Design of Ivermectin vs. Molnupiravir Trials

	Molnupiravir **PANORAMIC** *Gbinigie, isrctn.com*	***Ivermectin*** **PRINCIPLE** *isrctn.com (B)*
Investigator	Prof. Chris Butler	Prof. Chris Butler
Delay	≤5 days from onset median 2 days	≤14 days from onset median unknown
Population	50+ or 18+ w/comorbidities	18+ (mid-trial change)
Treatment	5 days, 2x per day	3 days, 1x per day, dose below real-world use
Administration	Per recommendation (with or without food)	Directed to take opposite of recommendation for COVID-19 - without food, greatly reducing concentration *c19ivm.org, Guzzo*
Patients	25,783	3,963 (inc. concurrent control)
Publication delay	4 months	19 months (26 months from expected end)
Enrollment	Dec 2021 - Apr 2022	May 2021 - Jul 2022
Mutagenic	Yes	No
Cost	$707 *fiercepharma.com*	<$1 *medrxiv.org*
Merck profit	>$7.2B sales to date *merck.com*, estimated $18 to produce *theintercept.com*	~$0 (potential, unlikely competitive with low cost manufacturers)

Design better for showing efficacy

It Gets Worse

1) Long delay between registration and enrollment

One participant reports filling out a form for the trial at the time of receiving a positive PCR result and not being called until much later on day 11 of COVID to complete enrollment twitter.com (C). A second participant reports waiting 9 days after online registration to receive an enrollment phone call twitter.com (D), twitter.com (E)."

2) Ability to pickup medication quickly removed from information sheet

Earlier versions of the patient information sheet (e.g., v3.1 c19ivm.org (K)) allowed patients to pickup the medication from a local pharmacy instead of waiting for delivery. This was removed sometime before the ivermectin arm and the sheet now only lists delivery, excluding the possibility of very quick pickup of the medication after enrollment c19ivm.org (L).

And Worse

3) Slow delivery

The patient information sheet for molnupiravir states that medication will be delivered by the next day c19ivm.org (H), Gbinigie, while the patient information sheet for ivermectin has deleted "next day" only stating that medication will be delivered c19ivm.org (I).

Despite all the above, they went even further:

4) Trial Schedule Change

As of February 11, 2022, the trial was open intermittently (twice daily between Sunday and Thursday), a change which further decreases the chance of participants receiving relatively early treatment.

C19early.com List of “crimes”

Severity	*Issue (most recent update 0 days ago)*
CRITICAL	1. 36% lower long COVID hidden in appendix ***(0 days ago)***
CRITICAL	2. False claims for long-term outcomes and recovery ***(0 days ago)***
CRITICAL	3. Significantly improved recovery is strongly associated with significantly lower mortality ***(0 days ago)***
CRITICAL	4. Superiority of ivermectin hidden ***(0 days ago)***
CRITICAL	5. Superiority of budesonide not hidden ***(0 days ago)***
CRITICAL	6. Pre-specified "meaningful effect" only for interim futility ***(0 days ago)***
CRITICAL	7. Pre-specified "meaningful effect" probability changed 0.01->0.25 ***(0 days ago)***
CRITICAL	8. Recovery benefit for ivermectin compared with budesonide ***(0 days ago)***
CRITICAL	9. Mortality results missing for concurrent control arm ***(0 days ago)***
CRITICAL	10. Details of hospitalizations and deaths not provided ***(0 days ago)***
CRITICAL	11. False claim on administration
CRITICAL	12. Very late treatment
CRITICAL	13. Inclusion changed from 50+ to 18+ w/COVID dyspnea or comorbidity before start of ivermectin arm
CRITICAL	14. Mid-trial change to include lower risk patients
CRITICAL	15. Exteme conflict of interest
CRITICAL	16. Pause due to supply but medicine was stored at every study site
CRITICAL	17. Supply issue contradicated by manufacturer
CRITICAL	18. Design favors null result in contrast to molnupiravir trial by the same chief investigator
CRITICAL	19. Other arm results not released over 1,380 days later
CRITICAL	20. Inclusion changed from 7 to 14 days
CRITICAL	21. "Gate-keeping" protection of serious outcome evaluation
CRITICAL	22. Long delay between registration and enrollment
CRITICAL	23. Subject to participant fraud
CRITICAL	24. Inconsistent analysis - Bayesian vs. frequentist statistics ***(3 days ago)***
SERIOUS	25. Lack of recovery inverted to reduce effect size ***(3 days ago)***
SERIOUS	26. Slow delivery
SERIOUS	27. Administration on an empty stomach
SERIOUS	28. Mismatch with original proposal
SERIOUS	29. Eligibility criteria worse than concurrent favipiravir arm
SERIOUS	30. Recruitment questions varied
MAJOR	31. Ivermectin from source chosen has shown lower efficacy
MAJOR	32. Ability to pickup medication quickly removed from information sheet
MAJOR	33. Only three different doses, lower µg/kg dose for higher weights

Responses: authors have not responded to any of these issues.

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19-month delay between trial completion and Publication??

