

Supplementary Material

Pathogen- and antibiotic-specific effects of prednisone in community-acquired pneumonia

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Supplementary Methods

Nasopharyngeal swabs, nucleic acid extraction, multiplex viral PCR.

Total nucleic acids were extracted from 489 nasopharyngeal swabs (eswab, Copan) between November 2011 and May 2014 by taking advantage the NucliSens miniMAG platform with the NucliSens magnetic extraction reagents (bioMérieux) according to the instructions of the manufacturer. Elution of these nucleic acid extracts was done in 20 µl. Amplification was performed using the Resplex v2 (Luminex technology, Qiagen, Hilden, Germany) and Anyplex II RV16 multiplex real-time RT-PCR test (Seegene, Seoul, South Korea) targeting influenza A, influenza B, parainfluenzavirus 1-3 (PIV), respiratory syncytial virus A and B (RSV A, RSV B), adenovirus (AdV), human rhinoviruses (HRVA/B/C), human coronaviruses (CoV 229E, OC43, NL69), human enterovirus (HEV), human metapneumovirus (MPV) and human bocavirus (HBoV).

Supplementary Table S1. Primary and secondary outcomes

1. Analysis by microbiological diagnosis

Pneumococcal Pneumonia

	Pneumococcal Pneumonia			All others			
Endpoints	Predni- sone (n= 53)	Placebo (n=53)	HR, OR or difference (95% CI)	Predni- sone (n=250)	Placebo (n=268)	HR, OR or difference (95% CI)	Interaction p-value
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	3.4 (1.5 - 8.5)	3.6 (2.0 - 5.9)	Unadjusted HR 0.97 (0.65 - 1.43) Adjusted HR 1.28 (0.85 - 1.94)	3 (2.0 - 5.3)	5 (2.5 - 8.3)	Unadjusted HR 1.48 (1.24 - 1.77) Adjusted HR 1.48 (1.24 - 1.77)	Unadjusted: 0.04 Adjusted: 0.14
Secondary Endpoints							
Time to effective hospital discharge	8.8 (6.0)	7.5 (5.5)	Unadjusted difference 1.26 days (-0.95 - 3.48) Adjusted difference 0.34 days (-1.61 - 2.30)	8.0 (6.0)	9.0 (6.1)	Unadjusted difference -1.02 days (-2.07 - 0.03) Adjusted difference -1.24 days (-2.22 - -0.26)	Unadjusted: 0.08 Adjusted: 0.16
Death from any cause	1 (2%)	3 (6%)	Unadjusted OR 0.32 (0.03 - 3.18) Adjusted OR 0.09 (0.005 - 1.48)	10 (4.0%)	10 (3.7%)	Unadjusted OR 1.08 (0.44 - 2.63) Adjusted OR 0.79 (0.30 - 2.12)	Unadjusted: 0.34 Adjusted: 0.28
ICU admission	6 (11%)	2 (4%)	Unadjusted OR 3.26 (0.63 - 16.93) Adjusted OR 3.88 (0.53 - 28.19)	7 (2.8%)	13 (4.9%)	Unadjusted OR 0.57 (0.22 - 1.44) Adjusted OR 0.48 (0.17 - 1.36)	Unadjusted: 0.07 Adjusted: 0.05
Re-hospitalization	5 (9%)	2 (4%)	Unadjusted OR 2.66 (0.49 - 14.35) Adjusted OR 2.45 (0.43 - 13.94)	23 (9.2%)	22 (8.2%)	Unadjusted OR 1.13 (0.61 - 2.09) Adjusted OR 1.07 (0.57 - 1.99)	Unadjusted: 0.35 Adjusted: 0.51
CAP complications	2 (4%)	3 (6%)	Unadjusted OR 0.65 (0.10 - 4.08) Adjusted OR 0.46 (0.06 - 3.49)	6 (2.4%)	14 (5.2%)	Unadjusted OR 0.45 (0.17 - 1.18) Adjusted OR 0.39 (0.14 - 1.06)	Unadjusted: 0.72 Adjusted: 0.76
Duration of total antibiotic treatment	11.4 (8.2)	10.2 (4.6)	Unadjusted difference 1.20 days (-1.42 - 3.82) Adjusted difference 1.13 days (-1.37 - 3.62)	9.5 (4.6)	10.1 (4.9)	Unadjusted difference -0.62 days (-1.46 - 0.22) Adjusted difference -0.70 days (-1.53 - 0.13)	Unadjusted: 0.10 Adjusted: 0.13
Duration of intravenous antibiotic treatment	7.3 (8.3)	5.6 (3.9)	Unadjusted difference 1.74 days (-0.81 - 4.29) Adjusted difference 1.62 days (-0.84 - 4.08)	5.2 (4.0)	6.4 (5.0)	Unadjusted difference -1.14 days (-1.95 - -0.34) Adjusted difference -1.25 days (-2.09 - -0.41)	Unadjusted: 0.01 Adjusted: 0.01

