Home-use Photobiomodulation Device Treatment Outcomes for COVID-19

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ABSTRACT

BACKGROUND

There is need for non-pharmaceutical treatments for COVID-19. A home-use photobiomodulation (PBM) device was tested as Treatment in a randomized clinical trial.

METHODS

294 patients were randomized with equal allocation to Treatment or Standard of Care (Control). 199 qualified for efficacy analyses. The Treatment group self-treated for 20 minutes twice daily, for the first 5 days, and subsequently once daily for 30 days. A validated respiratory questionnaire was used, and patients were monitored remotely. The primary endpoint was the time-to-recovery (3 consecutive days of no sickness) for general sickness. The Kaplan-Meier method and the Cox Proportional Hazards model were primary methods of analyses.

RESULTS

Treatment patients with collective 0-12 days of symptoms, at moderate-to-severe level on Day 1 of Treatment, did not recover significantly faster than Control. However, for patients with 0-7 days of symptoms there was a significant mean difference of 3 days: Treatment, 18 days (95% CI, 13-20) vs. Control, 21 days (95% CI, 15-28), P=0.050. The Treatment:Control hazard ratio at 1.495 (95% CI, 0.996-2.243), P=0.054 exceeded the pre-trial target of 1.44. Treated patients exceeding 7 days symptoms duration were more tired and had lower energy. None of the patients in the Treatment group suffered death or hospitalization while the Control group had 1 death and 3 severe adverse events requiring hospitalization.

CONCLUSIONS

Patients with up to 7 days of symptoms at moderate-to-severe levels on first day of Treatment can expect faster recovery for general sickness and several respiratory symptoms. (Funded by Vielight Inc.; ClinicalTrials.gov number, NCT04418505.)

INTRODUCTION

The National Institutes of Health reported that some people have sought "alternative" remedies to treat COVID-19[1], also supported by other reports[2]; hence a need to consider devices for treatment. We report on a randomized clinical trial (RCT) of a non-pharmaceutical option to treat COVID-19, a home-use device based on photobiomodulation (PBM).

The PBM device delivers red and near infrared (NIR) light to selected areas of the body, stimulating mitochondrial activity[3]. The mechanisms include the release of nitric oxide (NO) in the mitochondria[4 3] which has been shown to inhibit the replication of exposed coronavirus[5 6 7 8 9] and support endothelial function[10 11] , beneficial to patients with acute respiratory distress syndrome (ARDS) and impaired pulmonary function[12 13 14], which are features of acute COVID-19[15 16 17].

PBM may attenuate inflammation observed in cases of COVID-19[18 19 9]. NIR light may reach damaged lungs to accelerate healing[20]. The elevated cell count in bronchoalveolar lavage, inflammatory cytokines and neutrophil numbers were reduced in PBM experiments[21]. Systematic reviews[22 23 24 25 26] and case reports[27 28 29 30 31] warrant this RCT.

See Appendix 2, Supplement 1.2.

METHODS

TRIAL DESIGN

The Control group received standard of care, whereas the Treatment group added self-administered home treatment with a PBM device, the "Vielight RX Plus". The trial complied with the Declaration of Helsinki and the International Conference on Harmonization Guidelines for Good Clinical Practice. The protocol was approved by Health Canada and an institutional review board. Patients provided signed informed consent before enrollment. Information was posted on NIH National Library of Medicine website (ClinicalTrials.gov Identifier: NCT04418505).

The measures of COVID-19 improvement were based on the response to relevant questions (Q)1 through 43 on the Wisconsin Upper Respiratory Symptom Survey (WURSS)-44, scoring from 0 (not sick) to maximum 7 (severely sick) (Appendix 1 of the Protocol in Supplement 1).