PRINCIPLE trial treatments

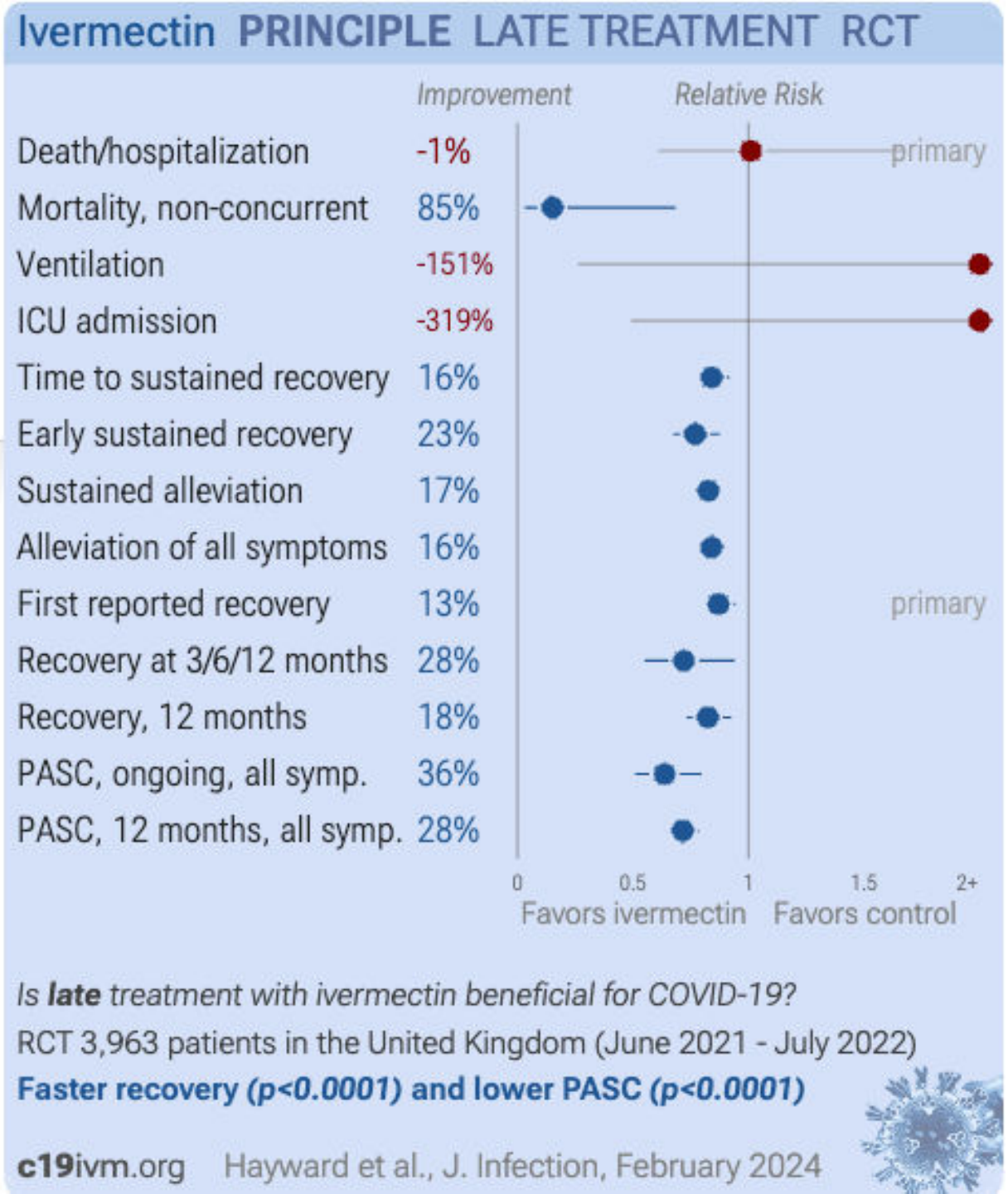
Treatment	*Treatment patients*	*Duration*	*Results delay*
HCQ	393-408 *dcricollab.dcri.duke.edu*	2 months	**over 1,350 days** *principletrial.org (B)*
Azithromycin *thelancet.com*	540	6 months	56 days *nihr.ac.uk*
Budesonide *thelancet.com (B)*	1,073	4 months	12 days *principletrial.org (C)*
Doxycycline *thelancet.com (C)*	780	5 months	42 days *nihr.ac.uk*
Colchicine *bjgp.org*	156	3 months	120 days *medrxiv.org (B)*
Ivermectin	2,157	14 months	**600 days (810 days from ~1,000 per arm enrollment)**
Favipiravir	~2,250	15 months	**over 600 days (over 820 days from ~1,000 per arm enrollment)**

Primary Outcome… was Positive For Ivermectin!!

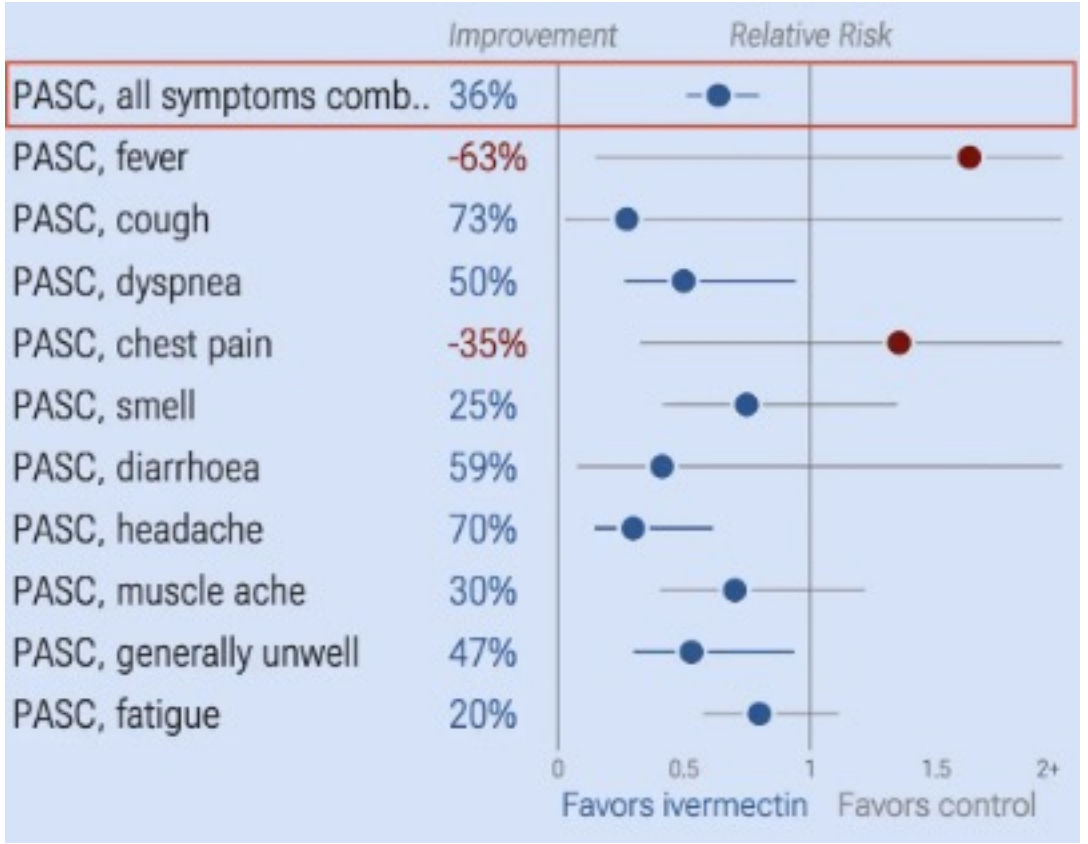
2 days shorter time to full recovery

Table 2 Primary and Secondary Outcomes.