Any CAP pathogen identified

Endpoints	Any CAP pathogen identified			All others			Interaction p-value
	Predni- sone (n=108)*	Placebo (n=113)**	HR, OR or difference (95% CI)	Predni- sone (n=254)	Placebo (n=251)	HR, OR or difference (95% CI)	
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	3.4 (2.0 – 7.0)	4.4 (2.4 – 8.0)	Unadjusted HR 1.16 (0.88 - 1.52) Adjusted HR 1.36 (1.03 – 1.80)	2.6 (1.9 – 5.0)	4.5 (2.2 – 8.0)	Unadjusted HR 1.50 (1.25 - 1.80) Adjusted HR 1.63 (1.36 – 1.96)	Unadjusted: 0.15 Adjusted: 0.26
Secondary Endpoints							
Time to effective hospital discharge	9.1 (6.9)	9.5 (7.2)	Unadjusted difference -0.32 days (-2.19 – 1.55) Adjusted difference -1.05 days (-2.76 – 0.66)	7.1 (5.3)	8.4 (5.6)	Unadjusted difference -1.33 days (-2.29 – -0.37) Adjusted difference -1.40 days (-2.29 – -0.52)	Unadjusted: 0.30 Adjusted: 0.58
Death from any cause	5 (4.6%)	6 (5.3%)	Unadjusted OR 0.87 (0.26 – 2.92) Adjusted OR 0.42 (0.10 – 1.78)	11 (4.3%)	7 (2.8%)	Unadjusted OR 1.58 (0.60 – 4.14) Adjusted OR 1.53 (0.55 – 4.25)	Unadjusted: 0.45 Adjusted: 0.19
ICU admission	10 (9.3%) ***	5 (4.4%) ***	Unadjusted OR 2.20 (0.73 – 6.67) Adjusted OR 2.29 (0.61 – 8.69)	4 (1.6%)	12 (4.8%)	Unadjusted OR 0.32 (0.10 – 1.00) Adjusted OR 0.31 (0.10 – 1.00)	Unadjusted: 0.02 Adjusted: 0.02
Re-hospitalization	14 (13%)	9 (8%)	Unadjusted OR 1.72 (0.71 – 4.16) Adjusted OR 1.47 (0.59 – 3.65)	16 (6.3%)	16 (6.4%)	Unadjusted OR 0.99 (0.48 – 2.02) Adjusted OR 0.95 (0.46 – 1.95)	Unadjusted: 0.34 Adjusted: 0.45
CAP complications	5 (4.6%)	8 (7.1%)	Unadjusted OR 0.64 (0.20 – 2.01) Adjusted OR 0.49 (0.14 – 1.69)	4 (1.6%)	10 (4%)	Unadjusted OR 0.39 (0.12 – 1.25) Adjusted OR 0.37 (0.11 – 1.19)	Unadjusted: 0.55 Adjusted: 0.67
Duration of total antibiotic treatment	10.5 (7.2)	11.2 (6.7)	Unadjusted difference -0.64 days (-2.54 – 1.26) Adjusted difference -1.03 days (-2.86 – 0.79)	9.2 (4.2)	9.5 (3.9)	Unadjusted difference -0.35 days (-1.08 – 0.38) Adjusted difference -0.38 days (-1.10 – 0.34)	Unadjusted: 0.73 Adjusted: 0.52
Duration of intravenous antibiotic treatment	6.7 (7.3)	7.2 (6.8)	Unadjusted difference -0.46 days (-2.36 – 1.44) Adjusted difference -0.95 days (-2.79 – 0.89)	4.6 (3.1)	5.6 (3.7)	Unadjusted difference -1.02 days (-1.63 – -0.41) Adjusted difference -1.04 days (-1.64 – 0.45)	Unadjusted: 0.48 Adjusted: 0.71

* contains the patients with pneumococcal pneumonia (n=53); ** contains the patients with pneumococcal pneumonia (n=53); *** ICU admission rate after removal of patients with pneumococcal pneumonia: 4 of 55 (7%) patients in prednisone arm vs. 3 of 60 (5%) patients in placebo arm

