Randomized trial of ultraviolet irradiation units installed in homes of children and adolescents with asthma

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Background: Asthma management involves medications with environmental control, but patient adherence to the latter is poor. A previous pilot study found an ultraviolet indoor air-irradiation system (CREON2000A) was effective in reducing asthma severity in children with mild to moderate asthma.
Objective: This trial's purpose was to confirm these results in a larger population over a longer time duration.
Methods: A 12-month randomized, sham device–controlled multicenter study enrolled 79 children with mild to moderate persistent asthma aged 6 to <18 years. Participants were randomized to have a CREON2000A ultraviolet air irradiation device or a sham device installed in their home's ventilation system. Enrolled children were assessed with the Composite Asthma Severity Index at baseline and every 4 months; asthma treatment was adjusted according to National Heart, Lung, and Blood Institute EPR-3 guidelines. The primary analysis compared the efficacy of the CREON2000A versus sham device from baseline to end of study (12-month visit). A sensitivity analysis compared efficacy across the 4-, 8-, and 12-month visits.
Trial registration: Investigate the Effect of the CREON2000A on Asthma Control in Children With Mild to Moderate Persistent Asthma (CREON2000A), ClinicalTrials.gov, NCT02715375.
Results: Baseline demographic characteristics of CREON2000A (n = 40) versus sham device (n = 39) groups were similar. The primary analysis estimated a difference in Composite Asthma Severity Index score for CREON2000A at 12 months relative to the sham device, which was not statistically significant ($\Delta_{Estimated}$ = 0.53; P = .404; 95% confidence interval, −0.576, 1.628). A sensitivity analysis detected a device benefit across all postbaseline values ($\Delta_{Estimated}$ = 0.76; P = .034; 95% confidence interval, 0.057, 1.465). A benefit was also observed for asthma daytime symptom score, average asthma exacerbations score, missed school days, rhinitis symptoms, and average number of respiratory infections (nominal P < .05 in all cases).
Conclusion: This small trial is inconclusive, but some results show promise, suggesting that this device and the concept of indoor air irradiation as an environmental intervention is worthy of further study in children with mild to moderate persistent asthma. (J Allergy Clin Immunol Global 2025;4:100427.)

Key words: *Asthma, CASI, CREON2000A, environmental intervention, ultraviolet*

Asthma represents the second most prevalent childhood condition and the single most common chronic condition among children.[1-3] The US Centers for Disease Control and Prevention estimates 1 in 12 children aged 5-14 years and 1 in 9 aged 15-19 years have asthma.[2] The burden of asthma is significant in these age groups. A 2013 survey reported that asthma was the primary reason for missed school days (~13.8 million days per year), and 50% of responders had one or more asthma exacerbations in the past year, which is similar to what has been reported more recently.[1-6] Despite increased knowledge regarding asthma pathogenesis and the availability of effective pharmacologic treatments, asthma prevalence and disease-related morbidity has steadily increased between 1997 and 2018, and it continues to remain high in children, resulting in significant health care costs.[1,4,7-10]

Asthma guidelines[11] recommend environmental control (EC) interventions to avoid or eliminate relevant indoor allergen and irritant triggers[12-18] that precipitate asthma symptoms or exacerbations.[19] Studies investigating the health effect of single interventions have yielded conflicting results.[20,21] Effective EC requires a multifaceted approach combining several interventions[19,22-25] tailored to the specific needs of each patient. The

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Abbreviations used

AE: Adverse event
CASI: Composite Asthma Severity Index
CI: Confidence interval
EC: Environmental control
FEV_1: Forced expiratory volume in 1 second
%FEV_1: Percentage predicted FEV_1
HEPA: High-efficiency particulate arrest
HVAC: Heating, ventilation, and air-conditioning
ICAC: Inner City Asthma Consortium
ITT: Intent to treat
MELRM: Mixed effects linear regression model
MID: Minimally important difference
MLR: Multiple linear regression
NIAID: National Institute of Allergy and Infectious Diseases
SD: Standard deviation
UV: Ultraviolet

economic impact of a combination of EC approaches can be costly over time, which leads to poor adherence.[20,26]

The CREON2000A (General Innovations and Goods, Columbus, Ohio) is a low-maintenance ultraviolet (UV) irradiation EC intervention designed to prevent or reduce asthma symptoms and exacerbations while improving overall health. Ultraviolet irradiation of indoor air effectively reduces bacteria, viruses, and other airborne microorganisms, thereby protecting against airborne infection transmission. The ability of UV irradiation to kill microbial, viral, and fungal organisms has been previously demonstrated by Menzies and colleagues, who conducted a double-blind multiple crossover trial investigating the health effect in 771 workers of cycling on and off UV germicidal irradiation lights installed in their office building.[27] They found a 99% reduction of microbial and endotoxin concentrations on irradiated surfaces in the ventilation systems, and workers reported significantly fewer work-related respiratory and mucosal symptoms. The authors speculated that the low cost of UV germicidal irradiation installation means it could be a cost-effective approach for reducing missed days from work or absenteeism related to building-related illness.

