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# **Online Supplement** The Azithromycin for Acute Exacerbations of Asthma (AZALEA) Randomized Clinical Trial

Sebastian L. Johnston<sup>1\*</sup> MBBS, PhD, Matyas Szigeti<sup>2</sup> MSc, Mary Cross<sup>2</sup> BA (Hons), Christopher Brightling<sup>3</sup> MBBS, PhD, Rekha Chaudhuri<sup>4, 5</sup> MBBS, MD, Timothy Harrison<sup>6</sup> MBBS, PhD, Adel Mansur<sup>7, 8</sup> MBBS, PhD, Laura Robison<sup>2</sup> BSc, Zahid Sattar<sup>2</sup> BSc, PhD, David Jackson<sup>1</sup> MBBS, PhD, Patrick Mallia<sup>1</sup> MBBS, PhD, Ernie Wong<sup>1</sup> MBBS, BSc, Christopher Corrigan<sup>9, 10</sup> MA, PhD, Bernard Higgins<sup>11</sup> MBBS, Philip Ind<sup>1, 12</sup> MB BChir, PhD, Dave Singh<sup>13</sup> MB BChir, MD, Neil C. Thomson<sup>4</sup> MBChB, MD, Deborah Ashby<sup>2</sup> PhD, CStat, Anoop Chauhan<sup>14</sup> MBBS, PhD on behalf of the AZALEA Trial Team.

- 1 National Heart and Lung Institute, Imperial College London, London, UK 2
  - Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, UK
- 3 Institute for Lung Health, University of Leicester, Leicester, UK
- 4 Institute of Infection Immunity and Inflammation, University of Glasgow, Glasgow, UK
- 5 Respiratory Medicine, NHS Greater Glasgow and Clyde, Glasgow, UK
- 6 Nottingham Respiratory Research Unit, University of Nottingham, Nottingham, UK
- 7 Respiratory Medicine, Heart of England Foundation Trust, Birmingham, UK
- 8 Severe and Brittle Asthma Unit, University of Birmingham, Birmingham, UK
- 9 Respiratory Medicine & Allergy, King's College London School of Medicine, London, UK
- 10 Department of Asthma, Allergy and Respiratory Science, Guy's & St. Thomas' NHS Foundation Trust, London, UK
- Respiratory Medicine, Newcastle University, Newcastle, UK 11
- Respiratory Medicine, Imperial College Healthcare NHS Trust, London, UK 12
- 13 Centre for Respiratory Medicine and Allergy, Medicines Evaluation Unit, University of Manchester and University Hospital of South Manchester NHS Foundation Trust, Manchester, UK
- 14 Respiratory Medicine, Portsmouth Hospitals NHS Trust, Portsmouth, UK

\*Corresponding author: Professor Sebastian Johnston, Airway Disease Infection Section,

National Heart and Lung Institute, Imperial College London, Norfolk Place, London W2 1PG; e mail:

s.johnston@imperial.ac.uk, telephone: +44 20 7594 3764, fax: +44 20 7262 8913.

Authors' contributions: Sebastian Johnston conception and design of study, analysis and interpretation of data, drafting/revising report, approval of report, guarantor for the study

Matyas Szigeti, Laura Robison, Zahid Sattar, David Jackson, Patrick Mallia, Ernie Wong, Deborah Ashby: analysis and interpretation of data, drafting/revising report, approval of report

Mary Cross: design of study, analysis and interpretation of data, drafting/revising report, approval of report Christopher Brightling, Rekha Chaudhuri, Timothy Harrison, Adel Mansur, Christopher Corrigan, Bernard Higgins, Philip Ind, Dave Singh, Neil Thomson, Anoop Chauhan: conception and design of study, analysis and interpretation of data, drafting/revising report, approval of report

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# **Supplementary methods**

## Study design

Visit 1 (day 1) occurred within 48 hours of initial presentation to medical care. Patients were then seen for Visits 2 (day  $5\pm1$  day, or exceptionally 2 days), 3 (day  $10\pm1$  day, or exceptionally 2 days) and 4 (day  $42\pm2$  weeks). At Visit 1 patients were instructed on symptom diary card recording and asked to complete the diary at the end of each day for 10 days. Symptom diary cards were reviewed at Visit 2 and 3. Convalescent serum was taken at Visit 4 for atypical bacterial serology.

We excluded subjects taking the following list of medications causing prolongation of the QT interval:

- 1. Amphetamines
- 2. Anti-emetics: Ondansetron, Dolasetron, Granisetron
- 3. Opioids: Methadone, Buprenorphine, Oxycodone
- 4. Antipsychotics: Droperidol, Thioridazine, Pimozide, Haloperidol, Chlorperazine
- 5. Antidepressants: Tricyclic Antidepressants, Trazodone
- 6. Antiarrhythmics: Quinidine, Disopyramide, Procainamide, Amiodarone, Sotalol
- 7. Antimalarials: Halofantrine
- 8. Cisapride
- 9. Cocaine

As there is no list that is regarded as definitive, this list was derived after consulting various different web-based sources and was agreed in consultation with all AZALEA PIs.

#### **Bacteriology/Virology**

We used in house PCR assays of nasal mucus samples, nasal and throat swabs and spontaneous or induced sputum to detect picornaviruses (mostly rhinoviruses); respiratory syncytial virus; coronaviruses 229E and OC43; parainfluenza viruses 1-3; influenza viruses AH1, AH3, and B; human metapneumoviruses; adenoviruses, bocavirus and the two atypical bacteria *Mycoplasma* (*M.*) *pneumoniae* and *Chlamydophila* (*C.*) *pneumoniae*, as described<sup>1</sup>. In addition we also used commercial MutaPLATE® real time (TaqMan) PCR kits for detection of *C. pneumoniae* and *M. pneumoniae* (Immundiagnostik, Bensheim, Germany) according to the manufacturer's instructions.

Serology for IgM for *M. pneumoniae* and *C. pneumoniae*, was performed on acute serum samples taken at exacerbation and for IgA and IgG for *M. pneumoniae* and *C. pneumoniae*, on acute serum samples taken at exacerbation and convalescent samples taken at Visit 4 using MEDAC *M. pneumoniae* and *C. pneumoniae* IgM, IgA and IgG ELISAs (Medac, Hamburg, Germany) according to the manufacturer's instructions.

All the above assays were performed centrally at Prof Johnston's laboratory at Imperial College London. Standard sputum quantitative bacterial cultures were performed locally at each site using local Microbiology Laboratory standard operating procedures.