Bacterial CAP pathogen identified

Endpoints	Bacterial CAP pathogen identified			All others			Interaction p-value
	Predni- sone (n= 78)*	Placebo (n=87)**	HR, OR or difference (95% CI)	Predni- sone (n= 258)	Placebo (n=245)	HR, OR or difference (95% CI)	
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	3 (1.5 - 7.0)	4 (2.4 - 9.0)	Unadjusted HR 1.18 (0.86 - 1.63) Adjusted HR 1.54 (1.11 - 2.14)	3 (2.0 - 5.0)	4.5 (2.3 - 7.5)	Unadjusted HR 1.38 (1.16 - 1.66) Adjusted HR 1.46 (1.22 - 1.75)	Unadjusted: 0.46 Adjusted: 1
Secondary Endpoints							
Time to effective hospital discharge	9.3 (7.3)	10.0 (7.7)	Unadjusted difference -0.61 days (-2.91 - 1.70) Adjusted difference -1.25 days (-3.37 - 0.87)	7.2 (5.3)	8.2 (5.4)	Unadjusted difference -0.95 days (-1.89 - -0.02) Adjusted difference -1.06 days (-1.93 - -0.19)	Unadjusted: 0.75 Adjusted: 0.98
Death from any cause	3 (4%)	5 (6%)	Unadjusted OR 0.66 (0.15 - 2.84) Adjusted OR 0.26 (0.04 - 1.53)	12 (4.7%)	7 (2.9%)	Unadjusted OR 1.66 (0.64 - 4.28) Adjusted OR 1.61 (0.57 - 4.50)	Unadjusted: 0.30 Adjusted: 0.12
ICU admission	8 (10%)	4 (5%)	Unadjusted OR 2.37 (0.69 - 8.21) Adjusted OR 2.23 (0.52 - 9.56)	6 (2.3%)	11 (4.5%)	Unadjusted OR 0.51 (0.18 - 1.39) Adjusted OR 0.49 (0.17 - 1.44)	Unadjusted: 0.06 Adjusted: 0.06
Re-hospitalization	10 (13%)	9 (10%)	Unadjusted OR 1.27 (0.49 - 3.32) Adjusted OR 1.07 (0.40 - 2.90)	16 (6.2%)	14 (5.7%)	Unadjusted OR 1.09 (0.52 - 2.29) Adjusted OR 1.05 (0.50 - 2.20)	Unadjusted: 0.80 Adjusted: 0.93
CAP complications	5 (6%)	8 (9%)	Unadjusted OR 0.68 (0.21 - 2.16) Adjusted OR 0.54 (0.15 - 1.92)	2 (0.8%)	8 (3.3%)	Unadjusted OR 0.23 (0.05 - 1.10) Adjusted OR 0.22 (0.04 - 1.04)	Unadjusted: 0.28 Adjusted: 0.31
Duration of total antibiotic treatment	11.5 (8.0)	11.8 (7.0)	Unadjusted difference -0.31 days (-2.69 - 2.07) Adjusted difference -0.77 days (-3.05 - 1.51)	9.0 (4.0)	9.5 (4.0)	Unadjusted difference -0.48 days (-1.20 - 0.24) Adjusted difference -0.51 days (-1.21 - 0.21)	Unadjusted: 0.86 Adjusted: 0.98
Duration of intravenous antibiotic treatment	7.7 (8.3)	7.5 (7.3)	Unadjusted difference 0.14 days (-2.30 - 2.58) Adjusted difference -0.37 days (-2.71 - 1.97)	4.6 (3.1)	5.8 (3.9)	Unadjusted difference -1.16 days (-1.78 - -0.54) Adjusted difference -1.19 days (-1.79 - -0.58)	Unadjusted: 0.15 Adjusted: 0.21

* contains the patients with pneumococcal pneumonia (n=53); ** contains the patients with pneumococcal pneumonia (n=53); *** ICU admission rate after removal of patients with pneumococcal pneumonia: 2 of 25 (8%) patients in prednisone arm vs. 2 of 34 (6%) patients in placebo arm

