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Efficacy of Topical Palmitoylethanolamide (Levagen+) for the Management of Eczema Symptoms: A Double-Blind, Comparator-Controlled, Randomized Clinical Trial

Amanda Rao[a, b] Amel A. Moussa[a] Jane Erickson[a] David Briskey[a, b]

[a]RDC Global, RDC Clinical, Newstead, Brisbane, QLD, Australia; [b]School of Human Movement and Nutrition Science, University of Queensland, Brisbane, QLD, Australia

Keywords
Dermatology · Allergy · Eczema · Atopic eczema · Palmitoylethanolamide · Alternative medicine · Anti-inflammation · Disease management · Skin disease

Abstract

Introduction: Eczema is a debilitating skin disorder clinically characterised by the development of itchy, dry, rough, and scaling skin caused by a series of rudimentary clinical phenotypes. ***Methods:*** This double-blind, randomised, comparator-controlled trial evaluated the effectiveness of topical application of a novel palmitoylethanolamide formulation (Levagen+) compared with a standard moisturiser (comparator) to reduce eczema severity and improve patient outcomes. Seventy-two participants aged over 18 years old with atopic eczema (symptoms including redness, dry skin, scaling, and/or itchiness) on their hands or arm were recruited. Participants were randomly allocated to one of two treatment groups (Levagen + or comparator). Treatment was applied to the affected area twice daily for 4 weeks. Outcome measures included Self-Assessed Eczema Area Severity Index (SA-EASI) scoring and Patient-Oriented Eczema Measure (POEM) from baseline to week 4. ***Results:*** Levagen+ was effective at alleviating symptom severity of eczema over 4 weeks. Levagen+ significantly reduced redness, dryness, and total POEM score compared to a comparator cream. ***Conclusion:*** Levagen+ can significantly reduce eczema symptom severity compared to a comparator product, supporting its use as a potential treatment for eczema. Trial registration: clinicaltrials.gov Identifier: NCT05003453.

Introduction

Eczema (atopic dermatitis) is a chronic, multifactorial inflammatory skin disease characterised by itchy, dry, rough, and scaling skin [1]. Depending on disease severity, eczema is associated with several comorbid chronic health disorders, impaired quality of life, and increased healthcare dependence [2]. Skin barrier dysfunction is recognised as the earliest sign in eczema development [3, 4]. Other underlying pathophysiology contributing to the aetiology of eczema include loss of water and lipid content, disturbed epidermal differentiation, immune dysregulation, elevated mast cells count, microbial imbalance, and hyperinflammation [5]. The complexity and numerous factors associated with eczema have made the development of therapies targeted at eczema management and relief difficult.

The persistent sensation of itching (pruritus) is the most reported clinical manifestation essential for eczema diagnosis

karger@karger.com
www.karger.com/spp

Correspondence to:
Amanda Rao, amanda@rdcglobal.com.au

[6]. Occurring in both acute and chronic stages, the molecular pathway responsible for pruritus in eczema remains poorly understood [7]. The sensory nerve fibres residing in the epidermis are reported to influence and control inflammation and pain in atopic eczema [6]. In the lesional skin, mast cells interact with the nerve fibres by releasing allogenic and puritogenic mediators that result in the release of inflammatory neuropeptides thus, creating a vicious negative feedback loop [8]. The negative feedback loop process is believed to instigate the redness, heat, itchiness, and inflammation associated with eczema, whilst simultaneously increasing sensory nerve ending sensitivity.

Current management of eczema therapies is primarily targeted to treat skin barrier dysfunction and immune dysregulation [9]. Based on disease severity and diagnosis, standard medical treatments currently include topical steroids, topical immunomodulators, oral antihistamines, and systemic therapy [10]. However, the use of some therapies is associated with the risk of long-term adverse effects leading to local, systemic, and psychological issues [11, 12]. Due to the risks associated with current eczema treatments, alternative treatments with minimal side effects are sought with the aim of establishing a "gold standard" natural treatment strategy [13, 14].

Palmitoylethanolamide (PEA) is a potential compound to treat the inflammatory pathologies of eczema, having anti-inflammatory, analgesic, and immunomodulatory effects [15]. PEA is an endocannabinoid-like bioactive signalling lipid expressed in plants, animal food sources, and mammalian body tissue [16]. PEA is often used to treat both acute and chronic disease stages and has been recognised for its ability to regulate numerous systems involved in inflammation, pruritus, and pain with no documented side effects [17, 18]. In eczema-lesioned skin, PEA is naturally recruited in high levels, and this is hypothesised to be a direct response to enable the down regulation of mast cell activity and function [19, 20].