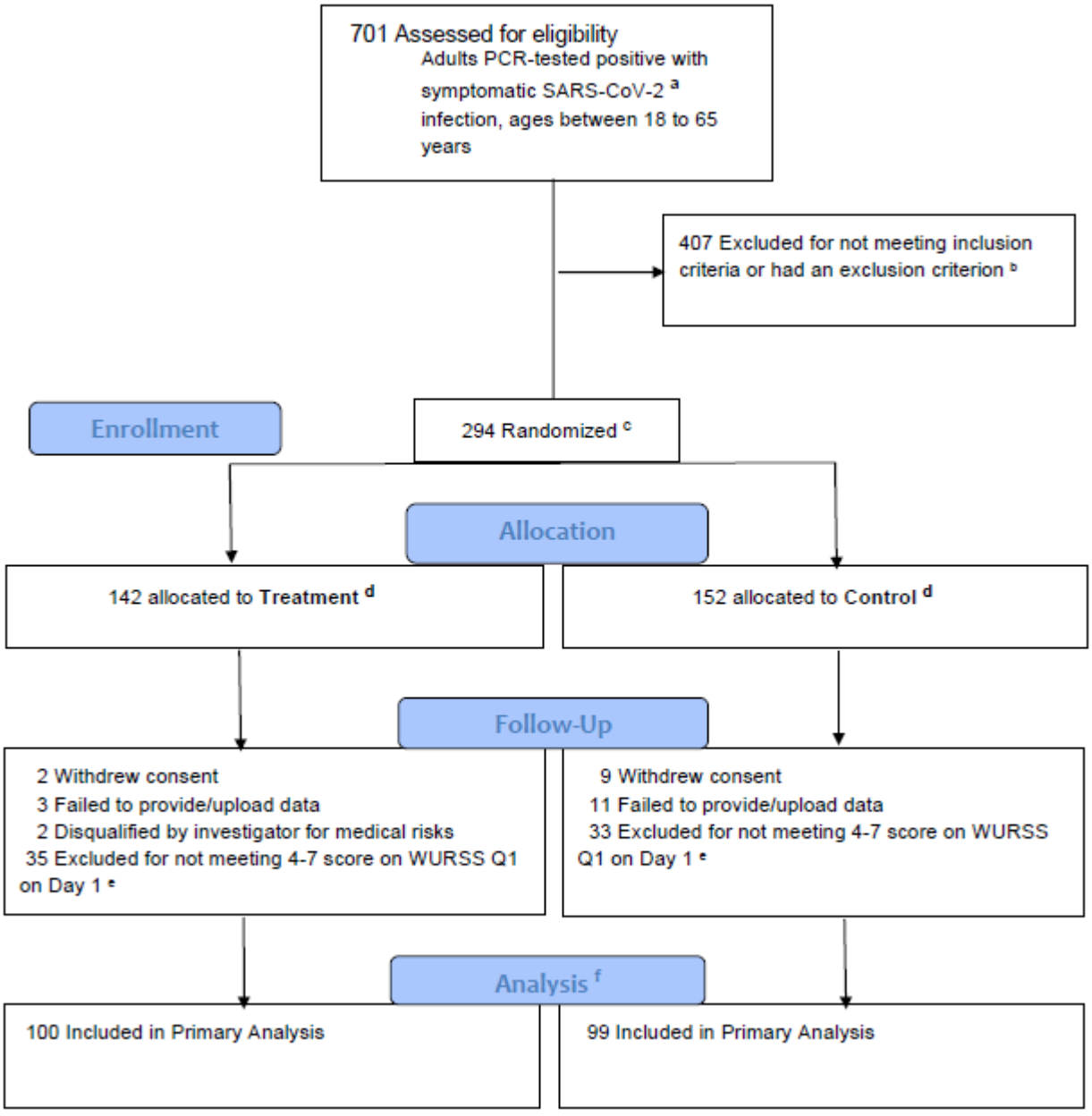
Patients uploaded answers daily through the REDCap Cloud electronic data capture (EDC) platform over 30 days.

PATIENTS AND PROCEDURES

All patients had tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection with reverse transcriptase–polymerase chain reaction (PCR) tests. Qualifying patients scored 4-7 on WURSS Q1 on Day 1 of treatment. Patients were registered via EDC software and then randomized

with equal allocation to the Treatment or Control group using the OxMAR minimization software[32] (See Figure).

