Clinical trial results:
A multi-centre open-label two-arm randomised superiority clinical trial of Azithromycin versus usual care In Ambulatory COVID-19 (ATOMIC2)

Summary

EudraCT number	2020-001740-26
Trial protocol	GB
Global end of trial date	20 April 2021

Results information

Result version number	v1 (current)
This version publication date	17 June 2022
First version publication date	17 June 2022

Trial information

Trial identification

Sponsor protocol code	ATOMIC2

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04381962
WHO universal trial number (UTN)	-
Other trial identifiers	IRAS: 282892

Notes:

Sponsors

Sponsor organisation name	University of Oxford
Sponsor organisation address	Clinical Trials and Research Governance, Boundary Brook House, Oxford, United Kingdom, OX3 7GB
Public contact	OCTRU, University of Oxford, +44 1865223469, ariel.wang@ndorms.ox.ac.uk
Scientific contact	OCTRU, University of Oxford, +44 1865223469, ariel.wang@ndorms.ox.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	13 April 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2021
Global end of trial reached?	Yes
Global end of trial date	20 April 2021
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Can a course of antibiotics reduce the number of people with COVID-19 symptoms who go to hospital but who doctors decide do not need to be admitted from getting worse?
(There is where worse is considered being admitted to hospital or dying).

Another more scientific way of describing this is:
Does giving patients who have a clinical diagnosis of COVID-19 who go to hospital with their symptoms, but who doctors decide to not need to be admitted and and are sent home, does giving these patients 14 days of an antibiotic called Azithromycin result in reducing the number of patients who then either die or get admitted to hospital, from any cause, in the period of 28 days from randomisation.

Protection of trial subjects:

Azithromycin has a very well-known safety profile.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 June 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 298
Worldwide total number of subjects	298
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	266

From 65 to 84 years	29
85 years and over	3

Subject disposition

Recruitment

Recruitment details:

From 3rd June 2020 to 29th January 2021, 1192 patients were screened, of whom 649 were ineligible, 84 declined consent, 161 were excluded for other reasons and 298 were enrolled in the trial. Three participants withdrew consent and requested removal of all data collected so are not presented in baseline data. 295 participants data was presented.

Pre-assignment

Screening details:

Eligible participants were adults, ≥18 years of age assessed in an acute hospital with a clinical diagnosis of highly-probable or confirmed COVID-19 infection made by the attending clinical team, with onset of first symptoms within the last 14 days, and assessed by the attending clinical team as appropriate for initial ambulatory management.

Period 1

Period 1 title	Baseline
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

ATOMIC2 is an open label study without blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	Azithromycin

Arm description:

Azithromycin 2x250mg capsules to be taken orally once daily for 14 days. The first dose will be within 4 hours of randomisation. This is in addition to standard care as per local hospital advice for those patients with suspected COVID who are not admitted: i.e. symptomatic relief with rest, as-required paracetamol (where appropriate) and advice to seek further medical attention if significant worsening of breathlessness. Azithromycin Capsule: Azithromycin 500 mg OD PO 14 days

Arm type	Intervention
Investigational medicinal product name	Azithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Azithromycin 2*250 mg orally once daily for 14 days. The first dose will be within 4 hours of randomisation.

Arm title	Standard care

Arm description:

Standard care as per local hospital advice for those patients with suspected COVID who are not admitted: i.e. symptomatic relief with rest, as-required paracetamol (where appropriate) and advice to seek further medical attention if significant worsening of breathlessness.

Arm type	Usual Standard Care

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Azithromycin	Standard care
Started	148	150
Completed	147	148
Not completed	1	2
Consent withdrawn by subject	1	2

Period 2

Period 2 title	Overall trial - Primary outcome
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Not blinded

Blinding implementation details:

ATOMIC2 is an open-label study without blinding

Arms

Are arms mutually exclusive?	Yes
Arm title	Azithromycin

Arm description: -

Arm type	Intervention
Investigational medicinal product name	Azithromycin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Azithromycin 2*250 mg orally once daily for 14 days. The first dose will be within 4 hours of randomisation.

