	-0.27 (-0.54; -0.00)	0.0393
Former GOLD (Interaction: p = 0.0672)				
I, II	[36] 0.43 (0.21; 0.64)	[42] 0.89 (0.57; 1.20)	-0.46 (-0.84; -0.08)	0.0029
III	[55] 0.77 (0.52; 1.02)	[59] 1.03 (0.74; 1.31)	-0.26 (-0.63; 0.12)	0.2501
IV	[38] 1.11 (0.71; 1.50)	[39] 1.13 (0.83; 1.44)	-0.03 (-0.53; 0.47)	0.7753
CRP at Screening (Interaction: p = 0.9186)				
Low CRP	[103] 0.74 (0.57; 0.92)	[104] 0.96 (0.75; 1.16)	-0.21 (-0.48; 0.05)	0.1635
High CRP	[44] 0.89 (0.52; 1.27)	[49] 1.17 (0.83; 1.52)	-0.28 (-0.79; 0.23)	0.1619
Anthonisen (Interaction: p = 0.4009)				
I	[43] 0.64 (0.37; 0.91)	[62] 0.88 (0.65; 1.10)	-0.23 (-0.59; 0.12)	0.0233
II	[46] 0.77 (0.51; 1.02)	[45] 1.29 (0.94; 1.65)	-0.53 (-0.97; -0.09)	0.3119
III	[53] 0.94 (0.62; 1.26)	[43] 0.93 (0.58; 1.28)	0.00 (-0.47; 0.48)	0.5788
ICS Use (Interaction: p = 0.1881)				
No	[29] 0.81 (0.41; 1.21)	[31] 0.70 (0.37; 1.03)	0.11 (-0.41; 0.63)	0.7840
Yes	[118] 0.78 (0.60; 0.96)	[123] 1.12 (0.91; 1.32)	-0.34 (-0.61; -0.07)	0.0308

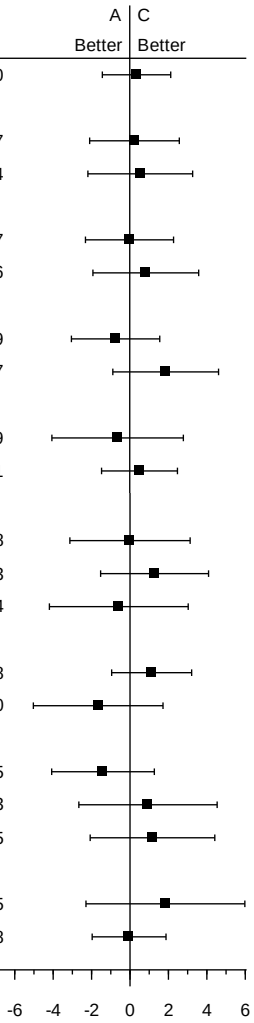


Recurrence rates are estimated by the Mean Cumulative Function (MCF). Treatment groups were compared by the the difference in MCFs.

NC = Not Calculated due to an insufficient number of patients in some groups.

Table E8. Subgroup analyses of the key hierarchical secondary endpoint, COPD assessment test score up to day 90, in the intention-to-treat population

Subgroup	Azithromycin [n] Est. (95% CI)	Control [n] Est. (95% CI)	Effect of Treatment (95% CI)	P
Total Population	[147] 17.70 (16.37; 19.03)	[153] 16.86 (15.46; 18.25)	0.35 (-1.43; 2.13)	0.6970
Age (Interaction: p = 0.8689)				
<= 65 years	[71] 17.29 (15.51; 19.08)	[86] 16.79 (14.97; 18.60)	0.25 (-2.09; 2.58)	0.8357
> 65 years	[76] 18.09 (16.14; 20.05)	[67] 16.95 (14.78; 19.12)	0.55 (-2.18; 3.28)	0.6934
Gender (Interaction: p = 0.6404)				
Male	[81] 16.94 (15.25; 18.63)	[87] 16.85 (15.05; 18.64)	-0.01 (-2.31; 2.28)	0.9917
Female	[66] 18.60 (16.52; 20.68)	[66] 16.87 (14.68; 19.07)	0.84 (-1.92; 3.59)	0.5516
Smoking (Interaction: p = 0.1542)				
Non-Smoker	[84] 16.96 (15.22; 18.70)	[88] 17.49 (15.71; 19.28)	-0.74 (-3.04; 1.56)	0.5299
Smoker	[63] 18.74 (16.71; 20.76)	[65] 15.98 (13.78; 18.18)	1.87 (-0.88; 4.62)	0.1827
GOLD (Interaction: p = 0.5716)				
A,B	[26] 12.75 (10.06; 15.44)	[30] 12.48 (10.45; 14.52)	-0.63 (-4.05; 2.79)	0.7179
C,D	[121] 18.85 (17.43; 20.28)	[123] 18.05 (16.44; 19.66)	0.51 (-1.47; 2.48)	0.6141
Former GOLD (Interaction: p = 0.6972)				
I, II	[36] 15.35 (12.82; 17.88)	[42] 15.19 (12.86; 17.53)	-0.00 (-3.13; 3.13)	0.9998
III	[55] 18.67 (16.71; 20.64)	[59] 16.66 (14.51; 18.81)	1.28 (-1.53; 4.09)	0.3723
IV	[38] 19.09 (16.06; 22.12)	[39] 19.13 (16.28; 21.97)	-0.58 (-4.20; 3.03)	0.7514
CRP at Screening (Interaction: p = 0.1704)				
Low CRP	[103] 18.42 (16.95; 19.89)	[104] 16.93 (15.20; 18.67)	1.13 (-0.96; 3.21)	0.2888
High CRP	[44] 15.74 (12.93; 18.54)	[48] 16.51 (14.23; 18.80)	-1.66 (-5.03; 1.72)	0.3360
Anthonisen (Interaction: p = 0.4046)				
I	[43] 15.92 (13.74; 18.10)	[62] 16.12 (14.07; 18.16)	-1.41 (-4.08; 1.27)	0.3025
II	[46] 18.20 (15.64; 20.76)	[45] 17.76 (15.27; 20.24)	0.94 (-2.66; 4.54)	0.6103
III	[53] 18.85 (16.63; 21.07)	[42] 17.29 (14.23; 20.36)	1.17 (-2.07; 4.41)	0.4795
ICS Use (Interaction: p = 0.4187)				
No	[29] 15.19 (12.32; 18.07)	[31] 13.04 (10.20; 15.87)	1.84 (-2.29; 5.98)	0.3825
Yes	[118] 18.35 (16.87; 19.82)	[122] 17.90 (16.37; 19.43)	-0.05 (-1.97; 1.87)	0.9608

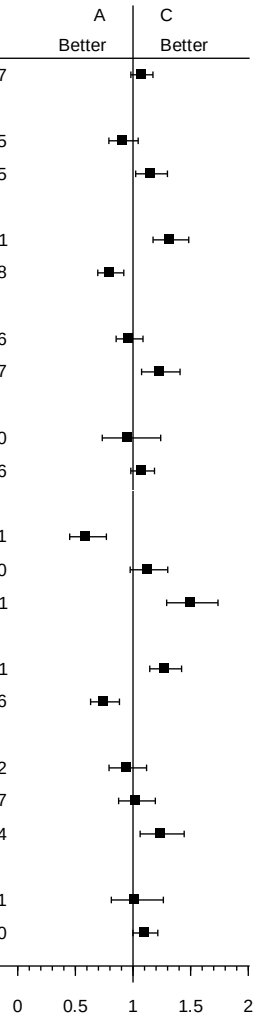


CAT scores were analysed using a GEE model for normal dadta including all visits and an independent variance-covariance matrix to account for interdepencies between the visits.

NC = Not Calculated due to an insufficient number of patients in some groups.

Table E9. Subgroup analyses of the key hierarchical secondary endpoint, total days of systemic corticosteroid use at 90 days, in the intention-to-treat population

Subgroup	Azithromycin [n] Est. (95% CI)	Control [n] Est. (95% CI)	Effect of Treatment (95% CI)	P
Total Population	[147] 15.87 (14.86; 16.93)	[154] 14.79 (13.91; 15.72)	1.07 (0.98; 1.17)	0.1217
Age (Interaction: p < 0.0001)				
<= 65 years	[71] 12.56 (11.24; 14.03)	[86] 13.82 (12.70; 15.03)	0.91 (0.79; 1.04)	0.1785
> 65 years	[76] 18.44 (17.01; 19.99)	[68] 16.00 (14.65; 17.47)	1.15 (1.02; 1.30)	0.0195
Gender (Interaction: p < 0.0001)				
Male	[81] 18.53 (17.09; 20.09)	[88] 14.04 (12.90; 15.28)	1.32 (1.17; 1.48)	<.0001
Female	[66] 12.53 (11.23; 13.99)	[66] 15.68 (14.36; 17.12)	0.80 (0.69; 0.92)	0.0018
Smoking (Interaction: p < 0.0001)				
Non-Smoker	[84] 14.90 (13.58; 16.35)	[89] 15.47 (14.33; 16.71)	0.96 (0.85; 1.09)	0.5416
Smoker	[63] 16.93 (15.45; 18.55)	[65] 13.76 (12.46; 15.20)	1.23 (1.07; 1.41)	0.0027
GOLD (Interaction: p = 0.1417)				
A,B	[26] 11.28 (9.18; 13.85)	[31] 11.83 (10.04; 13.93)	0.95 (0.73; 1.24)	0.7230
C,D	[121] 16.62 (15.52; 17.80)	[123] 15.41 (14.43; 16.45)	1.08 (0.98; 1.19)	0.1176
Former GOLD (Interaction: p < 0.0001)				
I, II	[36] 8.57 (6.76; 10.85)	[42] 14.55 (12.85; 16.48)	0.59 (0.45; 0.77)	0.0001
III	[55] 15.75 (14.27; 17.39)	[59] 13.98 (12.59; 15.53)	1.13 (0.98; 1.30)	0.1050
IV	[38] 21.66 (19.61; 23.93)	[39] 14.46 (12.96; 16.14)	1.50 (1.29; 1.74)	<.0001
CRP at Screening (Interaction: p < 0.0001)				
Low CRP	[103] 16.08 (14.93; 17.33)	[104] 12.60 (11.66; 13.63)	1.28 (1.15; 1.42)	<.0001
High CRP	[44] 15.20 (13.30; 17.39)	[49] 20.36 (18.44; 22.48)	0.75 (0.63; 0.88)	0.0006
Anthonisen (Interaction: p < 0.0001)				
I	[43] 13.23 (11.51; 15.20)	[62] 14.06 (12.69; 15.57)	0.94 (0.79; 1.12)	0.4882
II	[46] 14.38 (12.80; 16.15)	[45] 14.07 (12.69; 15.59)	1.02 (0.88; 1.19)	0.7817
III	[53] 19.58 (17.78; 21.56)	[43] 15.81 (14.03; 17.82)	1.24 (1.06; 1.44)	0.0064
ICS Use (Interaction: p = 0.0031)				
No	[29] 13.31 (11.47; 15.44)	[31] 13.14 (11.16; 15.48)	1.01 (0.81; 1.26)	0.9101
Yes	[118] 16.63 (15.46; 17.88)	[123] 15.09 (14.13; 16.11)	1.10 (1.00; 1.22)	0.0520



All results were obtained using a Poisson regression with the total number of days as offset.
Treatment, subgroup and their interaction were included as factors in the model.