#### Statistical analyses

#### Sample Size

The sample size calculations were based on the primary outcome: the telithromycin study<sup>2</sup> found a mean difference in symptom score of -0.3 (standard deviation [SD] 0.783) between active and placebo groups at 10 days. Using a two-sided t-test at 1% significance level, with 80% power, 161 patients in each group were needed to detect the same difference in asthma scores between the groups. The significance level of 1% in the above calculation was chosen to provide greater certainty in assessment of the primary outcome variable and to provide greater power for the subgroup analyses. Assuming a drop-out rate of  $15\%^2$ , we proposed to recruit 190 patients to each arm.

Randomization was via a secure server performed using the InForm ITM (Integrated Trial Management) System. Patient allocation was stratified by center in random length blocks. The randomization lists were generated by an Imperial Clinical Trials Unit (ICTU) statistician. Details such as block size were kept confidential. There was no requirement for unblinding during the AZALEA trial therefore no patients were unblinded before statistical analysis.

#### Multilevel modeling: the three main components of the model

Let  $DS_{id}$  represent the diary score for patient *i* on day d, d = 1, ..., 10, and *t*(*i*) represent the treatment given to individual *i* (azithromycin or placebo). Then model  $DS_{id}$  as the sum of three components: an intercept term, a change over time term and a residual error term, i.e.

 $DS_{id} = intercept_i + change over time_{t(i)d} + residual error_{id}$ 

Possible choices for each of these components are outlined below. The options explored for the primary analysis were determined by the results of the exploratory analysis, and the final choice will be the simplest model that satisfies standard checks of model fit (e.g. residual plots).

#### Intercept term

The intercept term will estimate the diary score on day 1 (the day of randomization and start of the study medication). This term will comprise an individual level random effect, which will be drawn from a distribution parameterized using the associated center level random effect. Hence the unexplained variation in the diary scores will be split into three components corresponding to the three levels of the model, i.e. the variation attributable to the center (between center variation) and the individual (between individual variation), as well as the residual variation (within individual variation).

Additionally, baseline covariates can be incorporated into the model at the individual level. None will be incorporated for the initial analysis unless the baseline characteristics analysis reveals a substantial imbalance. Further analyses will examine the effect of incorporating baseline variables (age, gender, asthma severity, smoking history and asthma exacerbation).

#### Change over time (cot) term

This term will capture the change in the diary score from the start of the study medication (day 1), hence time will enter the model as day 1. The simplest assumption would be a linear change over the period, however alternatives may need to be considered as the rate of change may not be constant over the 10 day period. Alternatives are to include a quadratic term or use splines. The coefficients in this term will be dependent upon treatment.

#### **Residual error term**

We were assuming that the residual errors have a Normal distribution. An alternative was to assume that these errors follow a heavier tailed distribution such as a t distribution with 4 degree of freedom, which will provide robustness to outliers. Normality of residual error was checked graphically.

#### Missing data

Before starting data analysis, the level and pattern of the missing data in the baseline variables and outcomes was analyzed by forming appropriate tables. Additionally, the likely causes of any omissions were investigated. This information was used to determine whether the level and type of missing data had the potential to introduce bias into the analysis or to substantially reduce the precision of estimates related to treatment effects. Missing data in the patient diary took one of several forms: no patient diary returned for any day (patient omissions), all data missing for one or more days (day omissions) and data missing for some but not all the individual questions for a particular day (item omissions). Of these, the level of item omissions was expected to be minimal. According to the SAP if any item omissions occurred in diary scores, the scores for the missing questions were interpolated from the previous and subsequent day scores. This process was conducted for 2 missing entries.

If any item omissions occurred in AQLQ scores the summary score for that day was treated as missing. Missing data for the pulmonary function tests were expected to be due to the spirometer not recording some measures. As this was unrelated to the patient outcome, it was reasonable to assume that these omissions were uninformative and that multi-level models fitted to all observed data would provide unbiased parameter estimates.

# **Supplementary results**

Of the 199 patients randomized, 193 (97%) were from secondary care hospitals and 6 (3%) from the primary care center.

#### Exploratory analysis of the primary outcome

As a check for outliers and imbalances, a series of longitudinal plots (one for each center) of diary score for each patient, differentiating between treatment arm were produced (see **Supplementary eFigure 1**). Boxplots of diary scores by treatment arm for each day were produced to show the distribution of the observed scores graphically in **Supplementary eFigure 2**. **Supplementary eTable 1** shows the observed mean diary scores and standard deviations for each treatment arm by day and the number of observations. Additionally, a table of summary statistics of the diary scores by day and treatment arm was produced, including the number of observations, mean, standard deviation, median, lower and upper quartiles (**Supplementary eTable 2**).

# Supplementary eFigure 1: Observed diary scores for each center by treatment arm



- Royal Berkshire Hospital
- A21 A22 Rowden Surgery
- A23 East Surrey Hospital
- A24
- Countess of Chester Musgrove Park Hospital A25
- A26 Worcester Acute Hospital
- A29 New Cross Hospital, Royal Wolverhampton
- A30 Ipswich Hospital, NHS Trust
- A32 . Telford
- A35 Gloucestershire Royal Hospital
- Heart of England NHS Foundation Trust Blackpool Victoria Hospital BIR
- BVH
- GLA Western Infirmary Glasgow
- LEI University Hospitals of Leicester NHS Trust
- NEW The Newcastle upon Tyne Hospitals NHS Foundation Trust
- NNU Norfolk and Norwich University Hospital
- NOC Nottingham City Hospital
- Queen's Medical Centre, Nottingham Portsmouth Hospitals NHS Trust NOT
- POR
- SMH St Mary's Hospital, Imperial College Healthcare NHS Trust
- St James's University Hospital
- STJ UNT University Hospital of North Tees