Respiratory Virus

	Respiratory virus identified			All others			
Endpoints	Predni- sone (n= 40)*	Placebo (n=35)**	HR, OR or difference (95% CI)	Predni- sone (n=174)	Placebo (n=183)	HR, OR or difference (95% CI)	Interaction p-value
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	4.0 (3.0 – 6.6)	4.4 (2.4 – 7)	Unadjusted HR 1.17 (0.74 - 1.86) Adjusted HR 1.21 (0.74 -1.98)	3.0 (2.0 – 5.3)	4.5 (2.3 – 8.0)	Unadjusted HR 1.37 (1.10 - 1.70) Adjusted HR 1.52 (1.22 – 1.89)	Unadjusted: 0.56 Adjusted: 0.40
Secondary Endpoints							
Time to effective hospital discharge	8.4 (5.5)	8.3 (6.0)	Unadjusted difference +0.19days (-2.45 – 2.83) Adjusted difference -0.67 days (-3.10 – 1.76)	7.3 (6.1)	8.2 (5.8)	Unadjusted difference -0.86 days (-2.10 – 0.37) Adjusted difference -0.97 days (-2.16 – 0.22)	Unadjusted: 0.48 Adjusted: 0.74
Death from any cause	2 (5%)	1 (3%)	Unadjusted OR 1.79 (0.16 – 20.63) Adjusted OR 0.06 (0.0003 – 10.32)	8 (4.7%)	9 (4.9%)	Unadjusted OR 0.93 (0.35 – 2.47) Adjusted OR 0.79 (0.26 – 2.40)	Unadjusted: 0.63 Adjusted: 0.98
ICU admission	3 (7.5%)	1 (3%)	Unadjusted OR 2.76 (0.27 – 27.79) Adjusted OR 7.42 (0.21 – 262.25)	6 (3.4%)	7 (3.8%)	Unadjusted OR 0.90 (0.30 – 2.73) Adjusted OR 1.09 (0.32 – 3.69)	Unadjusted: 0.39 Adjusted: 0.44
Re-hospitalization	4 (10%)	1 (3%)	Unadjusted OR 3.78 (0.40 – 35.51) Adjusted OR 3. 43 (0.34 – 34.38)	12 (7%)	13 (7.1%)	Unadjusted OR 0.97 (0.43 – 2.19) Adjusted OR 0.94 (0.41 – 2.17)	Unadjusted: 0.26 Adjusted: 0.35
CAP complications	0 (0%)	1 (3%)	Unadjusted OR 1 Adjusted OR 1	4 (2.3%)	10 (5.5%)	Unadjusted OR 0.41 (0.13 – 1.32) Adjusted OR 0.39 (0.11 – 1.38)	N.A. N.A.
Duration of total antibiotic treatment	8.8 (3.5)	10.2 (7.5)	Unadjusted difference -1.35 days (-4.07 – 1.36) Adjusted difference -1.30 days (-4.05 – 1.44)	9.8 (6.3)	9.8 (4.6)	Unadjusted difference 0.06 days (-1.11 – 1.23) Adjusted difference 0.002 days (-1.14 – 1.15)	Unadjusted: 0.34 Adjusted: 0.30
Duration of intravenous antibiotic treatment	5.0 (3.2)	6.7 (8.0)	Unadjusted difference -1.73 days (-4.47 – 1.01) Adjusted difference -1.83 days (-4. 63 – 0.96)	5.5 (6.0)	5.9 (4.4)	Unadjusted difference -0.42 days (-1.53 – 0.69) Adjusted difference -0.48 days (-1.56 – 0.60)	Unadjusted: 0.35 Adjusted: 0.24

* contains the patients with influenza virus (n=11); ** contains the patients with influenza virus (n=13)

Influenza virus

	Influenza virus			All others			
Endpoints	Predni- sone (n=11)	Placebo (n=13)	HR, OR or difference (95% CI)	Predni- sone (n=203)	Placebo (n=205)	HR, OR or difference (95% CI)	Interaction p-value
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	4.0 (1.4 - 7.0)	5.0 (3.0 - 10.4)	Unadjusted HR 1.26 (0.54 - 2.92) Adjusted HR 4.50 (1.17 - 17.25)	3.0 (2.0 - 5.5)	4.4 (2.3 - 7.5)	Unadjusted HR 1.33 (1.09 - 1.63) Adjusted HR 1.45 (1.18 - 1.77)	Unadjusted: 0.94 Adjusted: 0.91
Secondary Endpoints							
Time to effective hospital discharge	9.2 (9.4)	10.4 (8.0)	Unadjusted difference -1.57 days (-8.78 - 5.65) Adjusted difference -2.24 days (-9.61 - 5.12)	7.5 (5.8)	8.1 (5.8)	Unadjusted difference -0.60 days (-1.71 - 0.52) Adjusted difference -0.80 days (-1.86 - 0.27)	Unadjusted: 0.70 Adjusted: 0.56
Death from any cause	1 (10%)	1 (8%)	Unadjusted OR 1.2 (0.07 - 21.72) Adjusted OR 0.13 (N.A.)	9 (4.4%)	9 (4.4%)	Unadjusted OR 1.01 (0.39 - 2.60) Adjusted OR 0.79 (0.27 - 2.33)	Unadjusted: 0.91 Adjusted: 0.76
ICU admission	1 (10%)	1 (8%)	Unadjusted OR 1.2 (0.07 - 21.72) Adjusted OR N.A.	8 (3.9%)	7 (3.4%)	Unadjusted OR 1.16 (0.41 - 3.26) Adjusted OR 1.47 (0.47 - 4.64)	Unadjusted: 0.98 Adjusted: 0.77
Re-hospitalization	1 (10%)	1 (8%)	Unadjusted OR 1.20 (0.07 - 21.72) Adjusted OR 1.01 (0.03 - 37.26)	15 (7.4%)	13 (6.3%)	Unadjusted OR 1.18 (0.55 - 2.54) Adjusted OR 1.11 (0.51 - 2.44)	Unadjusted: 0.99 Adjusted: 0.98
CAP complications	0 (0%)	1 (8%)	Unadjusted OR 1 (N.A.) Adjusted OR 1 (N.A.)	4 (2%)	10 (4.9%)	Unadjusted OR 0.39 (0.12 - 1.27) Adjusted OR 0.37 (0.10 - 1.30)	Unadjusted: N.A. Adjusted: N.A.
Duration of total antibiotic treatment	7.8 (3.4)	13.0 (10.7)	Unadjusted difference -4.80 days (-12.21 - 2.61) Adjusted difference -4.63 days (-13.65 - 4.39)	9.7 (6)	9.6 (4.5)	Unadjusted difference 0.08 days (-0.97 - 1.14) Adjusted difference 0.02 days (-1.02 - 1.06)	Unadjusted: 0.04 Adjusted: 0.04
Duration of intravenous antibiotic treatment	3.4 (2.9)	9.8 (11.6)	Unadjusted difference -6.13 days (-13.60 - 1.33) Adjusted difference -6.13 days (-15.15 - 2.88)	5.5 (5.7)	5.8 (4.3)	Unadjusted difference -0.30 days (-1.30 - 0.70) Adjusted difference -0.39 days (-1.36 - 0.58)	Unadjusted: 0.01 Adjusted: <0.01