The CREON2000A UV air irradiation unit is mounted inside the ventilation duct and works in conjunction with the central heating, ventilation, and air-conditioning (HVAC) system to irradiate air circulating through the ducts and is a novel device because it is equipped with a pre–high-efficiency particulate arrest (HEPA) filter, which is designed to only protect the bulb from dust accumulation so that high microbicidal activity is maintained over 12 months.[28] The HEPA filter does not affect the air in the duct, as more than 99.5% of air traveling through the duct does not pass through the HEPA filter (see Fig E1 in the Online Repository available at www.jaci-global.org). A detailed explanation of the operational features of the CREON2000A device is provided in the Methods section in the Online Repository. A previous pilot study reported that this device, installed in asthmatic children's homes, improved asthma outcomes.[29]

The objective of this study was to conduct a larger randomized controlled clinical trial to confirm whether the CREON2000A technology is an effective nonpharmacologic intervention for reducing asthma severity and improving asthma control in children with mild to moderate persistent asthma over a 12-month study period.

METHODS

Trial design and oversight

A 12-month randomized, double-blind, sham-controlled study at 17 sites within the Midwest and Florida was conducted. Participants were randomized to install in their homes either a CREON2000A or sham device in a 1:1 allocation. The study was double blinded, so all clinical investigators, including General Innovations and Goods investigators, clinical research coordinators, study monitors, and anybody determining subject eligibility evaluating end points or assessing compliance with the study protocol, were not aware of the treatment assignment. This study was conducted under a National Institute of Allergy and Infectious Diseases (NIAID) clinical trial grant to General Innovations and Goods (the sponsor) (ClinTrials.gov, NCT02715375). The protocol was approved by a central institutional review board (Schulman Institutional Review Board), and written informed consent or assent was signed by all participants and/or their legal guardians before enrollment. The NIAID Allergy and Asthma Data and Safety Monitoring Board provided oversight of protocol safety. Device randomization and site-specific participant randomization were performed in 2 separate stages. The blinding codes were maintained in a secure area, and any unblinding for safety reasons or final unblinding after database lock had to be approved by the study NIAID medical officer and the study's protocol chair. Additional details of randomization and concealment are provided in the Methods section of the Online Repository.

Study participants

Children 6 to <18 years old with a physician diagnosis of mild or moderate persistent asthma, as determined by receiving inhaled corticosteroids per treatment steps 2 to 4, according to the National Heart, Lung, and Blood Institute EPR-3 guidelines, were enrolled.[19] All potential participants required a ≥60% predicted forced expiratory volume in 1 second (FEV_1) and a Composite Asthma Severity Index (CASI) score of ≥3. The CASI instrument is a multidimensional instrument developed by the NIAID-funded Inner City Asthma Consortium (ICAC) that incorporates risk and impairment outcomes as well as the amount of medication needed to maintain asthma control (see Table E1 in the Online Repository at www.jaci-global.org).[29] The protocol's inclusion criteria were subsequently modified with institutional review board approval to permit children living in homes with 2 HVAC systems to be enrolled. The final inclusion and exclusion criteria are summarized in the Methods section of the Online Repository.

Study visits and assessments

All randomized participants had a baseline clinic visit (day 1) and 3 subsequent clinic visits at 4 months (120 ± 7 days), 8 months (240 ± 7 days), and 12 months (360 ± 14 days) (see Fig E2 in the Online Repository available at www.jaci-global.org). During the trial, every 4 months, the prescribed dose of each participant's controller asthma medication was reassessed, and if needed, changes were made by the site's clinical investigator

using an algorithm that was modified from ICAC's.[30,31] Adverse events (AE) during the study were captured at each office and phone call visit. Asthma exacerbations were not considered AEs in this study but were documented.