Figure. Patient Enrollment and Treatment Allocations



a. *SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2.*
b. *The list of inclusion and exclusion criteria are presented in Sections 6.2 and 6.3 of the Protocol in Supplement 1.*

c. *For enrollment and randomization, patients met the inclusion criteria, which included scores of 4-7 on the WURSS-44 Q1. Patients were allocated equally to Treatment or Control.*
d. *Treatment involved following the standard of care (SoC) plus use of the Vielight RX Plus device, while Control only involved SoC. The allocations to Treatment and Control were managed by the OxMAR randomization software.*
e. *Between Enrollment and Baseline (Day 1 of Treatment), shipping added a mean of 2 days before "Day 1". 35 patients in Treatment and 33 in Control improved to the point that they no longer scored 4-7 for WURSS-44 Q1 and hence excluded from Baseline for analyses. However, they remained for safety monitoring with no bearing on efficacy.*
f. *Primary analyses were carried out on patients who had 4-7 on WURSS-44 Q1 on Day 1 of Treatment (Baseline). The primary time-to-event analyses along with the "intention-to-treat" started at this point.*

TRIAL INTERVENTION AND MONITORING

The intervention was the "Vielight RX Plus" device, shipped to Treatment patients within 24 hours of randomization. The Treatment was self-administered for 20 minutes twice a day for the first 5 days, and subsequently once daily. A pulse oximeter was shipped to all patients to measure oxygen saturation. See Section 5.9 of Supplement 1, product specifications in Supplement 2.

This trial was monitored remotely by a contract research organization, principal investigators, qualified investigators, and study staff.

EFFICACY OUTCOMES

The primary efficacy outcome was the time-to-recovery (days) for WURSS-44 Q1, "How sick do you feel today?". Recovery was defined as the first day of 3 consecutive days with 0 (not sick) score.

Secondary efficacy outcomes included time-to-recovery (days) for WURSS-44 Q2-Q43, and number of days with mild symptoms (0-3 scores). For Safety assessments, the number and percentages of patients reporting adverse events (AEs) and daily oxygen saturation with pulse oximetry were reported. See details in Section 7 of Supplement 1.

The trial targeted to enroll 280 patients in 1:1 randomization. The study was designed to detect the minimum Treatment:Control hazard ratio (HR) of 1.44, with approximately 80% power with 5% type 1 error.

STATISTICAL METHODS

Time-to-recovery (days) was estimated by the Kaplan-Meier (KM) method[33] overall and for baseline strata of 0-5 days and 6-10 days symptoms duration established on enrollment. A stratified log-rank test compared the outcome distributions between Treatment and Control by symptoms duration. An unstratified KM method and log-rank test were used to evaluate time-to-recovery over strata with terms for treatment and symptoms duration strata. Subjects who did not recover were censored on Day 30.

Supportive analyses included stratified and unstratified Cox Proportional Hazards models[34] with 95% confidence intervals (CI).

An analysis of variance (ANOVA) was used to compare mean days of mild symptoms with terms for treatment and symptoms strata. Unstratified analyses were by ANOVA with Treatment as the explanatory variable.

A linear mixed model repeated measures analysis of covariance[35] was used to compare percentage changes in oxygen saturation in safety monitoring. Model terms included treatment, days (7, 14, 21, 28), symptom days strata treatment-by-day interaction and baseline covariate.

Frequency distributions of adverse events were presented. A Poisson regression model was used to compare the mean number of episodes of adverse event (AE) and patients with AEs, between Treatment and Control[36].

The Statistical Analysis Plan and statistical methods are discussed in Supplement 3.1-3.3.

An interim analysis was conducted in January 2021. The results from 73 patients indicated that the study should continue and not stop for futility nor superiority (Supplements 5.1-5.2).

Missing data were not imputed. Kaplan-Meier estimates account for variable follow-up time under the assumption of non-informative censoring.

SAS software[37] was used for statistical analysis. All P-values were two-sided and a P-value <0.050 was used to declare statistical significance.

Sensitivity analysis by multiple imputation was not performed as the data were uniformly complete.

Results

PATIENTS

Recruitment started in September 2020 and data collection completed in August 2021. 701 adults who tested positive for COVID-19 were assessed for eligibility. 407 failed the initial inclusion/exclusion criteria, leaving 294 patients for enrollment, randomization, and allocation at screening. For efficacy analysis, Baseline ("Day 1") was established as the day of first-use of the Treatment device. Shipping added a mean of 2 days, extending the 0-5 days stratum to 0-7 days and 6-10 days stratum to 8-12 days. During this interval, 35 in Treatment and 33 in Control improved and scored below 4 on WURSS-44. Baseline with the intention-to-treat was then established with 199 patients (100 Treatment and 99 Control). See Figure, details in Supplements 4.1-4.3.