2. Analysis by antimicrobial subgroup

Beta-lactam + Macrolide

	Beta-lactam + Macrolide			All others			
Endpoints	Predni- sone (n=205)	Placebo (n=199)	HR, OR or difference (95% CI)	Predni- sone (n=156)	Placebo (n=162)	HR, OR or difference (95% CI)	Interaction p-value
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	3.0 (2.0 – 6.0)	5 (2.3 – 8.0)	Unadjusted HR 1.32 (1.08 - 1.61) Adjusted HR 1.52 (1.23 – 1.86)	2.4 (1.4 – 4.9)	4 (2.0 – 7.0)	Unadjusted HR 1.42 (1.13 - 1.77) Adjusted HR 1.46 (1.16 – 1.83)	Unadjusted: 0.46 Adjusted: 0.88
Secondary Endpoints							
Time to effective hospital discharge	8.0 (5.9)	8.7 (6.3)	Unadjusted difference -0.69 days (-1.90 – 0.51) Adjusted difference -1.25 days (-2.36 – -0.14)	7.3 (5.9)	8.7 (5.9)	Unadjusted difference -1.34 days (-2.63 – 0.46) Adjusted difference -1.14 days (-2.36 – 0.08)	Unadjusted: 0.47 Adjusted: 0.96
Death from any cause	12 (5.9%)	9 (4.5%)	Unadjusted OR 1.31 (0.54 – 3.19) Adjusted OR 0.93 (0.34 – 2.54)	4 (2.6%)	4 (2.5%)	Unadjusted OR 1.04 (0.26 – 4.23) Adjusted OR 1.07 (0.25 – 4.57)	Unadjusted: 0.78 Adjusted: 0.96
ICU admission	8 (3.9%)	13 (6.5%)	Unadjusted OR 0.58 (0.24 – 1.43) Adjusted OR 0.53 (0.20 – 1.40)	6 (3.8%)	4 (2.5%)	Unadjusted OR 1.58 (0.44 – 5.71) Adjusted OR 1.59 (0.36 – 7.06)	Unadjusted: 0.21 Adjusted: 0.17
Re-hospitalization	14 (6.8%)	18 (9%)	Unadjusted OR 0.74 (0.36 – 1.53) Adjusted OR 0.67 (0.32 – 1.40)	16 (10.3%)	7 (4.3%)	Unadjusted OR 2.53 (1.01 – 6.33) Adjusted OR 2.52 (0.98 – 6.48)	Unadjusted: 0.04 Adjusted: 0.03
CAP complications	4 (2%)	12 (6%)	Unadjusted OR 0.31 (0.10 – 0.98) Adjusted OR 0.25 (0.08 – 0.83)	5 (3.2%)	6 (3.7%)	Unadjusted OR 0.86 (0.26 – 2.88) Adjusted OR 0.86 (0.25 – 2.95)	Unadjusted: 0.23 Adjusted: 0.19
Duration of total antibiotic treatment	9.7 (4.2)	10.2 (4.7)	Unadjusted difference -0.46 days (-1.34 – 0.42) Adjusted difference -0.60 days (-1.46 – 0.26)	9.4 (6.5)	9.8 (5.3)	Unadjusted difference -0.41 days (-1.78 – 0.95) Adjusted difference -0.27 days (1.64 – 1.09)	Unadjusted: 0.95 Adjusted: 0.81
Duration of intravenous antibiotic treatment	5.4 (3.8)	6.3 (4.7)	Unadjusted difference -0.96 days (-1.80 – -0.12) Adjusted difference -1.19 days (-1.99 – -0.38)	5.0 (6.1)	5.8 (5.2)	Unadjusted difference -0.75 days (-2.02 – 0.53) Adjusted difference – 0.57 days (-1.81 – 0.68)	Unadjusted: 0.78 Adjusted: 0.48