Arm title	Standard care

Arm description: -

Arm type	Usual Standard Care

No investigational medicinal product assigned in this arm

Number of subjects in period 2	Azithromycin	Standard care
Started	147	148
Completed	145	147
Not completed	2	1
Consent withdrawn by subject	2	1

Baseline characteristics

Reporting groups	
Reporting group title	Azithromycin

Reporting group description:

Azithromycin 2x250mg capsules to be taken orally once daily for 14 days. The first dose will be within 4 hours of randomisation. This is in addition to standard care as per local hospital advice for those patients with suspected COVID who are not admitted: i.e. symptomatic relief with rest, as-required paracetamol (where appropriate) and advice to seek further medical attention if significant worsening of breathlessness. Azithromycin Capsule: Azithromycin 500 mg OD PO 14 days

Reporting group title	Standard care

Reporting group description:

Standard care as per local hospital advice for those patients with suspected COVID who are not admitted: i.e. symptomatic relief with rest, as-required paracetamol (where appropriate) and advice to seek further medical attention if significant worsening of breathlessness.

Reporting group values	Azithromycin	Standard care	Total
Number of subjects	148	150	298
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	134	129	263
From 65-84 years	13	16	29
85 years and over	0	3	3
Not reported	1	2	3
Age continuous			
adults, ≥18 years of age			
Units: years			
arithmetic mean	45.5	46.3	
standard deviation	± 14.2	± 15.5	-
Gender categorical Units: Subjects			
Female	71	72	143
Male	76	76	152
Not reported	1	2	3
Ethnicity Units: Subjects			
White	103	98	201
Mixed	0	4	4
Asian/Asian British	23	24	47
Black/Black British	6	5	11
Other Ethnic Group	15	17	32
Not recorded	1	2	3

Hypertension Units: Subjects			
Yes	25	27	52
No	122	121	243
Not reported	1	2	3
Diabetes Units: Subjects			
Yes	11	14	25
No	136	134	270
Not reported	1	2	3
Smoking Units: Subjects			
Never smoked	81	76	157
Ex-smoker	25	26	51
Current smoker	16	17	33
Ex-smoker & current vaper	3	4	7
Never smoked & current vaper	0	1	1
Not recorded	23	26	49
Residence Units: Subjects			
Non- residential care	132	137	269
Residential care	7	3	10
No fixed address	5	4	9
Not reported	4	6	10
Living alone Units: Subjects			
Yes	17	13	30
No	108	110	218
Not recorded	23	27	50
Work status Units: Subjects			
Retired	15	23	38
Working	101	95	196
Houseperson	22	21	43
Not reported	10	11	21
Occupation Units: Subjects			
Not healthcare related	77	69	146
Healthcare worker	20	23	43
Laboratory worker	1	1	2
Not reported	50	57	107
Have asthma Units: Subjects			
Yes	26	27	53
No	121	121	242
Not reported	1	2	3
History of previous myocardial infarction Units: Subjects			
Yes	5	7	12
No	142	141	283
Not reported	1	2	3

Currently undergoing any cancer treatment Units: Subjects			
Yes	1	0	1
No	146	148	294
Not reported	1	2	3
Have chronic pulmonary disease Units: Subjects			
Yes	7	5	12
No	140	143	283
Not reported	1	2	3
The severity scale score Units: Subjects			
Ambulatory, no limitation of activities	61	66	127
Limitation of simple activities	85	81	166
Hospitalised, mild disease, no oxygen therapy	1	1	2
Not reported	1	2	3
Pneumonia			
Pneumonia is defined as 'consolidation on a chest X-ray', if a chest X-ray was not taken it is assumed there was no pneumonia.			
Units: Subjects			
Yes	28	34	62
No	119	114	233
Not reported	1	2	3
Swab results			
SWAB test results are only available for those who had a Covid-19 swab at randomisation			
Units: Subjects			
Positive	76	76	152
Negative	41	38	79
Failed Assay	0	3	3
Not available	31	33	64
COVID-19 COS Score of clinical symptoms			
COVID-19 COS Score of clinical symptoms is a total score of six common and important clinical symptoms, including fever, cough, fatigue, shortness of breath, diarrhoea, and body pain, each of which can be scored as 0 (no), 1 (mild), 2 (moderate), or 3 (significant). COS scores range from 0 to 18, with higher scores indicating patient has more significant Covid symptoms.			
Units: scores on a scale			
arithmetic mean	6.4	7.0	
standard deviation	± 3.6	± 3.9	-
COVID-19 COS PLUS Score of clinical symptoms			
An amended version COVID-19 COS PLUS with 2 extra clinical symptoms that also considered as having clinical importance: changes to sense of smell and loss of taste. COS Plus scores range from 0 to 24. Higher scores indicating patient has more significant Covid symptoms.			
Units: Scores on a scale			
arithmetic mean	7.7	8.9	
standard deviation	± 4.6	± 5.2	-
The Charlson Comorbidity Index			
The Charlson Comorbidity Index assigns a numerical value or “weight” from 1,2,3 or 6 to nineteen specific chronic illnesses. The final score (range 0-42) is simply the sum of weighted values with higher scores indicating more comorbidities.			
Units: scores on a scale			

