1. Study Protocol

A Phase II open label, single arm, single centre clinical study on the effect of a moisturiser containing tocotrienol rich composition on mild to moderate atopic dermatitis in children

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4. Introduction

Natural extracts and actives are highly sought after for the management of skin disorders especially those that requires long-term, consistent usage: some to boost skin health, and some to prevent disturbing undesirable symptoms, including dry, itchy skin. Eczema is such long-term condition that causes the skin to become itchy, red, dry and cracked. The condition most often develops before a child's first birthday, although it can also appear in adults for the first time. Eczema symptoms vary between having small patches of dry skin, and having widespread inflamed, red skin. Earlier, it has been reported that patients could relieve signs of atopic dermatitis by taking daily Vitamin E supplements. It is reported that Vitamin E supports healthy skin due to its antioxidant activity besides working at the immune level to benefit the skin. Vitamin E specifically those from palm oil, is Generally Regarded as Safe (GRAS) (USFDA GRAS GRN 307). There are two types of Vitamin E i.e. tocopherol and tocotrienol where the latter has been found to be almost 60 times more potent an antioxidant than the former. Till date, study of Vitamin E, especially tocotrienol concentrated, as topical moisturiser for the management of atopic dermatitis is scarce. This study aimed to assess the effectiveness and safety of a moisturiser containing tocotrienol rich composition (REMDII® Sensitive, Malaysia) on children with mild-to-moderate atopic dermatitis in a period of 12 weeks. The endpoints of the study include changes in the severity of atopic dermatitis based on Investigator Global Assessment (IGA) score,

Scoring Atopic Dermatitis Index (SCORAD), Infant Dermatology Life Quality Index (IDLQI), Patient-oriented Scoring Atopic Dermatitis Index (PO-SCORAD) and pruritus score. Expectedly, REMDII® Sensitive would significantly improve the severity of atopic dermatitis in children.

5. Research Question

a) Could moisturiser with tocotrienol rich composition (REMDII® Sensitive, Malaysia) improve severity of atopic dermatitis of children with mild to moderate atopic dermatitis?

b) What is the extend of baseline changes in IGA, SCORAD, IDLQI, PO-SCORAD, HR-USI, TEWL, skin color and pruritus score in children upon usage of REMDII® Sensitive?

c) How well would children tolerate REMDII® Sensitive?

6. Research objectives and hypotheses

General objective

To assess the effectiveness and safety of a moisturiser containing tocotrienol rich composition (REMDII® Sensitive, Malaysia) on children with mild-to-moderate atopic dermatitis.

Specific objectives

- To assess the effectiveness and safety of REMDII® Sensitive as a supplement in mild-to-moderate atopic dermatitis in children based on the changes of IGA score and SCORAD.
- To assess correlation between patient-assessed PO-SCORAD and clinician-assessed IGA and SCORAD in children after 12 weeks of treatment using REMDII® Sensitive.
- To assess the changes in IDLQI.
- To assess the changes in patients' assessment of pruritus (based on a 100 mm Visual Analogue Scale and 0-3 ordinal scale).

- To assess the changes in skin properties, specifically high resolution ultrasound skin imaging (HR-USI), transepidermal water loss (TEWL) and skin color in children before and after application of REMDII® Sensitive.
- To assess the frequency of need for rescue medication in the event of an atopic dermatitis flare.

Hypotheses

Null: REMDII® Sensitive does not improve severity of atopic dermatitis of children with mild to moderate atopic dermatitis.

Alternative: REMDII® Sensitive significantly improves severity of atopic dermatitis of children with mild to moderate atopic dermatitis.

7. Literature review

Eczema is a general term used to describe numerous forms of epidermal inflammation or irritation that occurs regardless of gender, race and age. Among the various types of eczema, the most prevalent type is atopic dermatitis (AD). Currently, the prevalence rate of AD in children and adolescents was 15.0-20.0%, regardless of regions (Asher et al., 2006; Baek et al., 2013). Eczema poses significant impact and inconveniences to the patients' quality of life and health-care resources, mainly because of sleep deprivation and demoted self-esteemed (due to itchiness, scarring, lichenification, peer pressure and time to care), that would in turn affects the child's growth and development.

AD is a complex disease, and genetics has recently been shown to be an important risk factor for AD, and the strongest association so far with the gene encoding filaggrin has raised the recent interest in the role of skin barrier impairment in the development of AD (Nutten, 2015). There is no cure for AD yet, although a wide range of treatments have been introduced to ease the symptoms and keep the skin conditions under control. The most common treatment of AD involves the use of corticosteroids and in certain cases, immunosuppressants – both of which need strict monitoring of medical professionals and carelessness of application would lead to negative irreversible consequences (Liu et al.,

2013). Therefore, prevention is still regarded as the best management strategy for AD, some of the opinion that prevention should start as soon as possible (possibly even in utero), targeting both skin barrier, immune/ allergy and environmental aspects (Nutten, 2015). The application of emollients and moisturisers to maintain skin hydration is still by far the safest and most basic therapy of treating AD. Often, humectants and pharmacological compounds are also added into moisturisers or emollients as parts of AD skin treatment.