	Ivermectin	Usual Care	Estimated difference median TTR or hospitalisation/death rate (95% BCI)	Hazard Ratio/ Odds Ratio (95% BCI)	Pr(Superiority)	Pr (Meaningful)
Primary outcomes (Primary analysis: SARS-CoV-2 positive population)	(N=2157)	(N=3256)				
Time to first reported recovery, days	14 (7 to not reached)[a]	15 (7 to not reached)[a]	2·06 (1·00 to 3·06)[b]	1·15 (1·07 to 1·23)[b]	>0·999[b]	0·19[b]



Even more positive Results!



Budesonide

	Inhaled budesonide (95% BCI)	Usual care (95% BCI)	Estimated benefit median time to recovery or hospital admission or death rate (95% BCI)	Hazard ratio or odds ratio (95% BCI)	Probability of superiority
Primary analysis—SARS-CoV-2-positive participants					
Number of participants	787	1069	..	..	..
Time to first reported recovery, days*	11·8 (10·0 to 14·1)	14·7 (12·3 to 18·0)	2·94 (1·19 to 5·11)	1·21 (1·08 to 1·36)	>0·999
Hospital admission or death at 28 days†	6·8% (4·1 to 10·2)	8·8% (5·5 to 12·7)	2·0% (−0·2 to 4·5)	0·75 (0·55 to 1·03)	0·963

Ivermectin

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Good News Right? NO!

Interpretation

Ivermectin for COVID-19 is unlikely to provide clinically meaningful improvement in recovery, hospital admissions, or longer-term outcomes. Further trials of ivermectin for SARS-Cov-2 infection in vaccinated community populations appear unwarranted.

National Institutes of Health (NIH) (.gov)
https://www.ncbi.nlm.nih.gov › articles › PMC10008034

An evidence double standard for pharmacological versus ...

by TB Høeg · 2023 · Cited by 1 — The ACTIV-6 **trial** [17] identified no significant clinical benefits of **ivermectin**, though it was completed in a setting of very high degree ...

Videos

Ivermectin trial, Oxford University

YouTube · Dr. John Campbell
Feb 9, 2022

Misinformation about Ivermectin arm of PRINCIPLE trial for ...

YouTube · Biotech and Bioinformatics with Prof Greg
Feb 10, 2022

Feedback

View all →

Journal of Infection
https://www.journalofinfection.com › article › fulltext

Ivermectin for COVID-19 in adults in the community ...

3 days ago — In this multicentre, open-label, multi-arm, adaptive platform randomised controlled **trial**, we included participants aged ≥18 years in the ...

ScienceDirect.com
https://www.sciencedirect.com › science › article › pii

Ivermectin for COVID-19 in adults in the community ...

3 days ago — **PRINCIPLE** is the first UK randomised **trial** to evaluate the effect of **ivermectin** on time to recovery and hospital admission for mostly ...

PRINCIPLE Trial
https://www.principletrial.org › news › the-principle-tri...

The PRINCIPLE Trial - two years on

May 16, 2022 — It has tested five potential treatments so far, with a further two, favipiravir and **ivermectin**, still being studied in the **trial**. **PRINCIPLE** ...

ISRCTN86534580: PRINCIPLE: A clinical trial evaluating ...

The study treatment of **Ivermectin** will be 3mg tablets once daily (300µg/kg body weight) for 3 days. ... 14 days. The study treatment of **Ivermectin** will be 3mg ...

JAMA Network
https://jamanetwork.com › journals › jama › fullarticle

Effect of Higher-Dose Ivermectin for 6 Days vs Placebo on ...

by S Naggie · 2023 · Cited by 33 — ... **PRINCIPLE Trial** Collaborative Group. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK ...

National Institute for Health and Care Research
https://local.nihr.ac.uk › case-studies › taking-part-in-cov...

Case study: Taking part in COVID research: Michael's story

Jun 19, 2023 — The results for two further drugs, **Ivermectin** and Favipiravir, are being analysed prior to publication. ... **PRINCIPLE trial** gave me. Their stories ...

Liverpool School of Tropical Medicine
https://www.lstmed.ac.uk › news-events › news › iverme...

Ivermectin for COVID-19 review update: 11 trials and no ...

Jun 21, 2022 — Overall, the review found no evidence to support the use of **ivermectin** for treating or preventing COVID-19 infection. Review authors, Dr Maria ...

Medpage Today
https://www.medpagetoday.com › ... › Exclusives

Ivermectin Arm of PRINCIPLE Trial Put on Hold

Dec 14, 2021 — The **trial** is designed to "test a range of treatments in the community," according to the **PRINCIPLE** website, "with treatment arms that can be ...

Nuffield Department of Primary Care Health Sciences
https://www.phc.ox.ac.uk › news › 10-000-people-join-...

10000 people join the PRINCIPLE Trial – A huge 'Thank ...

Apr 4, 2022 — The **trial** is testing treatments for COVID-19 that can be used at home. Led by the University of Oxford, it began in March 2020 and investigates ...

PRINCIPLE Trial
https://www.principletrial.org › news › ivermectin-to-be...

Ivermectin to be investigated in adults aged 18+ as a ...

Jun 23, 2021 — Led by the University of Oxford, **PRINCIPLE** is investigating treatments for people at more risk of serious illness from COVID-19 which can speed ...