arithmetic mean	1.1	1.2	
standard deviation	± 1.5	± 1.8	-
Duration of symptoms (days) Units: Days			
arithmetic mean	5.8	6.3	
standard deviation	± 3.5	± 3.5	-

End points

End points reporting groups

Reporting group title	Azithromycin

Reporting group description:

Azithromycin 2x250mg capsules to be taken orally once daily for 14 days. The first dose will be within 4 hours of randomisation. This is in addition to standard care as per local hospital advice for those patients with suspected COVID who are not admitted: i.e. symptomatic relief with rest, as-required paracetamol (where appropriate) and advice to seek further medical attention if significant worsening of breathlessness. Azithromycin Capsule: Azithromycin 500 mg OD PO 14 days

Reporting group title	Standard care

Reporting group description:

Standard care as per local hospital advice for those patients with suspected COVID who are not admitted: i.e. symptomatic relief with rest, as-required paracetamol (where appropriate) and advice to seek further medical attention if significant worsening of breathlessness.

Reporting group title	Azithromycin
Reporting group description: -	
Reporting group title	Standard care
Reporting group description: -	
Subject analysis set title	Primary analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Efficacy and safety analyses were based on the intention-to-treat (ITT) population, defined as all randomised patients analysed according to their randomised allocation

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

Subject analysis set description:

Efficacy and safety analyses were based on the intention-to-treat (ITT) population, defined as all randomised patients analysed according to their randomised allocation.

Subject analysis set title	Secondary analysis (ITT+ve)
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

A supplementary ITT population (ITT +ve) is defined as all randomised patients with a positive COVID PCR result.

Primary: Proportion of Participants With Hospital Admission or Death From Any Cause Within 28 Days From Randomisation

End point title	Proportion of Participants With Hospital Admission or Death From Any Cause Within 28 Days From Randomisation

End point description:

The primary outcome for this study is the proportion of patients progressing to death or hospitalisation from any cause, by day 28 post-randomisation. The primary objective is to compare the effect of Azithromycin in participants with a clinical diagnosis of COVID-19 in reducing the proportion with either death or hospital admission from any cause over the 28 days from randomisation.

End point type	Primary

End point timeframe:

28 Days From Randomisation

End point values	Azithromycin	Standard care	Primary analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	145	147	292	
Units: Participants				
All cause hospitalisation or death	15	17	32	
Not hospitalised or died	130	130	260	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Unadjusted logistic regression	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.74 [1]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.88
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.84

Notes:

[1] - Unadjusted

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Adjusted logistic regression	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8 [2]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	1.92

Notes:

[2] - Adjust for stratification factors: centre, hypertension, diabetes, and sex. Hypertension, diabetes and sex were adjusted for as fixed effects. Centre was included as a random effect.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description: Fully adjusted logistic regression	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.82 [3]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	1.97

Notes:

[3] - Fully adjusted: Adjust for stratification factors and other important prognostic variables: centre, hypertension, diabetes, sex, and age ≥65 years, presence of chronic lung disease, and treatment for cancer

Statistical analysis title	Statistical Analysis 4
Statistical analysis description: Unadjusted Log Rank test	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.79 [4]
Method	Logrank

Notes:

[4] - Unadjusted

Statistical analysis title	Statistical Analysis 5
Statistical analysis description: Adjusted Cox's proportional hazard	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.89 [5]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.95
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.46
upper limit	1.96

Notes:

[5] - Adjust for stratification factors: hypertension, diabetes and sex were adjusted for as fixed effects; centre was included as a random effect.

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Fully adjusted Cox's proportional hazard	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.99 [6]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.99
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2

Notes:

[6] - Adjust for stratification factors and other important prognostic variables: centre, hypertension, diabetes, sex, and age ≥65 years, presence of chronic lung disease, and treatment for cancer.