Nutten (2015) found that environmental factors and specifically exposure to microbes are increasingly recognized to play a role in the development of AD. In this finding, the sole use of moisturisers, in the absence of sufficient topical anti-inflammatory therapy, would involve a significant concern over the risk of microbial infection. In addition, direct use of emollients on inflamed acute patches is poorly tolerated and may lead to stinging pain. Topical corticosteroids and calcineurin inhibitors are still the standard choice for topical anti-inflammatory therapy despite their risk of carcinogenicity (Arellano et al., 2009; Arellano, Wentworth, Arana, Fernández, & Paul, 2007). Although topical corticosteroids are useful in suppressing skin inflammation, long period of usage (which is usually the case to maintain a reasonable quality of life) are more likely to cause skin atrophy which further aggravates skin barrier functions. Consequently, there is still a need for a moisturiser containing natural anti-inflammatory properties with minimal or no side effect for the prevention or treatment of skin disorders.

Children's skin is very delicate. The need for a more natural topical moisturiser with maximal efficacy and minimal side effects and irritation potentials is highly demanded by the public. The latest search for a worldwide listing of AD medical research trials actively recruiting patient volunteers on CenterWatch yielded only 91 interventional studies and 25 observational studies where 14 are labeled as Phase I trials, 36 Phase IIs, 41 Phase IIIs, 10 Phase IVs, 3 Phase I/IIs, 4 Phase II/IIIs and the rest unknown (https://www.centerwatch.com/clinical-trials/listings/condition/695/atopic-dermatitis/). In Malaysia, only 3 dermatological-categorized clinical trials where reported for the year 2012-2017 (NPRA, 2018). Choices for clinically tested OTC moisturiser are scarce as compared to non-tested cosmetic grade moisturisers. Lai, Tan, Lai, and Khong (2016) have recently derived a natural antioxidant and preservative with selective antimicrobial

properties to hygiene-related pathogens from palm oil. The natural bioactive was found to exhibit higher and broader antimicrobial activity compared to virgin coconut oil and extra virgin olive oil *in vitro*. One of the apparent advantages of this active is the superior stability of the Vitamin E in an accelerated shelf life study (Figure 1).

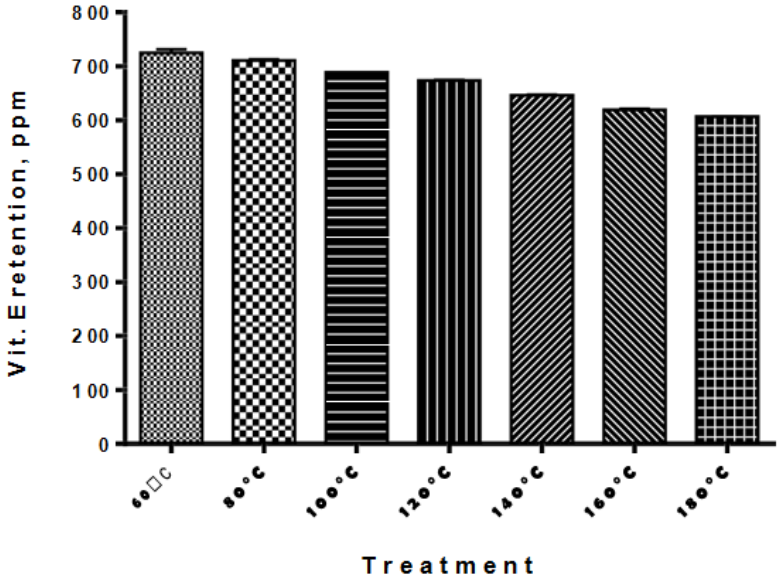


Figure 1. Retention of total Vitamin E content (α-tocopherol, α-tocotrienol, β-tocopherol, β- tocotrienol, ϒ-tocopherol, ϒ-tocotrienol) of processed active at different temperatures.

The IP of this study is a topical moisturiser containing tocotrienol rich composition from plant source (REMDII® Sensitive, Malaysia). REMDII® Sensitive contains both tocopherol (α, β, γ & δ) and tocotrienol (α, β, γ & δ). Serbinova, Kagan, Han, and Packer (1991) showed that tocotrienols can be 40-60 times more potent as antioxidant than tocopherols. Vitamin E especially palm-based has been proven repeated to exhibit no adverse effects in both normal as well as vulnerable subjects while potentially poses significantly high benefits with very low risks (Argyriou et al., 2006; Kappus & Diplock, 1992; Meydani et al., 1998). In a prospective, randomised, double-blinded trial involving 84 post-surgical subjects, no significant adverse effect was observed up to the dosage of 5% topical tocotrienol, applied twice-daily over 4 months post-surgery (Khoo et al., 2011). In another study, Hasan, Idris, Gani, and Basri (2018) concluded that palm tocotrienol rich fraction has no indication of irritancy to both ocular and dermal tissues and could be

