



## 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 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,  $\geq 18$  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          |
| <b>Arm title</b>             | 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.

|                  |               |
|------------------|---------------|
| <b>Arm title</b> | 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          |
| <b>Arm title</b>             | 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.

|   |                     |
|---|---------------------|
| <b>Arm title</b>  | 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<br>Units: Subjects                              |     |     |     |
| Yes  | 25  | 27  | 52  |
| No   | 122 | 121 | 243 |
| Not reported   | 1   | 2   | 3   |
| Diabetes<br>Units: Subjects                                  |     |     |     |
| Yes  | 11  | 14  | 25  |
| No   | 136 | 134 | 270 |
| Not reported   | 1   | 2   | 3   |
| Smoking<br>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<br>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<br>Units: Subjects                              |     |     |     |
| Yes  | 17  | 13  | 30  |
| No   | 108 | 110 | 218 |
| Not recorded   | 23  | 27  | 50  |
| Work status<br>Units: Subjects                               |     |     |     |
| Retired  | 15  | 23  | 38  |
| Working  | 101 | 95  | 196 |
| Houseperson  | 22  | 21  | 43  |
| Not reported   | 10  | 11  | 21  |
| Occupation<br>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<br>Units: Subjects                               |     |     |     |
| Yes  | 26  | 27  | 53  |
| No   | 121 | 121 | 242 |
| Not reported   | 1   | 2   | 3   |
| History of previous myocardial infarction<br>Units: Subjects |     |     |     |
| Yes  | 5   | 7   | 12  |
| No   | 142 | 141 | 283 |
| Not reported   | 1   | 2   | 3   |

|  |       |       |     |
|--|-------|-------|-----|
| Currently undergoing any cancer treatment<br>Units: Subjects   |       |       |     |
| Yes  | 1     | 0     | 1   |
| No   | 146   | 148   | 294 |
| Not reported   | 1     | 2     | 3   |
| Have chronic pulmonary disease<br>Units: Subjects  |       |       |     |
| Yes  | 7     | 5     | 12  |
| No   | 140   | 143   | 283 |
| Not reported   | 1     | 2     | 3   |
| The severity scale score<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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:<br>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 <sup>[1]</sup>        |
| 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:<br>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 <sup>[2]</sup>         |
| 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.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>                                       | Statistical Analysis 3       |
| Statistical analysis description:<br>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 <sup>[3]</sup>        |
| 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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>                             | Statistical Analysis 4       |
| Statistical analysis description:<br>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 <sup>[4]</sup>        |
| Method  | Logrank                      |

Notes:

[4] - Unadjusted

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>                                       | Statistical Analysis 5       |
| Statistical analysis description:<br>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 <sup>[5]</sup>        |
| 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.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>   | Statistical Analysis 6       |
| Statistical analysis description:<br>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  $\geq 65$  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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[7]</sup>           |
| 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                        |                              |

|  |                              |
|--|------------------------------|
| <b>Statistical analysis title</b>  | 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 <sup>[8]</sup>        |
| 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. |                              |

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[9]</sup>        |
| 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  $\geq 65$  years, presence of chronic lung disease, and treatment for cancer.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[10]</sup>       |
| Method                                  | Logrank                      |

Notes:

[10] - Unadjusted

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[11]</sup>       |
| 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

|  |                              |
|--|------------------------------|
| <b>Statistical analysis title</b>        | 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 <sup>[12]</sup> |
| 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 <sup>[13]</sup> |
| 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 <sup>[14]</sup>  |
| 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 <sup>[15]</sup> |
|---------------|-----------------------------|

|         |     |
|---------|-----|
| 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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[16]</sup>  |
| 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 <sup>[17]</sup> | 114 <sup>[18]</sup> | 233 <sup>[19]</sup>  |  |
| 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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[20]</sup>  |
| 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 <sup>[21]</sup> | 52 <sup>[22]</sup> | 110 <sup>[23]</sup>         |  |
| 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

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | 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 <sup>[24]</sup>  |
| 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 <sup>[25]</sup> | 34 <sup>[26]</sup> | 62 <sup>[27]</sup>   |  |
| 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 <sup>[28]</sup> | 131 <sup>[29]</sup> | 255 <sup>[30]</sup>  |  |
| 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 <sup>[31]</sup>  |
| P-value                                 | = 0.57 <sup>[32]</sup>       |
| 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 <sup>[33]</sup>  |
| P-value                                 | = 0.69 <sup>[34]</sup>       |
| 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 <sup>[35]</sup> | 70 <sup>[36]</sup> | 135 <sup>[37]</sup>         |  |
| 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:<br>Unadjusted ordinal logistic regression |                              |
| Comparison groups   | Azithromycin v Standard care |
| Number of subjects included in analysis                                     | 135                          |
| Analysis specification  | Pre-specified                |
| Analysis type   | superiority <sup>[38]</sup>  |
| P-value   | = 0.53 <sup>[39]</sup>       |
| 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:<br>Adjusted ordinal logistic regression |                              |
| Comparison groups   | Azithromycin v Standard care |
| Number of subjects included in analysis                                   | 135                          |
| Analysis specification  | Pre-specified                |
| Analysis type   | superiority <sup>[40]</sup>  |
| P-value   | = 0.29 <sup>[41]</sup>       |
| 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<sup>[1]</sup>

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:

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### 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:

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### Online references

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