Supplementary eFigure 2: Boxplots of observed symptom diary scores

Supplementary eTable 1: Observed mean symptom scores for each day by treatment group and their standard deviation

|         | day    |
|---------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
|         | 1      | 2      | 3      | 4      | 5      | 6      | 7      | 8      | 9      | 10     |
| Placebo | 4.18   | 3.45   | 3.12   | 3.04   | 2.87   | 2.79   | 2.80   | 2.43   | 2.32   | 2.20   |
| (SD)    | (1.48) | (1.62) | (1.47) | (1.57) | (1.58) | (1.56) | (1.69) | (1.53) | (1.55) | (1.51) |
| N       | 77     | 86     | 85     | 81     | 81     | 80     | 79     | 77     | 74     | 68     |
| Active  | 4.14   | 3.51   | 3.09   | 2.78   | 2.63   | 2.44   | 2.19   | 2.24   | 2.22   | 2.09   |
| (SD)    | (1.38) | (1.42) | (1.45) | (1.58) | (1.51) | (1.54) | (1.53) | (1.61) | (1.71) | (1.71) |
| N       | 71     | 85     | 86     | 84     | 80     | 78     | 81     | 80     | 78     | 71     |

| Placebo | )  |                              |                                    | Active |    |                              |                              |
|---------|----|------------------------------|------------------------------------|--------|----|------------------------------|------------------------------|
|         | Ν  | Diary<br>score,<br>mean (SD) | Diary<br>score,<br>median<br>(IQR) |        | Ν  | Diary<br>score,<br>mean (SD) | Diary score,<br>median (IQR) |
| day 1   | 77 | 4.18 (1.48)                  | 4.25<br>(3.00, 5.50)               | day 1  | 71 | 4.14 (1.38)                  | 4.25<br>(3.25, 5.00)         |
| day 2   | 86 | 3.45 (1.62)                  | 3.50<br>(2.25, 5.00)               | day 2  | 85 | 3.51 (1.42)                  | 3.75<br>(2.50, 4.75)         |
| day 3   | 85 | 3.12 (1.47)                  | 3.00<br>(2.00, 4.25)               | day 3  | 86 | 3.09 (1.45)                  | 3.00<br>(2.00, 4.25)         |
| day 4   | 81 | 3.04 (1.57)                  | 3.25<br>(1.75, 4.25)               | day 4  | 84 | 2.78 (1.58)                  | 2.50<br>(1.50, 4.00)         |
| day 5   | 81 | 2.87 (1.58)                  | 3.00<br>(1.50, 4.25)               | day 5  | 80 | 2.63 (1.51)                  | 2.50<br>(1.38, 3.75)         |
| day 6   | 80 | 2.79 (1.56)                  | 2.63<br>(1.50, 4.00)               | day 6  | 78 | 2.44 (1.54)                  | 2.25<br>(1.25, 3.75)         |
| day 7   | 79 | 2.80 (1.69)                  | 3.00<br>(1.25, 4.00)               | day 7  | 81 | 2.19 (1.53)                  | 2.25<br>(1.00, 3.25)         |
| day 8   | 77 | 2.43 (1.53)                  | 2.50<br>(1.00, 3.50)               | day 8  | 80 | 2.24 (1.61)                  | 2.00<br>(1.00, 3.50)         |
| day 9   | 74 | 2.32 (1.55)                  | 2.38<br>(1.00, 3.25)               | day 9  | 78 | 2.22 (1.71)                  | 2.00<br>(0.75, 3.25)         |
| day 10  | 68 | 2.20 (1.51)                  | 2.25<br>(0.88, 3.25)               | day 10 | 71 | 2.09 (1.71)                  | 1.75<br>(0.50, 3.50)         |

# Supplementary eTable 2: Detailed statistics of observed diary scores

A linear change was assumed in the model for the diary score over time with different slopes for the two treatment arms. Additionally, equal mean scores were assumed at baseline for the two groups as any inequality could only have occurred by chance, due to randomization. In order to reduce bias caused by the observed difference at baseline, the main effect of the interaction term was not included in the model as an independent covariate. Sensitivity analysis with the inclusion of this covariate was conducted. The estimated mean diary score at baseline (day 1) in the whole study population was 3.66 (95% CI: 3.41; 3.90). In addition to the decrease observed in the placebo group, the decrease of the diary score in the azithromycin group was slightly greater. On average the difference in change compared to the placebo group was -0.018 per day (95% CI: -0.074, 0.037). The estimated differences with their 95% confidence intervals for each day can be found in **Supplementary eTable 3**. The mean "natural" background daily decrease (decrease in placebo group) in diary score was -0.18 (95% CI for the first day alone: -0.22; 0.14). On day 10, the difference between the two groups was not statistically significant. The estimated mean diary score was lower in the azithromycin group by -0.166 (95% CI: -0.670; 0.337). On Day 5 the difference was -0.074 (95% CI: -0.298; 0.150) between the two groups.

|   | Day | Day        | Day        | Day        | Day        | Day        | Day        | Day        | Day        | Day        |
|---|-----|------------|------------|------------|------------|------------|------------|------------|------------|------------|
|   | 1   | 2          | 3          | 4          | 5          | 6          | 7          | 8          | 9          | 10         |
| Difference<br>in Change<br>from<br>baseline | 0   | -<br>0.018 | -<br>0.037 | -<br>0.055 | -<br>0.074 | -<br>0.092 | -<br>0.111 | -<br>0.129 | -<br>0.148 | -<br>0.166 |
| 95%   | -   | -          | -          | -          | -          | -          | -          | -          | -          | -          |
| Confidence                                  |     | 0.074      | 0.149      | 0.223      | 0.298      | 0.372      | 0.446      | 0.521      | 0.595      | 0.670      |
| Interval                                    |     | 0.037      | 0.075      | 0.112      | 0.150      | 0.187      | 0.224      | 0.262      | 0.299      | 0.337      |

# Supplementary eTable 3: Estimated difference in change of diary scores from baseline and 95% confidence intervals for azithromycin compared to the placebo

### **Model selection**

Different relationships between time and diary scores were compared including linear, quadratic and square root relationships. These models differed in their "time" covariate. Fixed and random effects and the use of splines were also investigated. The plots of level 1 and level 2 residuals (where appropriate) were assessed for these models, including the model with splines at day 3 and day 7 and the fitted and observed values were also investigated graphically. As it can be seen (**Supplementary eFigure 3**), the more complex alternative models gave more flexibility than the standard linear model, but overall the residuals were just barely lower and the pattern of residuals remain the same, so in order of simplicity a linear model was chosen to calculate the estimated scores.