classified as Category 1 according to United Nations Globally Harmonised System of Classification and labelling of Chemicals. Hasan, Ismail, and Ahmad (2008) also concluded that palm tocotrienol rich fraction do not induce any cutaneous reactions including irritation and dermatitis and it is safe to be used for topical applications. REMDII® Sensitive has been registered to the National Pharmaceutical Regulatory Agency (NPRA), Kementerian Kesihatan Malaysia with the notification number NOT181000506K, tested for its product stability and certified halal. Thus, subject could benefits freedom of better accessibility to the Vitamin E in the IP with lesser risk on exposure to unknown degradatory products resulted from product instability. Besides, REMDII® Sensitive has also been tested to have low risk of adverse effect (LC_{50} = >5000 μg/ mL) *in vivo*.

As a topical cosmetic or over-the-counter product, Vitamin E has been used in product concentration of 1%-5% (w/w) for almost half a century. The lipophilic nature of vitamin E makes it suitable for topical application and percutaneous absorption through the skin (Krol, Kramer-Stickland, & Liebler, 2000; Lin et al., 2003). When topically applied, vitamin E has been shown to hydrate the stratum corneum (SC), improve skin hydration and improve water-binding capacity (Ismail, Affandi Yusoff, & Hashim, 2009; Manela-Azulay & Bagatin, 2009). Topical vitamin E was also found to significantly reduced postoperative pain in a prospective randomized clinical trial involving 60 patients (Ruiz-Tovar et al., 2016). Thiele, Hsieh, and Ekanayake-Mudiyanselage (2005) summarised that Vitamin E could be considered an effective ingredient for imparting skin protection and treating atopic dermatitis (AD) based on experimental evidences suggesting that topical and oral vitamin E has anticarcinogenic, photoprotective, and skin barrier-stabilizing properties. In a 2015 randomized, controlled, double-blind, single center study involving 44 patients with mild to moderate AD in the perioral/periocular area and/or the neck, Patrizi et al. (2016) noted a significantly more rapid reduction in affected surface area with an emollient containing Vitamin E, compared with placebo; the product was found to be well tolerated and safe as well as effective for mild to moderate AD. Maarouf, Vaughn, and Shi (2018) also agrees that topical Vitamin E formulations appear to provide some benefit to AD individuals. In addition, Yap (2018) also showed that tocotrienol rich fraction is an effective anti-inflammatory agent that is safe to be applied daily. As nitric oxide (NO) has

been shown to be involved in the pathogenesis of vasodilation and erythema in atopic dermatitis (Taniuchi et al., 2001), REMDII® Sensitive could be as potential product with potential in the management of AD. REMDII® Sensitive is tested to have inhibited ~50% NO level in vivo, slightly lower to ~60% NO inhibition activity of hydrocortisone 1% (w/w) (Hydrocortisone® Cream, Xepa-Soul Pattinson) *in vivo* ($p>0.05$).

In a study involving 13 human subjects, Ekanayake-Mudiyanselage et al. (2005) studied the effect of applying a Vitamin E-enriched rinse-off product and found that application of Vitamin E, even in rinse-off products, raised Vitamin E levels in human skin, which remained consistent for at least 24 hours, as opposed to the reduced finding of Vitamin E in the Vitamin E–free vehicle control group. The product also significantly inhibited photo-oxidation of squalene. Foote et al. (2009) findings also agrees to the elevation of Vitamin E level in human subject's skin upon application of Vitamin E containing cream and further proved the chemoprevention properties of the topical Vitamin E via reductions in polyamine metabolism which is consistent with the reductions in tumorigenesis potential**.** Further, Julianto, Pereira, Yuen, and Majid (2011) demonstrated that the mean droplet sizes of nanoemulsion hydrogel containing palm tocotrienol extract affect skin penetration and consequently the systemic bioavailability of δ-, γ-, and α-tocotrienols, Nanoemulsion with smaller size was reported to have significantly heightened bioavailability of δ-tocotrienol. In agreement to this, total Vitamin E in a moisturizer with Vitamin E nanoemulsion (REMDII® Sensitive, Malaysia) was also observed to has significantly higher absorption in faster time compared to one with Vitamin E emulsion.