NC = Not Calculated due to an insufficient number of patients in some groups.

Table E10. Overview of most frequent adverse events

Gastrointestinal	**Trial phase**	**Azithromycin** (n=147)		**Placebo** (n=154)	
Diarrhea	Day 1 - day 90	20	(13.6)	15	(9.7)
	Day 90 - day 270	10	(6.8)	11	(7.1)
Nausea	Day 1 - day 90	12	(8.2)	11	(7.1)
	Day 90 - day 270	5	(3.4)	5	(3.3)
Anorexia	Day 1 - day 90	9	(6.1)	8	(5.2)
	Day 90 - day 270	10	(6.8)	12	(7.8)
Other					
Hearing loss	Day 1 - day 90	1	(0.7)	6	(3.9)
	Day 90 - day 270	3	(2.0)	6	(3.9)
Syncope	Day 1 - day 90	1	(0.7)	2	(1.3)
	Day 90 - day 270	2	(1.4)	1	(0.7)

Data are presented as number of patients with the specific adverse event during the given time period (no. (%)).
Note: day 1: randomization; day 90: end of intervention; day 270: end of follow-up.

Table E11. Overview of adverse events leading to study drug discontinuation

		Azithromycin	Placebo
Gastrointestinal	**Trial phase**	(n=147)	(n=154)
Diarrhea	Day 1 - day 90	2 (1.4)	0 (0)
	Day 90 - day 270	-	-
Nausea	Day 1 - day 90	1 (0.7)	0 (0)
	Day 90 - day 270	-	-
Abdominal discomfort	Day 1 - day 90	1 (0.7)	1 (0.6)
	Day 90 - day 270	-	-
Pancolitis	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Cardiovascular			
QTc prolongation	Day 1 - day 90	2 (1.4)	1 (0.6)
	Day 90 - day 270	-	-
(N)STEMI	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Takotsubo cardiomyopathy	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Other	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Respiratory			
AECOPD	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	-	-
Other			
Miscellaneous	Day 1 - day 90	2 (1.4)	6 (3.9)
	Day 90 - day 270	-	-

Data are presented as number of patients with the specific adverse event during the given time period (no. (%)).
Note: day 1: randomization; day 90: end of intervention; day 270: end of follow-up.

Table E12. Overview of serious adverse events

FATAL	Trial phase	Azithromycin (n=147)	Placebo (n=154)
All-cause	Day 1 - day 90	3 (2.0)	6 (3.9)
	Day 90 - day 270	4 (2.7)	3 (1.9)
Cardiovascular	Day 1 - day 90	3 (2.0)	2 (1.3)
	Day 90 - day 270	1 (0.7)	0 (0)
Respiratory	Day 1 - day 90	0 (0)	3 (1.9)
	Day 90 - day 270	2 (1.4)	3 (1.9)
Lung cancer	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	1 (0.7)	0 (0)
NON-FATAL			
Gastrointestinal	Day 1 - day 90	3 (2.0)	2 (1.3)
	Day 90 - day 270	1 (0.7)	3 (1.9)
Cardiovascular	Day 1 - day 90	3 (2.0)	6 (3.9)
	Day 90 - day 270	2 (1.4)	1 (0.6)
Laboratory investigations	Day 1 - day 90	1 (0.7)	0 (0)
	Day 90 - day 270	1 (0.7)	1 (0.6)
Oncology	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	2 (1.4)	1 (0.6)
Cerebrovascular	Day 1 - day 90	0 (0)	2 (1.3)
	Day 90 - day 270	2 (1.4)	2 (1.3)
Renal	Day 1 - day 90	0 (0)	0 (0)
	Day 90 - day 270	0 (0)	2 (1.3)
Psychological	Day 1 - day 90	1 (0.7)	0 (0)
	Day 90 - day 270	1 (0.7)	1 (0.6)
Musculoskeletal	Day 1 - day 90	0 (0)	1 (0.6)
	Day 90 - day 270	2 (1.4)	3 (1.9)

Data are presented as number of patients with the specific adverse event during the given time period (no. (%)).
Note: day 1: randomization; day 90: end of intervention; day 270: end of follow-up.

Table S13. Overview of obtained spontaneous sputum samples*

	Azithromycin	Placebo
Baseline	**(n=147)**	**(n=154)**
Number of patients with sputum samples	110	109
Number of patients with bacterial culture	109	103
Number of patients with pathogens in sputum	37 (33.9)	30 (29.1)
Haemophilus influenzae	18 (16.5)	5 (4.9) †
Streptococcus pneumoniae	12 (11.0)	8 (7.8)
Pseudomonas aeruginosa	3 (2.8)	5 (4.9)
Morexella catarrhalis	2 (1.8)	6 (5.8)
Staphylococcus aureus	4 (3.7)	2 (1.9)
Other gram-negative bacteria	10 (9.2)	11 (10.7)
Number of patients with macrolide resistant bacteria	6 (5.5)	2 (1.9)
Streptococcus pneumoniae	4 (3.7)	2 (1.9)
Morexella catarrhalis	0 (0)	0 (0)
Staphylococcus aureus	2 (1.8)	0 (0)
Day X	**(n=143)**	**(n=150)**
Number of patients with sputum samples	55	62
Number of patients with bacterial culture	53	61
Number of patients with newly acquired pathogens	9	11
Number of patients with newly acquired macrolide resistant bacteria	1	3
Day 90	**(n=131)**	**(n=129)**
Number of patients with sputum samples	24	22
Number of patients with bacterial culture	23	21
Number of patients with newly acquired pathogens	4	3
Number of patients with newly acquired macrolide resistant bacteria	0	1
Day 270	**(n=118)**	**(n=115)**
Number of patients with sputum samples	20	16
Number of patients with bacterial culture	19	15
Number of patients with newly acquired pathogens	4	3
Number of patients with newly acquired macrolide resistant bacteria	0	0

Date are presented as no. (%).

*Newly acquired pathogens and macrolide resistant bacteria were counted with regards to the preceding study visit.

Note: † p=0.006. baseline: hospital admission; day X: day of discharge, at the investigator's discretion; day 90: end of intervention; day 270: end of follow-up.

TITLE PAGE

Word count text: 3692

Word count abstract: 255

Title

Azithromycin during acute COPD exacerbations requiring hospitalization

Running title

The BACE trial

Author list

Kristina Vermeersch, Msc[1,2]; Maria Gabrovska, MD[3]; Joseph Aumann, MD[4]; Ingel K Demedts, MD, PhD[5]; Prof. Jean-Louis Corhay, MD, PhD[6]; Prof. Eric Marchand, MD, PhD[7,8]; Hans Slabbynck, MD[9]; Christel Haenebalcke, MD[10]; Michiel Haerens, MD[11]; Shane Hanon, MD[12]; Paul Jordens, MD[13]; Rudi Peché, MD[14]; Antoine Fremault, MD[15]; Tine Lauwerier, MD[16]; Anja Delporte, Msc[17]; Bert Vandenberk, MD, PhD[18]; Prof. Rik Willems, MD, PhD[18]; Stephanie Everaerts, MD, PhD[1,2]; Ann Belmans, Msc[19]; Kris Bogaerts, PhD[19]; Prof. Geert M Verleden, MD, PhD[1,2]; Prof. Thierry Troosters, PhD[1,20]; Prof. Vincent Ninane, MD, PhD[3]; Prof. Guy G Brusselle, MD, PhD[17]; Prof. Wim Janssens, MD, PhD[1,2] – *On behalf of the BACE trial investigators*

Corresponding author: Wim Janssens, MD, PhD

KU Leuven, Department of Chronic Diseases, Metabolism and Ageing

Herestraat 49, O&NI, box 706

B-3000 Leuven, Belgium

Phone: +32 16346812; Fax: +32 16346803

E-mail: wim.janssens@kuleuven.be

Affiliations

[1]KU Leuven, Laboratory of Respiratory Diseases, Department of Chronic Diseases, Metabolism and Ageing, B-3000 Leuven, Belgium

[2]University Hospitals Leuven, Department of Respiratory Diseases, B-3000 Leuven, Belgium

[3]Centre Hospitalier Universitaire Saint-Pierre, Université Libre de Bruxelles, Department of Pneumology, B-1000 Brussels, Belgium

[4]Jessa Ziekenhuis, Department of Pneumology, B-3500 Hasselt, Belgium

[5]AZ Delta Roeselare-Menen, Department of Respiratory Medicine, B-8800 Roeselare, Belgium

[6]Centre Hospitalier Universitaire, site Sart-Tilman, Department of Pneumology, B-4000 Liège, Belgium

[7]CHU-UCL-Namur, site Mont-Godinne, Department of Pneumology, B-5530 Yvoir, Belgium

[8]University of Namur, Faculty of Medicine, NARILIS, Laboratory of Respiratory Physiology, B-5000 Namur, Belgium

[9]ZNA Middelheim, Department of Respiratory Medicine, B-2020 Antwerpen, Belgium

[10]AZ Sint-Jan, Department of Pneumology, B-8000 Brugge-Oostende, Belgium

[11]AZ Groeninge, Department of Pneumology, B-8500 Kortrijk, Belgium

[12]UZ Brussel, Department of Pneumology, B-1090 Jette, Belgium

[13]Onze-Lieve-Vrouw ziekenhuis, Department of Pneumology, B-9300 Aalst, Belgium

[14]Centre Hospitalier Universitaire de Charleroi, Department of Pneumology, B-6110 Charleroi, Belgium

[15]Grand Hôpital de Charleroi, Department of Pneumology, B-6000 Charleroi, Belgium

[16]Imelda ziekenhuis, Department of Pneumology, B-2820 Bonheiden, Belgium

[17]Ghent University Hospital, Department of Respiratory Medicine, B-9000 Ghent, Belgium

[18]University Hospitals Leuven, Department of Cardiology, B-3000 Leuven, Belgium

[19]I-BioStat, KU Leuven, B-3000 Leuven, Belgium and Universiteit Hasselt, B-3500 Hasselt, Belgium

[20]KU Leuven, Department of Rehabilitation Sciences, Faculty of Kinesiology and Rehabilitation Sciences, Leuven, Belgium

Summary Conflict of Interest Statements

-KV is supported as a doctoral candidate by the Flemish Government Agency for Innovation by Science and Technology (Belgium).

-MG has nothing to disclose.

-JA has nothing to disclose.

-IKD has nothing to disclose.

-JLC has received speaker and consultancy fees from Boehringer-Ingelheim, AstraZeneca, Novartis, Chiesi and GlaxoSmithKline.

-EM has, within the last 5 years, received honoraria for lectures from Boehringer-Ingelheim, Chiesi and Novartis; he is a member of advisory boards for AstraZeneca, Chiesi, Boehringer-Ingelheim and Novartis.