Secondary: Proportion With All-cause Hospital Admission or Death (SARS-CoV-2 PCR Positive)

End point title	Proportion With All-cause Hospital Admission or Death (SARS-CoV-2 PCR Positive)

End point description:

Efficacy was determined through differences in the proportion with all-cause hospital admission or death in the 28 days from randomisation using a retrospective analysis of COVID-19 oropharyngeal swabs for those who had one taken at time of randomisation.

End point type	Secondary

End point timeframe:

Determined at day 28 from randomisation

End point values	Azithromycin	Standard care	Secondary analysis (ITT+ve)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	75	75	150	
Units: Participants				
All cause hospital admission or death	11	11	22	
Not hospitalised or died	64	64	128	

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description:	
Unadjusted logistic regression	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1 [7]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.47

Notes:

[7] - Unadjusted

Statistical analysis title	Statistical Analysis 2
Statistical analysis description:	
Adjusted linear regression	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.97 [8]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.4
upper limit	2.57

Notes:

[8] - Adjust for stratification factors: centre, hypertension, diabetes, and sex. Hypertension, diabetes and sex were adjusted for as fixed effects. Centre was included as a random effect.

Statistical analysis title	Statistical Analysis 3
Statistical analysis description:	
Adjusted logistic regression	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.83 [9]
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.11

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.43
upper limit	2.9

Notes:

[9] - Fully adjusted: adjust for stratification factors and other important prognostic variables: centre, hypertension, diabetes, sex, and age ≥65 years, presence of chronic lung disease, and treatment for cancer.

Statistical analysis title	Statistical Analysis 4
Statistical analysis description:	
Unadjusted Log Rank test	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.78 [10]
Method	Logrank

Notes:

[10] - Unadjusted

Statistical analysis title	Statistical Analysis 5
Statistical analysis description:	
Adjusted Cox's proportional hazard	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.72 [11]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.17
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.49
upper limit	2.77

Notes:

[11] - Adjusted for stratification factors (centre, hypertension, diabetes and sex). Hypertension, diabetes and sex were adjusted for as fixed effects. Centre was included as a random effect

Statistical analysis title	Statistical Analysis 6
Statistical analysis description:	
Fully adjusted Cox's proportional hazard	
Comparison groups	Azithromycin v Standard care

Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.57 [12]
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	1.3
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.52
upper limit	3.21

Notes:

[12] - Fully adjusted: adjust for stratification factors and other important prognostic variables: centre, hypertension, diabetes, sex, and age ≥65 years, presence of chronic lung disease, and treatment for cancer.

Secondary: Proportion Progressing to Respiratory Failure or Death

End point title	Proportion Progressing to Respiratory Failure or Death

End point description:

Efficacy was determined through differences in the proportion with either death or admission with respiratory failure requiring level 2 ventilatory support (NIV/CPAP/nasal high-flow) or level 3 (invasive mechanical ventilation) in the 28 days from randomisation.

End point type	Secondary

End point timeframe:

Determined at day 28 from randomisation.

End point values	Azithromycin	Standard care	Secondary analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	145	147	292	
Units: Participants				
Participants on level 2/3 ventilation or died	2	2	4	
Not on level 2/3 ventilation or died	143	145	288	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Fisher Exact test

Comparison groups	Azithromycin v Standard care

Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority[13]
P-value	= 1
Method	Fisher exact

Notes:

[13] - Due to the very low number of events Fisher's exact test was used to compare the Azithromycin and control groups.

Secondary: Proportion Progressing to Respiratory Failure or Death (SARS-CoV-2 PCR Positive)

End point title	Proportion Progressing to Respiratory Failure or Death (SARS-CoV-2 PCR Positive)

End point description:

Efficacy was determined through differences in the proportion with either death or admission with respiratory failure requiring level 2 ventilatory support (NIV/CPAP/nasal high-flow) or level 3 (invasive mechanical ventilation) in the 28 days from randomisation using a retrospective analysis of COVID-19 oropharyngeal swabs for those who had one taken at time of randomisation.

End point type	Secondary

End point timeframe:

Determined at day 28 from randomisation

End point values	Azithromycin	Standard care	Secondary analysis (ITT+ve)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	75	75	150	
Units: Participants				
Participants on level 2/3 ventilation or died	2	2	4	
Not on level 2/3 ventilation or died	73	73	146	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Fisher Exact test

Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority[14]
P-value	= 1
Method	Fisher exact

Notes:

[14] - Due to the very low number of events Fisher's exact test was used to compare the Azithromycin and control groups.