The proactive properties of Vitamin E to skin health promoting have widely been reported to be contributed by its antioxidative activity. Hayashi et al. (2012) demonstrated that lipid peroxidation in the skin and serum is significantly proportional to symptoms of atopic dermatitis and inflammation. Weber et al. (1997) found that tocotrienol rich fraction readily penetrate the skin of hairless mice and are protective against oxidative stress in vivo. Palm tocotrienol has also been demonstrated to promote wound healing by increasing superoxidase dismutase (SOD), catalase and glutathione (GSH) gene regulation (Shahrim, Omar, Zainal, & Hasan, 2016). Ex vivo study of tocotrienol against H_2O_2-induced oxidative stress found that the vitamin protects and prevents oxidation damages to the skin by upregulating of *COL1* and *COLIII* genes and increase in total collagen synthesis (Makpol,

Jam, Yusof, & Ngah, 2011). Anti-inflammatory properties of palm derived Vitamin E has been confirmed and it is reported to be caused by reducing pro-inflammatory cytokines, specifically IL-6, IL-8 and COX-2 in skin cells (Yap, 2018). As effective moisturization of the skin is a compulsory exercise for AD patients, Vitamin E played a role in improving AD by significantly increasing skin hydration and skin elasticity, while decreasing skin roughness in human subjects (Ismail et al., 2009). Besides, Tsuduki, Kuriyama, Nakagawa, and Miyazawa (2013) also found that tocotrienols reduces AD by suppressing degranulation of mast cells in vivo and tocotrienols' reduction of dermal inflammation follow similar mechanism as it's UV-B protection activity. Kapun et al. (2014) found that Vitamin E significantly improves atopic dermatitis in canine subjects due to improvements of oxidative stress.

Vitamin E has been attributed to positive properties especially to the skin. However, there is little clinical data on the effect of tocotrienol onto children's skin health especially in the treatment of AD. Therefore, the general aims of this study are:

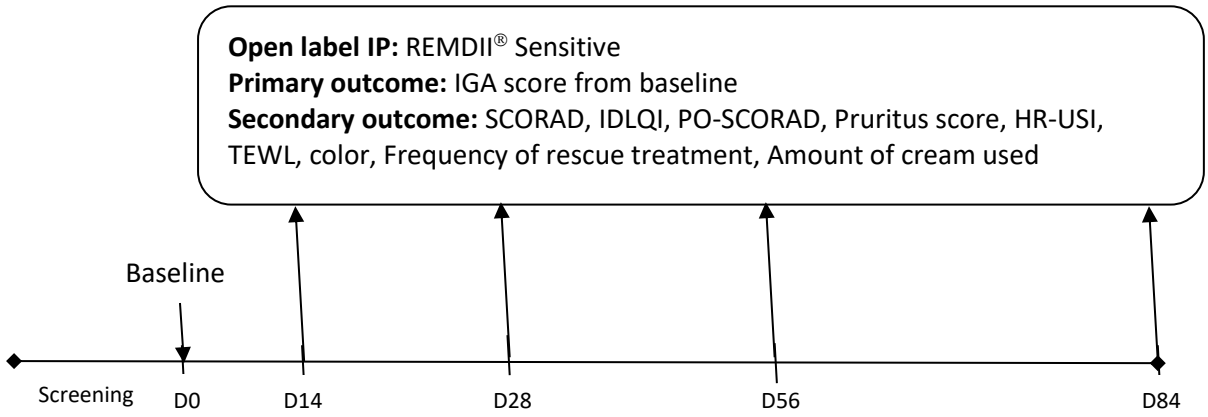
(1) To evaluate the efficacy of REMDII® Sensitive in treating AD topically;

(2) To evaluate the effect of REMDII® Sensitive on skin properties, especially on skin ultrasound properties, skin color and transepidermal water loss;

(3) To evaluate the safety of a REMDII® Sensitive in treating AD topically;

(4) To evaluate if the usage of REMDII® Sensitive improves the quality of life in patients with AD.

8. Conceptual framework



Recruitment: 1 July 2019-30 Aug 2019

Study site:

Hospital Pengajar UPM: Consultation, IGA, SCORAD, IDLQI, PO-SCORAD, Pruritus score, Rescue treatment (if any)

Lipidware Sdn Bhd: Skin analyser (Dermalab Series SkinLab Combo, Denmark), data compilation, measurement of cream, provision of REMDII® Sensitive and REMDII® Calming Body Wash, and diary.

Figure 2. Study outline

9. Research Methodology

9.1 Study Type and Design

9.1.1 Study design

A Phase 2, single arm, open label, single-centre trial will be conducted at Hospital Pengajar UPM, 43400 UPM Serdang, Selangor and Lipidware Sdn. Bhd. Participants fulfilling the eligibility criteria will be selected. Each participant will be examined for signs and symptoms of AD before and after using REMDII® Sensitive. Figure 2 shows the outline of the study.

9.1.2 Investigative product (IP)

Subjects will be provided with REMDII® Sensitive throughout the duration of the study.

9.1.3 Endpoints

Primary endpoint: Change from baseline the severity of atopic dermatitis – IGA score.

Secondary endpoints:

- Changes in SCORAD
- Changes from baseline the
  - IDQOL & CDLQI
  - PO-SCORAD
  - Pruritus score (VAS/ ordinal)
  - Frequency of rescue treatment needed
  - High resolution ultrasound skin-imaging (HR-USI), skin color & Transepidermal Water Loss (TEWL)
- Correlation between SCORAD index and PO-SCORAD or IDLQI at each baseline and follow-up visit and absolute changes from baseline.
- Efficacy and safety assessment of the study product.