Beta-lactam only

	Beta-lactam only			All others			
Endpoints	Predni- sone (n=103)	Placebo (n=96)	HR, OR or difference (95% CI)	Predni- sone (n=258)	Placebo (n=265)	HR, OR or difference (95% CI)	Interaction p-value
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	2.0 (1.3 - 4.4)	3.0 (2.0 - 6.0)	Unadjusted HR 1.28 (0.97 - 1.71) Adjusted HR 1.28 (0.96 - 1.71)	3.0 (2.0 - 6.0)	5.0 (2.4 - 8.4)	Unadjusted HR 1.36 (1.14 - 1.63) Adjusted HR 1.58 (1.32 - 1.89)	Unadjusted: 0.88 Adjusted: 0.33
Secondary Endpoints							
Time to effective hospital discharge	6.8 (4.3)	7.6 (4.4)	Unadjusted difference -0.81 days (-2.02 - 0.39) Adjusted difference -0.65 days (-1.80 - 0.50)	8.1 (6.4)	9.1 (6.6)	Unadjusted difference -1 day (-2.12 - 0.12) Adjusted difference -1.45 days (-2.49 - -0.41)	Unadjusted: 0.85 Adjusted: 0.36
Death from any cause	2 (1.9%)	3 (3.1%)	Unadjusted OR 0.61 (0.10 - 3.76) Adjusted OR 0.64 (0.10 - 4.18)	14 (5.4%)	10 (3.8%)	Unadjusted OR 1.46 (0.64 - 3.36) Adjusted OR 1.04 (0.41 - 2.62)	Unadjusted: 0.39 Adjusted: 0.65
ICU admission	1 (1%)	0 (0%)	Unadjusted OR 1 Adjusted OR N.A.	13 (5.0%)	17 (6.4%)	Unadjusted OR 0.77 (0.37 - 1.63) Adjusted OR 0.64 (0.28 - 1.44)	N.A.
Re-hospitalization	7 (6.8%)	1 (1%)	Unadjusted OR 6.93 (0.84 - 57.39) Adjusted OR 6.38 (0.76 - 53.84)	23 (8.9%)	24 (9.1%)	Unadjusted OR 0.98 (0.54 - 1.79) Adjusted OR 0.87 (0.47 - 1.61)	Unadjusted: 0.08 Adjusted: 0.07
CAP complications	3 (2.9%)	3 (3.1%)	Unadjusted OR 0.93 (0.18 - 4.72) Adjusted OR 0.93 (0.17 - 4.94)	6 (2.3%)	15 (5.7%)	Unadjusted OR 0.40 (0.15 - 1.04) Adjusted OR 0.31 (0.11 - 0.85)	Unadjusted: 0.38 Adjusted: 0.25
Duration of total antibiotic treatment	8.5 (3.6)	8.8 (3.6)	Unadjusted difference -0.31 days (-1.36 - 0.75) Adjusted difference -0.17 days (-1.22 - 0.88)	10.0 (5.8)	10.4 (5.3)	Unadjusted difference -0.41 days (-1.38 - 0.55) Adjusted difference -0.61 days (-1.55 - 0.34)	Unadjusted: 0.91 Adjusted: 0.63
Duration of intravenous antibiotic treatment	4.5 (2.8)	5.3 (3.2)	Unadjusted difference -0.73 days (-1.59 - 0.13) Adjusted difference -0.58 days (-1.43 - 0.27)	5.5 (5.5)	6.4 (5.4)	Unadjusted difference -0.87 days (-1.81 - 0.06) Adjusted difference -1.11 days (-2.02 - -0.21)	Unadjusted: 0.86 Adjusted: 0.47