Patient demographics, baseline characteristics and WURSS-44 severity scores are presented in Table 1.

Table 1. Patient Demographics, Baseline Characteristics and Symptom Severity Scores

	N		
	Treatment	Control	Combined
Characteristic	100	99	199
Age			
Mean (SD)	37.9 (13.16)	35.3 (11.82)	36.6 (12.54)
Median (IQR)	37 (22.4)	34 (18.7)	36 (20.7)
Sex N (%)			
Female	31 (31.0)	32 (32.3)	63 (31.7)
Male	68 (68.0)	67 (67.7)	135 (67.8)
Unstated	1 (1.0)	0	1 (0.5)
Ethnicity N (%)			
American Indian / Alaskan	2 (2.0)	0	2 (1.0)
Black	2 (2.0)	5 (5.1)	7 (3.5)
Hawaiian / Islander	4 (4.0)	4 (4.0)	8 (4.0)
Caucasian	82 (82.8)	78 (78.8)	160 (80.8)
Other	9 (9.1)	12 (12.1)	21 (10.6)
Anthropometrics			
Height (inches)			
Mean (SD)	66.7 (3.63)	66.6 (4.23)	66.7 (3.93)
Median (IQR)	66.0 (5.0)	66.0 (7.0)	66.0 (5.0)
Weight (pounds)			
Mean (SD)	181.4 (54.24)	173.0 (43.71)	177.2 (49.31)
Median (IQR)	172.0 (69.0)	165.0 (55.0)	170.0 (60.0)
BMI (kg/m^2)[a]			
Mean (SD)	28.7 (9.26)	27.3 (6.37)	28.0 (7.39)
Median (IQR)	27.0 (9.2)	26.2 (8.2)	26.6 (8.6)
Symptoms Duration Stratum at Baseline (%)[b]			
0-5	68 (68.0)	68 (68.7)	136 (68.3)
6-10	32 (32.0)	31 (31.3)	63 (31.7)
0-10 Combined Total	100 (100.0)	99 (100.0)	199 (100.0)
WURSS-44 Severity Score at Baseline N (%)[c]			
4	32 (32.0)	32 (31.3)	63 (31.7)
5	51 (51.0)	48 (48.5)	99 (49.7)
6	15 (15.0)	17 (17.2)	32 (16.1)
7	2 (2.0)	3 (3.0)	5 (2.5)
Residency N (%)			
Canada	8 (8.0)	5 (5.1)	13 (6.5)
United States	92 (92.0)	94 (94.9)	186 (93.5)

Abbreviations: BMI, body mass index; SD, standard deviation, IQR, interquartile range; WURSS, Wisconsin Upper Respiratory Symptoms Survey.
a Calculated as weight in kilograms divided by height in meters squared.
b Patients were stratified by symptoms duration strata 0-5 days or 6-10 days of having COVID-19 symptoms (established upon Enrollment).
c Qualifying patients at Baseline had WURSS-44 Q1 scores of 4-7.

PRIMARY EFFICACY OUTCOMES

For the 199 patients at Baseline (0-10 days symptoms duration), the median time-to-recovery for Treatment was 19 days (95% CI, 16-22) vs. Control of 21 days (95% CI, 19-25), P=0.197, a median difference of 2 days.

For the 0-5 days symptoms duration stratum, the median time-to-recovery for Treatment was 18 days (95% CI, 13-20) vs. Control of 21 days (95% CI, 15-28), P=0.050, a median difference of 3 days.

For the 6-10 days stratum, the median time-to-recovery for Treatment was 23 days (95% CI, 19-27) vs. Control of 21 days (95% CI, 15-23), a median difference of -2 days (P=0.507).

In summary, the 0-5 days stratum demonstrated a significant (P=0.050) 3 day improvement to recovery. The 6-10 days stratum was worse (slower recovery) by 2 days (P=0.507).

Results are in Table 2, full table in Supplement 6.3.