# Supplementary eFigure 3: Boxplot of residuals for linear and quadratic models

# Details of the models for diary and AQLQ Scores

# Supplementary eTable 4: Diary score

| Fixed-effects Para                           | ameters   |                                      |                  |        |                  |             |            |
|--|---|--------------------------------------|------------------|--------|------------------|-------------|------------|
| Covariates                                   |   | Coe                                  | fficient         | 95% CI |                  |             | P value    |
| Constant                                     | Mean score at baseline in the Placebo group                                       | 3.65                                 | 595 3.4169       |        | 9 3.9022         |             | 0.000      |
| Days (centered)                              | Daily change in Placebo group   | Daily change in Placebo group -0.179 |                  |        | 7 -0.136         | 67          | 0.000      |
| Treatment #Day<br>(interaction)              | (Treatment effect)<br>Difference in daily change<br>compared to the Placebo group | -0.0                                 | 185 -0.074       |        | 4 0.037          | '4          | 0.517      |
| Random-effects P                             | arameters   |                                      |                  |        |                  |             |            |
| Level  | variance  |                                      | Estimate         |        | 95% CI*          |             |            |
| Site   | Constant (intercept)  |                                      | 0.0412           |        | 0.0012           | 1.43        | 372        |
| Subject Constant (intercept)<br>Days (slope) |   |                                      | 1.6863<br>0.0334 |        | 1.3063<br>0.0251 | 2.1<br>0.04 | 769<br>443 |
|  | Covariance Days - Constant  |                                      | -0.0957          |        | -0.1461          | -0.0        | )453       |
|  | residuals   |                                      | 0.6941           |        | 0.6415           | 0.7         | 510        |

\*95% confidence intervals presented for the variance parameters should not be used to test the significance of the variance parameters as the lower limits of these intervals can never be smaller than zero since variances are strictly positive quantities

LR test vs. linear regression: p < 0.0001

# Supplementary eTable 5: Acute AQLQ

| Fixed-effects Parameters          |  |       |                |       |                |              |         |  |  |
|-----------------------------------|--|-------|----------------|-------|----------------|--------------|---------|--|--|
| Covariates                        |  | Coef  | fficient       | 95% C |                |              | P value |  |  |
| Constant                          | Mean score at baseline in the<br>Placebo group | 4.727 |                | 4.491 | 4.962          |              | 0.000   |  |  |
| Visits (centered)                 | Per visit change in Placebo group              | 0.42  | 0.429          |       | 0.583          |              | 0.000   |  |  |
| Treatment #Visit<br>(interaction) | (Treatment effect)                             | 0.065 |                |       | 0.269          |              | 0.530   |  |  |
| Random-effects P                  | arameters                                      |       |                |       |                |              |         |  |  |
| Level                             | variance                                       |       | Estimate       |       | 95% CI*        |              |         |  |  |
| Site                              | Constant (intercept)                           |       | 0.063          |       | 0.009          | 0.45         | 0       |  |  |
| Subject                           | Constant (intercept)<br>Visits (slope)         |       | 0.888<br>0.165 |       | 0.583<br>0.059 | 1.35<br>0.46 | 3<br>4  |  |  |
|                                   | Covariance Visits - Constant                   |       | -0.074         |       | -0.272         | 0.12         | 25      |  |  |
|                                   | residuals                                      |       | 0.903          |       | 0.727          | 1.12         | 3       |  |  |

\*95% confidence intervals presented for the variance parameters should not be used to test the significance of the variance parameters as the lower limits of these intervals can never be smaller than zero since variances are strictly positive quantities

# Supplementary eTable 6: Mini AQLQ

| Fixed-effects Para             | meters   |                     |          |                |         |              |         |  |
|--------------------------------|--|---------------------|----------|----------------|---------|--------------|---------|--|
| Covariates                     |  | Coef                | fficient | 95% CI         |         |              | P value |  |
| Constant                       | Mean score at baseline in the<br>Placebo group | 3.35                | 5        | 3.196          | 3.514   |              | 0.000   |  |
| Visits (centered)              | Per visit change in Placebo group              | 0.35                | 0        | 0.214          | 0.486   |              | 0.000   |  |
| Treatment #Visit (interaction) | (Treatment effect)                             | -0.02               | -0.204   |                | 0.163   |              | 0.823   |  |
| Random-effects Parameters      |  |                     |          |                |         |              |         |  |
| Level                          | variance                                       |                     | Estimat  | te             | 95% CI* |              |         |  |
| Site                           | Constant (intercept)                           |                     | 0.000    |                | 0.000   | 0.00         | 0       |  |
| Subject                        | Constant (intercept)<br>Visits (slope)         | ntercept) C<br>e) C |          | 0.803<br>0.185 |         | 1.13<br>0.35 | 3<br>0  |  |
| Covariance Visits - Constant   |  |                     | -0.076   |                | -0.220  | 0.0          | 69      |  |
| residuals                      |  |                     | 0.566    |                | 0.457   | 0.70         | 3       |  |

\*95% confidence intervals presented for the variance parameters should not be used to test the significance of the variance parameters as the lower limits of these intervals can never be smaller than zero since variances are strictly positive quantities

### Secondary outcome analysis

For all secondary outcomes, an exploratory analysis and assessment of missing data was completed prior to the main analysis. This was analogous to that outlined for the primary outcome. Multilevel models, similar to those specified for the primary outcome, were used to analyze the acute asthma and mini-asthma questionnaires and also for the pulmonary function tests. Details of the models used for AQLQ and mini AQLQ respectively can be found in **Supplementary eTables 5 and 6**.

## Acute AQLQ and mini AQLQ analysis

Boxplots of acute AQLQ by treatment arm for each visit are shown in Supplementary eFigure 4.



# Supplementary eFigure 4: Boxplots of observed acute AQLQ scores

**Supplementary eTable 7** shows the observed mean and standard deviation of Acute AQLQ scores for each treatment arm by visit and the number of observations.

| Placebo |     |         |     |        |     |     |
|---------|-----|---------|-----|--------|-----|-----|
|         |     | Acute A | QLQ |        |     |     |
| Visit   | Ν   | Mean    | Sd  | Median | P25 | P75 |
| 1       | 100 | 4.8     | 1.3 | 5.0    | 4.0 | 5.6 |
| 2       | 87  | 5.3     | 1.4 | 5.7    | 4.2 | 6.4 |
| 3       | 83  | 5.6     | 1.5 | 6.1    | 4.8 | 6.7 |
| Active  |     |         |     |        |     |     |
|         |     | Acute A | QLQ |        |     |     |
| Visit   | N   | Mean    | Sd  | Median | P25 | P75 |
| 1       | 96  | 4.6     | 1.4 | 4.6    | 3.6 | 5.8 |
| 2       | 84  | 5.4     | 1.3 | 5.7    | 4.6 | 6.6 |
| 3       | 80  | 56      | 15  | 61     | 49  | 68  |

# Supplementary eTable 7: Detailed statistics of observed acute AQLQ scores

As for the primary outcome, multilevel modeling was carried out assuming equal mean scores at baseline and linear change for the acute AQLQ and mini-AQLQ scores over time with different slopes for the two treatment arms. Differences in the change of acute AQLQ scores for each visit with the 95% confidence intervals can be found in **Supplementary eTable 8**. At visit 3 (day 10) there was no statistically significant difference between the two groups. According to the model, at visit 3, there was 0.130 (95% CI: -0.276; 0.539) greater acute AQLQ score estimated in the azithromycin group than the placebo group.