Inhaled budesonide

Summary:

Early treatment with inhaled budesonide shortens recovery time by a median of three days in patients with COVID-19 who are at higher risk of more severe illness and are treated in the community. A common corticosteroid, budesonide is the first widely available, inexpensive drug found to shorten recovery times in COVID-19 patients aged over 50 who are treated at home and in other community settings. The findings are based on an interim analysis, which included 751 people in the budesonide group and 1028 in the usual care group who were SARS-CoV-2 positive.

Research paper:

Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

PRINCIPLE Trial Collaborative Group
The Lancet, August 10, 2021: DOI: https://doi.org/10.1016/S0140-6736(21)01744-X

Press release:

Asthma drug budesonide shortens recovery time in non-hospitalised patients with COVID-19

12 April 2021

UK therapeutic alert:

NHS / MHRA COVID-19 Therapeutic Alert - Inhaled Budesonide for Adults (50 Years and Over) with COVID-19

12 April 2021

Azithromycin

Summary:

Azithromycin is not generally an effective treatment for reducing the time to recovery or risk of hospital admission for people with suspected COVID-19 in the community. The analysis included data from 500 patients assigned to receive azithromycin and usual NHS care, who were compared with 823 patients who were assigned to usual NHS care only.

Research paper:

Azithromycin for community treatment of suspected COVID-19 in people at increased risk of an adverse clinical course in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

PRINCIPLE Trial Collaborative Group
The Lancet, March 4 2021. DOI: https://doi.org/10.1016/S0140-6736(21)00461-X

Press release:

Azithromycin and doxycycline are not generally effective against COVID-19 in patients treated at home, shows PRINCIPLE trial
January 25, 2021

UK therapeutic alert:

NHS / MHRA COVID-19 Therapeutic Alert - Antimicrobials (azithromycin and doxycycline) Not Beneficial in the Management of COVID-19 (SARS-CoV-2) Positive Patients
January 28, 2021

Doxycycline

Summary:

Doxycycline is not generally an effective treatment for reducing the time to recovery or risk of hospital admission from COVID-19. The finding is based on an interim analysis of 798 patients assigned to receive doxycycline and usual NHS care who were compared with 994 patients assigned to receive usual NHS care only.

Research Paper:

Doxycycline for community treatment of suspected COVID-19 in people at high risk of adverse outcomes in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial

PRINCIPLE Trial Collaborative Group
Lancet Respir Med , July 27 2021.

DOI: https://doi.org/10.1016/ S2213-2600(21)00310-6

Press release:

Azithromycin and doxycycline are not generally effective against COVID-19 in patients treated at home, shows PRINCIPLE trial
January 25, 2021

UK therapeutic alert:

NHS / MHRA COVID-19 Therapeutic Alert - Antimicrobials (azithromycin and doxycycline) Not Beneficial in the Management of COVID-19 (SARS-CoV-2) Positive Patients
January 28, 2021

Colchicine

Summary:

Colchicine did not improve time to recovery in people at higher risk of complications with COVID-19 in the community. The analysis included data from 156 patients assigned to receive Colchicine and usual NHS care, who were compared with 1145 patients who were assigned to usual NHS care only, and 1454 to other treatments.

Research Paper:

Colchicine for COVID-19 in adults in the community (PRINCIPLE): a randomised, controlled, adaptive platform trial

PRINCIPLE Trial Collaborative Group
medRxiv , September 23 2021.

DOI: https://doi.org/10.1101/2021.09.20.21263828

(n=3398) from June 23, 2021 to July 1, 2022. Time to self-reported recovery was shorter in the ivermectin group compared with usual care (hazard ratio 1·15 [95% Bayesian credible interval, 1·07 to 1·23], median decrease 2.06 days [1·00 to 3·06]), probability of meaningful effect (pre-specified hazard ratio ≥1.2) 0·192). COVID-19-related hospitalisations/deaths (odds

Table 2. Secondary Outcomes in a Trial of Vitamin C Infusion in Patients With Sepsis and Severe Acute Respiratory Failure

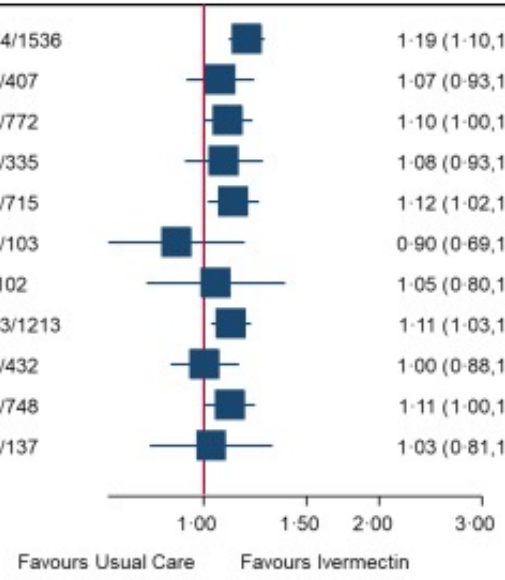
Table 2. Secondary Outcomes in a Trial of Vitamin C Infusion in Patients With Sepsis and Severe Acute Respiratory Failure