For all patients on Day 1, the hazard ratio (HR) was 1.252 (95% CI, 0,888-1.764), P=0.199. For the 0-5 days stratum, HR was 1.495 (95% CI, 0.996-2.243), P=0.052. For the 6-10 days stratum, HR was 0.803 (95% CI, 0.425-1.517), P=0.499. See Table 2 and Supplement 7.1. The HR of 1.495 for the 0-5 days stratum exceeded the pre-trial target, while the 6-10 days stratum and full population did not.

Table 2. Primary Outcome – Time-to-Recovery and Hazard Ratio by Symptoms Duration Strata

Symptoms Duration	No.			Days-to-Recovery with Kaplan-Meier Method				Cox Proportional Hazards Model Hazard Ratio (HR)		
Stratum	Treatment	Control	Total	Treatment	Control	Difference	P-value	HR	95% CI	P-value
0-10 days (All)	100	99	199	19	21	2	0.197	1.252	(0.888, 1.764)	0.199
0-5 days	68	68	136	18	21	3	0.050	1.495	(0.996, 2.243)	0.052
6-10 days	32	31	63	23	21	-2	0.507	0.803	(0.425, 1.517)	0.499

"Recovery" in Time-to-recovery is defined as the first of 3 consecutive days with WURSS-44 Q1 score of 0. The medians of the days-to-recovery were estimated at 95% confidence intervals (CI). Significance in the difference between the Treatment and Control groups (P-values) was estimated using the log-rank test stratified by symptoms duration, and unstratified log-rank test within stratum. The full table is presented in Supplement 6.3. The Treatment:Control hazard ratios (HR) and 95% CI were estimated with

a Cox Proportional Hazards model. The table covering the full set of symptoms estimated with this method is presented in Supplement 7.1.

SECONDARY EFFICACY OUTCOMES

As secondary efficacy outcomes, patients with WURSS-44 Q1 scores of 4-7 at Baseline were assessed for time-to-recovery for Q2-Q43 (Table 3).

For the full population, statistical significance favoring Treatment was observed for sinus pain, chest congestion, body aches, think clearly, ear discomfort, sinus drainage, headache, coughing up stuff and sneezing.

For the 0-5 days symptoms duration stratum, significance was observed for headache, sinus pain, thinking clearly, chest congestion and body aches.

For the 6–10 days stratum, the Treatment group recovered significantly more slowly for feeling tired and lack of energy.

We also assessed the Treatment effectiveness in reducing symptom severity, expressed as the mean number of days of mild symptoms (WURSS-44 Q1-43 scores of 0-3). For all patients, Treatment results were significantly better for runny nose, sneezing, body aches, irritability, and ear discomfort. For the 0-5 days stratum, Treatment showed significance for headache. For the 6-10 days stratum, Treatment showed significance for runny nose, sneezing, body aches, sinus drainage and plugged ears. See Supplement 8.

Table 3. Secondary Outcomes of Patients with P<0.050 Log-rank for Time-to-recovery and Hazard Ratio