# Supplementary eTable 8: Estimated difference in acute AQLQ score by visits

| Acute AQLQ score                                     | Visit 1<br>(Day 1) | Visit 2<br>(Day 5) | Visit 3<br>(Day 10) |
|--|--------------------|--------------------|---------------------|
| Difference in change<br>compared to Placebo<br>group | 0                  | 0.065              | 0.130               |
| 95% Confidence<br>Interval                           | -                  | -0.138; 0.269      | -0.276; 0.539       |

The same analyses were conducted for mini AQLQ scores as for acute AQLQ scores. Boxplots of Mini-AQLQ, by treatment arm, for each visit, are shown in **Supplementary eFigure 5**. **Supplementary eTable 9** shows the observed mean and standard deviation of mini AQLQ scores for each treatment arm by visit.



Supplementary eFigure 5: Boxplots of observed mini AQLQ scores

# Supplementary eTable 9: Detailed statistics of observed mini AQLQ scores

| Placebo  |           |     |        |     |     |  |  |  |  |
|----------|-----------|-----|--------|-----|-----|--|--|--|--|
|          | Mini AQLQ |     |        |     |     |  |  |  |  |
| Visit    | Mean      | Sd  | Median | P25 | P75 |  |  |  |  |
| 1        | 3.4       | 1.1 | 3.2    | 2.6 | 4.0 |  |  |  |  |
| 2        | 3.6       | 1.2 | 3.4    | 2.7 | 4.3 |  |  |  |  |
| 3        | 4.1       | 1.3 | 3.9    | 3.1 | 4.9 |  |  |  |  |
| Azithrom | iycin     |     |        |     |     |  |  |  |  |
|          | Mini AC   | LQ  |        |     |     |  |  |  |  |
| Visit    | Mean      | Sd  | Median | P25 | P75 |  |  |  |  |
| 1        | 3.4       | 1.2 | 3.1    | 2.5 | 4.2 |  |  |  |  |
| 2        | 3.6       | 1.1 | 3.6    | 2.9 | 4.3 |  |  |  |  |
| 3        | 4.1       | 1.3 | 4.1    | 3.1 | 5.1 |  |  |  |  |

Differences in the change of mini AQLQ scores for each visit with 95% confidence intervals are shown in **Supplementary eTable 10**. At visit 3 (day 10) there was no statistically significant difference between the two groups. According to the model, at visit 3 there was -0.042 (95% CI: -0.409; 0.325) lower mini AQLQ score estimated in the azithromycin group than the placebo group.

# Supplementary eTable 10: Estimated difference in mini AQLQ score azithromycin compared to placebo by visits

| Mini AQLQ  | Visit 1 | Visit 2       | Visit 3       |
|--|---------|---------------|---------------|
|  | (Day 1) | (Day 5)       | (Day 10)      |
| Difference in change<br>compared to Placebo<br>group | 0       | -0.020        | -0.042        |
| 95% Confidence<br>interval                           | -       | -0.204; 0.163 | -0.409; 0.325 |

### Pulmonary function test analysis

For the pulmonary function tests similar exploratory analyses and multilevel modelling was conducted as for AQLQ scores. **Supplementary eTable 11** shows the observed pulmonary function test values (mean and standard error) for each visit by treatment arm.

**Supplementary eTable 12** shows the estimated differences in change for azithromycin compared to placebo group with 95% confidence intervals by visit for each pulmonary function test.

# Supplementary eTable 11: Observed mean (SD) pulmonary function test results by visit and treatment arm

| Active G | roup    |         |                                      | Placebo g | roup    |         |
|----------|---------|---------|--------------------------------------|-----------|---------|---------|
| Visit 1  | Visit 2 | Visit 3 |                                      | Visit 1   | Visit 2 | Visit 3 |
| Day 1    | Day 5   | Day 10  |                                      | Day 1     | Day 5   | Day 10  |
| 97       | 85      | 80      | Ν                                    | 101       | 90      | 83      |
| 1.94     | 2.23    | 2.30    | FEV <sub>1</sub> (liters), mean (SD) | 2.11      | 2.34    | 2.38    |
| (0.74)   | (0.77)  | (0.83)  |                                      | (0.79)    | (0.83)  | (0.91)  |
| 2.80     | 3.13    | 3.25    | FVC(liters), mean (SD)               | 3.09      | 3.40    | 3.38    |
| (1.03)   | (1.00)  | (1.08)  |                                      | (1.05)    | (1.10)  | (1.09)  |
| 69.66    | 71.71   | 71.00   | FEV₁/FVC ratio, mean                 | 68.83     | 69.28   | 70.02   |
| (13.33)  | (12.02) | (12.38) | (SD)                                 | (13.71)   | (12.24) | (12.71) |
| 1.59     | 1.85    | 1.77    | FEF <sub>25-75%</sub> (liters/sec),  | 1.74      | 1.83    | 1.94    |
| (0.89)   | (0.94)  | (0.92)  | mean (SD)                            | (1.14)    | (1.08)  | (1.20)  |
| 1.92     | 2.12    | 2.19    | FEF <sub>50%</sub> (liters/sec),     | 2.04      | 2.15    | 2.32    |
| (1.06)   | (1.05)  | (1.08)  | mean (SD)                            | (1.26)    | (1.24)  | (1.35)  |
| 288.0    | 345.0   | 363.3   | PEF(liters/min), mean                | 320.2     | 349.5   | 356.8   |
| (107.5)  | (109.0) | (108.4) | (SD)                                 | (102.6)   | (110.1) | (118.1) |