Variable	Hour	Vitamin C			Placebo			Difference, Coefficient (95% CI)	*P* Value
		No.	Median or %	IQR	No.	Median or %	IQR		
Oxygenation index,* median (IQR)	0	76	0.082	0.090	80	0.089	.077	0.129 (−0.096 to 0.353)	.26
	48	53	0.058	0.062	57	0.056	.054	0.004 (−0.016 to 0.023)	.71
	96	42	0.079	0.084	33	0.045	.040	0.016 (−0.017 to 0.049)	.33
	168	28	0.052	0.051	16	0.074	.066	−0.003 (−0.050 to 0.044)	.90
VE-40† to median (IQR)	0	78	0.126	0.044	81	0.115	.058	0.013 (−0.002 to 0.028)	.09
	48	59	0.109	0.049	60	0.110	.061	0.001 (−0.017 to 0.019)	.94
	96	46	0.129	0.060	39	0.105	.047	0.036 (−0.015 to 0.086)	.16
	168	29	0.114	0.043	17	0.118	.057	−0.020 (−0.055 to 0.015)	.26
Net fluid balance to median (IQR), mL	0	83	1604	2927	79	1901	3034	−3759 (−1123 to 373)	.32
	48	81	768	2471	73	473	1797	545 (−255 to 1345)	.18
	96	76	134	2168	66	−659	2560	792 (208 to 1376)	.01
	168	57	190	2076	54	−380	2213	496 (−206 to 1198)	.16
All-cause mortality to day 28, %			84	29.8	38	82	46.3	−0.17	.03
Ventilator-free days to day 28, median (IQR), d		84	17	24	82	8	22	2.5 (−0.9 to 5.9)	.15
ICU-free days to day 28, median (IQR), d		83	11	21	82	0	18	3.2 (0.3 to 6.0)	.03
Hospital-free days, to day 60, median (IQR), d		82	22	46	80	0	39	7.0 (0.3 to 13.8)	.04

Figure S6 Secondary time-to-event outcomes (concurrent randomisation and eligible population)

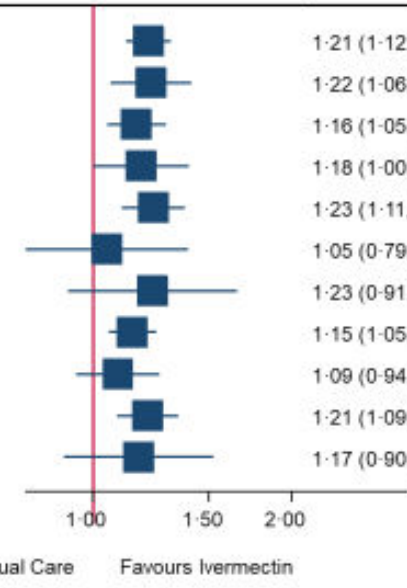
a) Time to alleviation of all symptoms, and each symptom

Time to Alleviation of Symptom[1]	Ivermectin	Usual Care	Adjusted HR (95% CI)	P-value
All symptoms	1677/1826	1374/1536	1·19 (1·10,1·27)	<0·0001
Fever	482/487	397/407	1·07 (0·93,1·22)	0·33
Cough	878/911	742/772	1·10 (1·00,1·21)	0·059
Shortness of breath	355/384	310/335	1·08 (0·93,1·26)	0·31
Muscle ache	806/832	691/715	1·12 (1·02,1·25)	0·024
Nausea-vomiting	119/125	101/103	0·90 (0·69,1·18)	0·44
Diarrhoea	115/120	99/102	1·05 (0·80,1·38)	0·73
Generally unwell	1404/1451	1163/1213	1·11 (1·03,1·20)	0·0069
Loss of smell or taste	471/531	379/432	1·00 (0·88,1·15)	0·96
Headache	842/870	725/748	1·11 (1·00,1·22)	0·043
Abdominal pain	132/136	135/137	1·03 (0·81,1·31)	0·81



(b) Time to sustained alleviation of all symptoms, each symptom

ime to Sustained lleviation[1]	Ivermectin	Usual Care	Adjusted HR (95% CI)	P-value
ll symptoms	1460/1826	1158/1536	1·21 (1·12,1·31)	<0·0001
ever	450/487	354/407	1·22 (1·06,1·41)	0·0049
ough	810/911	653/772	1·16 (1·05,1·29)	0·0043
hortness of breath	311/384	253/335	1·18 (1·00,1·40)	0·049
luscle ache	723/832	599/715	1·23 (1·11,1·38)	0·0002
ausea-vomiting	108/125	89/103	1·05 (0·79,1·39)	0·74
iarrhoea	105/120	83/102	1·23 (0·91,1·65)	0·17
enerally unwell	1246/1451	1018/1213	1·15 (1·05,1·24)	0·0014
oss of smell or taste	426/531	325/432	1·09 (0·94,1·26)	0·24
eadache	760/870	627/748	1·21 (1·09,1·34)	0·0005
bdominal pain	121/136	112/137	1·17 (0·90,1·52)	0·23



(c) Time to initial reduction of severity of all symptoms, and each symptom

Time to Initial Reduction of Severity of Symptom[1]	Ivermectin	Usual Care	Adjusted HR (95% CI)	P-value
All symptoms	1824/2193	1473/1838	1·16 (1·08, 1·24)	<0·0001
Fever	1378/1406	1161/1183	1·08 (1·00, 1·16)	0·065
Cough	1819/1960	1521/1650	1·07 (1·00, 1·15)	0·050
Shortness of breath	1104/1241	894/1032	1·15 (1·06, 1·26)	0·0016
Muscle ache	1709/1776	1394/1464	1·14 (1·06, 1·22)	0·0004
Nausea-vomiting	551/566	465/473	1·08 (0·95, 1·22)	0·23
Diarrhoea	475/483	405/411	1·08 (0·95, 1·24)	0·24
Generally unwell	2069/2158	1741/1815	1·09 (1·02, 1·16)	0·011
Loss of smell or taste	925/1022	764/856	1·08 (0·98, 1·19)	0·11
Headache	1797/1850	1453/1496	1·10 (1·02, 1·18)	0·0082
Abdominal pain	584/596	458/469	1·16 (1·02, 1·31)	0·021

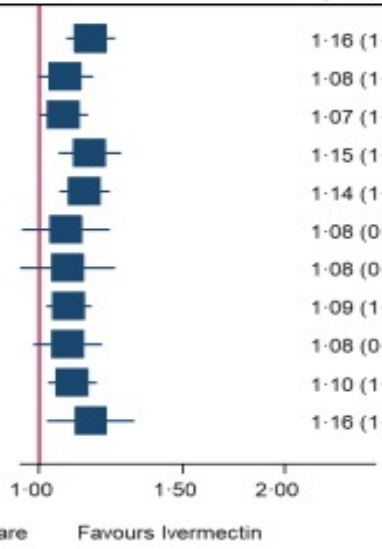


Table 2 Primary and Secondary Outcomes.