Although PEA is known to benefit several disorders including psoriasis, fibromyalgia, arthritis, and traumatic brain injury, its therapeutic application has been limited due to its poor bioavailability [16, 21–23]. Bioavailability is a critical factor to achieve a therapeutic level in systemic circulation, and therefore elicit a notable therapeutic response [24]. We previously showed PEA combined with a novel dispersion technology (Levagen+) resulted in a significant increase in PEA plasma concentration [25] compared to a standard PEA formulation.

Therefore, the aim of this study was to assess the efficacy of Levagen+ in reducing eczema severity compared to a comparator moisturiser. We hypothesise that topical PEA application will reduce eczema severity and improve patient outcome and overall health.

Methods

A double-blind, randomised, comparator-controlled trial conducted over 4 weeks with two treatment arms, an active product (Levagen+) and comparator product (comparator). Sample size was calculated using G*power (v3.0.10), accounting for an α probability of 0.05 and powered to 0.80 for a 50% reduction in SA-EASI scores compared to a comparator. The resulting effect size, calculated from values obtained from published studies (baseline SA-EASI score of 30 for both treatment and comparator), a post-intervention SA-EASI score of approximately 12 and 21 for Levagen+ and comparator treatment, respectively, with a standard deviation (SD) of 15, was d = 0.73. The required group sizes given were at least 24. Allowing for approximately 30% dropouts, group sizes of 35 were chosen (n = 70). Any participant that withdrew without providing any data was replaced. Randomisation was conducted using a random allocation software (www.sealedenvelope.com) by an individual not involved in the trial. For each segment of the body (i.e., forearm, upper arm, hand), one to three pumps of the allocated treatment were used to cover the affected area with a thin layer. All clinical procedures were approved by Bellberry Limited (approval number 2020-08-789) and strictly confirmed to the current International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) guidelines. This study is registered on clinicaltrials.gov (Identifier NCT05003453).

The trial products in this study were either an active product, consisting of a moisturising base cream with 1.5% PEA (Levagen+), or a comparator group, consisting of the same moisturising base cream used in the Levagen+ product. The moisturising base cream was a water-based white viscous cream containing water, *Camellia oleifera* oil, mango seed butter, Jojoba oil, almond oil, calendula oil, panthenol, tocopherol, and a blend of essential oils for fragrance (lavender, geranium, and vanilla). All trial products were supplied by Pharmako Biotechnologies Pty Ltd (Sydney, Australia).

All participants applied their allocated product to the affected area twice daily. An appropriate amount of the study product was to be applied to each affected area such that following some gentle rubbing, no residual product remained on the skin surface.

Seventy-two participants aged over 18 years old were recruited from databases and public media outlets between November 2021 (summer) and June 2022 (winter). Participants were recruited if they presented otherwise healthy, capable of providing informed consent, and suffered from atopic eczema with symptoms including redness, dry skin, scaling, and/or itchiness on their hands or arm. Exclusion criteria included those with active allergic skin responses, pregnant or lactating women, active smokers, or chronic past and/or current alcohol use (>14 alcoholic drinks per week). Participants were also excluded if they suffered from an unstable or serious illness that included renal. Hepatic, gastrointestinal, cardiovascular, diabetes, mood disorders, cancer, using or used immunosuppressive medication within the last 3 months, or allergies to any of the ingredients in the Levagen+ or comparator formula. Following preliminary screening, potential participants were provided with a copy of the participant information form before a telehealth interview being contacted by a trial