9.1.4 Study Population

Children (1 month – 12 years old) will be recruited through three routes i.e. patients who see the trial advertisements on bulletins made available in UPM (specifically Pusat Kesihatan Universiti, Hospital Pengajar UPM's Family Medicine Clinic, Medical Specialist Clinic, or Paediatric Clinic) that will contact the sponsor voluntarily; Patients who see the trial advertisements in social media, specifically Malaysia Eczema Support Community on Facebook, that will contact the sponsor voluntarily; and Patients who obtained words of mouth of the trial that will contact the sponsor voluntarily during the period of 1 July 2019 – 30 August 2019.

9.1.5 Inclusion Criteria

9.1.5.1 Male and female ages 1 month to 12 years with a diagnosis of atopic dermatitis based on UK Working Party Criteria of Atopic Dermatitis (Williams, Jburney, Pembroke, Hay, & Party, 1994).

9.1.5.2 Individuals with IGA score of at least mild (IGA= 2) or moderate (IGA= 3) and have at least 5% of body surface area affected during the inclusion time.

9.1.5.3 Individuals with a carer reported pruritus score based on VAS of at least 40 mm and above.

9.1.5.4 Individuals with no other chronic health condition other than atopic dermatitis e.g. asthma, allergic rhinitis or allergy.

9.1.5.5 Individuals with no objection towards use of topical corticosteroids as prescribed by attending medical officer during the study.

9.1.5.6 Written informed consent for participation in the trial.

9.1.6 Exclusion Criteria

9.1.6.1 Individuals with confounding skin diseases other than atopic dermatitis in the affected area which could interfere with assessment of treatment (e.g. psoriasis, rosacea, erythroderma, ichthyosis, acne, Netherton's syndrome, scabies, seborrheic dermatitis, and cutaneous lymphoma).

9.1.6.2 Individuals with severe atopic dermatitis (IGA = 4).

9.1.6.3 Individuals with active ongoing secondary infection of atopic dermatitis.

9.1.6.4 Individuals with any physical attributes or skin conditions that might interfere with the clear visual or instrumental assessments (i.e. cuts, sunburn, birth marks, tattoos, extensive scarring, excessive hair growth or acne).

9.1.6.5 Individuals with diabetes, severe liver disability (2.5-fold the normal high range value for ALT, AST) or severe renal disability (sCr > 2.0 mg/dl).

9.1.6.6 Individuals with immunodeficiency disorder or infectious disease (e.g. hepatitis, tuberculosis, HIV or AIDS, lupus rheumatoid arthritis.

9.1.6.7 Subjects who are not keen to start on corticosteroid on screening, despite informing that it is the first line treatment option according to the National Atopic Dermatitis guideline.

9.1.6.8 Use of other topical or systemic medications that could affect the course of their atopic dermatitis during the study period (except inhaled steroids and/or stable antihistamines for asthma or allergies for the past 30 days).

9.1.6.9 Use of steroids, oral antibiotics, immunosuppressants, other systemic treatments (i.e. retinoids, methotrexate, cyclosporine, hydroxycarbamide (hydroxyurea) and azathioprine) or physical therapy (i.e excimer laser, NBUVB, or PUVA) that could affect AD within 30 days or 5 half- lives.

9.1.6.10 History of drug abuse.

9.1.6.11 Hypersensitivity to Vitamin A, Vitamin C, Vitamin E or oil palm derived products.

9.1.6.12 Poorly controlled bronchial asthma, as mentioned according to GINA guideline.

9.1.6.13 Individuals with any other condition or factor the Investigator or their duly assigned representative believes may affect the ability of the subject to complete the study or the interpretation.

9.1.7 Withdrawal Criteria

The subjects who meet the criteria listed in Subject Withdrawal Criteria section will be discontinued from treatment or they may can choose to withdraw voluntarily at any time. Subjects may be withdrawn if the investigator deems that it is detrimental or risky for the subject to continue. All withdrawn subjects should attend the final study visit. Withdrawn subjects after randomization will not be replaced and will be followed for outcomes.

Subject Withdrawal Criteria

9.1.7.1 Patients with exacerbation which is not controlled by per protocol rescue medicine in 2 weeks.

9.1.7.2 Infection failed to be treated with per protocol oral antibiotic. Or those who develop cutaneous sepsis, as defined by skin infection + >/= 2 meets SIRS definition, as defined below:

9.1.7.2.1 Temp >38.5°C or > 36°C.

9.1.7.2.2 Tachycardia or bradycardia (if <1 year).

9.1.7.2.3 Tachypnea or requiring mechanical ventilation.

9.1.7.2.4 Abnormal leukocyte count or >10% bands.

9.1.7.3 Infection which are not deemed related to atopic eczema <i.e pneumonia, UTI, AGE, will not be withdrawn even if fulfilled sepsis criteria.

9.1.7.4 The development of any severe adverse event, as defined by the Malaysian GCP.

9.1.7.5 Use of any forbidden medication or treatment, and/or other use moisturisers or emollients during the trial that could affect the study result.

9.1.7.6 Subjects who did not comply with the protocol of at least two times-per-day application of cream.

9.1.7.7 Subject's withdrawal of consent.

9.1.7.8 Detection of eligibility violations, occurrence of other significant protocol violations during the trial.

9.1.7.9 Investigator's decision to terminate the process for the sake of the subject's health.

9.1.7.10 Dropouts are defined as patients who did not attend for follow-up visit within the designated visit window (+/- 3 days) and whose outcomes are unknown by the end of the trial.

9.1.8 Sample Size

Sample size calculations were performed according to Cheon et al. (2013) using the following formula, where the mean difference and standard deviation of the scoring atopic dermatitis (SCORAD) index will be 10 and 13.576, respectively.

$$
\begin{aligned}
n &= \frac{2\left(z_{\alpha/2} + z_{\beta}\right)^2 \sigma^2}{\left(\mu_c - \mu_t\right)^2} \\
&= \frac{2 \times (1.96 + 0.84)^2 \times 13.576^2}{10^2} \\
&= 28.932
\end{aligned}
$$

Using 80% power, a 5% significance level, and a 10% dropout rate, the required sample size will be corrected to approximately 33 participants for a group. Therefore, a total of ***33 participants*** will be needed for this trial.

9.1.9 Study Duration and Timeline

Stage 1, review of medical records – 0.5 months

Stage 2, data collection and data analysis – 1-12 months

Stage 3, presentation and publication - 6-18 months

The participation duration for each subject is 3 months.

9.1.10 Study Visits and Procedures

9.1.10.1 Subjects who are eligible to take part in this trial will need to attend to the study site for a total of 5 compulsory visits, as illustrated in Fig. 3.

9.1.10.2 During the screening/baseline visit, it will take about 1 hours where the investigators will take note of the subjects conditions for evaluation of study acceptability.

9.1.10.3 Prior to any baseline measurement, the correct usage of the cream will be explained by the investigator and the investigator's team. Subjects will be required to apply at least 1 fingertip unit to 2% body surface area. The subjects will receive treatment with the IP for topical application for 3 times a day for 12 weeks (according to the guideline that emphasize the important of using sufficient emollient).

9.1.10.4 Subjects will be provided with non-soap-based shower product (REMDII® Calming Body Wash, Malaysia) for subject's shower purpose throughout

the study. Subjects should avoid the usage of soap-based products throughout the study.

9.1.10.5 Subjects will also be provided with a diary, for recording of any application of rescue treatment and deviation from the study protocols.

9.1.10.6 Subjects who have flare up, will be managed using hydrocortisone 1% cream for a duration of 7 days. Those who are not responding to hydrocortisone end of 7 days will be prescribed with clobetasone butyrate 0.05% cream for additional 7 days. Those who doesn't respond to the treatment shall be withdrawn. However, subjects need to record the application in the provided diary. As well, any deviation or illness that occurs during the study will need to be recorded in the same diary as well.

9.1.10.7 Those who acquired secondary bacterial infection will be treated with a week of cloxacillin (50-100mg/kg/day po in 4 divided dose). For those who are above 20kg, will receive the usual adult dose.

9.1.10.8 In patients with penicillin allergy will be given a week of erythromycin ethylsuccinate at a dose of 30mg/kg/day in divided dose (up to a max 2gm/day).

9.1.10.9 Patients who have eczema herpeticum will received a week of oral acyclovir, in which subjects 1 month till 2 years will receive 100mg 5×/day; while subjects age 2 to 12 years old will received 200mg 5×/day dosage.

9.1.10.10 After the explanation of the "Dos and Don'ts" to the guardians/parents, baseline measurement of atopic dermatitis severity of subjects using SCORAD index will be conducted.

9.1.10.11 Initial weight of cream provided to subjects will be recorded and weighed.

9.1.10.12 Subjects will be required to pay their visit to the study site, as stipulated, which takes about 45 minutes for each visit.

9.1.10.13 Measurement of atopic dermatitis severity using IGA and SCORAD index will be conducted. DLQI will be answered by subjects at each visit too.

9.1.10.14 Measurement of high resolution ultrasound skin-imaging (HR-USI), skin color and transepidermal water loss (TEWL) will be conducted using DermaLab® Series SkinLab Combo (DermaLab®, Denmark).

9.1.10.15 Subjects need to submit the old bottles of cream to investigator where they will be weighed in every visits. New cream will be provided to subjects, when necessary, in which the weight will be recorded too.