Secondary: All Cause Mortality

End point title	All Cause Mortality

End point description:

All-cause mortality was assessed and reported based on data ascertained at 28 days after randomisation. Hospitalised patients were followed up until discharge or death where possible. Data on vital status (alive / dead, with date and presumed cause of death if appropriate) was collected at day 14 and at 28 days post-randomisation.

End point type	Secondary

End point timeframe:

Ascertain data at 28 days after randomisation

End point values	Azithromycin	Standard care	Secondary analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	145	147	292	
Units: Participants				
Died	1	1	2	
Alive	144	146	290	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Fisher Exact test

Comparison groups	Standard care v Azithromycin
Number of subjects included in analysis	292
Analysis specification	Pre-specified
Analysis type	superiority[15]
P-value	= 1
Method	Fisher exact

Notes:

[15] - Due to the very low number of events Fisher’s exact test was used to compare the Azithromycin and control groups

Secondary: All-cause Mortality (SARS-CoV-2 PCR Positive)

End point title	All-cause Mortality (SARS-CoV-2 PCR Positive)

End point description:

All-cause mortality was assessed and reported based on data ascertained at 28 days after randomisation. Hospitalised patients were followed up until discharge or death where possible. Data on vital status (alive / dead, with date and presumed cause of death if appropriate) was collected at day 14 and at 28 days post-randomisation.

End point type	Secondary

End point timeframe:

Ascertain data at 28 days after randomisation

End point values	Azithromycin	Standard care	Secondary analysis (ITT+ve)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	75	75	150	
Units: Participants				
Died	1	1	2	
Alive	74	74	148	

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Fisher Exact test

Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	150
Analysis specification	Pre-specified
Analysis type	superiority[16]
P-value	= 1
Method	Fisher exact

Notes:

[16] - Due to the very low number of events Fisher's exact test was used to compare the Azithromycin and control groups

Secondary: Proportion Progressing to Pneumonia

End point title	Proportion Progressing to Pneumonia

End point description:

Progression to pneumonia as diagnosed by chest x-ray (or CT thorax), with compatible clinical findings, if no pneumonia was presented at time of enrolment. Pneumonia was diagnosed by a medically qualified doctor and data obtained from review of case-notes and relevant radiology.

End point type	Secondary

End point timeframe:

Ascertain this information at time of pneumonia diagnosis, or at 28 days after randomisation (whichever is sooner)

End point values	Azithromycin	Standard care	Secondary analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	119[17]	114[18]	233[19]	
Units: Participants				
Progression to pneumonia	0	2	2	
No pneumonia	119	112	231	

Notes:

[17] - This is the number of participants that did not have pneumonia presented at baseline

[18] - This is the number of participants that did not have pneumonia presented at baseline

[19] - This is the number of participants that did not have pneumonia presented at baseline

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Fisher Exact test

Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	233
Analysis specification	Pre-specified
Analysis type	superiority[20]
P-value	= 0.24
Method	Fisher exact

Notes:

[20] - Due to the very low number of events Fisher's exact test was used to compare the Azithromycin and control groups

Secondary: Proportion Progressing to Pneumonia (SARS-CoV-2 PCR Positive)

End point title	Proportion Progressing to Pneumonia (SARS-CoV-2 PCR Positive)

End point description:

Progression to pneumonia as diagnosed by chest x-ray (or CT thorax), with compatible clinical findings, if no pneumonia was presented at time of enrolment. Pneumonia was diagnosed by a medically qualified doctor and data obtained from review of case-notes and relevant radiology.