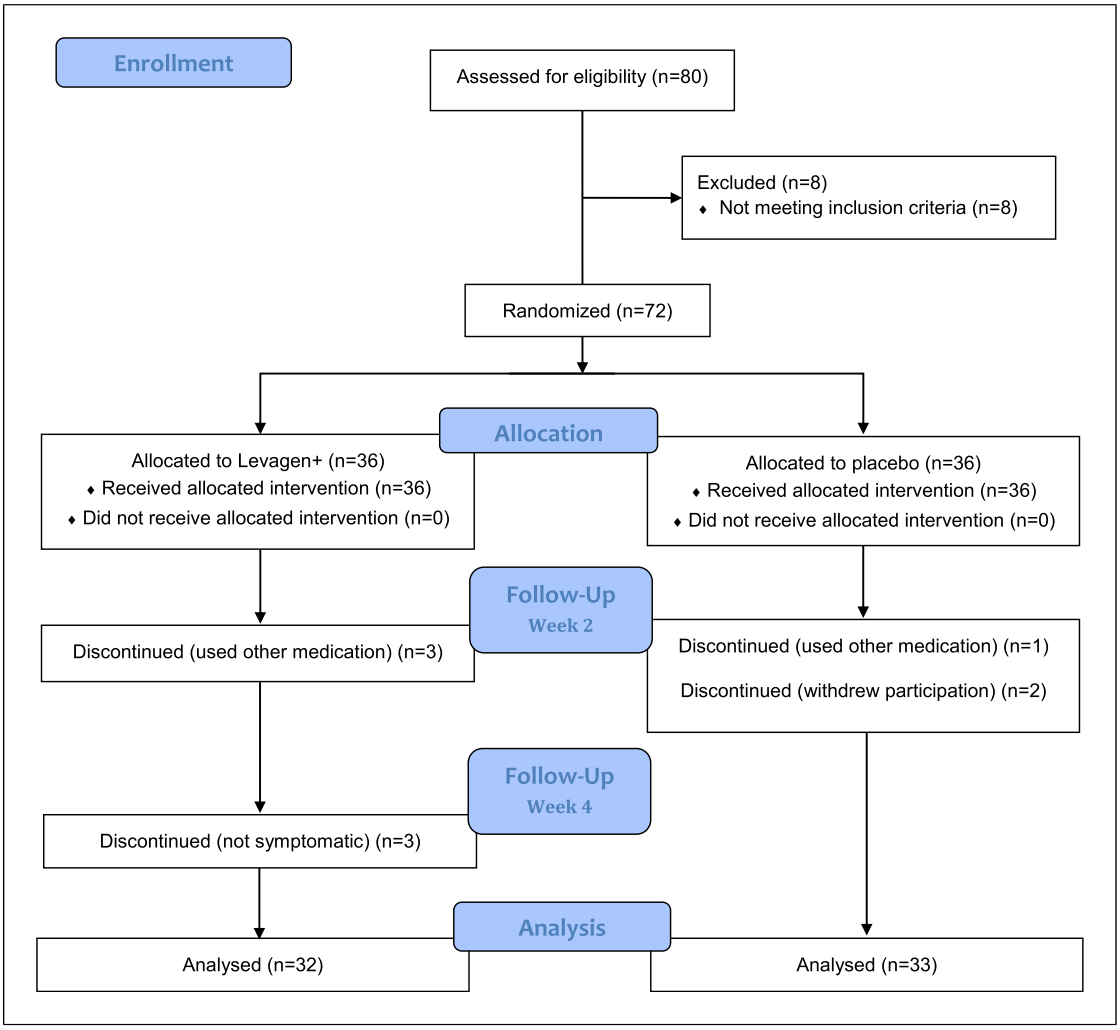

Fig. 1. Participant flowchart.

Table 1. Baseline demographics

	Levagen+	Comparator
Participants, *n*	32	33
Females, *n*	27	21
Males, *n*	5	12
Average age, years	37.4 (11.7)	36.0 (10.6)

Data presented as mean (SD).

coordinator for full screening. Following screening, eligible participants were asked to sign a consent form and allocated to one of two treatment groups at according to the randomisation list.

Once randomised, participants completed a baseline assessment including the Self-Assessed Eczema Area and Severity Index (SA-EASI), pruritus Numerical Rating Scale (NRS), Patient-Oriented Eczema Measure (POEM), and Dermatology Quality of Life Index (DLQI) questionnaires. Participants completed the same baseline measures and reported any use of a topical anti-inflammatory creams at week 2 (mid-point) and 4 (end point).

During the study, participants were asked to avoid any other topical medication for eczema (not including basic moisturising creams). If any topical anti-inflammatories were used, participants were to document the product and frequency. Basic moisturising creams could still be used by both the Levagen+ and comparator groups as desired daily if they were documented. Any product that was normally used to protect the skin, such as sunscreen, was also still permitted to be used.

The primary outcome measure for this study was a reduction in SA-EASI score. SA-EASI is used as an instrument to assess eczema disease severity and quantifies the intensity score (from 0 for absent to 100 for severe) based on redness, thickness, dryness, scratches, and itchiness. Secondary measures included reduction in itchiness (pruritus NRS; recorded as an average score over the past 24-h), reduction in self-reported topical anti-inflammatory use, improvement in self-reported eczema severity (POEM), and improvement in quality of life (DLQI).