-HS has received consultancy fees from Boehringer-Ingelheim and GlaxoSmithKline.

-CH has received speaker and consultancy fees from Boehringer-Ingelheim, Chiesi, AstraZeneca, GlaxoSmithKline and Novartis.

-MH has nothing to disclose.

-SH has received research grants from UCB Pharma and Chiesi, as well as speaker and consultancy fees from AstraZeneca, GlaxoSmithKline and Novartis.

-PJ has nothing to disclose.

-RP has nothing to disclose.

-AF has nothing to disclose.

-TL has nothing to disclose.

-AD has nothing to disclose.

-BV has nothing to disclose.

-RW is supported as a senior clinical researcher by the Fund for Scientific Research Flanders (Belgium).

-SE was supported as a doctoral candidate by the Fund for Scientific Research Flanders (Belgium) (11V9417N).

-AB's institute received consultancy fees from Boehringer-Ingelheim and UCB Pharma.

-KB's institute received consultancy fees from Boehringer-Ingelheim and UCB Pharma.

-GMV has nothing to disclose.

-TT is vice president of the European Respiratory Society (2018-2019). His institute received speaker and consultancy fees from Boehringer-Ingelheim, AstraZeneca and Chiesi.

-VN has received speaker and consultancy fees from Boehringer-Ingelheim, AstraZeneca, Novartis, MSD, GlaxoSmithKline and Chiesi.

-GGB has, within the last 5 years, received honoraria for lectures from AstraZeneca, Boehringer-Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer, Teva, UCB Pharma and Zambon; he is a member of advisory boards for AstraZeneca, Boehringer-Ingelheim, GlaxoSmithKline, Novartis, Sanofi/Regeneron and Teva.

-WJ is supported as a senior clinical researcher by the Fund for Scientific Research Flanders (Belgium); and has received research funding, speaker and consultancy fees from Boehringer-Ingelheim, AstraZeneca, Novartis, Chiesi and GlaxoSmithKline.

Author's contributions

The protocol was initiated by WJ, designed in collaboration with GGB and modified on the basis of input from the Consortium. The data were gathered by study personnel at each participating hospital, overseen by the local investigator. The statistical analysis plan was implemented by independent biostatisticians AB and KB. The cardiac safety assessment was performed by independent cardiologists BV and RW. All authors participated in interpreting the results. The first and final draft were written by KV and revised on the basis of input from the other authors and the Steering Committee. All the authors made the decision to submit the manuscript for publication and assume responsibility for the data, the accuracy of the analyses, and vouch for the fidelity of the study to the protocol.

Descriptor number classifying the manuscript's subject

9.7 COPD: Exacerbations < Lung diseases

Funding information

This work was funded by the Flemish Government Agency for Innovation by Science and Technology (IWT) through the '*Toegepast Biomedisch onderzoek met een primair Maatschappelijke finaliteit*' (TBM) program (grant number: IWT-TBM130233). The trial was approved and supported by the Belgian Thoracic Society (BVP-SBP) which provided logistic support for the organization of the investigator meetings. Financial support for study logistics was also received from TEVA, Belgium. Neither the IWT, the BVP-SBP, nor TEVA were involved in the study design, in the collection, analysis, and interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

Notation of prior abstract presentation

Data have been presented at the European Respiratory Society Conference (Paris, 16 September 2018).

Online data supplement

This article has an online data supplement, which is accessible from this issue's table of content online at www.atsjournals.org.

ABBREVIATION LIST

AECOPD	acute exacerbation of chronic obstructive pulmonary disease
BACE	Belgian trial with azithromycin for COPD exacerbations requiring hospitalization
CAT	COPD assessment test
COPD	chronic obstructive pulmonary disease
Δ	symbol used to indicate the difference
ECG	electrocardiogram
EQ5D	European Quality of Life – 5 Dimensions questionnaire
FEV1	forced expiratory volume in 1 second
GOLD	global initiative for chronic obstructive lung disease
GP	general practitioner
HR	hazard ratio
ICS	inhaled corticosteroids
ICU	intensive care unit
LABA	long-acting ß-agonist
LAMA	long-acting muscarinic antagonist
mMRC	modified Medical Research Council questionnaire
RCT	randomized controlled trial
SH	step-up in hospital care
SSQ5	Speech, Spatial and Qualities of Hearing Scale – 5 items questionnaire
STEMI	ST elevation myocardial infarction
TI	treatment intensification
TF	treatment failure
QTcB	QT interval corrected according to Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula

ABSTRACT

Rationale. Azithromycin prevents acute exacerbations in COPD (AECOPD); however, its value in the treatment of AECOPD requiring hospitalization is yet to be defined.

Objective. We investigated whether a 3-month intervention with low-dose azithromycin could decrease treatment failure (TF) when initiated at hospital admission and added to standard care.

Methods. In an investigator-initiated, multi-centre, randomized, double-blind, placebo-controlled trial, patients hospitalized for an AECOPD, with a smoking history of ≥10 pack-years and ≥1 exacerbation in the previous year, were randomized (1:1) within 48-hours of admission to azithromycin or placebo. The study drug (500mg/day for 3 days) was administered on top of a standardized acute treatment of systemic corticosteroids and antibiotics, and subsequently continued for 3 months (3m) (250mg/2days). Patients were followed-up for 6m thereafter. Time-to-first event analyses evaluated the TF rate within 3m as a novel primary endpoint in the intention-to-treat population, with TF defined as the composite of treatment intensification with systemic corticosteroids and/or antibiotics (TI), step-up in hospital care or readmission for respiratory reasons (SH) or all-cause mortality.

Main results. 301 patients were randomized to azithromycin (n=147) or placebo (n=154). The TF rate within 3m was 49% in the azithromycin and 60% in the placebo group (HR=0.73; 95%CI 0.53-1.01; p=0.0526). TI, SH and mortality rates within 3m were 47% *vs* 60% (p=0.0272), 13% *vs* 28% (p=0.0024) and 2% *vs* 4% (p=0.5075), respectively. Clinical benefits were lost 6m after withdrawal.

Conclusions. 3m of azithromycin for infectious AECOPD requiring hospitalization may significantly reduce TF during the highest risk period. Prolonged treatment seems needed to maintain clinical benefits.

Word count abstract. 255 words

Funding. Flemish Government Agency for Innovation by Science and Technology

ClinicalTrials.gov number. NCT02135354

Keywords: *Macrolide, Composite, Time-to-event, Treatment failure, Readmission*

AT A GLANCE SUMMARY

Scientific knowledge of the subject.

Clinical trials in stable COPD and patients with increased risk of exacerbations have proven long-term (6–12 months) continuous and intermittent use of macrolide antibiotics effective in the prevention of acute exacerbations (AECOPD). Safety concerns associated with long-term use in the general COPD population, however, require new studies to define the optimal dose, treatment duration and target population.

What this study adds to the field.

The present double-blind RCT is the first to evaluate the effect of macrolide treatment by positioning the intervention in the acute setting of a severe AECOPD requiring hospitalization, in addition to a time-limited low-dose intermittent administration to prevent relapse. Though formally negative (p=0.0526), our findings show that a low-dose azithromycin intervention, initiated at the onset of a severe AECOPD requiring hospitalization (500mg/day for 3 days) and subsequently administered for 3 months (250mg/2 days), may strongly reduce the recurrence of exacerbations, especially those leading to hospital admission and transfer to intensive care, in patients at risk. Prolonged treatment, however, seems needed to maintain clinical benefits. By providing a cross-continuum between the acute treatment phase in the hospital and ambulatory therapeutic prolongation for 3 months, the proposed intervention may help to address the highest risk period for readmission and provide a new treatment strategy for severe infectious AECOPD requiring hospitalization.

INTRODUCTION

Acute exacerbations of chronic obstructive pulmonary disease (AECOPD) requiring hospitalization are associated with a 6% risk of in-hospital mortality. Of those who survive, 35% are likely to be readmitted within 3 months after hospital discharge (80% of which is directly related to recurrent disease or relapse), during which they face a 12% risk of all-cause mortality.[1,2] The management of AECOPD requiring hospitalization has therefore been studied extensively.[3,4] However, with the exception of non-invasive ventilation administered to patients with acute respiratory acidosis,[5] no intervention has been shown to improve the prognosis over the last 40 years.[6]

Long-term treatment with 250mg azithromycin once daily has been proven effective in the prevention of AECOPD by decreasing the exacerbation rate and increasing the inter-exacerbation interval.[7,8] Despite confirmation of efficacy with an intermittent dose (500mg three times weekly) in a restricted subgroup of frequent exacerbators,[9] safety concerns associated with long-term use in the general COPD population[10] (e.g. the induction of antibiotic resistance,[11] cardiac toxicity[12] and ototoxicity[13]) require new studies to define the optimal dose, treatment duration and target population.

Published randomized controlled trials (RCT) of azithromycin therapy in COPD have focused exclusively on stable disease with increased risk of exacerbations. To date, few RCTs are evaluating new acute interventions in patients hospitalized for a severe exacerbation, facing the highest risk period for deterioration, relapse and death. We therefore performed a large investigator-initiated RCT to evaluate whether a 3-month intervention with low-dose azithromycin, initiated at the onset of a severe AECOPD requiring hospitalization, could effectively and safely decrease treatment failure (TF) in the highest risk period during and immediately after the acute event. Time-to-first event analyses evaluated TF as a novel composite primary endpoint to capture clinically relevant short-term and long-term outcomes of our intervention. Some of the results of the study have been previously reported in the form of an abstract.[14]

METHODS

STUDY DESIGN

An investigator-initiated, multi-centre, randomized, double-blind, placebo-controlled trial was performed in 6 academic and 14 non-academic hospitals within Belgium, to prove the effectiveness of azithromycin in the acute treatment of COPD exacerbations requiring hospitalization. Between August-2014 and April-2017, patients were randomized (1:1) to receive azithromycin or placebo on top of a standardized acute treatment of systemic corticosteroids and antibiotics (Online Supplement). Within 48-hours of hospital admission, a 3-month (or 90-day) intervention with azithromycin or matching placebo was initiated at a loading dose of 500mg once daily for 3 days (hypothesis: maximizing both acute anti-microbial and anti-inflammatory effects) and subsequently administered at a lower intermittent maintenance dose of 250mg every 2 days (hypothesis: prolonging anti-inflammatory effects). Patients were followed-up for 9 months, including 6 months after study drug withdrawal to evaluate whether potential effects of the 3-month intervention could be maintained long term (Figure 1).[15] The study consisted of 3 assessments during hospitalization of the index event: randomization (day 1), start of maintenance dose (day 4) and day of discharge (day X, at the investigator's discretion). After discharge, out-patient visits occurred at one month after discharge (day X+28), end of intervention (day 90) and end of follow-up (day 270). Telephone calls were scheduled bimonthly (day 150 and day 210) between day 90 and day 270.

Written informed consent was obtained from all participants. The study was approved by the competent authorities, the central (Commissie Medische Ethiek UZ-KU Leuven, ML10232) and local ethics committees of each participating hospital.