Outcome measures

The primary efficacy end point was the difference between study arms in the change in asthma severity measured by CASI from baseline (visit 1) to the 12-month follow up (visit 5).[30,32] CASI scores include 5 individually scored domains (daytime symptoms and albuterol receipt, nighttime symptoms and albuterol receipt, asthma controller treatment, percentage predicted FEV_1 [%FEV_1] asthma exacerbations) that are summed to determine a total score, which ranges from 0 to 20, with 0 reflecting very mild, well-controlled asthma. In most published studies using CASI, the score in children with moderate and severe asthma is in the range of 4 to 6—that is, much smaller than 20 (as in the Asthma Phenotypes in Inner City and other ICAC studies).[33] A CASI score of 3 was previously determined to be the optimal cut point discriminating a low from a medium or high severity rating.[30,32] A minimally important difference (MID) of 0.49 points in effect size was previously defined.[32] This particular MID value referred to the minimum difference between populations, as opposed to a change within an individual, which, by definition, can be no smaller than 1.

The secondary efficacy end points were the differences between study arms in mean change over time in each of the CASI components (daytime asthma symptoms score, nighttime asthma symptoms score, %FEV_1, asthma exacerbation score, receipt controller and rescue medications, respiratory infections, rhinitis scores, and the number of missed schooldays or workdays; see the Methods section in the Online Repository). For all of these outcomes, values from baseline (visit 1), 4-month (visit 3), 8-month (visit 4), and the final 12-month (visit 5) visits were to be assessed.

Statistical analysis

The primary and secondary end point analyses were performed as an intent-to-treat (ITT) analysis (see the Methods section in the Online Repository). The prespecified primary analysis used a multiple linear regression (MLR) model that used only CASI scores at baseline and at 12 months. Secondary analyses were to be conducted using a gatekeeping approach and thus were not formally tested if the primary analysis was not significant. Secondary end point *P* values should be considered descriptive.

While this primary analysis model fit the protocol requirement, its power to detect a difference was greatly reduced because of the curtailed sample size. In addition, the MLR model did not include as an independent variable changes in pharmacologic treatment of asthma that were made on the basis of the standardized algorithm, because these changes are incorporated in the CASI. To address the latter limitation, a prespecified sensitivity analysis of CASI scores using a mixed effects linear regression model (MELRM) was conducted that incorporated responses to the intervention measured at baseline and 4, 8, and 12 months, allowing for the potential detection of treatment benefit over the entire year. Both MLR and MELRM were analyzed with protocol-specified predictors including baseline CASI score, device (CREON2000A vs sham device), patient age, and season. Five missing values were imputed at the final 12-month visit for CASI values by device by implementing the AMELIA II program, which uses simulations of multivariate normal distributions. This program multiplies imputed data through the bootstrap expectation and minimization (aka EM) algorithm approach.[34] Imputed dataset *P* values were combined by the harmonic mean method.[35] For the subgroup with CASI ≥ 4, in a *post hoc* analysis, multiple imputation chain equation (aka MICE) was used for imputation.[36] Chi-square test of association or Fisher exact test was performed for categorical variables, and 2-sample *t* test was performed for continuous variables. The MLR and MELRM were implemented in SAS 9.4.2 (SAS Institute, Cary, NC) and through the 'lme4' package in R (R Project; www.r-project.org). Two-sided $P < .05$ was considered statistically significant for the primary analysis (MLR); the *P* values for secondary end points should only be considered descriptive because of the gatekeeping approach (see the Methods section in the Online Repository).

Sample size calculation

Sample size was calculated to identify the number of participants per group to detect a 30% decline in CASI scores in the treated group, starting from a baseline of 4.8. This hypothesized effect size was based on the original CASI validation work.[30] This corresponds to an assumption of 4.8 and 3.4 as the 12-month means, and thus a difference of 1.4 between the average CASI score from baseline to 12 months for the CREON2000A versus the sham device group with 80% power (2 tailed, $\alpha = 5\%$).[30,31] For different values of standard deviation (SD) based on the change in CASI scores, per-group sample sizes were calculated by applying an unpaired (2 sample) *t* test and using different assumptions about the correlation of CASI scores between baseline and 12 months, and a SD of 2.5 (G*Power 3.1.9.7, www.psychologie.hhu.de/arbeitsgruppen/allgemeine-psychologie-und-arbeitspsychologie/gpower).[30] These sample sizes were increased to allow for inclusion of a 15% subject dropout rate.[37] From these calculations, an initial sample size of 160 subjects (80 per group) was determined.

