A Phase 1, Open-label Study to determine Safety and Tolerability of the Topical Application of Mesenchymal stem/stromal cell (MSC) Exosome Ointment to Treat Psoriasis in Healthy Volunteers

The trial was conducted under a clinical trial authorization (Authorisation No.: CTA2200019) approved by the Health Sciences Authority (HSA) Singapore. The clinical protocol and informed consent form (ICF) were approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB reference number: 2021/00905).

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Introduction

Globally, 125 million people have psoriasis, estimating 2 to 3% of the total population[1]. Generally, first-line therapy for the treatment of mild to moderate psoriasis includes a topical regimen containing vitamin D analogues and glucocorticoids, and phototherapy. Whereas, for the treatment of moderate to severe psoriasis, systemic therapy is required, including small-molecule therapies and biologics [2-4]. However, the long-term use of systemic treatment is associated with some toxic adverse events (AEs) like nephrotoxicity, hepatotoxicity, hyperkalemia, hypomagnesemia, hypertension, tremors, malignancies, and loss of drug response [5-9]. A new treatment option is needed.

Mesenchymal stem cells (MSCs) exosome ointment, PTD 2021P, is being developed as a potential and promising treatment for the management of psoriasis. MSCs are one of the extensively employed cells in clinical trials with established safety profiles in humans and are approved for treating extremely inflexible inflammatory diseases [10, 11]. MSC exosomes are highly known for their potent immunomodulatory properties and have the potential to mitigate inflammation by promoting the secretion of anti-inflammatory cytokines, stimulating Treg polarization, and preventing complement activation [12-14].

We previously showed that topical application of MSC exosome not only reduced C5b-9 but also IL-17, and IL-23 in the IMQ-induced psoriasis mouse model [10]. As psoriatic and IMQ-treated stratum corneum is rich in activated complements and complement-activated neutrophils, and neutrophils are now implicated as the major source of IL-17 in psoriasis [15], it was postulated that topically applied MSC exosome inhibits C5b-9 formation in psoriatic and IMQ-treated stratum corneum, and this, in turn, reduces IL-17 secretion by neutrophils. When topically applied TID, the MSC exosome ointment, on mouse skin for 20 days at 10x higher than the clinical dose, the MSC exosome ointment elicited minimal systemic and local adverse effects (unpublished).

Before the conduct of this study, PTD 2021P has not been administered to humans thus far. Therefore, this phase 1 study was the first to evaluate the safety and tolerability of the application of the MSC exosome ointment with repeated topical application on adult healthy subjects (TID from Day 1 to 20). The results of this study were to provide the first clinical information on the drug's safety and inform the selection of administration of exosome ointment to be evaluated in subsequent clinical studies. The endpoints included to assess the safety and tolerability of exosome ointment for topical application in healthy adult volunteers are:

- Frequency of treatment-emergent adverse events (TEAEs)
- The incidence rate of local skin responses (LSR, i.e., erythema, flaking/scaling, crusting, swelling, vesiculation/pustulation, erosion/ulceration, hyperpigmentation, hypopigmentation, and scarring) [Time Frame: Days 1 and 21]
- Changes from baseline in blood parameters (including hematology, chemistry, and other inflammation parameters such as C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) [Time Frame: Days 1 and 21]

Materials and Methods

Study Design

The trial was conducted under a clinical trial authorization (Authorisation No.: CTA2200019) approved by the Health Sciences Authority (HSA) Singapore. The clinical protocol and informed consent form (ICF) were approved by the National Healthcare Group Domain Specific Review Board (NHG DSRB reference number: 2021/00905).

This study was conducted in accordance with the protocol and consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines, applicable International Conference on Harmonization (ICH), Good Clinical Practice (GCP) Guidelines, and other applicable laws and regulations.

This was a Phase 1, single center, open-label study. After signing an ICF, subjects underwent screening procedures on Day 1 prior to the first study product application to determine eligibility. Once eligible, all subjects (n=10) received topical treatment with the MSC exosome ointment immediately followed by Vesiderm liposome cream TID on the forearm with a gap of 4 hours between doses.

The study consisted of the following periods:

- A Screening Period of 1 day (Day 1)
- A Treatment Period of 20 days (Day 1 to 20)
- An End of Study (EOS) Period of 1 day (Day 21 [+3 days]).

Screening Period

Screening

The subjects were screened for eligibility on Day 1 prior to the application of the study product. Subjects were asked to sign the ICF after having the study described to them. After obtaining written informed consent, subjects underwent the following screening procedures for participation in the study:

- Inclusion/exclusion criteria assessments
- Vital signs
- Medical history
- Demographic data review
- Standard hematology panel
- Renal panel
- Liver function test
- Inflammatory blood examinations
- Pregnancy test (if applicable)
- Concomitant medications

Identification, visual assessment, and photography of application area

A trained expert evaluator (an Investigator or designee) identified the area of study product application and performed visual assessments which were carried out using an adapted version of SCORing Atopic Dermatitis (SCORAD) scale and visual assessment score (VAS). A photograph of the area of application was also taken using a dedicated compact digital camera at the clinic where subject visits were done.

Treatment Period

After confirmation of the application site, the subjects applied exosome ointment along with Vesiderm liposome cream (TID per day). The study product was applied daily (Day 1 to 20) with a gap of 4 hours between each dose to an area of healthy skin (one palm size) on the forearm using 1 fingertip unit (FTU). The Vesiderm liposome cream was applied in the same area immediately after.

All through the treatment period, the subjects completed the daily Subject Diary to capture adverse events (AEs; skin-related and other), concomitant medications, and time of study product application.

Follow-up calls were made every 3 days (Days 3, 6, 9, 12, 15, and 18) to check on compliance to the investigational product's (IP), and if subjects had any adverse events or taken any concomitant medications during the period. Any AEs reported by the subject during the calls were to be referred to the investigator for appropriate review and follow-up.

End of Study (EOS) Period

The EOS period was on Day 21 (+3 days). The subjects visited the clinic on this day for the assessments such as vital signs, blood examinations (hematology, chemistry, and inflammatory blood examinations), photograph of the area of application, visual assessment of the area of application, AEs, and concomitant medications used.

The assessments at this visit were also to be conducted in case of early termination or withdrawal of any subject.

Study Participants

Subjects were eligible to be included in the study only if they met all the following criteria:

1. Signed ICF prior to entering the study or undergoing any study procedures.
2. Male or female, >21 years of age at the time of signing the informed consent.
3. Subject who had been fully vaccinated for COVID-19 and was not under quarantine or Stay Home Notice or on a medical leave.
4. Subject who was willing and able to comply with scheduled visits, treatment plan, laboratory tests, and other study procedures.
5. Subject was able to read and write in the English language.
6. For women who were not postmenopausal (> 12 months of non-therapy induced amenorrhea) or surgically sterile (absence of ovaries and/or uterus):
    a. had a negative pregnancy test at screening
    b. remained abstinent or used contraceptive methods during the treatment period and continued for at least 30 days (one menstrual cycle) after the last treatment dose.

Subjects were to be excluded from the study if there was evidence of any of the following at screening or check-in, as appropriate:

1. Subject had any serious skin condition that was not well controlled.
2. Subject was currently using topical treatments.

3. Pregnant or breast-feeding women.
4. