AHUS-NO-COVID-19 Secondary Endpoints

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This report presents the results of additional analyses of the secondary endpoints of the AHUS-NO-COVID-19 trial. The analysis was performed as response to the reviewer comments on the manuscript submitted to Nature Communication. The analyses are based on the Full Analysis Set (FAS) including all randomised subjects who have had at least one baseline and one post-randomisation evaluation of efficacy of the primary endpoint (N=51).

The analysis is performed based on the pre-specified short description of analysis of secondary continuous, categorical and time-to-event data in the study protocol. The analysis of the ordinal endpoint was not specified in the protocol and was decided posthoc (but before looking at any results of the secondary endpoints). Protocol Version 1.3, dated 26.03.2020.

Data extraction Viedoc electronic data capture system, time stamped: 26.05.2020 12:06 UTC. Additional data on secondary endpoints received from the study group, 11.09.2020

# 1. Clinical status 14 days after randomisation

Ordinal logistic regression model with 7-point scale as outcome and allocation as exposure. Output set to OR.

**Number and proportion of participants in each level of the 7-point clinical state scale, stratified by group allocation**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  | | --- | --- | --- | --- | |  | | Standard of care | Chloroquine therapy + standard of care | |  | | (N = 25) | (N = 26) | |
| |  |  |  |  | | --- | --- | --- | --- | | **7-point clinical status scale** | |  |  | | 1 | | 1 (4.0%) | 1 (3.8%) | | 2 | | 1 (4.0%) | 0 (0.0%) | | 3 | | 0 (0.0%) | 1 (3.8%) | | 4 | | 2 (8.0%) | 0 (0.0%) | | 5 | | 0 (0.0%) | 1 (3.8%) | | 6 | | 2 (8.0%) | 3 (11.5%) | | 7 | | 19 (76.0%) | 20 (76.9%) | |

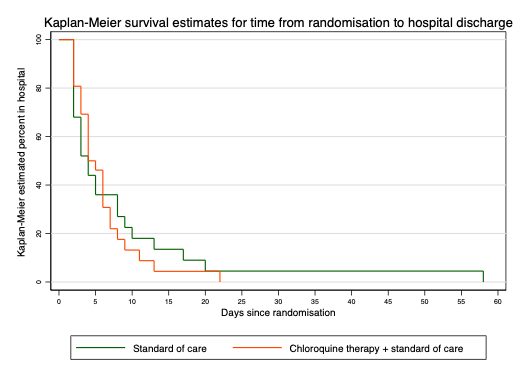
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| --- | --- | --- | --- | --- | --- | --- |
| Table 1. Results from ordinal logistic regression model | | | | | | |
| scale\_7 | Odds Ratio | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| allocation | 1.114987 | .7284604 | 0.17 | 0.868 | .3098486 | 4.012267 |
| /cut1 | -3.144622 | .7887927 |  |  | -4.690627 | -1.598616 |
| /cut2 | -2.718138 | .6764048 |  |  | -4.043867 | -1.392409 |
| /cut3 | -2.409181 | .6128039 |  |  | -3.610254 | -1.208107 |
| /cut4 | -1.959556 | .5439166 |  |  | -3.025613 | -.8934989 |
| /cut5 | -1.782529 | .5236083 |  |  | -2.808782 | -.7562756 |
| /cut6 | -1.122753 | .467223 |  |  | -2.038494 | -.2070132 |

# 2. Duration of hospital stay

Kaplan Meier method to estimate time from randomisation to hospital discharge by allocation. Comparison of the two groups with a log rank test.

**Description of overall survival data**

51 observations, 49 failures (=discharges), 347 days of total analysis time at risk and under observation



**Results from log-rank test for equality of survivor functions**

Standard of care arm: observed events=24, expected events=25.15; Chloroquine therapy + standard of care arm: observed events=25; expected events=23.85; p-value=0.7137

# 3. Change in NEWS score from randomisation to 96 hours

Change in the NEWS score from baseline to 96 hours post-randomisation. Analysed using a linear mixed model with fixed and random intercept. Time in days was entered categorical in the model.

**Number of available NEWS assessments per day, stratified by group allocation**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | | Standard of care | Chloroquine therapy + standard of care | Total | |  | | (N = 84) | (N = 100) | (N = 184) | |
| |  |  |  |  |  | | --- | --- | --- | --- | --- | | **Day** | |  |  |  | | Randomisation | | 25 (29.8%) | 26 (26.0%) | 52 (27.4%) | | 24 hours | | 25 (29.8%) | 26 (26.0%) | 53 (27.9%) | | 48 hours | | 15 (17.9%) | 22 (22.0%) | 38 (20.0%) | | 72 hours | | 11 (13.1%) | 16 (16.0%) | 29 (15.3%) | | 96 hours | | 8 (9.5%) | 10 (10.0%) | 18 (9.5%) | |