RESULTS

Study enrollment

A total of 83 participants were enrolled (43 onto the CREON2000A arm and 40 onto the sham device arm) into this study before discontinuation due to slow enrollment and administrative delays. The study's CONSORT flow diagram is illustrated in Fig 1.[38] All but 4 randomized participants were included in the final analyses. Three participants were excluded from the ITT analysis, as stipulated in the protocol, because the CREON2000A or sham devices were not installed correctly or not functioning properly during the study, as this was considered random and unrelated to any participant characteristics or decision. One participant not fulfilling all inclusion criteria was excluded. Five participants from the sham device study group who did not attend visit 5 despite multiple attempted contacts were considered lost to follow-up, but their data were included in the ITT analysis and their missing values imputed.

Demographics and other baseline characteristics

Table I summarizes demographic and baseline characteristics of participants randomized to the CREON2000A and sham device groups. There were no statistically significant differences between

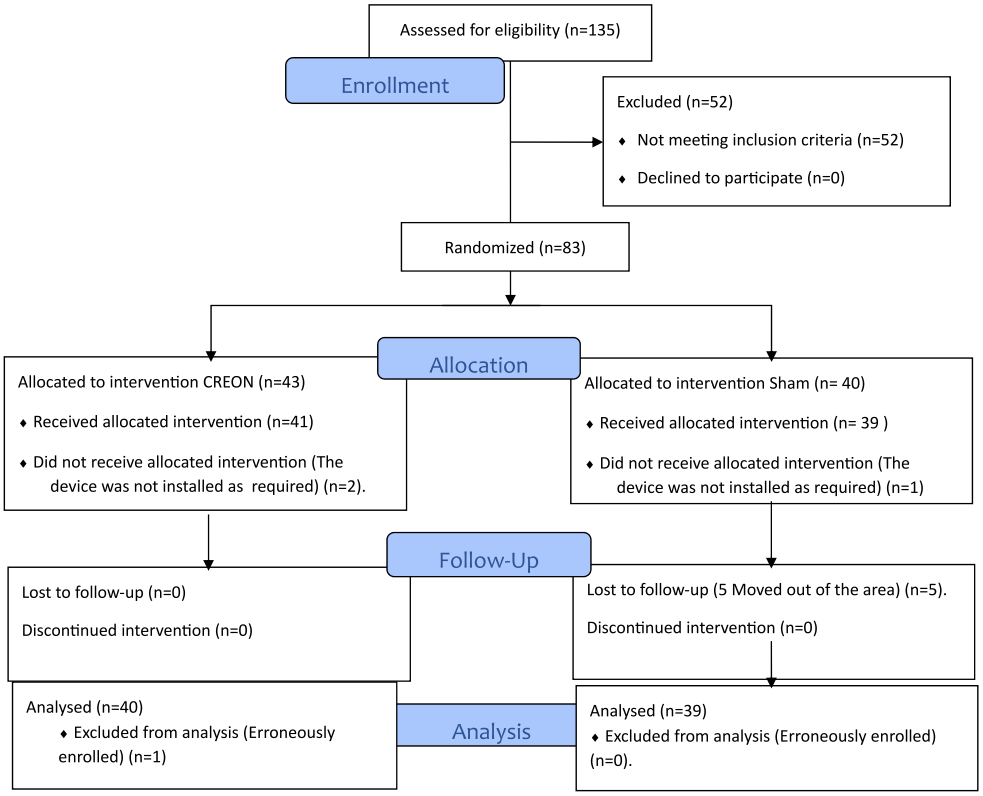

FIG 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing study enrollment, randomization, and allocation of subjects.

groups in sex, race, age, household education, income level, season of enrollment, atopic status, baseline CASI score, or housing characteristics, indicating that our randomization process was effective. Of note, two thirds of enrollees had atopic disease and one third nonatopic; they were evenly distributed between groups.

Primary end point

The primary efficacy end point determined for the ITT population revealed an estimated benefit in reduction of asthma severity, or $\Delta CASI_{(baseline\text{-}12\ months)}$, from baseline to 12 months for CREON2000A (n = 40) versus sham device (n = 39) groups of 0.53 (95% confidence interval [CI], −0.576, 1.628), which was not statistically significant (P = .404) (Table II).

Sensitivity analyses

Although the primary end point was not significant, it was observed that the change in CASI was 0.53, which is larger than the previously established minimum important difference of 0.49.[30] Interestingly, a *post hoc* MLR model demonstrated a significant interaction between the CREON2000A and baseline CASI score (P = .003) estimating that the benefit of the device was larger as the baseline CASI score became higher. In view of this finding, a *post hoc* subgroup analysis with CASI ≥ 4 using the MLR (data from visits 1 and 5) and MELRM (data from visit 1, 3, 4, and 5 models) was performed using the protocol-specified covariates (CASI score at visit 1, device, age, and season). Applying the MLR model in the subgroup with 2 imputed values yielded a P value of .124, whereas applying the MELRM model yielded a P value of .005 favoring the CREON2000A over the sham device (see Fig E12 and Fig E13 in the Online Repository available at www.jaci-global.org).