All other antibiotics

	All other antibiotics			All others			
Endpoints	Predni- sone (n=47)	Placebo (n=62)	HR, OR or difference (95% CI)	Predni- Sone (n=314)	Placebo (n=299)	HR, OR or difference (95% CI)	Interaction p-value
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	3.0 (1.4 – 6.0)	5.0 (3.0 – 9.0)	Unadjusted HR 1.47 (1.00 - 2.17) Adjusted HR 1.78 (1.18 – 2.69)	3.0 (2.0 – 5.4)	4.3 (2.0 – 7.6)	Unadjusted HR 1.31 (1.11 - 1.54) Adjusted HR 1.42 (1.20 – 1.67)	Unadjusted: 0.60 Adjusted: 0.44
Secondary Endpoints							
Time to effective hospital discharge	9.0 (8.3)	10.4 (7.4)	Unadjusted difference -1.40 days (-4.40 – 1.59) Adjusted difference -1.93 days (-4.77 – 0.92)	7.5 (5.5)	8.3 (5.8)	Unadjusted difference -0.81 days (-1.70 – 0.08) Adjusted difference -1.04 days (-1.86 – -0.21)	Unadjusted: 0.64 Adjusted: 0.55
Death from any cause	2 (4%)	1 (2%)	Unadjusted OR 2.71 (0.24 – 30.83) Adjusted OR 1.61 (0.11 – 23.7)	14 (4.5%)	12 (4%)	Unadjusted OR 1.12 (0.51 – 2.45) Adjusted OR 0.92 (0.39 – 2.19)	Unadjusted: 0.50 Adjusted: 0.62
ICU admission	5 (11%)	4 (6%)	Unadjusted OR 1.73 (0.44 – 6.82) Adjusted OR 0.94 (0.17 – 5.33)	9 (2.9%)	13 (4.3%)	Unadjusted OR 0.65 (0.27 – 1.54) Adjusted OR 0.67 (0.26 – 1.70)	Unadjusted: 0.24 Adjusted: 0.53
Re-hospitalization	9 (19%)	6 (10%)	Unadjusted OR 2.09 (0.73 – 6.72) Adjusted OR 1.70 (0.51 – 5.69)	21 (6.7%)	19 (6.4%)	Unadjusted OR 1.06 (0.56 – 2.01) Adjusted OR 0.98 (0.51 – 1.87)	Unadjusted: 0.26 Adjusted: 0.29
CAP complications	2 (4%)	3 (5%)	Unadjusted OR 0.87 (0.14 – 5.45) Adjusted OR 0.14 (0.003 – 5.05)	7 (2.2%)	15 (5%)	Unadjusted OR 0.43 (0.17 – 1.07) Adjusted OR 0.40 (0.16 – 1)	Unadjusted: 0.50 Adjusted: 0.67
Duration of total antibiotic treatment	12.7 (9.6)	12.0 (6.3)	Unadjusted difference 0.71 days (-2.38 – 3.81) Adjusted difference 0.46 days (-2.72 – 3.65)	9.1 (4.2)	9.6 (4.5)	Unadjusted difference -0.48 days (-1.19 – 0.23) Adjusted difference -0.54 days (-1.22 – 0.15)	Unadjusted: 0.27 Adjusted: 0.41
Duration of intravenous antibiotic treatment	6.7 (10.0)	6.9 (7.1)	Unadjusted difference -0.20 days (-3.49 – 3.09) Adjusted difference -0.74 days (-3.98 – 2.50)	5 (3.5)	5.9 (4.3)	Unadjusted difference -0.90 days (-1.54 – -0.27) Adjusted difference -0.98 days (-1.59 – -0.37)	Unadjusted: 0.50 Adjusted: 0.66

Sensitivity Analysis: Patients who received any macrolide

	Patients who <u>ever</u> received a macrolide			All others			
Endpoints	Predni- sone (n=225)	Placebo (n=234)	HR, OR or difference (95% CI)	Predni- Sone (n=136)	Placebo (n=127)	HR, OR or difference (95% CI)	Interaction p-value
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	3.0 (2.0 - 6.0)	5.0 (2.0 - 8.4)	Unadjusted HR 1.36 (1.12 - 1.64) Adjusted HR 1.58 (1.30 - 1.92)	2.0 (1.4 - 4.5)	3.4 (2.0 - 6.0)	Unadjusted HR 1.31 (1.02 - 1.67) Adjusted HR 1.31 (1.02 - 1.68)	Unadjusted: 0.98 Adjusted: 0.98
Secondary Endpoints							
Time to effective hospital discharge	8.1 (6.3)	9.0 (6.7)	Unadjusted difference -0.84 days (-2.04 - 0.35) Adjusted difference -1.40 days (-2.50 - -0.29)	7.0 (5.1)	8.1 (4.9)	Unadjusted difference -1.13 days (-2.35 - 0.08) Adjusted difference -0.85 dys (-2 - 0.30)	Unadjusted: 0.75 Adjusted: 0.59
Death from any cause	13 (5.8%)	10 (4.3%)	Unadjusted OR 1.37 (0.59 - 3.20) Adjusted OR 0.90 (0.35 - 2.34)	3 (2.2%)	3 (2.4%)	Unadjusted OR 0.93 (0.18 - 4.71) Adjusted OR 1.09 (0.20 - 5.90)	Unadjusted: 0.68 Adjusted: 0.89
ICU admission	11 (4.9%)	15 (6.4%)	Unadjusted OR 0.75 (0.34 - 1.67) Adjusted OR 0.62 (0.26 - 1.48)	3 (2.2%)	2 (1.6%)	Unadjusted OR 1.41 (0.23 - 8.58) Adjusted OR 1.41 (0.18 - 11.06)	Unadjusted: 0.53 Adjusted: 0.28
Re-hospitalization	19 (8.4%)	22 (9.4%)	Unadjusted OR 0.89 (0.47 - 1.69) Adjusted OR 0.80 (0.41 - 1.54)	11 (8.1%)	3 (2.4%)	Unadjusted OR 3.64 (0.99 - 13.35) Adjusted OR 3.57 (0.94 - 13.53)	Unadjusted: 0.06 Adjusted: 0.04
CAP complications	6 (2.7%)	14 (6.0%)	Unadjusted OR 0.43 (0.16 - 1.14) Adjusted OR 0.34 (0.12 - 0.96)	3 (2.2%)	4 (3.1%)	Unadjusted OR 0.69 (0.15 - 3.16) Adjusted OR 0.67 (0.14 - 3.17)	Unadjusted: 0.60 Adjusted: 0.47
Duration of total antibiotic treatment	10.1 (5.7)	10.5 (5.2)	Unadjusted: -0.38 (-1.40 - 0.64) Adjusted: -0.61 (-1.62 - 0.39)	8.6 (4.4)	9 (4.2)	Unadjusted: -0.40 (-1.49 - 0.70) Adjusted: -0.24 (-1.32 - 0.84)	Unadjusted: 0.99 Adjusted: 0.72
Duration of intravenous antibiotic treatment	5.7 (5.5)	6.6 (5.5)	Unadjusted difference -0.96 days (-1.97- 0.06) Adjusted difference -1.25 days (-2.24 - -0.26)	4.5 (3.4)	5.0 (3.3)	Unadjusted difference -0.58 days (-1.43 - 0.26) Adjusted difference -0.38 days (-1.21 - 0.45)	Unadjusted: 0.63 Adjusted: 0.27