End point type	Secondary

End point timeframe:

Ascertain this information at time of pneumonia diagnosis, or at 28 days after randomisation (whichever is sooner)

End point values	Azithromycin	Standard care	Secondary analysis (ITT+ve)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	58[21]	52[22]	110[23]	
Units: Participants				
Progression to pneumonia	0	2	2	
No pneumonia	58	50	108	

Notes:

[21] - This is the number of participants that did not have pneumonia presented at baseline

[22] - This is the number of participants that did not have pneumonia presented at baseline

[23] - This is the number of participants that did not have pneumonia presented at baseline

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Fisher Exact test

Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	110
Analysis specification	Pre-specified
Analysis type	superiority[24]
P-value	= 0.22
Method	Fisher exact

Notes:

[24] - Due to the very low number of events Fisher's exact test was used to compare the Azithromycin and control groups

Secondary: Proportion Progressing to Severe Pneumonia

End point title	Proportion Progressing to Severe Pneumonia

End point description:

Evolution of pneumonia, as diagnosed by chest x-ray or CT thorax, if pneumonia was presented at time of enrolment. Pneumonia was diagnosed by a medically qualified doctor and data obtained from review of case-notes and relevant radiology. Severe pneumonia is defined as BTS CURB-65 score of 3-5.

Note: No statistical analysis was undertaken as there were no instances of participants progressing to severe pneumonia.

End point type	Secondary

End point timeframe:

Ascertain this information at time of pneumonia diagnosis, or at 28 days after randomisation (whichever is sooner)

End point values	Azithromycin	Standard care	Secondary analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	28[25]	34[26]	62[27]	
Units: Participants				
Progression to severe pneumonia	0	0	0	
Not progressed to severe pneumonia	28	34	62	

Notes:

[25] - This is the number of participants who had pneumonia presented at time of enrolment.

[26] - This is the number of participants who had pneumonia presented at time of enrolment.

[27] - This is the number of participants who had pneumonia presented at time of enrolment.

Statistical analyses

No statistical analyses for this end point

Secondary: Differences in the Peak Severity of Illness

End point title	Differences in the Peak Severity of Illness

End point description:

The 9-point ordinal scoring system is described in the protocol reflects the severity of respiratory illness. The maximum severity scores during the entire study period were compared.
The severity scale scores range from 0 to 8 with higher scores indicating the most severe status, death.

End point type	Secondary

End point timeframe:

Ascertain from day 14 and day 28 telephone call and from retrospective ePR/medical notes data at 28 days after randomisation.

End point values	Azithromycin	Standard care	Secondary analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	124[28]	131[29]	255[30]	
Units: Participants				
Ambulatory, no limitation of activities	62	60	122	
Limitation of simple activities	49	57	106	
Hospitalised, mild disease, no oxygen therapy	3	2	5	
Hospitalised, oxygen ≤40% mask	5	10	15	
Hospitalised, oxygen >40% mask	3	0	3	
Hospitalised receiving NIV or high-flow oxygen	1	1	2	
Death	1	1	2	

Notes:

[28] - This is the number of participants completed the severity scale scores.

[29] - This is the number of participants completed the severity scale scores.

[30] - This is the number of participants completed the severity scale scores.

Statistical analyses

Statistical analysis title	Statistical Analysis 1

Statistical analysis description:

Unadjusted ordinal logistic regression

Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[31]
P-value	= 0.57 [32]
Method	ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.87
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.54
upper limit	1.4

Notes:

[31] - The difference between the treatment arms in terms of peak severity score was assessed using ordinal logistic regression.

[32] - Unadjusted

Statistical analysis title	Statistical Analysis 2

Statistical analysis description:

Adjusted ordinal logistic regression

Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	255
Analysis specification	Pre-specified
Analysis type	superiority[33]
P-value	= 0.69 [34]
Method	ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	0.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.57
upper limit	1.46

Notes:

[33] - The difference between the treatment arms in terms of peak severity score was assessed using ordinal logistic regression.

[34] - Adjust for stratification factors: centre, hypertension, diabetes, and sex. Hypertension, diabetes and sex were adjusted for as fixed effects. Centre was included as a random effect.

Secondary: Differences in Peak Severity of Illness (SARS-CoV-2 PCR Positive)

End point title	Differences in Peak Severity of Illness (SARS-CoV-2 PCR Positive)

End point description:

The 9-point ordinal scoring system is described in the protocol reflects the severity of respiratory illness.
The maximum severity scores during the entire study period were compared.
The severity scale scores range from 0 to 8 with higher scores indicating the most severe status, death.

End point type	Secondary

End point timeframe:

Ascertain from day 14 and day 28 telephone call and from retrospective ePR/medical notes data at 28 days after randomisation.