9.1.10.16 Subjects also have to submit their diaries to investigator. New sets of diaries will be provided to subjects.

9.1.10.17 All adverse events that happened throughout the study will be recorded.

9.2 Risk and benefit to study participants

Tocotrienol rich composition used in the topical is GRAS. As stated in the literature above, there are no adverse effects known to be caused by the IP. REMDII® Sensitive has been registered to the National Pharmaceutical Regulatory Agency (NPRA), Kementerian Kesihatan Malaysia with the notification number NOT181000506K and certified halal. All topicals shall expect to have irritation, burning, stinging sensation and folliculitis. There is low risk of sensitization to the topical ingredients. The study procedures are all routine procedures for the disease/condition studied. There is thus minimal risk for subjects. All parties will be insured by trial insurance paid for by the sponsor.

9.2.1 Potential benefits

- All subjects will be provided with free moisturisers and gentle body cleanser (REMDII®, Malaysia) for 3 months.
- Each subjects will be provided with an emolument of RM30/visit which will cover for their transportation. F & B will be provided at site.
- Access to promising new treatments often not available outside the clinical-trial setting.
- Treatment that may be more effective than the standard approach, Vitamin E has been tested to be safe and without known negative side effects.
- Close monitoring, advice, care, and support by a research team of doctors and other health care professionals who understand your disease or condition, free of charge.
- The opportunity to be the first to benefit from a new method under study.

- The chance to play an active role in your own health care and gain a greater understanding of your disease or condition.
- The chance to help society by contributing to medical research. Even if you don't directly benefit from the results of the clinical trial you take part in, the information gathered can help others and adds to scientific knowledge. People who take part in clinical trials are vital to the process of improving medical care.

9.2.2 Potential risks

- The clinical trial may require more time and hassle than a non-clinical trial treatment such as visits to the clinical trial site and potential waiting period prior to investigator's assessment.
- There may be possible risk of burning and stinging sensation on scratch wounds, irritation, and allergic reaction which is common of topical applications.

9.2.3 Risk Benefit Assessment

There is minimal risk from the IP and study procedures are non-invasive. Study findings shall potentially greatly improve treatment outcomes. The expected benefit outweighs the minimal risk to subjects and thus this study should be supported. All parties are insured by trial insurance provided and paid for by the sponsor.

9.2.4 Informed Consent/Assent Process

All interested party shall be informed and briefed of the study during the advertisement period by the investigator team. All parents will be properly informed and allowed a fixed time period to consider and inquire prior to consent. Two consents will be taken from children above 7 years where they will also be properly informed and allowed a fixed time period to consider and inquire prior to consent. All participation is strictly voluntary based. An appointment will be made where the patient information sheet will be provided and explained to them. If they are willing to participate, the consent forms will be signed and dated. If they need to, they are allowed to take the information sheet home to consult with their family members, and another day for getting consent arranged.

9.2.5 Privacy and Confidentiality

All subjects' personal data will be kept confidential. Subject's names will be kept on a password-protected database and will be linked only with a study identification number for this research. The identification number instead of patient identifiers will be used on subject data sheets. All data will be entered into a computer that is password protected. On completion of study, data in the computer will be copied to CDs and the data in the computer erased. CDs and any hardcopy data will be stored in a locked office of the investigators and maintained for a minimum of three years after the completion of the study. The CDs and data will be destroyed after that period of storage. Subjects will not be allowed to view their personal study data, as the data will be consolidated into a database. Subjects can write to the investigators to request access to study findings

9.2.7 Publication Policy

No personal information will be disclosed and subjects will not be identified when the findings of the survey are published.

9.2.8 Termination of Study

The sponsor may decide to terminate the study at any time. Subjects will be informed if the study is terminated and follow-up visits will be arranged if needed.

10. Statistical Analysis Plan

All data obtained at baseline will be given a coded ID-number before they are used in further statistical analyses.

10.1 The data analysis will be performed using Minitab 16. Descriptive date will be expressed as mean ± standard deviation (SD) unless otherwise stated. A value of $P < 0.05$ is considered statistically significant.

10.2 Prior to the statistical analysis, investigator needs to determine whether intention-to-treat analysis or modified intended-to-treat analysis is used for the statistical analysis. As well per-protocol analysis also can be carried out for comparison purpose. In

addition, the distribution of the data needs to be checked if it is following Gaussian distribution.

10.3 Comparison of SCORAD index between baseline and follow-up visits (if data is following Gaussian distribution, ANOVA will be used. If it is not following Gaussian distribution, Kruskal-Wallis test will be used.)

10.4 Comparison of POEM between baseline and follow-up visits (if data is following Gaussian distribution, ANOVA will be used. If it is not following Gaussian distribution, Kruskal-Wallis test will be used.)

10.5 Comparison of DLQI between baseline and follow-up visits (if data is following Gaussian distribution, ANOVA will be used. If it is not following Gaussian distribution, Kruskal-Wallis test will be used).