3. Analysis by initial serum procalcitonin level

Endpoints	Patients with procalcitonin <u>above</u> the median population level			All others			Interaction p-value
	Predni- sone (n=141)	Placebo (n=148)	HR, OR or difference (95% CI)	Predni- Sone (n=148)	Placebo (n=158)	HR, OR or difference (95% CI)	
Primary Endpoint							
Per protocol, time to clinical stability, median (IQR)	2.6 (1.9 - 5.4)	4.5 (2.5 - 8.7)	Unadjusted HR 1.54 (1.21 - 1.96) Adjusted HR 1.75 (1.37 - 2.25)	2.4 (1.5 - 4.5)	4.0 (2.0 - 7.0)	Unadjusted HR 1.40 (1.11 - 1.76) Adjusted HR 1.44 (1.14 - 1.82)	Unadjusted: 0.53 Adjusted: 0.51
Secondary Endpoints							
Time to effective hospital discharge	7.6 (5.9)	9.1 (6.4)	Unadjusted difference -1.57 days (-3.01 - -0.14) Adjusted difference -1.84 days (-3.17 - -0.53)	6.8 (5.7)	8.2 (6.2)	Unadjusted difference -1.40 days (-2.74 - -0.05) Adjusted difference -1.26 days (-2.54 - 0.01)	Unadjusted: 0.86 Adjusted: 0.64
Death from any cause	6 (4.3%)	6 (4.1%)	Unadjusted OR 1.05 (0.33 - 3.34) Adjusted OR 0.75 (0.20 - 2.84)	4 (2.7%)	5 (3.2%)	Unadjusted OR 0.85 (0.22 - 3.23) Adjusted OR 0.97 (0.23 - 4.08)	Unadjusted: 0.81 Adjusted: 0.98
ICU admission	6 (4.3%)	9 (6.1%)	Unadjusted OR 0.69 (0.24 - 1.98) Adjusted OR 0.68 (0.22 - 2.17)	3 (2%)	5 (3.2%)	Unadjusted OR 0.63 (0.15 - 2.70) Adjusted OR 0.56 (0.12 - 2.58)	Unadjusted: 0.93 Adjusted: 0.87
Re-hospitalization	12 (8.5%)	7 (4.7%)	Unadjusted OR 1.87 (0.72 - 4.90) Adjusted OR 1.60 (0.59 - 4.30)	11 (7.4%)	13 (8.2%)	Unadjusted OR 0.90 (0.39 - 2.07) Adjusted OR 0.98 (0.41 - 2.34)	Unadjusted: 0.26 Adjusted: 0.30
CAP complications	3 (2.1%)	11 (7.4%)	Unadjusted OR 0.27 (0.07 - 0.99) Adjusted OR 0.25 (0.07 - 0.96)	4 (2.7%)	6 (3.8%)	Unadjusted OR 0.70 (0.19 - 2.54) Adjusted OR 0.75 (0.20 - 2.83)	Unadjusted: 0.31 Adjusted: 0.28
Duration of total antibiotic treatment	9.5 (4.4)	11.1 (5.8)	Unadjusted difference -1.61 days (-2.85 - -0.38) Adjusted difference -1.82 days (-3.03 - -0.62)	8.9 (4.9)	9 (4.4)	Unadjusted difference -0.11 days (-1.18 - 0.97) Adjusted difference -0.03 days (-1.11 - 1.06)	Unadjusted: 0.07 Adjusted: 0.04
Duration of intravenous antibiotic treatment	5.5 (3.6)	7.2 (6.1)	Unadjusted difference -1.80 days (-2.99 - -0.60) Adjusted difference -2.01 days (-3.16 - -0.85)	4.4 (4.5)	5 (3.7)	Unadjusted difference -0.63 days (-1.57 - 0.31) Adjusted difference -0.53 days (-1.46 - 0.40)	Unadjusted: 0.13 Adjusted: 0.07