**Results from linear mixed model**

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| --- | --- | --- | --- | --- | --- | --- |
| Table 2. Model results | | | | | | |
| news\_mean | Coef. | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| Study\_Day |  |  |  |  |  |  |
| 24 hours | .4786667 | .3899393 | 1.23 | 0.220 | -.2856004 | 1.242934 |
| 48 hours | .0605587 | .4697168 | 0.13 | 0.897 | -.8600694 | .9811867 |
| 72 hours | 1.010652 | .5279533 | 1.91 | 0.056 | -.0241169 | 2.045422 |
| 96 hours | .292297 | .5974441 | 0.49 | 0.625 | -.8786718 | 1.463266 |
|  |  |  |  |  |  |  |
| allocation |  |  |  |  |  |  |
| Chloroquine therapy + standard of c.. | -.0348407 | .573036 | -0.06 | 0.952 | -1.157971 | 1.088289 |
|  |  |  |  |  |  |  |
| Study\_Day#allocation |  |  |  |  |  |  |
| 24 hours# |  |  |  |  |  |  |
| Chloroquine therapy + standard of c.. | -.4395557 | .5461293 | -0.80 | 0.421 | -1.509949 | .630838 |
| 48 hours# |  |  |  |  |  |  |
| Chloroquine therapy + standard of c.. | .6465381 | .620341 | 1.04 | 0.297 | -.5693079 | 1.862384 |
| 72 hours# |  |  |  |  |  |  |
| Chloroquine therapy + standard of c.. | -.9359865 | .6955399 | -1.35 | 0.178 | -2.29922 | .4272467 |
| 96 hours# |  |  |  |  |  |  |
| Chloroquine therapy + standard of c.. | .1812375 | .8049881 | 0.23 | 0.822 | -1.39651 | 1.758985 |
|  |  |  |  |  |  |  |
| \_cons | 3.903476 | .4091509 | 9.54 | 0.000 | 3.101555 | 4.705397 |

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| Table 3. Estimated change from baseline at each time point | | | | | | |
|  |  | Delta-method |  |  |  |  |
|  | dy/dx | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| 0.Study\_Day | (base outcome) |  |  |  |  |  |
| 1.Study\_Day |  |  |  |  |  |  |
| allocation |  |  |  |  |  |  |
| Standard of care | .4786667 | .3899393 | 1.23 | 0.220 | -.2856004 | 1.242934 |
| Chloroquine therapy + standard of c.. | .0391109 | .382367 | 0.10 | 0.919 | -.7103146 | .7885364 |
| 2.Study\_Day |  |  |  |  |  |  |
| allocation |  |  |  |  |  |  |
| Standard of care | .0605587 | .4697168 | 0.13 | 0.897 | -.8600694 | .9811867 |
| Chloroquine therapy + standard of c.. | .7070968 | .4052025 | 1.75 | 0.081 | -.0870855 | 1.501279 |
| 3.Study\_Day |  |  |  |  |  |  |
| allocation |  |  |  |  |  |  |
| Standard of care | 1.010652 | .5279533 | 1.91 | 0.056 | -.0241169 | 2.045422 |
| Chloroquine therapy + standard of c.. | .0746659 | .4528147 | 0.16 | 0.869 | -.8128346 | .9621664 |
| 4.Study\_Day |  |  |  |  |  |  |
| allocation |  |  |  |  |  |  |
| Standard of care | .292297 | .5974441 | 0.49 | 0.625 | -.8786718 | 1.463266 |
| Chloroquine therapy + standard of c.. | .4735345 | .5395057 | 0.88 | 0.380 | -.5838773 | 1.530946 |

|  |  |  |  |
| --- | --- | --- | --- |
| Table 4. Estimated difference of the change between the treatment groups at each time point | | | |
|  | df | chi2 | P>chi2 |
| 0b.Study\_Day |  |  |  |
| allocation | (omitted) |  |  |
| 1.Study\_Day |  |  |  |
| allocation | 1 | 0.65 | 0.4209 |
| 2.Study\_Day |  |  |  |
| allocation | 1 | 1.09 | 0.2973 |
| 3.Study\_Day |  |  |  |
| allocation | 1 | 1.81 | 0.1784 |
| 4.Study\_Day |  |  |  |
| allocation | 1 | 0.05 | 0.8219 |

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Table 4. Estimated difference of the change between the treatment groups at each time point | | | | |
|  | Contrast | Delta-method |  |  |
|  | dy/dx | Std. Err. | [95% Conf. Interval] | |
| 0.Study\_Day | (base outcome) |  |  |  |
| 1.Study\_Day |  |  |  |  |
| allocation |  |  |  |  |
| (Chloroquine therapy + standard of care |  |  |  |  |
| vs |  |  |  |  |
| Standard of care) | -.4395557 | .5461293 | -1.509949 | .630838 |
| 2.Study\_Day |  |  |  |  |
| allocation |  |  |  |  |
| (Chloroquine therapy + standard of care |  |  |  |  |
| vs |  |  |  |  |
| Standard of care) | .6465381 | .620341 | -.5693079 | 1.862384 |
| 3.Study\_Day |  |  |  |  |
| allocation |  |  |  |  |
| (Chloroquine therapy + standard of care |  |  |  |  |
| vs |  |  |  |  |
| Standard of care) | -.9359865 | .6955399 | -2.29922 | .4272467 |
| 4.Study\_Day |  |  |  |  |
| allocation |  |  |  |  |
| (Chloroquine therapy + standard of care |  |  |  |  |
| vs |  |  |  |  |
| Standard of care) | .1812375 | .8049881 | -1.39651 | 1.758985 |

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| Table 5. Estimated marginal mean by treatment group at time point 96 hours | | | | | | |
|  |  | Delta-method |  |  |  |  |
|  | Margin | Std. Err. | z | P>|z| | [95% Conf. Interval] | |
| allocation |  |  |  |  |  |  |
| Standard of care | 4.195773 | .6101567 | 6.88 | 0.000 | 2.999888 | 5.391658 |
| Chloroquine therapy + standard of c.. | 4.34217 | .5530169 | 7.85 | 0.000 | 3.258277 | 5.426063 |

**Figure 2. Marginsplot to illustrate the estimated mean NEWS score with 95% CIs over time and by treatment arm**