PATIENTS

Eligible patients were 18 years or older, had an established diagnosis of COPD (based on clinical history and a pulmonary function test), had a history of ≥1 exacerbation treated with systemic corticosteroids and/or antibiotics in the previous year, had a current or past smoking history of ≥10 pack-years, had a

normal QT interval corrected according to Bazett's formula (QTcB; ≤450msec for male or ≤470msec for female) and were hospitalized for an AECOPD deemed infectious by the local investigator within the 48-hour screening period from hospital admission, qualifying them for the standardized acute treatment of systemic corticosteroids and antibiotics. Investigators were to rely on the available evidence obtained from routine assessments (laboratory, chest X-ray and clinical presentation) in the emergency department, as the trial protocol was embedded in a real-life hospitalization setting. The main exclusion criteria were contraindications to azithromycin, respiratory insufficiency requiring mechanical or non-invasive ventilation at the time of randomization, chronic systemic corticosteroid use (>4mg methylprednisolone/day for ≥2 months) and the use of macrolide antibiotics during ≥2 weeks preceding inclusion. None of the patients were taking phosphodiesterase-4 inhibitors (not commercialized in Belgium). Full list of exclusion criteria is provided in the Online Supplement.

EFFICACY OUTCOMES

The primary endpoint was the TF rate within 90 days analyzed using time-to-first event methods, with TF defined as the composite of 3 endpoints: (1) treatment intensification (TI) with systemic corticosteroids and/or antibiotics for respiratory reasons, (2) step-up in hospital care (SH) including transfer to the intensive care unit (ICU) or readmission for respiratory reasons or (3) all-cause mortality. Date of TF was defined as the time of first occurrence of one of these events. TI and SH were further specified for the hospitalization period of the index event (day 1 to day X), and the period after discharge (day X to day 90), as outlined in Table 1. Three key secondary endpoints were assessed in following hierarchical order: the number of TFs, COPD assessment test (CAT) score and total days of systemic corticosteroid use at day 90. Other secondary endpoints, including the evaluation of the composite endpoint and its 3 components 6 months after study drug withdrawal, are listed in the Online Supplement.

SAFETY OUTCOMES

Standard 12-lead resting electrocardiograms (ECG), obtained at hospital admission (baseline), day 4, day X+28 and day 90 were inspected manually. The QT interval values were corrected using Bazett's formula and verified using Fridericia's (QTcF) formula, reflecting a more accurate correction in patients with tachycardia.[16] Safety outcomes also included the assessment of (serious) adverse events, the Speech, Spatial and Qualities of Hearing Scale – 5 items (SSQ5) questionnaire[17] and spontaneous sputum samples for detection of macrolide-resistant pathogens. Details are provided in the Online Supplement.

STATISTICAL ANALYSES

The required sample size was calculated at 250 patients per group, 500 in total, to show a significant difference in the primary endpoint at a two-sided significance level of 0.05 with 80% power. Calculations were based on a survival analysis using a log-rank test assuming proportional hazards, a clinical failure within 90 days of at least 45% in the placebo arm, a 35% relative improvement with azithromycin (hazard ratio [HR]=0.65) and taking into account a maximal drop-out of 25%. Due to slow recruitment and unavailability of funds, it was decided to stop enrolment early at 301 inclusions (moment of interim safety analysis, pre-specified after 300 inclusions) and the final analysis was performed once all patients reached their 270-day follow-up.

All analyses were performed in the intention-to-treat population, the primary endpoint was also assessed in the per-protocol population, excluding patients with one or more major protocol violations (which included a standardized acute treatment which was not respected, a concomitant use of macrolide antibiotics for more than 10 days and a unverifiable compliance with regards to study drug intake). Outcomes were analyzed using time-to-event methods. TF and mortality were analyzed by Kaplan-Meier survival analysis and compared between groups using a log-rank test. TI and SH were analyzed by a Cumulative Incidence Function taking mortality as a competing risk into account and compared between groups using Gray's test. Patients without an event within 90 days were censored at day 90, early terminations at their time of withdrawal. The treatment effect was estimated by the HR, obtained from a Cox regression. The treatment effect of the secondary endpoints were estimated by

the difference in means using the Mean Cumulative Function, the difference in expected means using a weighted Generalized Estimating Equations model and the rate ratio using a Poisson Regression model, as specified in the Statistical Analysis Plan. To control the overall Type I Familywise Error Rate of the key secondary endpoints, a serial gatekeeping method was used.

ECG data were analyzed as repeated measures of differences (Δ) compared to baseline with Bonferroni post-hoc correction for multiple testing. Other safety outcomes were compared between groups using a Chi-square or Fisher's exact test. All analyses were performed using SAS software version 9.4.

RESULTS

PATIENTS

A total of 2063 patients were screened by 15 centers within the Consortium, 301 (15%) of whom were randomized to azithromycin (n=147) or placebo (n=154). The study was completed by 118 (80%) *vs* 115 (75%) patients, respectively (Figure 2). The baseline characteristics of the 301 randomized patients are summarized in Table 2. Mean study drug adherence was 95.7% *vs* 96.2%, respectively.

PRIMARY ENDPOINT AND COMPONENTS

Within 3 months after randomization, 69 patients in the azithromycin and 86 in the placebo group experienced TF. TI, SH and mortality occurred in 66 patients *vs* 85, 18 *vs* 39 and 3 *vs* 6, respectively. The unadjusted TF rate within 3 months was 49% in the azithromycin and 60% in the placebo group (HR=0.73, 95%CI 0.53;1.01, p=0.0526) (Figure 3). The unadjusted TI, SH and mortality rates were 47% *vs* 60% (HR=0.70, 95%CI 0.51;0.97, p=0.0272), 13% *vs* 28% (HR=0.43, 95%CI 0.25;0.75, p=0.0024) and 2% *vs* 4% (HR=0.62, 95%CI 0.15;2.59, p=0.5075), respectively. Differences between treatment groups were lost 6 months after study drug withdrawal (Figure 4). Results from the per-protocol analyses were almost identical to those from the intention-to-treat analyses (Online Supplement).

SECONDARY ENDPOINTS

The effect of azithromycin on the secondary endpoints is summarized in Table 3. Within 3 months after randomization, the mean cumulative number of TFs (first key hierarchical secondary endpoint) was reduced in the azithromycin group as compared to the placebo group (Δ=-0.24, 95%CI -0.48;0.00, p=0.0395). No significant differences were found in quality of life (European Quality of Life – 5 Dimensions [EQ5D] questionnaire) or symptom assessment scores (CAT, modified Medical Research Council [mMRC] and SSQ5 questionnaires). The unadjusted rate of new exacerbations (defined as the composite of a new course of systemic corticosteroids and/or antibiotics, or hospitalization for respiratory reasons, all after the index event) within 3 months was reduced in the azithromycin as compared to the placebo group (HR=0.70, 95%CI 0.49;1.00, p=0.0497). Within 3 months after randomization, the total hospital and ICU days were reduced (rate ratio=0.76, 95%CI 0.63;0.92,

p=0.0061 and rate ratio=0.26, 95%CI 0.15;0.47, p<0.0001, respectively). Notably, the latter remained reduced 6 months after study drug withdrawal (p<0.0001). Furthermore, the total dose of systemic corticosteroid use and total days of non-study antibiotic use were respectively higher (rate ratio=1.06, 95%CI 1.04;1.08, p<0.0001) and lower (rate ratio=0.77, 95%CI 0.68;0.86, p<0.0001) in the azithromycin as compared to the placebo group. No significant group differences were found in pre-bronchodilator forced expiratory volume in 1 second (FEV1) or number of general practitioner (GP) visits.

Upon hospital discharge, the COPD inhaled maintenance therapy in both groups was adjusted compared to hospital admission with a step-up to triple therapy (combination of inhaled corticosteroids (ICS), long-acting muscarinic antagonists (LAMA), and long-acting ß-agonists (LABA)) and step-down in ICS/LABA. Three months after randomization, a slightly greater percentage of azithromycin-treated patients received triple therapy as compared to placebo (80.9% vs 71.3%), however, no significant difference in the distribution of concurrent inhaled maintenance therapy was found (Online Supplement).

SUBGROUP ANALYSES

Eight subgroups were assessed for the primary and key secondary endpoints. We found no statistically significant interaction between the intervention and any of the subgroups (Online Supplement).

SAFETY OUTCOMES

All-cause mortality at 3 months was 2% in the azithromycin and 4% in the placebo group (p=0.5023). Mortality from respiratory and cardiovascular causes at 3 months were 0% *vs* 2% (p=0.2479) and 2% *vs* 1% (p=0.6783), respectively. No significant differences were observed in the frequency of serious adverse events or adverse events leading to study drug discontinuation. Reported gastro-intestinal adverse events occurred more frequently during the treatment period as compared to the follow-up period, however, no significant group differences were found (Online Supplement).

A total of 228 patients, 114 (50%) receiving azithromycin, had all 4 ECGs available. Heart rate at baseline was significantly higher compared to the other time points (p<0.001), with no difference between treatment groups (p=0.552). The overall mean QTcB at baseline was 427.4±21.6msec, and

400.8±21.3msec for QTcF (Δ=-26.6±12.8msec, p<0.001). Overall, neither with QTcB nor with QTcF significant QTc prolongation was observed in the azithromycin group (Online Supplement). The study medication was stopped due to prolongation of the QTcB interval >500msec or ΔQTcB>60msec in 3 patients (1%): 2 in the azithromycin group at day 4 and 1 in the placebo group at day X+28. However, when using QTcF, 2 of these patients no longer had significant QTc prolongation and only for 1 patient (receiving azithromycin) the decision to discontinue the study remained valid. No patients developed clinical serious arrhythmia.

Bacterial cultures on spontaneous sputum samples were obtained in 74% in the azithromycin and 67% in the placebo group at baseline, 37% *vs* 41% at day X, 12% *vs* 17% at day 90 and 17% *vs* 13% at day 270. At baseline, the most commonly cultured bacteria were *Haemophilus influenzae* (11%), *Streptococcus pneumoniae* (9%), *Pseudomonas aeruginosa* (4%), *Morexella catarrhalis* (4%) and *Staphylococcus aureus* (2%). While no significant differences were observed in the proportion of macrolide sensitive and macrolide resistant bacteria, a significant group difference at baseline was found for *Haemophilus influenzae* (16.5% in the azithromycin *vs* 4.9% in the placebo group, p=0.006). During follow-up, no significant group differences were found for positive sputum cultures with newly acquired pathogens, neither for the acquisition of macrolide-resistant bacteria (Online Supplement).