# Supplementary eTable 12: Estimates of pulmonary function mean differences and 95% CI in brackets

|                                    | Difference in<br>change compared<br>to Placebo at visit 3<br>(Day 10) | Difference in<br>change<br>compared to<br>Placebo at visit 2<br>(Day 5) | Per visit<br>change in<br>Placebo | Baseline<br>mean        |
|------------------------------------|---|---|-----------------------------------|-------------------------|
| FEV <sub>1</sub> (liters)          | 0.050<br>(-0.132: 0.231)  | 0.024<br>(-0.067: 0.116)  | 0.164 (0.099: 0.228)              | 2.011 (1.875: 2.146)    |
| FVC(liters)                        | 0.038<br>(-0.166; 0.243)  | 0.019<br>(-0.083; 0.122)  | 0.200 (0.127; 0.272)              | 2.959<br>(2.809; 3.110) |
| FEV <sub>1</sub> /FVC ratio        | 1.379<br>(-1.559; 4.316)  | 0.689<br>(-0.779; 2.158)  | 0.365 (-0.732;<br>1.463)          | 69.5<br>(67.7; 71.4)    |
| FEF <sub>25-75%</sub> (liters/sec) | 0.036<br>(-0.192; 0.265)  | 0.018<br>(-0.096; 0.132)  | 0.116<br>(0.035; 0.197)           | 1.631<br>(1.470; 1.792) |
| FEF <sub>50%</sub> (liters/sec)    | 0.045<br>(-0.234; 0.324)  | 0.022<br>(-0.117; 0.162)  | 0.161 (0.062; 0.260)              | 1.931<br>(1.750; 2.112) |
| PEF(liters/min)                    | 18.03<br>(-8.56; 44.62)   | 9.016<br>(-4.278; 22.31)  | 24.66<br>(15.01; 34.31)           | 296.3<br>(272.0; 321.6) |

### Subgroup studies

The same model as outlined for the primary outcome was used for subgroup analyses which including the following:

- Bacteria culture positive or negative in sputum: Supplementary eTable 13
- Viral tests positive or negative in nasal mucus, nasal swab, throat swab or sputum: **Supplementary** eTable 14
- Atypical bacteria positive or negative in nasal mucus, nasal swab, throat swab, sputum or serological testing: **Supplementary eTable 15**

Sputum bacterial culture was positive in 6% of subjects (4.1% active, 7.8% placebo). Nasal/throat swab/mucus and/or sputum atypical bacterial PCR and/or atypical bacterial serology were positive in 4.5% of patients (5.2% active, 3.9% placebo). Overall a bacteria/atypical bacterial test positive occurred in 10.6% of patients (9.3% active, 11.8% placebo). Nasal/throat swab/mucus and/or sputum virus PCR were positive in 18.1% of patients (16.5% active, 19.6% placebo).

# Supplementary eTable 13: Estimated Day 10 difference in change of diary scores from baseline with 95% confidence intervals with azithromycin compared to the placebo group in sputum culture bacteria positive or negative subgroup

| Group                             | Whole study<br>population<br>(N=176) | Sputum bacterial<br>culture missing<br>(N=93) | Sputum bacterial<br>culture positive<br>(N= 12) | Sputum bacterial<br>culture negative<br>(N= 71) |
|-----------------------------------|--------------------------------------|---|---|---|
| Day 10<br>difference in<br>change | -0.166                               | -0.114  | 1.178   | -0.410  |
| 95% CI                            | -0.670; 0.337                        | -0.821; 0.594                                 | -0.497; 2.853                                   | -1.183; 0.364                                   |

# Supplementary eTable 14: Estimated Day 10 difference in change of diary scores from baseline with 95% confidence intervals for azithromycin compared to placebo in virus PCR test positive or negative subgroups

| Group                          | Whole study<br>population<br>(N=176) | Virus PCR positive<br>(N=31) | Virus PCR negative<br>(N= 138) |
|--------------------------------|--------------------------------------|------------------------------|--------------------------------|
| Day 10 difference in<br>change | -0.166                               | -0.100                       | -0.106                         |
| 95% CI                         | -0.670; 0.337                        | -1.170; 0.969                | -0.683; 0.472                  |

Supplementary eTable 15: Estimated Day 10 difference in change of diary scores from baseline with 95% confidence intervals for azithromycin compared to the placebo group in atypical bacteria and any bacteria positive or negative subgroups

| Group                             | Whole study<br>population<br>(N=176) | Atypical* bacteria<br>positive (N=8†) | Atypical* bacteria<br>negative (N=157) | Any bacterial test positive (N=20) |
|-----------------------------------|--------------------------------------|---------------------------------------|--|------------------------------------|
| Day 10<br>difference in<br>change | -0.166                               | 1.391                                 | 0.044                                  | 0.198                              |
| 95% ČI                            | -0.670; 0.337                        | -1.214; 3.996                         | -0.465; 0.554                          | -1.546; 1.942                      |

\* C. pneumoniae or M. pneumoniae

†There were 9 patients with positive atypical bacteriology test results, but one of them had no diary score records





Supplementary eFigure 7: Observed mean diary scores and standard errors of the atypical bacterial test positive subgroup (N=8) by treatment arm



Supplementary eFigure 8: Observed mean diary scores and standard errors of the Bacteria culture positive in sputum subgroup (N=12) by treatment arm



#### Subgroup analysis based on time to receipt of study drug

A subgroup analysis on those who received study drug within 24hrs of initial presentation to medical care (N=104, 52 azithromycin, 52 placebo, difference at day 10 0.001 (95% CI: -0.634 to 0.636) and those who received study drug 24hrs or more after initial presentation (N=72, 35 azithromycin, 37 placebo, difference at day 10 -0.356 (95% CI: -1.128 to - 0.417) suggested there was no evidence that benefit may have been greater in those that received study drug earlier.

#### **Post Hoc analysis**

The AZISAST study reported that azithromycin prophylaxis reduced exacerbations in subjects with non-eosinophilic severe asthma (blood eosinophilia  $\leq 200/\mu$ L): 0.44 (95% CI 0.25 to 0.78) versus 1.03 (95% CI 0.72 to 1.48) (*P*=0.013)<sup>3</sup>. We therefore carried out a similar post hoc analysis. There were 166 patients with blood eosinophil results and diary score records. Multilevel modeling of our primary outcome revealed no significant benefit in those with blood eosinophils  $<200/\mu$ L (N=103: difference -0.265; 95% CI -0.873 to 0.363) or  $<300/\mu$ L (N=118: difference: -0.180; 95% CI -0.791 to 0.432).

#### Safety data analysis

Protocol reporting of adverse events were from the time the patient gave informed consent until seven days after the last dose of study medication. Using the information recorded on the adverse event eCRF, each adverse event was categorized using MedDRA coding System Organ Class (SOC) terms by a designee of the Chief Investigator. The number of adverse events and patients affected in each category by treatment arm can be found in **Supplementary eTable 16** and **Supplementary eTable 17**.