Table 2. Self-Administered Eczema Area and Severity Index scoring (0–100 visual analogue scale [VAS])

	Baseline			Week 2			Week 4		
	comparator	Levagen	*p* value	comparator	Levagen	*p* value	comparator	Levagen	*p* value
Thickness	43.4 (25.9)	33.5 (19.7)	0.16	32.4 (22.4)[b]	27.8 (20.0)	0.46	31.2 (24.9)[b]	20.8 (21.2)[b,c]	0.17
Scratches	51.4 (31.0)	44.7 (26.5)	0.30	38.8 (29.7)[b]	29.5 (22.5)[b]	0.19	32.9 (31.2)[b]	21.1 (20.7)[b,c]	0.09
Itchiness	49.2 (25.6)	52.0 (20.6)	0.50	42.8 (29.5)	35.8 (25.2)[b]	0.36	36.3 (29.0)[b]	25.6 (22.6)[b,c]	0.12

All values are mean (SD). *p* values presented are between group values for the reported period. [b]Significant within group difference compared to baseline ($p < 0.05$). [c]Significant within group difference compared to week 2 ($p < 0.05$).

Table 3. Dermatology Life Quality Index (DLQI) scoring (0–3 effect of symptoms on patients' life)

	Baseline			Week 2			Week 4		
	comparator	Levagen	*p* value	comparator	Levagen	*p* value	comparator	Levagen	*p* value
Symptoms and feelings	2.91 (1.52)	2.81 (1.12)	0.66	2.09 (1.44)[b]	2.06 (1.34)[b]	0.81	1.91 (1.62)[b]	1.5 (0.88)[b,c]	0.26
Daily activities	1.30 (1.14)	1.63 (1.62)	0.50	0.88 (1.30)[b]	1.13 (1.24)	0.53	0.94 (1.67)	0.66 (0.94)[b,c]	0.42
Work and school	0.88 (0.88)	0.94 (0.80)	0.89	0.61 (0.81)	0.47 (0.51)[b]	0.38	0.70 (1.00)	0.5 (0.80)[b]	0.39
Personal relationships	0.52 (0.74)	0.81 (1.35)	0.36	0.52 (1.05)	0.44 (0.80)	0.72	0.39 (1.15)	0.34 (0.60)	0.81
Treatment	0.64 (0.73)	0.78 (0.75)	0.60	0.39 (0.65)[b]	0.28 (0.46)[b]	0.52	0.36 (0.69)[b]	0.28 (0.46)[b]	0.52
Total	7.30 (4.76)	8.41 (5.03)	0.57	5.21 (5.46)[b]	5.28 (4.23)[b]	0.95	5.09 (6.33)[b]	3.71 (3.22)[b,c]	0.28
Category	2.73 (0.93)	3.00 (0.92)	0.54	2.33 (1.15)[b]	2.28 (0.96)[b]	0.68	2.15 (1.08)[b,c]	1.93 (0.88)[b,c]	0.42

All values are mean (SD). *p* values presented are between group values for the reported period. [b]Significant within group difference compared to baseline ($p < 0.05$). [c]Significant within group difference compared to week 2 ($p < 0.05$).

Data analysis was conducted using GraphPad Prism 7.0 and SPSS 22. Data were tested for normality using the Shapiro-Wilk test. For analysis, questionnaire data were pooled and averaged within each category and analysed using a paired *t* test comparing the symptoms across comparator and Levagen+ groups at varying time points. Analysing data independently within treatment groups was conducted using a 2-way ANOVA test. Significance was set to $p < 0.05$. Data were represented as mean ± SD.

Results

Sixty-five of the 72 enrolled (90.3%) participants completed the study. Two participants were lost to follow up following consent without providing any data and were replaced (Fig. 1). There were no significant differences between groups at baseline (Tables 1–4). No side effects or adverse events were reported by either group during the study.

There was a significant reduction in SA-EASI scores between treatment groups at weeks 2 and 4 (Fig. 2; Table 2). Participants in the Levagen+ group reported an average 52% greater improvement in symptoms compared to the comparator group. The redness and dryness experienced at baseline was significantly reduced by week 4 within the Levagen+ treatment group (Fig. 2).