DISCUSSION

The Belgian trial with Azithromycin for acute COPD Exacerbations requiring hospitalization (BACE) is the first to evaluate macrolide treatment as an acute intervention for patients hospitalized for a severe AECOPD. In this trial, the 18% reduction in TF rate within 3 months after hospital admission in the azithromycin group, as compared with the placebo group, did not meet the predetermined level of statistical significance (p=0.0526), as the trial was underpowered due to early termination for slow recruitment. While formally negative, there is a strong trend in favor of the 3-month intervention with low-dose azithromycin, significantly reducing the number of TFs, as well as the rate of TI and SH for respiratory reasons with more than 20% and 50% respectively. Although methodological heterogeneity prevents direct comparison of results, the observed risk reduction in new exacerbation rate (30%) was of similar magnitude to that in other long-term macrolide studies in COPD.[7,18] We documented a 57% risk reduction for SH (comprising transfer to the ICU during the index event and readmission for new exacerbation after discharge) over a 3 month period. This effect translated in a 24% and 74% reduction in the total hospital and ICU days respectively, with the latter remaining significantly reduced 6 months after azithromycin withdrawal. Preventing COPD readmissions following an exacerbation is an international priority aimed at slowing down disease progression and limiting health care costs.[6,19] Apart from the recently published IMPACT trial showing a 34% reduction in hospital admissions with ICS,[20] and the REACT trial showing a 24% reduction with phosphodiesterase-4 inhibitors,[21] no other evidence-based chronic intervention has demonstrated such a large potential on top of maintenance therapy.[22] Moreover, acute interventions initiated for severe AECOPD are mostly restricted to the hospitalization period and are often completed before full clinical resolution. Consequently, they may leave an active inflammatory process smoldering at the time of discharge and the patient vulnerable to relapse.[23,24] By providing a cross-continuum between the acute treatment phase in the hospital and ambulatory therapeutic prolongation for 3 months, our proposed intervention may help to address the highest risk period for readmission and provide a new treatment strategy for severe infectious AECOPD requiring

hospitalization. Future post-hoc analyses are required to elucidate the underlying mechanism by assessing the added value of positioning azithromycin in the acute setting (potentially maximizing both anti-microbial and anti-inflammatory effects) in addition to a limited prolonged administration to prevent relapse. Intriguingly, the total days of antibiotic use was significantly decreased by the intervention, whereas the total dose of systemic corticosteroid use was increased. This might indicate a shift in the type of exacerbations experienced by patients under azithromycin therapy, which could also be observed in the COLUMBUS trial data.[9] While bacterial infections and exacerbations might be prevented by azithromycin therapy,[25,26] these patients remain prone to exacerbations of different etiology which may be more refractory to standard care and requiring a higher dose of systemic corticosteroids.[27,28] It may also explain why no statistically significant differences were found in quality of life or symptom assessment scores, as assessed by the EQ5D, CAT and mMRC questionnaires.

The BACE trial is also the first to explore azithromycin withdrawal after a prolonged course in high-risk patients with COPD. Time-to-event curves of TF and TI appear to diverge up to 1 month after azithromycin withdrawal and even 3 months for SH. This observation is supported by the molecule's prominent pharmacokinetic features, i.e. a long half-life and high lung tissue concentrations following repeated administration.[29] While these findings support the BACE trial rationale for dose and treatment duration to establish and maintain therapeutic benefits, they may not exclude that a maximal effect was not yet reached under the proposed 3 month duration and a reduced dosage of 250 mg of azithromycin every other day. Clear convergence of the time-to-event curves 6 months after withdrawal demonstrates that prolonged treatment appears to be needed to sustain its clinical benefits. This pleads against our hypothesis that prolonged treatment for 3 months may sufficiently interrupt the vicious circle of inflammation to alter the phenotype of 'frequent exacerbator'. Cautioned use of intermittent treatment courses of azithromycin is therefore warranted.

The intervention was well tolerated, with no significant differences in the frequency of (serious) adverse events. Gastrointestinal symptoms were most often reported and results were comparable to those

observed in long-term studies.[30] Significant QTc prolongation necessitating study drug discontinuation is rare, particularly when excluding patients with a prolonged QTc before treatment. A prolonged QTcB at admission excluded 13% of the screened population and ECG monitoring led to treatment interruption in only 2 patients treated with azithromycin, supporting earlier findings.[31] The use of QTcF could minimize false-positive cases[16] and better justify patient access to azithromycin therapy without impairing safety. The main risk of chronic use of azithromycin is the induction of bacterial resistance.[11,32] In the trial by *Albert et al.* 81% versus 41% of colonizing pathogens in the placebo group were resistant to macrolides.[7] A related concern is the wider spread of macrolide resistance to the general population and the potential risk of losing azithromycin as part of the first-line treatment for non-tuberculous mycobacterial infections.[33,34] Macrolide resistance was monitored, however, as induced sputum was not required per protocol, the limited number of spontaneous sputum samples did not allow for thorough evaluation of antibiotic resistance induced by azithromycin on top of a standardized acute treatment of systemic corticosteroid and antibiotics in the acute setting.

In analogy with MACE (major adverse cardiovascular events) for cardiovascular research,[35] the BACE trial provides first results on a composite endpoint to evaluate interventions during an AECOPD requiring hospitalization. In addition to reducing the required sample size in a difficult setting, the use of TF allowed for the evaluation of in-hospital outcomes, as well as the relapse rate during 3 months after discharge. Although TI during hospital admission is often neglected, it may capture important differences in the resolution of the index event. As we defined TI in a continuum of 3 months, it also incorporated transfer to the ICU, readmission and new exacerbations, as these events are unavoidably associated and often preceded with new courses of systemic corticosteroids and/or antibiotics. In fact, TI was covering 96% and 99% of the total event rate of TF over 3 months in the azithromycin and placebo group, respectively. Future studies in this setting may therefore consider TI, which includes prolongation, up-titration or new courses of medication as a major single endpoint.

By reducing the dose and treatment duration, and by restricting the intervention to subgroups with the most unmet needs, a more favorable benefit-risk ratio can be obtained for azithromycin interventions. The potential for a significant and clinically relevant reduction in total hospital and ICU days within 3 months of hospital admission, merits further investigation in large real-life pragmatic RCTs to validate the important health economic impact of prolonged low-dose treatment in such high risk groups.

The BACE trial had several limitations – First, target enrolment was not met due to a high screen failure rate (85.4%), as well as various non-scientific and funding challenges associated with investigator-initiated clinical research, which leaves the trial underpowered. Second, due to the low inclusion rate (14.6%) the obtained results are limited in their external validity and generalizability to other populations of COPD patients. In particular, the findings do not support the extrapolation to non-infectious exacerbations. Third, the 48-hour screening period to assess the infectious nature of the index AECOPD resulted in the inclusion of AECOPD of viral and bacterial aetiology. While viral AECOPD can facilitate subsequent bacterial infections,[36] procalcitonin might have provided guidance as to which events would have required antibiotics as part of the standardized acute treatment.[37,38] As most subgroup analyses were not significant when testing for interaction, these findings provide no insight into which type of infectious exacerbation, viral or bacterial, would benefit most from the intervention. Fourth, while all TFs were carefully adjudicated by the blinded study team, judgement on the necessity of TI is subjective and was left to the physician caring for the patient. This might have introduced between-site inhomogeneity. Fifth, although patients were actively asked about hearing loss and questionnaires were regularly completed, no standard audiometry was performed. Finally, spontaneous sputum samples were obtained in less than 20% at days 90 and 270 in both groups so that no conclusions can be made on shifts in bacterial resistance.

CONCLUSIONS

A 3-month intervention with low-dose azithromycin may effectively and safely reduce TF (i.e. TI and SH) during and immediately after hospital admission for a severe exacerbation, to overcome in COPD the highest risk period for deterioration, relapse and death. Prolonged treatment, however, appears to be needed to sustain clinical benefits. A careful and individualized approach to the selection of patients, with regards to pro-arrhythmic effects and the development of antibiotic resistance, would be recommended.

ACKNOWLEDGEMENTS

We would like to thank the Flemish Government Agency for Innovation by Science and Technology (IWT) for funding the BACE trial through the *Toegepast Biomedisch onderzoek met een primair Maatschappelijke finaliteit* (TBM) program: IWT-TBM number 130233. The trial was also approved and supported by the Belgian Thoracic Society (BVP-SBP) which provided logistic support for the organization of the investigator meetings. Financial support for study logistics was also received from TEVA, Belgium. Neither the IWT, BVP-SBP nor TEVA were involved in the study design, in the collection, analysis and interpretation of data, in the writing of the manuscript, or in the decision to submit the manuscript for publication.

At the KU Leuven and associated University Hospital Gasthuisberg Leuven, we thank: Eline Lahousse and Anita Vandeborne from the laboratory of respiratory diseases; Geert Verleden, Pascal Van Bleyenbergh, Lieven Dupont, Paul Van Den Brande, Nathalie Lorent, Karen Denaux and Kristien De Bent from the service of respiratory medicine; Christine Mathieu, Sabien Vanlangendonck and Birgit Peeters from the legal department, and Johan Meeus and Evelyne Van Etten from the financial department of the KU Leuven Research and Development; and the Clinical Trial Centre of UZ-KU Leuven.

At the University Hospital Ghent, we thank: Bénédicte Demeyere, Stefanie Vermeersch, Leen Raman, Anja Delporte and Bart Coucquyt from the service of respiratory medicine; Véronique Bégérem, Els Kestens and Charline Paepens from the hospital pharmacy; and Lieselot Burggraeve, Tom Verschoore and Barbara van Aelst from Bimetra – Clinical Research Centre.

Special thanks goes to Jurgen Silence (Sibetec) for the continuous support in the development and management of the electronic case report form.

We thank the BACE trial patients for their participation, and the BACE trial investigators and supporting staff for their contributions in the Consortium: Vincent Ninane (CHU St.-Pierre – Brussel), Joseph Aumann (Jessa ziekenhuis – Hasselt), Ingel K Demedts (AZ Delta – Roeselare-Menen), Hans Slabbynck (ZNA Middelheim – Antwerpen), Eric Marchand (CHU-UCL Namur – Yvoir), Christel Haenebalcke (AZ St-

Jan ziekenhuis – Brugge), Rudi Peché (CHU de Charleroi – Charleroi), Guy G Brusselle (UZ Gent - Gent), Walter Vincken (UZ Brussel – Brussel), Jean-Louis Corhay (CHU de Liège – Luik), Michiel Haerens (AZ Groeninge – Kortrijk), Antoine Fremault (Grand Hôpital de Charleroi – Charleroi), Tine Lauwerier (Imelda ziekenhuis – Bonheiden), Alix Debrock (St-Augustinus ziekenhuis – Antwerpen), Jan Lamont (Maria Middelares ziekenhuis – Gent), Geert Tits (St-Andriesziekenhuis – Tielt), Paul Jordens (Onze-Lieve-Vrouwziekenhuis – Aalst), Alain Delobbe (Clinique Reine Astrid – Malmedy), Jean-Benoît Martinot (Clinique Ste.-Elisabeth – Namur).

TABLES

During hospitalization of the index event	After hospital discharge
day 1 to day X	day X to day 90
Treatment intensification for respiratory reasons (TI)	
Additional dose of systemic corticosteroids	New course of systemic corticosteroids
Prolongation of systemic corticosteroids >8 days	New course of antibiotics
Upgrade of antibiotics*	
Step-up in hospital care or readmission for respiratory reasons (SH)	
Transfer to the intensive care unit	Readmission
All-cause mortality	

Table 1 – Definition of the composite primary endpoint, treatment failure (TF)

*Change or narrowing of the initial antibiotics given as part of the standardized acute treatment during the index event – *consisting of 5 days of fixed dose systemic corticosteroids and 5 to 7 days of antibiotics* – based on proven bacterial cultures was not considered as treatment failure, but as good clinical practice.