The prespecified sensitivity analysis of the CASI scores using the MELRM, which compares the baseline value to responses from all postbaseline clinical visits and accommodates for missing values, yielded a statistically significant device effect (P = .034; $\Delta_{Estimated}$ = 0.76; 95% CI, 0.057, 1.465) using the above protocol-specified covariates. The P values for the 3 covariates were visit 1 CASI score (P = .002), visit times (P = .002), and age (P = .287). The mean asthma severity (CASI) scores over 12 months are summarized in Fig 2.

Secondary and exploratory end points

CREON2000A compared to sham device reduced the number of daytime asthma symptoms score (P = .016), exacerbations score (P = .034), and Modified Rhinitis Symptom Utility Index scores (P = .016), with effects of the number of missed school days (P = .051) and improvement in $\%FEV_1$ (P = .089) in the same direction. No differences in the mean change in number of nighttime asthma symptoms score, (P = .670), short-acting β-agonist receipt (P = .701), and the prescribed treatment score (P = .116) were observed (Table II, and see Figs E3 to E10 in the Online Repository available at www.jaci-global.org).

The overall incidence of respiratory infections was reduced by almost 50% in the CREON2000A group (30.0%) compared to the sham device group (56.4%). Over the period of 12 months, the relative risk of respiratory infection with the CREON2000A

TABLE I. Demographic and baseline characteristics of randomized subjects

Characteristic	CREON2000A group	Sham device group	Total	*P* value
No. of subjects	40	39	79	
Sex				
Male	20 (50.0)	25 (64.10)	45 (57.0)	.299
Female	20 (50.0)	14 (35.9)	34 (43.0)	
Race or ethnic group				
Black or African American	7 (17.5)	9 (23.1)	16 (20.2)	.821
White	30 (75.0)	27 (69.2)	57 (72.2)	
Other	3 (7.5)	3 (7.7)	6 (7.6)	
Season of enrollment				
Winter	7 (17.5)	6 (15.4)	13 (16.4)	.680
Spring	4 (10.0)	5 (12.8)	9 (11.4)	
Summer	3 (7.5)	6 (15.4)	9 (11.4)	
Fall	26 (65.0)	22 (56.4)	48 (60.8)	
Education level of mother				
Master's and/or more	7 (17.5)	7 (17.9)	14 (17.7)	.107
College	31 (77.5)	24 (61.5)	55 (69.6)	
High school	2 (5.0)	8 (20.5)	10 (12.7)	
Household income				
<$50,000	15 (37.5)	14 (35.9)	29 (36.7)	.989
$50,000 to $100,000	11 (27.5)	11 (28.2)	22 (27.8)	
>$100,000	14 (35.0)	14 (35.9)	28 (35.4)	
Housing characteristics				
Attached family home	5 (12.5)	4 (10.3)	9 (11.4)	1.00
Detached family home	35 (87.5)	35 (89.7)	70 (88.6)	
Carpet in subject's bedroom				
Yes	34 (85.0)	26 (66.7)	60 (75.9)	.06
No	6 (15.0)	13 (33.3)	19 (24.1)	
Location of house				
Rural	4 (10.0)	5 (12.8)	9 (11.4)	.922
Urban	12 (30.0)	11 (28.2)	26 (32.9)	
Suburban	24 (60.0)	23 (59.0)	47 (59.4)	
Atopic status				
Yes	26 (65)	27 (69.2)	53 (67.1)	.689
No	14 (35)	12 (30.8)	26 (32.9)	
Age (years) at consent	11.36 ± 3.02	11.34 ± 3.31	11.35 ± 3.15	.982
Duration (years) of asthma	7.45 ± 3.66	5.82 ± 3.24	6.64 ± 3.97	.068
Mean CASI score at visit 1	5.10 ± 2.67	4.92 ± 1.79	5.01 (2.27)	.73
Time spent in home (h/d per subject)	15.46 ± 2.87	15.56 ± 3.65	15.49 (3.05)	.89
No. of household members	4.35 ± 1.05	4.18 ± 1.23	4.31 (1.20)	.51
No. of household members under 21 years	2.37 ± 0.98	2.15 ± 1.11	2.33 (1.08)	.35

Data are presented as nos. (%) or means ± SDs unless otherwise indicated.