		Kaplan-Meier							Cox Proportional Hazards		
Symptom	Symptoms Duration at Baseline (Days)	Treatment	N Total	N Recovered	N Censored	Median Days to Recovery	95% CI	KM Log-rank P-value	Hazard Ratio	95% CI	Cox P-value
Patients with 0-10 Days Symptoms Duration (all at Baseline)											
Sinus pain	0 to 10	Treatment	39	35	4	10	(8, 13)	0.005	2.001	(1.203, 3.328)	0.008
		Control	42	30	12	17	(9, 25)				
		Total	81	65	16	7					
Chest congestion	0 to 10	Treatment	43	38	5	15	(9, 18)	0.017	1.878	(1.105, 3.193)	0.020
		Control	35	22	13	21	(17, 30)				
		Total	78	60	18	6					
Body aches	0 to 10	Treatment	60	52	8	12	(9,15)	0.019	1.652	(1.084, 2.519)	0.020
		Control	59	39	20	15	(12, 20)				
		Total	119	119	28	3					
Think clearly	0 to 10	Treatment	44	34	10	11	(9, 15)	0.020	1.893	(1.013, 3.248)	0.021
		Control	41	23	18	21	(12, 30)				
		Total	85	57	28	10					
Ear discomfort	0 to 10	Treatment	24	21	3	12.5	(8, 17)	0.023	2.325	(1.104, 4.893)	0.026
		Control	21	11	10	24.0	(12, 36)				
		Total	45	32	13	13.5					
Sinus drainage	0 to 10	Treatment	28	22	6	12	(10, 17)	0.026	2.14	(1.088, 4.203)	0.028
		Control	27	15	12	23	(10, 36)				
		Total	55	37	18	11					
Headache	0 to 10	Treatment	67	53	14	14	(11, 20)	0.031	1.586	(1.036, 2.429)	0.034
		Control	61	36	25	21	(14, 28)				
		Total	128	89	39	7					
Coughing up stuff	0 to 10	Treatment	27	25	2	13	(10, 20)	0.037	1.817	(1.013, 3.261)	0.045
		Control	32	21	11	21	(14, 27)				
		Total	59	46	13	8					
Sneezing	0 to 10	Treatment	33	29	4	13	(9, 18)	0.049	1.92	(1.064, 3.467)	0.030
		Control	22	14	8	17	(10, 24)				
		Total	55	43	12	4					
Patients with 0-5 Days Symptoms Duration											
Headache	0 to 5	Treatment	50	43	7	13	(10, 16)	0.006	2.027	(1.216, 3.378)	0.007
		Control	40	23	17	19	(14, 24)				
		Total	90	66	24	6					
Sinus pain	0 to 5	Treatment	28	24	4	9	(7, 13)	0.022	1.926	(1.074, 3.452)	0.028
		Control	32	22	10	15	(9, 25)				
		Total	60	46	14	6					
Think clearly	0 to 5	Treatment	29	22	7	10	(9, 15)	0.024	2.067	(1.093, 3.909)	0.025
		Control	30	17	13	21	(12, 30)				
		Total	59	39	20	11					
Swollen glands	0 to 5	Treatment	20	19	1	8	(6, 10)	0.029	2.436	(1.046, 5.676	0.039
		Control	13	9	4	10	(7, 13)				
		Total	33	28	5	2					
Chest congestion	0 to 5	Treatment	32	28	4	15	(9, 20)	0.042	1.847	(1.008, 3.384)	0.047
		Control	27	17	10	21	(10. 32)				
		Total	59	45	14	6					
Body aches	0 to 5	Treatment	46	39	7	12	(9, 17)	0.050	1.641	(0.996, 2.704)	0.052
		Control	39	26	13	15	(12, 23)				
		Total	85	65	20	3					
Patients with 6-10 Days Symptoms Duration											
Feeling tired	6 to 10	Treatment	25	9	16	25.5	(24, 27)	0.037	0.432	(0.192, 0.972)	0.094
		Control	29	17	12	20	(13, 27)				
		Total	54	26	28	4.5					
Lack of energy	6 to 10	Treatment	25	10	15	26.5	(27, 26)	0.049	0.47	(0.220, 0.996)	0.049
		Control	27	16	11	20	(15, 25)				
		Total	52	26	26	3.5					

Time-to-recovery outcomes were estimated with the Kaplan-Meier (KM) method. Hazard ratios were estimated with the Cox Proportional Hazards model. The full table for time-to-recovery estimates using the KM method is presented in Supplement 6.3. The full table for hazard ratios estimated with Cox, are presented in Supplement 7.1.

SAFETY OUTCOMES

After initial follow-up, 267 enrolled patients (135 in Treatment and 132 in Control) were monitored for adverse events. The safety population included all randomized subjects with a response of 4+ to WURSS Q1 on enrollment.

None of the Treatment patients suffered death or severe adverse events (SAEs). In Control, there were 4 (3.0%) SAEs that required hospitalization, including 1 death (Tables 4(1)-4(2)).

AEs occurring in >5% of patients are listed in Table 4(3). Patients in Treatment had significantly lower AEs in Tachycardia and Dysgeusia but not for other AEs.

In the assessment of percentage changes in oxygen saturation, Treatment produced improvements with a mean difference of 0.32%, P=0.018 (Supplements 9.1-9.3).