There was no significant between group differences seen in the DLQI (Table 3). Both the Levagen+ and comparator groups reduced baseline DLQI scores at weeks 2 and 4 (Table 3). Participants in both treatment groups reported a reduction in the level of itchiness,

Table 4. Patient-Oriented Eczema Measure (POEM), total scoring (0–7 = mild, 8–16 = moderate, 17–28 = severe to very severe)

	Baseline			Week 2			Week 4		
	Comparator	Levagen	*p* value	Comparator	Levagen	*p* value	Comparator	Levagen	*p* value
Over the last week, on how many days has your skin been itchy because of your eczema?	2.70 (1.34)	2.53 (1.27)	0.68	2.21 (1.34)[b]	2.19 (1.18)	0.92	2.06 (1.39)[b]	1.47 (1.02)[b,c]	0.07
Over the last week, on how many nights has your sleep been disturbed because of your eczema?	1.18 (1.09)	1.25 (1.08)	0.68	0.79 (1.17)	0.94 (1.08)	0.66	0.70 (1.00)[b]	0.50 (0.67)[b,c]	0.32
Over the last week, on how many days has your skin been bleeding because of your eczema?	1.12 (1.17)	0.65 (0.83)	0.08	0.79 (1.32)[b]	0.50 (0.76)	0.22	0.82 (1.24)	0.38 (0.83)[b]	0.06
Over the last week, on how many days has your skin been weeping or oozing clear fluid because of your eczema?	1.00 (1.30)	0.44 (0.56)[a]	0.03	0.76 (1.37)	0.47 (0.67)	0.16	0.61 (1.15)[b]	0.19 (0.47)[a,b,c]	0.04
Over the last week, on how many days has your skin been cracked because of your eczema?	2.39 (1.48)	2.00 (1.30)	0.31	1.36 (1.37)[b]	1.13 (0.94)[b]	0.51	1.52 (1.50)[b]	1.00 (1.11)	0.10
Over the last week, on how many days has your skin been flaking off because of your eczema?	2.27 (1.52)	1.59 (1.41)	0.07	1.58 (1.48)[b]	1.09 (1.09)[b]	0.17	1.48 (1.46)[b]	0.94 (1.05)[b]	0.08
Over the last week, on how many days has your skin felt dry or rough because of your eczema?	3.12 (1.20)	2.84 (1.25)	0.42	2.52 (1.46)[b]	2.03 (1.23)[b]	0.17	2.48 (1.46)[b]	1.75 (1.30)[a,b]	0.04

All values are mean (SD). *p* values presented are between group values for the reported period. [a]Significant between group difference for same reporting period ($p < 0.05$). [b]Significant within group difference compared to baseline ($p < 0.05$). [c]Significant within group difference compared to week 2 ($p < 0.05$).

soreness and the level of pain experienced. The Levagen+ group reporting a 56% reduction and the comparator group reporting a 30% reduction for total symptoms score at week 4. Overall, participants reported their eczema symptoms had reduced and had minimal debilitating effect on their life and living activities (Table 3).

At the completion of the study, the Levagen+ group reported a significant reduction in total symptom score compared to the comparator group (Fig. 3). Both the comparator and Levagen+ group had significant reductions from baseline in POEM scores at week 2 and 4 (Table 4; Fig. 3). The comparator group reported a significantly higher score for skin weeping or oozing at baseline compared to the Levagen+ group (Table 4). The difference for skin weeping or oozing was not seen at week 2 but was again at week 4. The Levagen+ group had a significantly lower score at week 4 for skin feeling dry or rough and total POEM score compared to the comparator group (Table 4).

Discussion

Mast cell recruitment and activation is extensively cited as one of the most influential factors relevant in the pathogenesis of eczema [26, 27]. Significant association has