TABLE II. Mean CASI score over 12-month study period

Time point	CREON2000A group	Sham device group	Effect size*	MLR		MELRM	
				$\Delta_{Estimated}$	*P* value	$\Delta_{Estimated}$	*P* value
Baseline	5.10 ± 2.67	4.92 ± 1.79	0.079	0.53	.404	0.76	.034
4 months	3.99 ± 1.76	4.96 ± 2.58	0.440				
8 months	3.35 ± 1.53	4.15 ± 2.32	0.408				
12 months	3.41 ± 2.01	3.82 ± 2.66	0.174				

Data are presented as averages ± SDs unless otherwise indicated. Mean ± SD CASI at baseline (visit 1); and at 4-month (120 ± 7 days), 8-month (240 ± 7 days), and 12-month (360 ± 14 days) follow-up office visits.
*Mean difference in CASI scores between CREON2000A and sham device in terms of SD.

device compared to the sham device was 0.53 (95% CI, 0.31, 0.92; $P = .024$). This effect was primarily due to a substantial reduction in respiratory infections during the winter season (relative risk = 0.19; 95% CI, 0.044, 0.81; $P = .025$) (see Table III and, in the Online Repository available at www.jaci-global.org, Fig E3 and Fig E11).

AEs

There were 96 AEs in 52 of 79 participants over the 12-month study period for all research sites; 39 were observed in the CREON2000A group and 57 in the sham device group (Table E3 and the Methods section in the Online Repository). The most common AE was upper respiratory infection

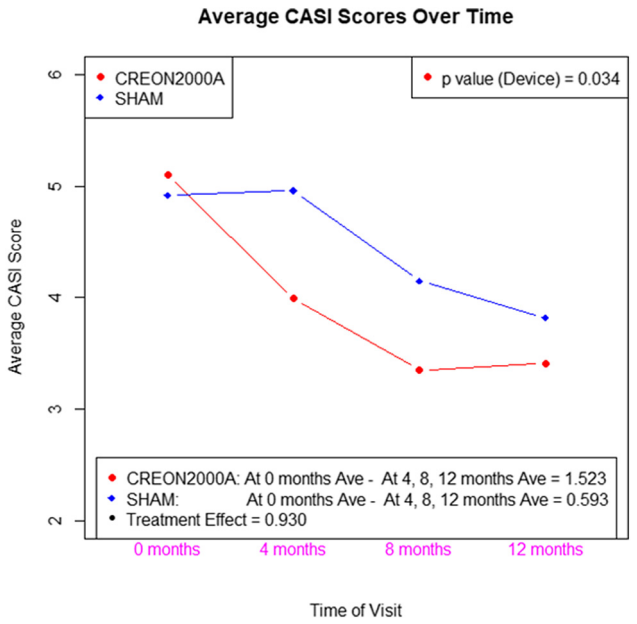

FIG 2. CASI scores over time. Average CASI score at each study visit by intervention arm (sensitivity analysis). Mean asthma severity (CASI) scores over 12 months are also summarized.

(bacterial or viral). There were two serious AEs; in one, a participant in the sham device group experienced a life-threatening allergic reaction after eating food containing shrimp; in the other, a participant in the CREON2000A group was admitted to the hospital for a major depressive episode. None of the AEs or serious AEs was assessed as being related to the study intervention. No participants withdrew from the study because of an AE.

DISCUSSION

The primary end point, which compared mean CASI score at baseline and at 12 months, showed that the estimated benefit of the intervention was not statistically significant, as the study fell well short of achieving the planned sample size and was thus underpowered. Because of this finding, we cannot make an efficacy claim.

Notably, the prespecified sensitivity analysis, which used all data collected at baseline and at 4, 8, and 12 months, and secondary end points identified several potential health benefits. It is also useful to point out several aspects of the primary analysis result despite the lack of statistical significance: first, the point estimate of the treatment effect exceeded the MID, and second, the upper end of the CI was consistent with a large treatment effect—more than 3 times the MID, a numerical difference in CASI of 1.6. That said, we also note that the CI of this treatment effect was wide and statistical significance was not close to being attained. However, the potential effect of the device is supported by the sensitivity analysis, which compared the baseline CASI values to all postbaseline (4, 8, and 12 months) scores and found reduced CASI scores in the CREON2000A group versus the sham device group.