Note: day 1: randomization; day X: day of discharge, at the investigator's discretion; day 90: end of intervention.

	Azithromycin (N=147)	Placebo (N=154)
Demographics		
Age – years	66 ± 9	67 ± 10
Female sex – no. (%)	66 (45)	66 (43)
Weight – kg	67 ± 20	70 ± 18
Height – m	1.66 ± 9	1.66 ± 9
BMI – kg/m²	24.5 ± 5.9	25.1 ± 6.5
Comorbidity		
Charlson comorbidity index	4 [3-5]	4 [3-5]
COPD comorbidity index	1 [0-2]	1 [1-2]
Lung disease		
mMRC dyspnea score	4 [2-4]	4 [2-4]
Pre-bronchodilator FEV1 – L	0.90 [0.69-1.23]	0.95 [0.71-1.36]
Pre-bronchodilator FEV1 – % pred.	36.0 [26.3-53.8]	38.5 [29.0-52.0]
Pre-bronchodilator FVC – L	2.26 [1.77-3.19]	2.24 [1.80-2.89]
Pre-bronchodilator FVC – % pred.	73.0 [58.3-93.8]	71.5 [56.3-88.8]
Pre-bronchodilator FEV1/FVC – %	40.3 [33.6-48.0]	45.0 [37.0-52.8]
GOLD stage – no. (%)††		
A	0 (0)	1 (1)
B	26 (18)	30 (20)
C	1 (1)	2 (1)
D	120 (82)	121 (79)
Current smoker – no. (%)	63 (43)	65 (42)
Smoking history – pack-years	44 [37-50]	43 [35-50]
Number of AECOPD in previous year – no. (%)		
1	38 (26)	51 (33)
2	41 (28)	37 (24)
3	31 (21)	19 (12)
>3	37 (25)	47 (31)
Of which number of hospitalization due to AECOPD – no. (%)		
0	64 (44)	64 (42)

1	55	(37)	58	(38)
2	15	(10)	16	(10)
3	6	(4)	6	(4)
>3	7	(5)	10	(6)
Inhaled therapy for COPD – no. (%)				
LABA	136	(93)	145	(94)
LAMA	118	(80)	123	(80)
Inhaled corticosteroids	118	(80)	123	(80)
SABA	108	(73)	109	(71)
Admission presentation				
Lower respiratory symptoms – no. (%)				
Cough	115	(78)	108	(70)
Sputum production	97	(66)	86	(56)
Sputum purulence	67	(46)	57	(37)
GP intervention prior to admission				
Systemic corticosteroids	48	(33)	37	(24)
Antibiotics	50	(34)	54	(35)
Laboratory				
C-reactive protein (mg/L)	14.2	[3.5-61.4]	21.6	[4.5-59.6]
Leucocytes ($x10^9$/L)	10.95	[9.00-13.89]	9.90	[8.20-13.70]
Neutrophils ($x10^9$/L)	8.20	[6.00-11.20]	7.70	[5.60-11.20]
Eosinophils ($x10^9$/L)	0.06	[0.00-0.20]	0.07	[0.00-0.20]
Standardized acute treatment				
Respected – no. (%)	134	(91)	141	(92)
Received antibiotic – no. (%)	145	(99)	152	(99)
Antibiotic group – no. (%)				
ß-lactam antibiotics	91	(62)	87	(57)
Quinolone antibiotics	61	(42)	71	(46)
Clindamycin	1	(1)	1	(1)
Macrolides	2	(1)	4	(3)
Antibiotic susceptible to pathogen † – no. (%)	136	(94)	144	(95)

Table 2 – Baseline characteristics

Data are presented as no. (%), mean ± SD and median [Q1-Q3 interquartile range].

Note: † Susceptibility was determined based on the need for antibiotic upgrade prior to discharge. Change or narrowing of the initial antibiotic based on proven bacterial cultures was considered good clinical practice. ††GOLD stages are not taking the current hospital admission into consideration.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; COPD, chronic obstructive pulmonary disease; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; GOLD, Global initiative for chronic Obstructive Lung Disease, guideline 2017; GP, general practitioner; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; mMRC, modified Medical Research Council questionnaire; SABA, short-acting beta-agonist.

	Visit	Azithromycin (n=147)	Placebo (n=154)	Estimator	Treatment effect (95% CI)	P-value
Primary endpoint						
Treatment failure rate †	Day 90	49.5 (41.5;58.1)	60.4 (52.4;68.5)	HR	0.73 (0.53;1.01)	0.0526
Key hierarchical secondary endpoints						
Number of treatment failures ‡	Day 90	0.79 (0.62;0.95)	1.03 (0.85;1.20)	Δ in MCF	-0.24 (-0.48;0.00)	0.0395
CAT score ¥	Day 90	17.7 (16.4;19.0)	16.9 (15.5;18.3)	Δ in means	0.35 (-1.43;2.13)	0.6970
Total days of steroid use *	Day 90	15.9 (14.9;16.9)	14.8 (13.9;15.7)	Rate ratio	1.07 (0.98;1.17)	0.1217
Other secondary endpoints						
Treatment failure rate †	Day 270	82.2 (75.2;88.2)	84.8 (78.3;90.3)	HR	0.83 (0.64;1.08)	0.1570
Number of treatment failures ‡	Day 270	2.41 (2.08;2.73)	2.54 (2.21;2.87)	Δ in MCF	-0.13 (-0.60;0.34)	0.1103
CAT score ¥	Day 270	18.3 (16.8;19.8)	18.5 (17.0;20.0)	Δ in means	-0.87 (-2.85;1.12)	0.3921
Total days of steroid use *	Day 270	27.1 (26.1;28.2)	27.2 (26.2;28.3)	Rate ratio	1.00 (0.94;1.05)	0.8817
Treatment intensification rate $	Day 90	47.4 (38.8;55.4)	59.7 (51.1;67.4)	HR	0.70 (0.51;0.96)	0.0272
	Day 270	79.2 (71.2;85.3)	84.1 (76.7;89.4)	HR	0.79 (0.61;1.02)	0.0709
Step-up in hospital care rate $	Day 90	13.2 (8.2;19.5)	27.7 (20.6;35.3)	HR	0.43 (0.25;0.75)	0.0030
	Day 270	36.5 (28.3;44.7)	45.2 (36.6;53.3)	HR	0.69 (0.48;1.01)	0.0536
Mortality rate †	Day 90	2.2 (0.7;6.5)	3.6 (1.5;8.3)	HR	0.62 (0.15;2.59)	0.5075
	Day 270	5.3 (2.6;10.8)	6.7 (3.5;12.5)	HR	0.78 (0.29;2.09)	0.6170
New exacerbation rate $	Day 90	39.6 (31.3;47.7)	51.0 (42.3;59.0)	HR	0.70 (0.49;1.00)	0.0497
	Day 270	75.1 (66.6;81.7)	79.5 (71.5;85.5)	HR	0.81 (0.62;1.06)	0.1324
Number of new exacerbations ‡	Day 90	0.57 (0.44;0.70)	0.75 (0.60;0.90)	Δ in MCF	-0.18 (-0.37;0.02)	0.0770
	Day 270	2.08 (1.80;2.36)	2.18 (1.92;2.45)	Δ in MCF	-0.10 (-0.49;0.28)	0.5997
Total dose of steroid use (mg) *	Day 90	340.2 (335.4;345.1)	321.8 (317.6;326.0)	Rate ratio	1.06 (1.04;1.08)	<0.0001
	Day 270	603.4 (598.4;608.5)	603.5 (598.4;608.6)	Rate ratio	1.00 (0.99;1.01)	0.9903
Total days of non-study antibiotics *	Day 90	10.5 (9.6;11.5)	13.7 (12.8;14.7)	Rate ratio	0.77 (0.68;0.86)	<0.0001
	Day 270	21.1 (20.2;22.1)	21.6 (20.7;22.6)	Rate ratio	0.98 (0.92;1.04)	0.4592
Total hospital days *	Day 90	10.7 (9.3;12.3)	14.0 (12.3;16.1)	Rate ratio	0.76 (0.63;0.92)	0.0061
	Day 270	22.2 (18.3;27.0)	28.5 (23.8;34.2)	Rate ratio	0.78 (0.60;1.01)	0.0631

Total ICU days *	Day 90	3.0 (1.8;5.1)	11.4 (9.1;14.3)	Rate ratio	0.26 (0.15;0.47)	<0.0001
	Day 270	5.1 (4.0;6.5)	11.1 (9.2;13.3)	Rate ratio	0.46 (0.34;0.63)	<0.0001
Number of GP contacts *	Day 90	2.4 (2.0;2.7)	2.6 (2.3;3.0)	Rate ratio	0.90 (0.74;1.10)	0.3119
	Day 270	6.1 (5.7;6.6)	6.6 (6.1;7.1)	Rate ratio	0.92 (0.83;1.03)	0.1511
Pre-bronchodilator FEV1 (L) ¥	Day 90	1.3 (0.9;1.7)	1.2 (1.1;1.3)	Δ in means	0.13 (-0.26;0.53)	0.5008
	Day 270	1.1 (1.0;1.2)	1.2 (1.1;1.3)	Δ in means	-0.09 (-0.23;0.05)	0.1933
mMRC score ¥	Day 90	3.1 (3.0;3.3)	3.2 (3.0;3.4)	Δ in means	-0.08 (-0.33;0.17)	0.5389
	Day 270	3.3 (3.2;3.5)	3.2 (3.0;3.4)	Δ in means	0.08 (-0.20;0.35)	0.5886
EQ5D score ¥	Day 90	61.6 (58.3;65.0)	61.2 (57.7;64.6)	Δ in means	0.34 (-4.28;4.97)	0.8842
	Day 270	57.3 (53.7;60.9)	60.2 (56.3;64.1)	Δ in means	-2.73 (-7.86;2.40)	0.2967
SSQ5 score ¥	Day 90	8.1 (7.8;8.4)	7.9 (7.6;8.2)	Δ in means	0.18 (-0.13;0.49)	0.2559
	Day 270	8.2 (7.8;8.5)	8.0 (7.7;8.3)	Δ in means	0.20 (-0.12;0.52)	0.2140

Table 3 – Primary, key hierarchical and other secondary endpoints in the intention-to-treat population

Data are presented as follows: †Event rate (95% CI) obtained using Kaplan-Meier methodology. Groups were compared using a log-rank test. Treatment effect presented as hazard ratio (HR). ‡Mean Cumulative Function (MCF) (95% CI). Groups were compared using a log-rank test for MCFs. Treatment effect presented as difference in MCF. ¥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. Groups were compared using GEE by a Chi-squared test. Treatment effect presented as difference in expected means. *Analyzed using a Poisson regression model. The natural logarithm of the total number of days up to the visit day was used as offset. Treatment effect presented as rate ratio. $Cumulative Incidence Function (CIF) (95% CI), using overall mortality as competing risk. Groups were compared using Gray's test. Treatment effect presented as HR. New exacerbation is defined as the composite of TI and SH for respiratory reasons after the index event.