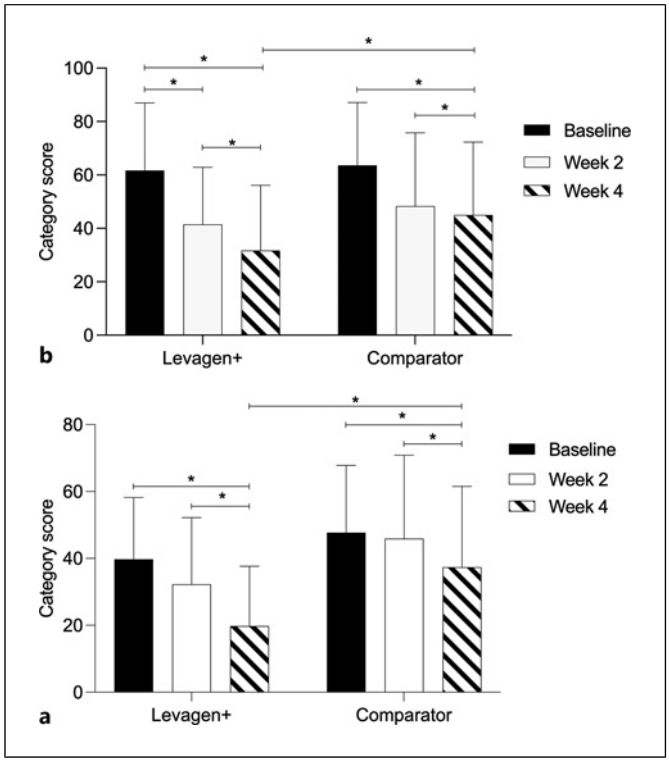

Fig. 2. Reduction in the severity index score for (**a**) redness and (**b**) dryness over 4 weeks. Levagen+ had a significant reduction in both redness and dryness compared to the comparator. Significant within group differences were also seen. *Significant difference $p < 0.05$.

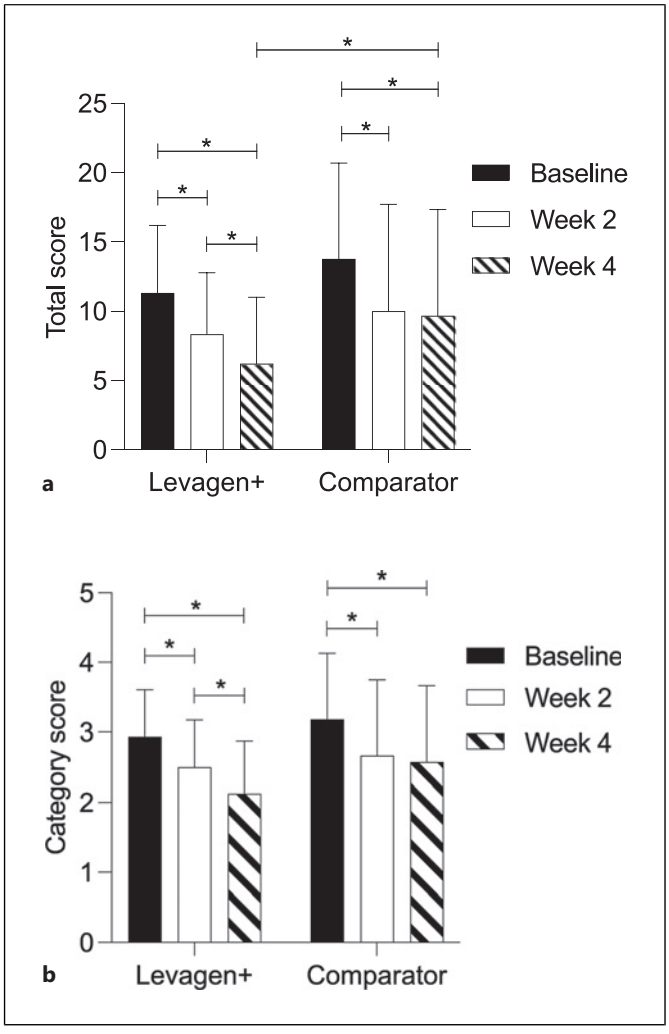

Fig. 3. Patient-Oriented Eczema Measure (POEM) questionnaire outcomes. **a** Total POEM outcome score at baseline, week 2 and week 4 for Levagen+ and comparator treatment groups. **b** POEM severity scoring at baseline, week 2 and week 4 for Levagen+ and comparator treatment groups. A reduction was seen in both groups. No significant difference was seen between groups at any time point. *$p < 0.05$.

previously been shown between the number of mast cells and eczema severity level [28]. The pathological interaction between these cells and nerve fibres exacerbates the most disruptive symptoms reported by eczema patient (pruritus and dryness) during chronic skin inflammation [29]. In eczema-lesioned skin, there is a marked proliferation in pro-inflammatory interleukin 6 (IL-6) mast cell expression which is responsible for upregulating histamine production and causing skin irritation [30, 31]. However, the pathogenesis of eczema is multifactorial, and the disease course can vary depending on a plethora of factors, requiring further elucidation to improve therapeutic options.