End point values	Azithromycin	Standard care	Secondary analysis (ITT+ve)	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	65[35]	70[36]	135[37]	
Units: Participants				
Ambulatory, no limitation of activities	26	32	58	
Limitation of simple activities	29	28	57	
Hospitalised, mild disease, no oxygen therapy	2	1	3	
Hospitalised, oxygen ≤40% mask	3	7	10	
Hospitalised, oxygen >40% mask	3	0	3	
Hospitalised receiving NIV or high-flow oxygen	1	1	2	
Death	1	1	2	

Notes:

[35] - This is the number of participants who completed the severity scale scores.

[36] - This is the number of participants who completed the severity scale scores.

[37] - This is the number of participants who completed the severity scale scores.

Statistical analyses

Statistical analysis title	Statistical Analysis 1
Statistical analysis description: Unadjusted ordinal logistic regression	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority[38]
P-value	= 0.53 [39]
Method	ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.23
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.65
upper limit	2.32

Notes:

[38] - The difference between the treatment arms was assessed using ordinal logistic regression.

[39] - Unadjusted

Statistical analysis title	Statistical Analysis 2
Statistical analysis description: Adjusted ordinal logistic regression	
Comparison groups	Azithromycin v Standard care
Number of subjects included in analysis	135
Analysis specification	Pre-specified
Analysis type	superiority[40]
P-value	= 0.29 [41]
Method	ordinal logistic regression
Parameter estimate	Odds ratio (OR)
Point estimate	1.43
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.73
upper limit	2.78

Notes:

[40] - The difference between the treatment arms was assessed using ordinal logistic regression.

[41] - Adjust for stratification factors: centre, hypertension, diabetes, and sex. Hypertension, diabetes, and sex were adjusted for as fixed effects. Centre was included as a random effect.

Secondary: Safety and Tolerability

End point title	Safety and Tolerability

End point description:

Serious adverse events and concomitant medications. Recorded at enrolment, emergently during study period and proactively elicit at day 14 and at day 28.

Note: No statistical analysis was undertaken as there were no instances of SAE

End point type	Secondary

End point timeframe:

Emergent data collection days 0-28 and elicit proactively at day 14 and day 28 post randomisation.

End point values	Azithromycin	Standard care	Secondary analysis	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	145	147	292	
Units: Participants				
SAE	0	0	0	
No SAE	145	147	292	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

From randomisation until 14 days of IMP administration

Adverse event reporting additional description:

All SAEs (other than those defined as foreseeable below) occurring within the first 14 days of the IMP administration were recorded. Deaths due to COVID-19 disease during the study were exempt from reporting as SAEs since they were captured as part of the primary outcome.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.0

Reporting groups

Reporting group title	Azithromycin

Reporting group description:

Azithromycin 2x250mg capsules to be taken orally once daily for 14 days. The first dose will be within 4 hours of randomisation. This is in addition to standard care as per local hospital advice for those patients with suspected COVID who are not admitted: i.e. symptomatic relief with rest, as-required paracetamol (where appropriate) and advice to seek further medical attention if significant worsening of breathlessness.

Reporting group title	Usual Standard Care

Reporting group description:

Standard care as per local hospital advice for those patients with suspected COVID who are not admitted: i.e. symptomatic relief with rest, as-required paracetamol (where appropriate) and advice to seek further medical attention if significant worsening of breathlessness.

Serious adverse events	Azithromycin	Usual Standard Care	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 145 (0.00%)	0 / 147 (0.00%)	
number of deaths (all causes)	1	1	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Azithromycin	Usual Standard Care	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 145 (0.00%)	0 / 147 (0.00%)	

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: Only non-serious adverse events were collected.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
14 May 2020	Increased information in Clinical Trial Label due to some pharmacies wanting to re-pack in one box.
16 June 2020	Addition of sites: ELHT, Royal Derby, Royal London, Royal Berkshire and change of PI at OUH.
22 July 2020	Protocol – change to inclusion criteria (symptoms <14 days, confirmed COVID & include participants on SSRIs) and clarification of safety reporting. Addition of compulsory ECG.
29 July 2020	Addition of new sites: South Tees and King's College
21 August 2020	Addition of new sites: North Tees, Darlington, St Georges and UCLH
03 March 2021	Change to primary endpoint and sample size recalculation. Halt to recruitment.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

This trial was open-label, and is at risk of bias particularly on patient reported outcomes.
We used a clinical diagnosis for inclusion, rather than requiring PCR confirmation.
No data on microbiology and no long term outcomes beyond 28 days.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34252378