Abbreviations: CAT, COPD assessment test; Δ: symbol indicating difference; FEV1, forced expiratory volume in 1 second; GP, general practitioner; ICU, intensive care unit; MCF, mean cumulative function; mMRC, modified Medical Research Council questionnaire; EQ5D, European Quality of Life – 5 dimensions questionnaire; SSQ5, the Speech, Spatial and Qualities of Hearing Scale – 5 items questionnaire.

Note: day 90: end of intervention; day 270: end of follow-up.

FIGURES

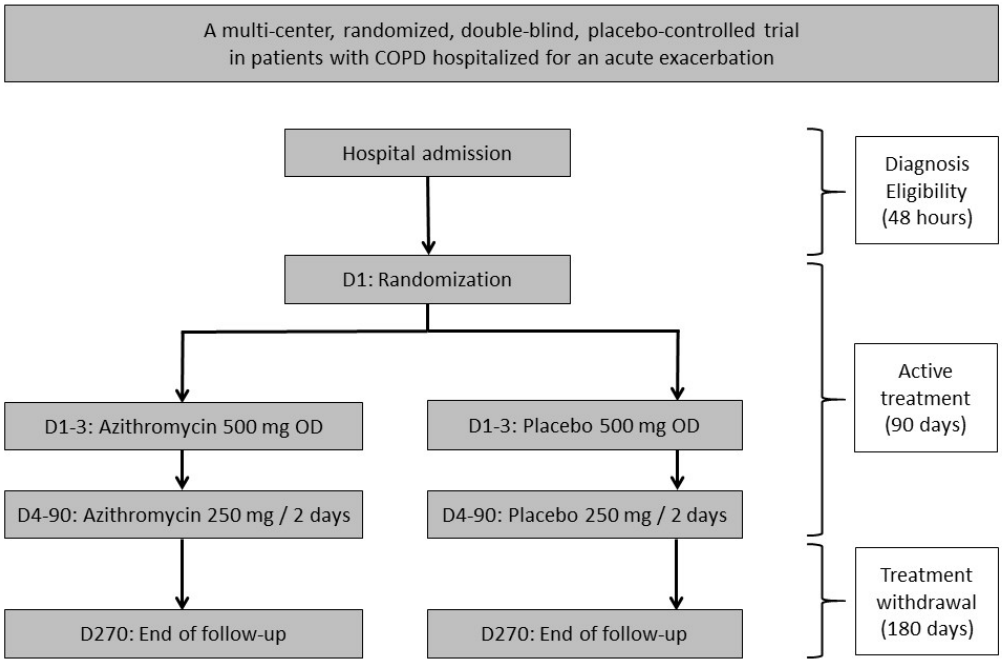


Figure 1 – The BACE trial study design.

Abbreviations: BACE, the Belgian trial with azithromycin for acute COPD exacerbations requiring hospitalization; COPD, chronic obstructive pulmonary disease; D1, day 1; D1-3, days 1-3; D4-90, days 4-90; D270, days 270; OD, once a day.

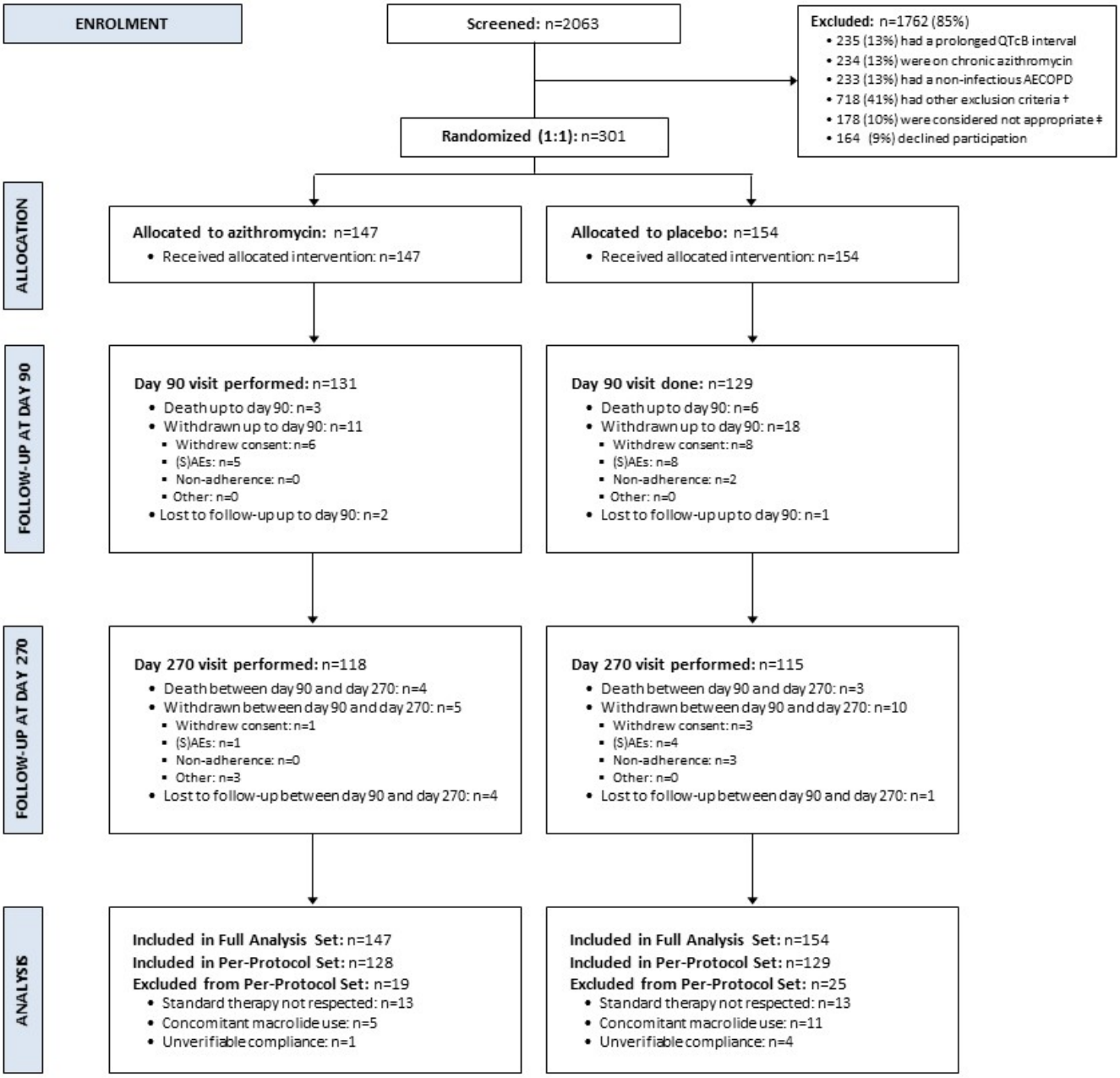


Figure 2 – Enrolment, allocation, follow-up and analysis of the trial participants.

Abbreviations: AECOPD, acute exacerbation of chronic obstructive pulmonary disease; (S)AE, (serious) adverse event; QTcB, QT interval corrected according to Bazett's formula.

Note: † Exclusion based on ≥1 of the exclusion criteria, with the exception of a prolonged QTcB, a chronic azithromycin intake and a non-infectious AECOPD; ‡ exclusion based on criteria limiting the ability of the patient to participate in the study (e.g. comorbidities, social circumstances, etc.); day 90, end of intervention; day 270, end of follow-up.

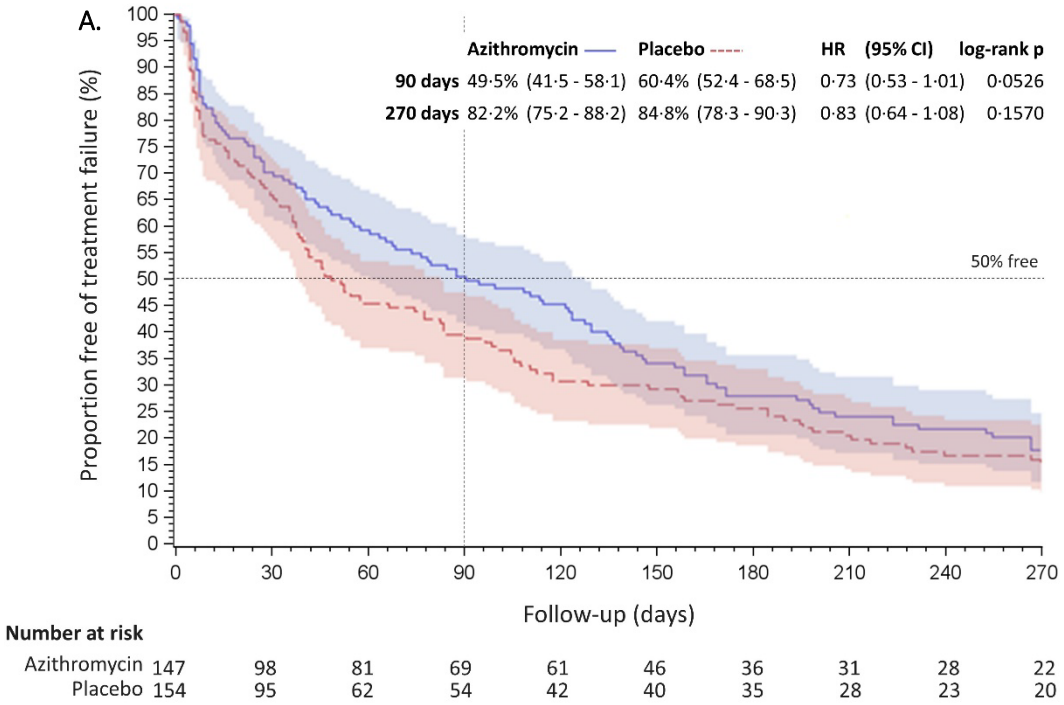


Figure 3 – Primary composite endpoint, treatment failure rate.

Percentage of patients free from treatment failure during 9 months (or 270 days) of follow-up since randomization, according to the study group. Participants who did not have an event within 270 days as well as early terminations were censored, respectively at day 270 and the time of termination.