The numerical differences between groups were larger at 4 and 8 months compared to 12 months, partly leading to the difference in the results of the primary versus sensitivity analyses. When analyzed by season, the data suggest greater difference in CASI between arms at the winter postbaseline visits than at postbaseline visits during other seasons, probably as a result of the sham device arm's scores being higher in the winter compared to all other seasons (Fig E3). Because 61% of participants entered the trial in the autumn months and only 14% in the winter (Table I), it may have been more difficult to show a benefit because the primary analysis only compared like-season values (autumn to autumn and winter to winter, etc), potentially limiting the power to detect a significant change.

The *post hoc* observation strongly suggested a possible interaction between treatment effect and baseline CASI score. If future studies are conducted to investigate evidence of a treatment effect, the above analyses should be limited to participants with baseline CASI of at least 4.

The apparent improvement observed in several secondary end points, including daytime asthma symptom score, average asthma exacerbation score, rhinitis symptoms, and a trend for missed school days, strengthens the possibility that the CREON2000A device may show efficacy in a future larger trial. Another interesting observation was that the average asthma exacerbation score decreased from 0.55 to 0 at 8 months in the CREON2000A group versus little to no change in the sham device group (Fig E6). This is reflected in the reduction of systemic glucocorticoid receipt by the CREON2000A intervention group.[1,2,4,9] Importantly, because the CASI algorithm allows the investigator to adjust asthma controller therapy for all subjects over the course of the study to permit optimal asthma control, receipt of controller therapy as a potential confounding variable is automatically accounted for in all primary or secondary end point analyses. In fact, when CASI components were analyzed separately, the medication component was not significantly reduced in the CREON2000A compared to sham device group.

Both allergic and nonallergic subjects in homes randomized to receive the CREON2000A unit appeared to improve in their asthma severity and control. This could be partially explained by the reduction in the number of respiratory infections observed during the winter months. A recent study investigating the use of a UV light disinfection device in a long-term care nursing facility found it successfully reduced surface microbes while also reducing overall infection rates and hospitalization rates for infection.[39] Although airborne or surface bacteria or virus particles were not specifically measured in our study, previous investigations have demonstrated that the CREON2000A device has sustained and reliable microbicidal activity over 12 months.[28] Given the coronavirus disease 2019 pandemic and the abundance of emerging information related to the potential viricidal benefits of UV irradiation,[40] further work to better understand the effect of whole-house irradiation systems on preventing viral infections is warranted for asthma and health in general.

A survey previously distributed to allergists found that the majority perceived EC interventions to be as equally important as medication for controlling asthma.[26] However, they also perceived that the need for multiple interventions such as frequent vacuuming, dust mite encasements, and HEPA filters that required tailoring to the specific sensitivities of each patient were difficult for patients to maintain in the long term.[26] In this regard, the ability to utilize a single environmental intervention that requires little maintenance and appears to benefit children with both atopic and nonatopic asthma addresses concerns related to patient adherence with EC measures. Previously, we and others

TABLE III. Secondary efficacy end points

Differences between study arms in:	Time point	CREON2000A group	Sham device group	*P* value
Mean %FEV_1	Baseline	91.94 (17.34)	93.26 (15.97)	.089*
	4 months	99.08 (15.15)	92.90 (16.88)	
	8 months	97.40 (17.12)	93.76 (13.85)	
	12 months	95.16 (18.49)	94.63 (17.99)	
Mean daytime asthma symptoms score	Baseline	0.85 (1.03)	0.62 (0.84)	.016*
	4 months	0.21 (0.47)	0.63 (1.10)	
	8 months	0.20 (0.41)	0.19 (0.40)	
	12 months	0.18 (0.59)	0.21 (0.54)	
Mean nighttime asthma symptoms score	Baseline	0.45 (0.81)	0.51 (0.97)	.670*
	4 months	0.10 (0.50)	0.24 (0.75)	
	8 months	0.20 (0.69)	0.08 (0.49)	
	12 months	0.12 (0.56)	0.21 (0.64)	
Mean no. of daily puffs/inhalations of short-acting β-agonist rescue medication	Baseline	10.6 (20.3)	7.4 (12.6)	.701*
	4 months	3.4 (5.9)	6.6 (11.3)	
	8 months	2.7 (4.8)	4.2 (9.6)	
	12 months	6.2 (18.7)	2.7 (5.4)	
Mean CASI controller treatment score (EPR-3 treatment step)	Baseline	3.22 (0.97)	3.33 (0.98)	.116*
	4 months	2.59 (1.11)	3.21 (1.32)	
	8 months	2.15 (1.12)	2.43 (1.30)	
	12 months	1.93 (1.51)	2.35 (1.61)	
Mean asthma exacerbation score	Baseline	0.55 (1.28)	0.36 (0.78)	.032*
	4 months	0.26 (0.68)	0.26 (0.83)	
	8 months	0.00 (0.00)	0.38 (1.04)	
	12 months	0.10 (0.44)	0.23 (1.07)	
Mean no. of missed days from school or work in 2 weeks before visit	Baseline	0.37 (1.6)	0.05 (0.22)	.051*
	4 months	0.00 (0.0)	0.18 (0.69)	
	8 months	0.02 (0.16)	0.05 (0.33)	
	12 months	0.02 (0.16)	0.09 (0.38)	
Modified Rhinitis Symptom Utility Index	Baseline	9.25 (6.55)	6.79 (6.13)	.016*
	4 months	5.79 (5.32)	7.44 (5.81)	
	8 months	5.27 (5.17)	6.51 (4.75)	
	12 months	6.60 (4.95)	4.52 (3.86)	
Respiratory infections over 12 months, no. of infections/no. of participants (%)		12/40 (30.0)	22/39 (56.41)	.024†
Respiratory infections by season, no. of infections/ no. of participants (%)	Winter	2/40 (5.0)	10/38 (26.3)	.025†
	Spring	1/40 (2.5)	1/37 (2.7)	.925
	Summer	1/40 (2.5)	2/37 (5.4)	.462
	Autumn	8/39 (20.5)	9/35 (25.7)	.798
Mean duration of respiratory infection over 12 months		9.00 ± 4.16	7.59 ± 5.22	.427