# Supplementary eTable 1: Number of adverse events by SOC category and treatment arm

|   | Arm    |         |       |
|---|--------|---------|-------|
| Adverse Event Category*                         | Active | Placebo | Total |
|   | No.    | No.     | No.   |
| Cardiac disorders                               | 4      | 2       | 6     |
| Eye disorders                                   | 2      | 1       | 3     |
| Gastrointestinal disorders                      | 35     | 24      | 59    |
| General disorders                               | 18     | 25      | 43    |
| Infections and infestations                     | 0      | 1       | 1     |
| Musculoskeletal and connective tissue disorders | 4      | 6       | 10    |
| Nervous system disorders                        | 15     | 14      | 29    |
| Psychiatric disorders                           | 1      | 2       | 3     |
| Reproductive system and breast disorders        | 0      | 1       | 1     |
| Respiratory, thoracic and mediastinal disorders | 27     | 37      | 64    |
| Skin and subcutaneous disorders                 | 0      | 1       | 1     |
| Total   | 106    | 114     | 220   |

\*as advised by Chief Investigator or designee, based on description

# Supplementary eTable 17: Number of patients affected by SOC category (a patient is only shown once in each category)

|  | Arm    |         |           |
|--|--------|---------|-----------|
| Adverse Event Category*                            | Active | Placebo | Total     |
|  | No.    | No.     | No.       |
| Cardiac disorders                                  | 4      | 2       | 6         |
| Eye disorders                                      | 2      | 1       | 3         |
| Gastrointestinal disorders                         | 25     | 20      | 45        |
| General disorders                                  | 16     | 19      | 35        |
| Infections and infestations                        | 0      | 1       | 1         |
| Musculoskeletal and connective tissue<br>disorders | 3      | 4       | 7         |
| Nervous system disorders                           | 14     | 13      | 27        |
| Psychiatric disorders                              | 1      | 2       | 3         |
| Reproductive system and breast disorders           | 0      | 1       | 1         |
| Respiratory, thoracic and mediastinal disorders    | 20     | 28      | 48        |
| Skin and subcutaneous disorders                    | 0      | 1       | 1         |
| Total† (number of patients affected)               | 85(51) | 92 (52) | 177 (103) |

\*as advised by Chief Investigator or designee, based on description †a patient may have more than one adverse event in any category **Supplementary eTable 18** shows the number of adverse events by category and relationship to study medication. The relationship is missing for four adverse events, and these are shown as "Unknown". No adverse events were definitely related to the study medication.

| Relationship to study Medication                |                |          |              |          |         |       |  |
|---|----------------|----------|--------------|----------|---------|-------|--|
| Adverse Event Category*                         | Not<br>related | Unlikely | Possibl<br>e | Probable | Unknown | Total |  |
|   | No.            | No.      | No.          | No.      | No.     | No.   |  |
| Cardiac disorders                               | 3              | 2        | 1            | 0        | 0       | 6     |  |
| Eye disorders                                   | 1              | 2        | 0            | 0        | 0       | 3     |  |
| Gastrointestinal disorders                      | 9              | 5        | 36           | 7        | 2       | 59    |  |
| General disorders                               | 20             | 11       | 11           | 0        | 1       | 43    |  |
| Infections and infestations                     | 1              | 0        | 0            | 0        | 0       | 1     |  |
| Musculoskeletal and<br>connective               |                |          |              |          |         |       |  |
| tissue disorders                                | 6              | 3        | 1            | 0        | 0       | 10    |  |
| Nervous system disorders                        | 8              | 13       | 8            | 0        | 0       | 29    |  |
| Psychiatric disorders                           | 0              | 3        | 0            | 0        | 0       | 3     |  |
| Reproductive system and<br>breast disorders     | 1              | 0        | 0            | 0        | 0       | 1     |  |
| Respiratory, thoracic and mediastinal disorders | 49             | 14       | 0            | 0        | 1       | 64    |  |
| Skin and subcutaneous<br>disorders              | 0              | 0        | 1            | 0        | 0       | 1     |  |
| Total   | 98             | 53       | 58           | 7        | 4       | 220   |  |

# Supplementary eTable 18: Number of Adverse Events by SOC category and Relationship to Study Medication

\*as advised by Chief Investigator or designee, based on description

Multiple adverse events were reported for some patients, with 51 patients (just less than half of those with adverse events) reporting more than one. Ten adverse events were reported for one subject. **Supplementary eTable 19** provides further detail about the distribution of the 220 adverse events between the 103 patients who reported adverse events.

# Supplementary eTable 19: Number of Adverse Events Reported for Individual patients

|                             | Treatme |         |       |
|-----------------------------|---------|---------|-------|
| Number of Adverse<br>Events | Active  | Placebo | Total |
|                             | No.     | No.     | No.   |
| 1                           | 24      | 28      | 52    |
| 2                           | 12      | 9       | 21    |
| 3                           | 7       | 6       | 13    |
| 4                           | 4       | 4       | 8     |
| 5                           | 3       | 2       | 5     |
| 6                           | 1       | 1       | 2     |
| 8                           | 0       | 1       | 1     |
| 10                          | 0       | 1       | 1     |
| Total                       | 51      | 52      | 103   |

Details of the adverse events classified as cardiac disorders are given in **Supplementary eTable 20**. None of these were classified as a serious adverse event.

| Age<br>(years<br>) | Arm     | Description                               | Site* | Relation       | Severity | Outcome              | Action<br>† | Duration       |
|--------------------|---------|---|-------|----------------|----------|----------------------|-------------|----------------|
| 26                 | PLACEBO | chest pain                                | NOC   | Not<br>related | Moderate | Recovered            | None        | Intermittent   |
| 36                 | ACTIVE  | chest pain                                | NOC   | Not<br>related | Mild     | Not yet<br>recovered | None        | Continuous     |
| 22                 | ACTIVE  | palpitations                              | POR   | Unlikely       | Mild     | Recovered            | None        | Intermittent   |
| 38                 | ACTIVE  | chest pain and pain<br>under left arm pit | POR   | Unlikely       | Mild     | Recovered            | None        | Single Episode |
| 55                 | ACTIVE  | chest pain                                | POR   | Not<br>related | Mild     | Recovered            | None        | Single Episode |
| 42                 | PLACEBO | feeling of tachycardia                    | SMH   | Possible       | Mild     | Recovered            | None        | Single Episode |

# Supplementary eTable 20: Listing of adverse events classified as Cardiac Disorders

\*NOC = Nottingham City Hospital; POR = Portsmouth Hospitals NHS Trust; SMH = St Mary's Hospital, Imperial College Healthcare NHS Trust †Action taken concerning study medication

Details of the serious adverse events are given in **Supplementary eTables 21 and 22**. There were 3 in the placebo group and one in the azithromycin group. All were related to the asthma exacerbations being studied and were considered unlikely or not related to study drug.