	Ivermectin	Usual Care	Estimated difference median TTR or hospitalisation/death rate (95% BCI)	Hazard Ratio/ Odds Ratio (95% BCI)	Pr(Superiority)	Pr (Meaningful)
Primary outcomes (Primary analysis: SARS-CoV-2 positive population)	(N=2157)	(N=3256)				
Time to first reported recovery, days	14 (7 to not reached)[a]	15 (7 to not reached)[a]	2·06 (1·00 to 3·06)[b]	1·15 (1·07 to 1·23)[b]	>0·999[b]	0·19[b]
Hospitalisation/death at 28 days	34/2157 (1.6%)[a]	144/3256 (4.4%)[a]	0% (-1% to 0·6%)[c]	1·02 (0·63 to 1·62)	0·472[c]	0·22[c]
Primary outcomes (Secondary analysis: all participants population)	(N=2192)	(N=4099)				
Time to first reported recovery, days	14 (7 to not reached)[a]	14 (6 to not reached)[a]	2·07 (1·02 to 3·06)[b]	1·15 (1·07 to 1·23)[b]	>0·999[b]	0·20[b]
Hospitalisation/death at 28 days	34/2192 (1.6%)[a]	162/4100 (4.0%)[a]	0% (-0·9% to 0·6%)[c]	1·02 (0·64 to 1·62)	0·472[c]	0·22[c]
Primary outcomes (Sensitivity analysis: concurrent and eligible analysis population)	(N=2157)	(N=1806)				
Time to first reported recovery, days	14 (7 to not reached)[a]	16 (8 to not reached)[a]	2·07 (0·97 to 3·11)[b]	1.15 (1·06 to 1·24)[b]	>0·999[b]	0·21[b]
Hospitalisation/death at 28 days	34/2157 (1.6%)[a]	27/1806 (1.5%)[a]	0% (-1% to 0·6%)[c]	1·01 (0·61 to 1·68)[c]	0·481[c]	0·24[c]

Table 3 Long term follow-up: Primary and Secondary Outcomess.

	Ivermectin (N=2157)	Usual Care (N=1806)	Estimated treatment effect [95% CI]	P-value
Primary outcome:				
Feeling fully recovered[a], n/N(%)				
3 months	1265/1766 (71.6%)	993/1486 (66.8%)	1·06 [1·03 to 1·10]	0·0002
6 months[b]	1301/1750 (74.3%)	1037/1455 (71.3%)	1·05 [1·02 to 1·08]	0·0035
12 months	1431/1848 (77.4%)	1113/1533 (72.6%)	1·06 [1·03 to 1·09]	0·0001
Primary outcome: sensitivity analysis	(N=2250)	(N=1869)		
Feeling fully recovered[a], n/N(%)				
3 months	1267/1769 (71.6%)	996/1490 (66.8%)	1·06 [1·03 to 1·09]	0·0002
6 months[b]	1304/1753 (74.4%)	1042/1461 (71.3%)	1·05 [1·01 to 1·08]	0·0039
12 months	1436/1853 (77.5%)	1120/1540 (72.7%)	1·06 [1·03 to 1·09]	0·0001

Differences Across Symptom Clusters

Analysis of Long COVID-19 Symptom cluster

Table S5 Summary statistics for the long COVID-19 symptom clusters and the adjusted odds ratios between the randomised groups

	Ivermectin	Usual Care	Adjusted Relative Risk [95% CI]*	P-value†
Chest/heart symptoms‡, n/N (%)				
3 months	336/1601 (21·0)	340/1356 (25·1)	0·82 [0·73 to 0·94]	0·0031
6 months‡‡	329/1588 (20·7)	314/1306 (24·0)	0·86 [0·75 to 0·98]	0·0217
12 months‡‡	339/1653 (20·5)	351/1370 (25·6)	0·79 [0·70 to 0·90]	0·0004
Ear, nose, or throat symptoms§, n/N (%)				
3 months	440/1601 (27·5)	396/1356 (29·2)	0·93 [0·83 to 1·05]	0·24
6 months‡‡	444/1588 (28·0)	384/1306 (29·4)	0·95 [0·85 to 1·06]	0·36
12 months‡‡	427/1653 (25·8)	371/1370 (27·1)	0·95 [0·84 to 1·07]	0·36
Stomach/gut/digestive system symptomsǁ, n/N (%)				
3 months	273/1601 (17·1)	273/1356 (20·1)	0·84 [0·72 to 0·97]	0·0189
6 months‡‡	276/1588 (17·4)	250/1306 (19·1)	0·90 [0·77 to 1·05]	0·19
12 months‡‡	303/1653 (18·3)	266/1370 (19·4)	0·93 [0·80 to 1·08]	0·34
Mood/memory/brain and nervous system symptoms¶, n/N (%)				
3 months	527/1601 (32·9)	532/1356 (39·2)	0·83 [0·75 to 0·91]	0·0001
6 months‡‡	548/1588 (34·5)	528/1306 (40·4)	0·85 [0·77 to 0·93]	0·0005
12 months‡‡	552/1653 (33·4)	577/1370 (42·1)	0·78 [0·72 to 0·86]	<0·0001
Body pains/musculoskeletal symptoms, n/N (%)**				
3 months	570/1601 (35·6)	532/1356 (39·2)	0·90 [0·82 to 0·99]	0·0313
6 months‡‡	604/1588 (38·0)	523/1306 (40·0)	0·95 [0·87 to 1·04]	0·27
12 months‡‡	676/1653 (40·9)	577/1370 (42·1)	0·97 [0·90 to 1·06]	0·54
Feeling generally unwell/low energy levels††, n/N (%)				
3 months	602/1601 (37·6)	568/1356 (41·9)	0·89 [0·81 to 0·97]	0·0069
6 months‡‡	606/1588 (38·2)	535/1306 (41·0)	0·93 [0·85 to 1·01]	0·09
12 months‡‡	621/1653 (37·6)	549/1370 (40·1)	0·97 [0·90 to 1·06]	0·54