PEA acts as a putative analgesic and agonist of the nuclear receptor PPAR-α which regulates and controls pain and inflammation [32]. The PPAR-α family of receptors regulates several inflammatory genes and following activation, maintains mast cell homeostasis by suppressing their activity and function during an inflammatory response [33]. In studies by Patzer's and colleagues and Serrano-Marco and colleagues [34, 35], PPAR-α receptors also suppressed the expression of IL-6 during the acute phase of cerebral ischaemia. In mouse models of acute and chronic inflammation, topical PEA exhibited a promising ability to mediate mast cell activity. This study investigated the efficacy of PEA as an effective anti-inflammatory reagent in the treatment of eczema. Our findings aim to support published data and establish potential therapies for eczema treatments incorporating PEA.

Levagen+ was shown to significantly reduce redness, itchiness, dryness, and improve patient outcome

compared to the use of a comparator cream. Previous research has shown IL-6 to cause redness and pigmentation in multiple skin disorders [30, 31]. It is therefore possible that Levagen+ plays a role in modulating IL-6 expression to reduce skin irritation. When scores were assessed for severity, Levagen+ significant decreased the number of participants reporting severe eczema and increased participants reporting mild eczema compared to the comparator. These results are consistent with those reported by Del Rosso and Yuan, who observed improved symptom outcomes in patients using PEA emollient with clearance of disease flares after 3 weeks [1, 36]. This suggests a clinical efficacy of PEA to increase skin hydration and strengthen the skin barrier to reduce itching and pain. PEA may achieve effective relief from eczema symptoms by monitoring mast cells pathophysiology and allowing an appropriate anti-inflammatory response to occur. However, in the absence of biochemistry measures, these mechanisms are not yet known. Future studies on PEA for eczema relief would benefit by incorporating biochemistry with eczema symptom scoring to enable a definitive link to proposed mechanisms to be established.

A limitation of this study is that it relied on self-assessment of eczema symptoms and symptom severity. The lack of assessment of eczema symptoms and severity by a clinician could potentially create data variability and accuracy. While future studies incorporate participant assessment by a clinician to score the degree of eczema severity would allow for a more accurate assessment of outcome measures, it is not always practical. Eczema can affect a person's general health (i.e., via the compromised skin barrier), quality of life and potentially mental health. Therefore, along with clinical improvements, self-reported relief and improvement in subjective symptoms resulting in increased reported comfort and quality of life should be presented with equal emphasis and qualitative detail. Another limitation of the study may be the study duration. Results from the current study appear to show the symptoms scores to be steadily decreasing at week 4, whereas the comparator product appears to be plateauing. Had the study continued to be conducted for an additional 2 or 4 weeks, the differences between groups may have become more pronounced and additional findings may have been possible.

This study demonstrates the ability of Levagen+ to reduce and manage the most common and debilitating symptoms of eczema with no reported side effects. Compared with a comparator cream, the application of Levagen+ in individuals with eczema can significantly improve symptoms. The findings of this study together with the lack of any reported side effects or adverse events provide evidence for the potential for Levagen+ to regulate inflammatory skin reactions by influencing the pathophysiological systems involved in the pathogenesis and acceleration of eczema. Levagen+ appears to be a promising therapeutical option in the treatment of eczema and understanding the interplay between this compound and inflammatory pathogenesis is integral to improve and deliver disease-modifying treatment.

Statement of Ethics

This study was approved by Bellberry Limited (approval number 2020-08-789) and executed in agreement with the current International Conference on Harmonization Guideline for Good Clinical Practice. Written informed consent was obtained from all participants prior to enrolment and entry into the clinical trial.

Conflict of Interest Statement

The authors declare that they have no known conflict of interest for disclosure.

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Author Contributions

Conceptualization: methodology, resources, supervision, and funding acquisition: A.R. and D.B. Project administration: A.R., J.E., and D.B. Formal analysis: A.M. and A.R. Investigation: J.E. and D.B. Data curation: A.M. Writing – original draft preparation: A.M. Writing – review and editing: D.B. Visualisation: A.R. All authors have read and agreed to the published version of the manuscript.

Data Availability Statement

The data reported in the findings of this study are not openly available due to commercial agreements. However, on equitable request, data can be made available from the corresponding author. Further inquiries can be directed to the corresponding author.

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