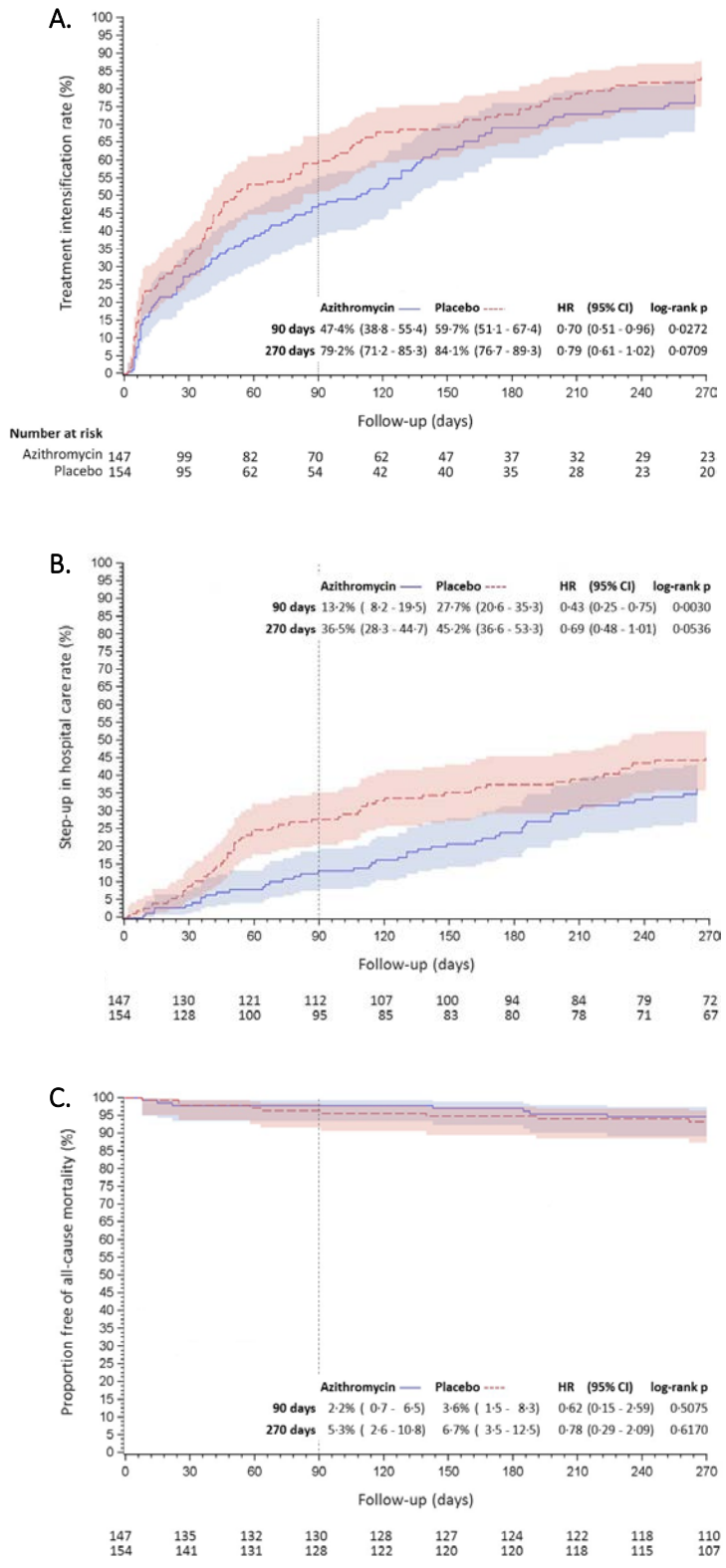


Figure 4 – The three components of treatment failure.

Percentage of patients requiring (B) treatment intensification for respiratory reasons, (C) step-up in hospital care for respiratory reasons and (D) percentage free from mortality during 9 months (or 270 days) of follow-up since randomization, according to the study group. Participants who did not have an event within 270 days as well as early terminations were censored, respectively at day 270 and the time of termination.

REFERENCES

1. Hartl S, Lopez-Campos JL, Pozo-Rodriguez F, et al. Risk of death and readmission of hospital-admitted COPD exacerbations: European COPD Audit. *Eur Respir J* 2016; **47**: 113–21.
2. Hoogendoorn M, Hoogenveen RT, Rutten-van Mölken MP, Vestbo J, Feenstra TL. Case fatality of COPD exacerbations: A meta-analysis and statistical modelling approach. *Eur Respir J* 2011; **37**: 508–15.
3. Lodewijckx C, Sermeus W, Vanhaecht K, et al. Inhospital management of COPD exacerbations: a systematic review of the literature with regard to adherence to international guidelines. *J Eval Clin Pract* 2009; **15**: 1101–10.
4. Chow L, Parulekar AD, Hanania NA. Hospital management of acute exacerbations of chronic obstructive pulmonary disease. *J Hosp Med* 2015; **10**: 328–39.
5. Soo Hoo GW, Esquinas AM. Risk trajectories of readmission and death in the first year after hospitalization for chronic obstructive pulmonary disease: don't shortchange noninvasive ventilation. *Am J Respir Crit Care Med* 2018; **198**: 282–83.
6. Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD). Global strategy for the diagnosis, management, and prevention of COPD, 2018 report [Internet]. 2018. Available from: http://goldcopd.org.
7. Albert RK, Connett J, Bailey WC, et al. Azithromycin for prevention of exacerbations of COPD. *N Engl J Med* 2011; **365**: 689–98.
8. Ni W, Shao X, Cai X, et al. Prophylactic use of macrolide antibiotics for the prevention of chronic obstructive pulmonary disease exacerbation: A meta-analysis. *PLoS One* 2015; **10**: 1–13.
9. Uzun S, Djamin RS, Kluytmans JAJW, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): A randomised, double-blind, placebo-controlled trial. *Lancet Respir Med* 2014; **2**: 361–8.

10. Li H, Liu DH, Chen LL, et al. Meta-Analysis of the adverse effects of long-term azithromycin use in patients with chronic lung diseases. *Antimicrob Agents Chemother* 2014; **58**: 511–7.

11. Serisier DJ. Risks of population antimicrobial resistance associated with chronic macrolide use for inflammatory airway diseases. *Lancet Respir* 2013; **1**: 262–74.

12. FDA Drug Safety Communication: azithromycin (Zithromax or Zmax) and the risk of potentially fatal heart rhythms [safety announcement 3-12-2013]. U.S. Food and Drug Aministration [Internet].Available from: https://www.fda.gov/downloads/Drugs/DrugSafety/UCM343347.pdf

13. Wallace M, Miller L, Nguyen M, Shields A. Ototoxicity with azithromycin. *Lancet* 1994; **343**: 241.

14. Vermeersch K, Gabrovska M, Aumann J, et al. Late breaking abstract: Azithromycin for acute COPD exacerbations requiring hospitalization – the BACE trial results. *Eur Resp J* 2018; 52: Suppl. 62, OA1654.

15. Vermeersch K, Gabrovska M, Deslypere G, et al. The Belgian trial with azithromycin for acute COPD exacerbations requiring hospitalization: An investigator-initiated study protocol for a multicenter, randomized, double-blind, placebo-controlled trial. *Int J COPD* 2016; **11**: 687–96.

16. Vandenberk B, Vandael E, Robyns T, et al. Which QT correction formulae to use for QT monitoring? *J Am Heart Assoc* 2016; **5**: 1–10.

17. Demeester K, Topsakal V, Hendrickx J, et al. Hearing disability measured by the speech, spatial, and qualities of hearing scale in clinically normal-hearing persons, and hearing-impaired middle-aged persons, and disability screening by means of a reduced SSQ (the SSQ5). *Ear & Hear* 2012; **32**: 1–12.

18. Seemungal TAR, Wilkinson TMA, Hurst JR, et al. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. *Am J Respir Crit Care Med* 2008; **178**: 1139–47.

19. Khakban A, Sin DD, FitzGerald M, et al. The projected epidemic of chronic obstructive pulmonary disease hospitalizations over the next 15 years. A population-based perspective. *Am J Respir Crit Care Med* 2017; **195**: 287–91.

20. Lipson DA, Barnhart F, Brealey N, et al. Once-daily single-inhaler triple versus dual therapy in patients with COPD. *N Engl J Med* 2018; **378**: 1671–80.

21. Martinez FJ, Calverley PMA, Goehring UM, et al. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): A multicentre randomised controlled trial. *Lancet* 2015; **385**: 857–66.

22. Braman S. Hospital Readmissions for COPD: We Can Meet the Challenge. *Chronic Obstr Pulm Dis J COPD Found* 2015; **2**: 4–7.

23. Mantero M, Rogliani P, Pasquale M Di, et al. Acute exacerbations of COPD: risk factors for failure and relapse. *Int J COPD* 2017; **12**: 2687–93.

24. Miravitlles M, Anzueto A. Antibiotics for acute and chronic respiratory infection in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; **188**: 1052–1057.

25. Altenburg J, De Graaff CS, Van Der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics - Part 1: Biological mechanisms. *Respiration* 2010; **81**: 67–74.

26. Altenburg J, De Graaff CS, Van Der Werf TS, Boersma WG. Immunomodulatory effects of macrolide antibiotics - Part 2: Advantages and disadvantages of long-term, low-dose macrolide therapy. *Respiration* 2010; **81**: 75–87.

27. Celli BR, Barnes PJ. Exacerbations of chronic obstructive pulmonary disease. *Eur Respir J* 2007; **29**: 1224–38.

28. Papi A, Bellettato CM, Braccioni F, et al. Infections and airway inflammation in chronic obstructive pulmonary disease severe exacerbations. *Am J Respir Crit Care Med* 2006; **173**: 1114–21.

29. Lode H. The pharmacokinetics of azithromycin and their clinical significance. *Eur J Clin Microbiol Infect Dis* 1991; **10**: 807–12.

30. Brown BA, Griffith DE, Girard W, Levin J, Wallace RJ. Relationship of adverse events to serum drug levels in patients receiving high-dose azithromycin for mycobacterial lung disease. *Clin Infect Dis* 1997; **24**: 958–64.

31. Albert RK, Schuller JL. Macrolide antibiotics and the risk of cardiac arrhythmias. *Am J Respir Crit Care Med* 2014; **189**: 1173–80.

32. Malhotra-Kumar S, Lammens C, Coenen S, Van Herck K, Goossens H. Effect of azithromycin and clarithromycin therapy on pharyngeal carriage of macrolide-resistant streptococci in healthy volunteers: a randomised, double-blind, placebo-controlled study. *Lancet* 2007; **369**: 482-490.

33. Wenzel RP, Fowler AA, Edmond MB. Antibiotic prevention of acute exacerbations of COPD. *N Engl J Med* 2012; **367**: 340-347.

34. Desai H, Richter S, Doern G, et al. Antibiotic resistance in sputum isolates of Streptococcus pneumoniae in chronic obstructive pulmonary disease is related to antibiotic exposure. *COPD* 2010; **7**: 337-344.

35. Lim E, Brown A, Helmy A, Mussa S, Altman DG. Composite outcomes in cardiovascular research: A survey of randomized trials. *Ann Intern Med* 2008; **149**: 612–18.

36. Molyneaux PL, Mallia P, Cox MJ, et al. Outgrowth of the bacterial airway microbiome after rhinovirus exacerbation of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2013; **188**: 1224–31.

37. Lin C, Pang Q. Meta-analysis and systematic review of procalcitonin-guided treatment in acute exacerbation of chronic obstructive pulmonary disease. *Clin Respir J* 2016; **12**: 10–5.

38. Corti C, Fally M, Fabricius-Bjerre A, et al. Point-of-care procalcitonin test to reduce antibiotic exposure in patients hospitalized with acute exacerbation of COPD. *Int J Chron Obstruct Pulmon Dis* 2016; **11**: 1381–9.