SHORTNESS OF BREATH

Table S7 Summary statistics for the severity and relatedness of shortness of breath

Shortness of breath, n/N (%)		Ivermectin	Usual Care	Adjusted Relative Risk [95% CI]†	P-value‡
3 Months	**Severity**			0·70 [0·54 to 0·91]	0·0086
	None/mild	1403/1492 (94·0)	1168/1276 (91·5)		
	Moderate/major	89/1492 (6·0)	108/1276 (8·5)		
	Relatedness				
	Yes	161/1588 (10·1)	200/1345 (14·9)		
	No	1323/1588 (83·3)	1059/1345 (78·7)		
	Unsure	104/1588 (6·5)	86/1345 (6·4)		
6 Months	**Severity**			0·83 [0·62 to 1·09]	0·18
	None/mild	1376/1463 (94·1)	1110/1196 (92·8)		
	Moderate/major	87/1463 (5·9)	86/1196 (7·2)		
	Relatedness				
	Yes	154/1567 (9·8)	142/1300 (10·9)		
	No	1334/1567 (85·1)	1067/1300 (82·1)		
	Unsure	79/1567 (5·0)	91/1300 (7·0)		
12 months	**Severity**			0·75 [0·58 to 0·97]	0·0305
	None/mild	1417/1513 (93·7)	1132/1238 (91·4)		
	Moderate/major	96/1513 (6·3)	106/1238 (8·6)		
	Relatedness				
	Yes	133/1647 (8·1)	138/1357 (10·2)		
	No	1410/1647 (85·6)	1107/1357 (81·6)		
	Unsure	104/1647 (6·3)	112/1357 (8·3)		

†Logistic regression model adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status; RR < 1 favours Ivermectin; ‡Level of significance = 0·05.

ANXIETY

Table S21 Summary statistics for the severity and relatedness of feeling anxious

Feeling anxious, n/N (%)		Ivermectin	Usual Care	Adjusted Relative Risk [95% CI]†	P-value‡
3 Months	**Severity**			0·68 [0·52 to 0·88]	0·0042
	None/mild	1176/1264 (93·0)	924/1026 (90·1)		
	Moderate/major	88/1264 (7·0)	102/1026 (9·9)		
	Relatedness				
	Yes	78/1361 (5·7)	78/1114 (7·0)		
	No	1171/1361 (86·0)	912/1114 (81·9)		
	Unsure	112/1361 (8·2)	124/1114 (11·1)		
6 Months	**Severity**			0·83 [0·63 to 1·08]	0·16
	None/mild	1132/1227 (92·3)	881/972 (90·6)		
	Moderate/major	95/1227 (7·7)	91/972 (9·4)		
	Relatedness				
	Yes	74/1332 (5·6)	68/1083 (6·3)		
	No	1145/1332 (86·0)	889/1083 (82·1)		
	Unsure	113/1332 (8·5)	126/1083 (11·6)		
12 months	**Severity**			0·72 [0·54 to 0·94]	0·0164
	None/mild	1198/1287 (93·1)	879/973 (90·3)		
	Moderate/major	89/1287 (6·9)	94/973 (9·7)		
	Relatedness				
	Yes	63/1412 (4·5)	68/1109 (6·1)		
	No	1226/1412 (86·8)	929/1109 (83·8)		
	Unsure	123/1412 (8·7)	112/1109 (10·1)		

†Logistic regression model adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status; RR < 1 favours Ivermectin; ‡Level of significance = 0·05.

DEPRESSION

Table S22 Summary statistics for the severity and relatedness of feeling low or depressed

Feeling low or depressed, n/N (%)		Ivermectin	Usual Care	Adjusted Relative Risk [95% CI]†	P-value‡
3 Months	**Severity**			0·60 [0·45 to 0·79]	0·0004
	None/mild	1208/1283 (94·2)	942/1042 (90·4)		
	Moderate/major	75/1283 (5·8)	100/1042 (9·6)		
	Relatedness				
	Yes	84/1398 (6·0)	98/1132 (8·7)		
	No	1189/1398 (85·1)	914/1132 (80·7)		
	Unsure	125/1398 (8·9)	120/1132 (10·6)		
6 Months	**Severity**			0·71 [0·54 to 0·93]	0·0134
	None/mild	1154/1240 (93·1)	889/983 (90·4)		
	Moderate/major	86/1240 (6·9)	94/983 (9·6)		
	Relatedness				
	Yes	69/1364 (5·1)	71/1116 (6·4)		
	No	1164/1364 (85·3)	911/1116 (81·6)		
	Unsure	131/1364 (9·6)	134/1116 (12·0)		
12 months	**Severity**			0·78 [0·60 to 1·03]	0·08
	None/mild	1203/1298 (92·7)	900/992 (90·7)		
	Moderate/major	95/1298 (7·3)	92/992 (9·3)		
	Relatedness				
	Yes	66/1438 (4·6)	61/1145 (5·3)		
	No	1241/1438 (86·3)	946/1145 (82·6)		
	Unsure	131/1438 (9·1)	138/1145 (12·1)		

†*Logistic regression model adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status; RR < 1 favours Ivermectin;* ‡*Level of significance = 0·05*

BRAIN FOG

Table S24 Summary statistics for the severity and relatedness of inability to concentrate/brain fog

Inability to concentrate/ brain fog, n/N (%)		Ivermectin	Usual Care	Adjusted Relative Risk [95% CI]†	P-value‡
3 Months	**Severity**			0·66 [0·53 to 0·83]	0·0004
	None/mild	1253/1369 (91·5)	1004/1148 (87·5)		
	Moderate/major	116/1369 (8·5)	144/1148 (12·5)		
	Relatedness				
	Yes	201/1489 (13·5)	208/1244 (16·7)		
	No	1152/1489 (77·4)	879/1244 (70·7)		
	Unsure	136/1489 (9·1)	157/1244 (12·6)		
6 Months	**Severity**			0·88 [0·70 to 1·11]	0·28
	None/mild	1213/1349 (89·9)	944/1065 (88·6)		
	Moderate/major	136/1349 (10·1)	121/1065 (11·4)		
	Relatedness				
	Yes	188/1492 (12·6)	163/1203 (13·5)		
	No	1144/1492 (76·7)	882/1203 (73·3)		
	Unsure	160/1492 (10·7)	158/1203 (13·1)		
12 months	**Severity**			0·71 [0·57 to 0·89]	0·0025
	None/mild	1247/1376 (90·6)	962/1105 (87·1)		
	Moderate/major	129/1376 (9·4)	143/1105 (12·9)		
	Relatedness				
	Yes	153/1548 (9·9)	162/1253 (12·9)		
	No	1245/1548 (80·4)	911/1253 (72·7)		
	Unsure	150/1548 (9·7)	180/1253 (14·4)		

†Logistic regression model adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status; RR < 1 favours Ivermectin; ‡Level of significance = 0·05.