# Supplementary eTable 21: Serious Adverse Events

| Age<br>(years) | Arm     | Classification | Action<br>taken             | Event Description  | Site | Relation to study drug | Severity |
|----------------|---------|----------------|-----------------------------|--|------|------------------------|----------|
| 18             | PLACEBO | Serious        | Hospitalisation required    | Pt became wheezy and short of breath, 13/10/12,<br>presented to accident and emergency on<br>14/10/2012 and was admitted overnight.<br>Diagnosis exacerbation of asthma. | GLA  | Unlikely               | Moderate |
| 22             | PLACEBO | Serious        | Hospitalisation required    | Exacerbation of underlying asthma. Admitted<br>to Hospital at 9am on 7/Oct/2013 with extreme<br>symptoms of breathlessness.  | NNU  | Not related            | Severe   |
| 47             | PLACEBO | Serious        | Hospitalisation<br>required | Acute exacerbation of asthma   | A32  | Not related            | Moderate |
| 49.            | ACTIVE  | Serious        | Hospitalisation<br>required | Shortness of breath and wheeze- non- infective<br>exacerbation of asthma   | A29  | Not related            | Moderate |

| Frequency         | Comments   | Ongoing | Outcome              | Category   |
|-------------------|--|---------|----------------------|--|
| Single<br>Episode |  | No      | Recovered            | Respiratory,<br>thoracic and<br>mediastinal<br>disorders |
| Unknown           | Continuation of<br>patients existing<br>underlying<br>condition. Classed<br>as AE  | No      | Recovered            | Respiratory,<br>thoracic and<br>mediastinal<br>disorders |
| Single<br>Episode | Admitted to hospital<br>in Chester with<br>asthma<br>exacerbation for 3<br>nights. | No      | Recovered            | Respiratory,<br>thoracic and<br>mediastinal<br>disorders |
| Single<br>Episode | Patient was<br>admitted with<br>shortness of breath<br>and kept in<br>overnight    | Yes     | Not yet<br>recovered | Respiratory,<br>thoracic and<br>mediastinal<br>disorders |

# Supplementary eTable 22: Serious Adverse Events continued

### References

- 1. Bisgaard H, Hermansen MN, Bonnelykke K, et al. Association of bacteria and viruses with wheezy episodes in young children: prospective birth cohort study. *Bmj*. 2010;341:c4978.
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# Membership of the AZALEA Trial Team:

Miss Maria-Belen Trujillo-Torralbo, Research Nurse, Imperial College, London, London, UK Mr Ajerico del Rosario, Research Nurse, Imperial College, London, London, UK Dr Alexina Mason, Statistician, Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, UK Dr Jane Warwick, Senior Statistician, Imperial Clinical Trials Unit, School of Public Health, Imperial College London, London, UK Dr James Griffiths, PI, Barnsley Hospital, UK Dr Tarek Saba, PI, Blackpool Victoria Hospital, UK Sister Judith Saba, Research Nurse, Blackpool Victoria Hospital, UK Dr Stephen Scott, PI, Countess of Chester Hospital, UK Jillian Andrews, Senior Respiratory Nurse, Countess of Chester Hospital, UK Dr Duncan Fullerton, Leighton Hospital, Crewe, UK Dr Edward Cetti, PI, East Surrey Hospital, UK Patricia Clark, Research Nurse, Western & Royal Infirmary, Glasgow, UK Dr Simon Message, PI, Gloucestershire Royal Hospital, UK Dr Jonathan Douse, PI, Ipswich Hospital, UK Dr Ian Clifton, PI, St James Hospital, Leeds, UK Dr Richard Harrison, PI, University Hospital of North Tees, UK Dr Andrew Wilson, PI, Norfolk and Norwich Hospitals, UK Janet Oborne, Research Nurse, Notttingham University Hospitals NHS Trust, Nottingham, UK Dr Matthew Masoli, PI, Derriford Hospital, Plymouth, UK Dr Thomas Brown, Consultant Respiratory Physician, Portsmouth Hospitals NHS Trust, Portsmouth, UK Dr Jonathan Owen, Consultant Respiratory Physician, Portsmouth Hospitals NHS Trust, Portsmouth, UK Dr Dominic Revnish, Clinical Research Fellow, Portsmouth Hospitals NHS Trust, Portsmouth, UK Dr Heena Mistry, Clinical Research Fellow, Portsmouth Hospitals NHS Trust, Portsmouth, UK Dr Gavin Durrant, PI, Rowden Surgery, Chippenham, UK Dr Grace Robinson, PI, Royal Berkshire Hospital, Reading, UK Dr Jonathan Mann, PI, Royal Wolverhampton NHS Trust, UK Dr Ramamurthy Sathyamurthy, PI, James Cook University Hospital, South Tees, UK Dr Andrew Stanton, PI, Great Western Hospital, Swindon, UK Dr Justin Pepperill, PI, Musgrove Park Hospital, Taunton, UK Dr Harmesh Moudgil, PI, Princess Royal Hospital, Telford, UK Dr Steve O'Hickey, PI, Worcestershire Royal Hospital, UK

# **Data Monitoring and Ethics Committee**

An independent Data Monitoring and Ethics Committee (DMEC) was established to review adverse event reports and any ongoing safety issues. The DMEC membership is listed below:

## Independent members

Professor Jonathan Grigg – Chair Dr Stephen Bremner – Independent Statistician Dr Peter Howarth – Independent Member

## **Trial Steering Committee**

A Trial Steering Committee (TSC) was established to oversee the conduct of the study. The TSC membership is listed below:

## Independent members

Professor Wisia Wedzicha – Chair Professor Peter Calverley - Independent Member Professor Ratko Djukanovic – Independent Member Ms Leanne Metcalf, Asthma UK – Patient representative, Independent Member Professor Mike Thomas – Independent Member

# Non-members in attendance

Professor Deborah Ashby – Senior Statistician Professor Chris Brightling – Principal Investigator, Leicester Mrs Mary Cross – Operations Manager, Imperial Clinical Trials Unit Professor Sebastian Johnston – Chief Investigator Ms Laura Robison – Trial Manager (until February 2013) Dr Zahid Sattar – Trial Manager (until April 2015) Dr Jane Warwick – Senior Statistician (until June 2014) Dr Alexina Mason – Junior Statistician (until Jan 2015) Dr Ernie Wong – Research Fellow, Imperial College