Table 4. Summary Tables of Adverse Events

1. All-cause Mortality

No of patients	Treatment or Control[1]	Diagnoses on expiration
1	Control	- septic shock - COVID-19 pneumonia - bilateral pneumonia - hypoxic respiratory failure - left-sided pneumothorax - severe subcutaneous emphysema - Type 2 diabetes - (history of) hypertension - hyperlipidemia - history of coronary artery disease (post 2 stents placement to the left anterior descending artery) - sick sinus syndrome (post permanent pacemaker placement) - moderate protein-calorie malnutrition due to acute illness - acute kidney injury, likely due to acute tubular necrosis due to septic shock

2. Serious Adverse Events requiring Hospitalization (Excluding Deaths)

No of patients	Treatment or Control[1]	Diagnosis
1	Control	COVID pneumonia
1	Control	Respiratory decomposition
1	Control	Unspecified COVID symptoms

3. Adverse Events Not Requiring Hospitalization[2 3 4 5]

	Monitored from Enrollment									
	Treatment Group, N=135			Control Group, N=132			Differences in % of Patients, Treatment-Control			
	Number of	% in	Number of	Number of	% in	Number of	Difference	95% CI		
Adverse Event	Patients	Treatment	Events	Patients	Control	Events	in %	Lower	Upper	P-value
Significant Symptom										
Tachycardia	40	29.63	107	58	43.94	180	-14.30	-25.90	-1.87	0.016
Dysgeusia	7	5.19	7	24	18.18	24	-13.00	-21.20	-4.63	0.001
Other Symptoms >5% of Patients										
Bradycardia	38	28.15	100	38	28.79	102	-0.64	-11.60	10.51	0.940
Diarhea	19	14.07	23	24	18.18	27	-4.11	-13.30	4.89	0.529
Nausea	16	11.85	18	27	20.45	31	-8.60	-17.90	0.36	0.058
Anosmia/parosmia	11	8.15	11	15	14.35	19	-6.25	-14.30	1.55	0.126
Emesis	8	5.93	8	10	7.58	12	-1.65	-8.28	4.75	0.683

1. Events in "Control" would be unrelated to the investigational agent.

2. "Adverse Events Not Requiring Hospitalization" covered all severity levels of adverse events not requiring hospitalization.

3. Symptoms occurring in >5% of monitored patients are listed. The full table is shown in Supplement 10.2.
4. Patients were monitored for safety and adverse events from the time of Enrollment and after initial Follow-up. As the result 267 were monitored, 135 in Treatment and 132 in Control.
5. Upon Enrollment all these patients qualified with WURSS-44 severity scores of 4-7. They continued to be monitored throughout their 30-day assessment period although some would fail to be included in the Baseline for Final Analysis due to improvements before Day 1 of treatment.
Fuller discussions on AEs are presented in Supplements 10.1-10.4.

Discussion

The assessment of patients with combined symptoms duration of 0-10 days (established on enrollment) did not show significance for the primary outcome of time-to-recovery for general sickness. However, those with 0-5 days presented significant Treatment vs Control difference with P=0.050, supported by hazard ratios exceeding the pre-trial target.

The strata of 0-5 days and 6-10 days symptoms duration were reset to 0-7 days and 8-12 days respectively at Baseline due to device shipment time, allowing the same start for Control and Treatment patients for analyses.

By interpretation, patients with symptoms of up to 7 days can expect to recover more quickly than those with longer symptoms duration; and avoid the side effects of tiredness and energy deficits.

Patients with 0-7 days symptoms duration are also more likely to experience quicker recovery for headache, sinus pain, think clearly, swollen glands, and chest congestion; and experience more mild days with headache.

Fewer treated patients are expected to experience tachycardia and ageusia which were the most frequent adverse events reported.

There were several limitations. Firstly, the RCT was not double-blinded with a placebo device. Attempts at masking the efficacious visible red light of this device would likely fail with alert users. Secondly, the methodology was based on self-reporting. However, the WURSS-44 questionnaire had performed well as an illness-specific quality-of-life evaluative outcome instrument.[38] Thirdly, the statistical power to detect differences in each WURSS-44 Q1-Q43 was reduced due to the sample size presenting with WURSS-44 4-7 severity scores for each item at Baseline.

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