Data are presented as means (SDs or %) unless otherwise indicated.
*Mixed effects linear regression model.
†Seasonal relative risk (95% CI) is as follows: overall, 0.53 (0.31-0.92); winter, 0.19 (0.044-0.81); spring, 0.925 (0.06-14.26); summer, 0.462 (0.044-4.89); and autumn, 0.798 (0.346-1.84).

reported the effect of UV irradiation on altering allergen structure. An exploratory end point of this study that will be subsequently reported is to assess and compare microbiome profiles in dust samples collected at baseline and end of study from each child's bedroom.[29,41] It is important to note that over 90% of participants who received either the active or sham units requested an active unit be installed in their home after completion of the study, which was provided in accordance with the study protocol suggesting they thought it had an impact on their health.

There are several strengths of this study worth noting. First, the study was well designed, with rigorous clinical and environmental inclusion and exclusion criteria with regular clinical follow-up. The study excluded any additional environmental interventions in the home and used a composite end point, CASI, as the primary end point, which has been previously validated and successfully used in pediatric asthma,[30] in conjunction with a standardized treatment algorithm for adjusting controller medications by stepping therapy up or down to provide asthma management according to national guidelines.[31]

The major limitation of this study was the lower-than-targeted sample size (79/160), which considerably diminished the statistical power of the primary outcome analysis. The difficulty in recruitment primarily reflects the many clinical and environmental requirements for study participation, which aimed to eliminate confounding variables. Therefore, future studies should include better strategies for recruitment of participants with more

active disease that incorporates analyses utilizing information collected at baseline and all subsequent clinical visits. In addition, because improvements in all secondary efficacy end points were noted for both the CREON2000A and sham device groups, study participants (or their families) may have behaved differently because of their study participation (ie, the Hawthorne effect).

In conclusion, although we did not detect a statistically significant effect of reducing asthma severity end point, possibly as a result of lower-than-expected enrollment, the findings suggest that additional studies may provide more definitive outcomes, and the data would be helpful in the design of such trials. Simple EC approaches, such as central UV irradiation intervention, may improve asthma control in a more cost-effective manner compared to long-term asthma controller therapy; they are consistent with recommendations by current EPR-4 and Global Initiative for Asthma guidelines[42,43] and should continue to be tested.

DISCLOSURE STATEMENT

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Disclosure of potential conflict of interest: J. A. Bernstein reports acting as PI for GI&G; PI or sub-PI and consultant for ALK, Allergy Therapeutics, Amgen, Areteia Therapeutics, AstraZeneca, Boehringer Ingelheim, Genentech, GSK, Merck, Novartis, Sanofi-Regeneron, and TEVA; is immediate past president of the American Academy of Allergy, Asthma & Immunology (AAAAI); is Chairperson of the AAAAI Foundation; is a Joint Task Force member; is a GINA Guideline Advocate; and is on the board of directors of WAO and Interasma. A. Seth, J. C. Katz, and M. Glazman are employees of GI&G, the study's sponsor. The rest of the authors declare that they have no relevant conflicts of interest.

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