10.6 Correlation between SCORAD index with POEM or DLQI at baseline will be analysed using correlation coefficient (r) test. The cut-off values to interpret the correlations were as follows: < 0.5 = no correlation, > 0.5 = correlation, > 0.7 = high correlation. (If it is following Gaussian distribution, Pearson correlation will be used. If it is not following Gaussian distribution, Spearman correlation will be used)

11. Expected outcome

- REMDII® Sensitive will be effective in improving mild-to-moderate atopic dermatitis in children based on the positive changes of IGA score and SCORAD.
- Clinician-assessed IGA and SCORAD is directly correlated with patient-assessed SCORAD after 12 weeks of treatment using IP.
- IDLQI of subjects significantly improved compared to baseline as well as vehicle group.
- REMDII® Sensitive improves skin properties (HR-USI, color & TEWL) in children.
- REMDII® Sensitive will has no negative side effects on children with mild-to-moderate atopic dermatitis.

12. Gantt chart & milestone

Gantt chart

Activities	2019								2020								
	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9
Ethical clearance																	
Recruitment																	
Screening																	
Trial study																	
Data collection & analysis																	
Presentation & publication																	

Milestone

Stage 1, review of medical records – 0.5 months

Stage 2, data collection and data analysis – 1-12 months

Stage 3, presentation and publication - 6-18 months

The participation duration for each subject is ***3 months***.

13. Ethical consideration

All procedures will be conducted in compliance with ethical principles outlined in the Declaration of Helsinki and Malaysian Good Clinical Practice Guideline and will be well explained to subjects prior to signing of subject informed consent. Any subjects could withdraw at any time during the clinical trial, even without explanation.

The study involves no greater than minimal risk as the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests. Vulnerable group involves baby and children. All subjects will involves permission of one parent, while informed consent will also be obtained from children above 7 years old.

14. Declaration of conflict of interest

The investigators declare they have no conflict of interest. Prof. Dr. Lai Oi Ming, Dr. Nicholas Khong and Dr. Lai Wee Ting are representatives from Lipidware Sdn. Bhd.

15. Honoranium and incentives to respondents

- **Token of appreciation**

  Free moisturisers will be given to respondents that completes the 12 weeks study for the period of one year (including the study period).

- **Cost of transportation**

  All subjects will be provided RM30 each, for every visits, as incentive.

16. Other ethical review board approval (if applicable)

N/A

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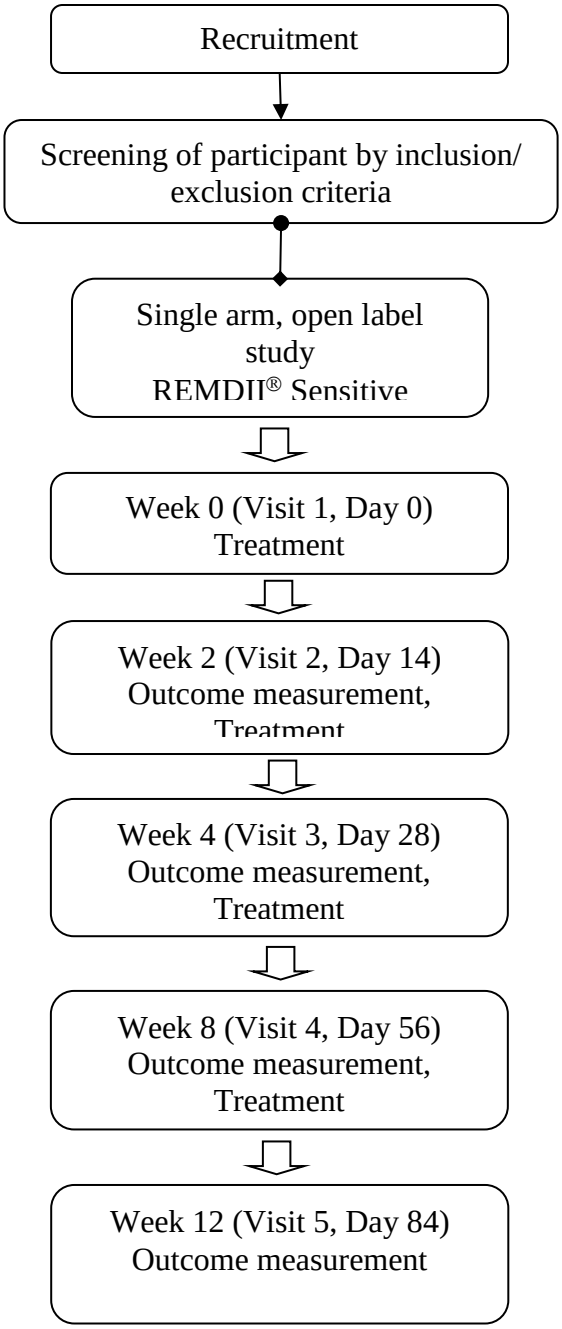

Figure 3. Study flow chart