FATIGUE

Table S34 Summary statistics for the severity and relatedness of fatigue

Fatigue, n/N (%)		Ivermectin	Usual Care	Adjusted Relative Risk [95% CI]†	P-value‡
3 Months	**Severity**			0·78 [0·67 to 0·91]	0·0019
	None/mild	1226/1459 (84·0)	996/1247 (79·9)		
	Moderate/major	233/1459 (16·0)	251/1247 (20·1)		
	Relatedness				
	Yes	298/1652 (18·0)	297/1391 (21·4)		
	No	1133/1652 (68·6)	884/1391 (63·6)		
	Unsure	221/1652 (13·4)	210/1391 (15·1)		
6 Months	**Severity**			0·93 [0·79 to 1·10]	0·39
	None/mild	1154/1393 (82·8)	950/1164 (81·6)		
	Moderate/major	239/1393 (17·2)	214/1164 (18·4)		
	Relatedness				
	Yes	237/1634 (14·5)	218/1365 (16·0)		
	No	1180/1634 (72·2)	925/1365 (67·8)		
	Unsure	217/1634 (13·3)	222/1365 (16·3)		
12 months	**Severity**			0·82 [0·69 to 0·97]	0·0220
	None/mild	1193/1398 (85·3)	972/1181 (82·3)		
	Moderate/major	205/1398 (14·7)	209/1181 (17·7)		
	Relatedness				
	Yes	199/1706 (11·7)	195/1411 (13·8)		
	No	1296/1706 (76·0)	1012/1411 (71·7)		
	Unsure	211/1706 (12·4)	204/1411 (14·5)		

†Logistic regression model adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status; RR < 1 favours Ivermectin; ‡Level of significance = 0·05.

JOINT PAINS

Table S33 Summary statistics for the severity and relatedness of joint pains

Joint pains, n/N (%)		Ivermectin	Usual Care	Adjusted Relative Risk [95% CI]†	P-value‡
3 Months	**Severity**			0·67 [0·54 to 0·83]	0·0004
	None/mild	1134/1255 (90·4)	932/1088 (85·7)		
	Moderate/major	121/1255 (9·6)	156/1088 (14·3)		
	Relatedness				
	Yes	69/1464 (4·7)	94/1241 (7·6)		
	No	1240/1464 (84·7)	977/1241 (78·7)		
	Unsure	155/1464 (10·6)	170/1241 (13·7)		
6 Months	**Severity**			0·82 [0·66 to 1·02]	0·08
	None/mild	1073/1209 (88·8)	872/1009 (86·4)		
	Moderate/major	136/1209 (11·2)	137/1009 (13·6)		
	Relatedness				
	Yes	75/1453 (5·2)	63/1202 (5·2)		
	No	1228/1453 (84·5)	976/1202 (81·2)		
	Unsure	150/1453 (10·3)	163/1202 (13·6)		
12 months	**Severity**			0·80 [0·65 to 0·99]	0·0421
	None/mild	1084/1220 (88·9)	889/1035 (85·9)		
	Moderate/major	136/1220 (11·1)	146/1035 (14·1)		
	Relatedness				
	Yes	72/1513 (4·8)	59/1272 (4·6)		
	No	1270/1513 (83·9)	1030/1272 (81·0)		
	Unsure	171/1513 (11·3)	183/1272 (14·4)		

†Logistic regression model adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status; RR < 1 favours Ivermectin; ‡Level of significance = 0·05.

DIFFICULTY SLEEPING

Table S30 Summary statistics for the severity and relatedness of problems sleeping

Problems sleeping, n/N (%)		Ivermectin	Usual Care	Adjusted Relative Risk [95% CI]†	P-value‡
3 Months	**Severity**			0·79 [0·63 to 0·99]	0·0397
	None/mild	1150/1283 (89·6)	908/1041 (87·2)		
	Moderate/major	133/1283 (10·4)	133/1041 (12·8)		
	Relatedness				
	Yes	89/1447 (6·2)	90/1182 (7·6)		
	No	1203/1447 (83·1)	934/1182 (79·0)		
	Unsure	155/1447 (10·7)	158/1182 (13·4)		
6 Months	**Severity**			0·83 [0·66 to 1·05]	0·11
	None/mild	1113/1240 (89·8)	857/977 (87·7)		
	Moderate/major	127/1240 (10·2)	120/977 (12·3)		
	Relatedness				
	Yes	79/1428 (5·5)	80/1152 (6·9)		
	No	1197/1428 (83·8)	922/1152 (80·0)		
	Unsure	152/1428 (10·6)	150/1152 (13·0)		
12 months	**Severity**			0·77 [0·61 to 0·98]	0·0297
	None/mild	1165/1288 (90·5)	861/982 (87·7)		
	Moderate/major	123/1288 (9·5)	121/982 (12·3)		
	Relatedness				
	Yes	80/1515 (5·3)	73/1181 (6·2)		
	No	1305/1515 (86·1)	963/1181 (81·5)		
	Unsure	130/1515 (8·6)	145/1181 (12·3)		

†Logistic regression model adjusted for randomised group, age, presence of comorbidity, duration of illness at randomisation, and vaccination status; RR < 1 favours Ivermectin; ‡Level of significance = 0·05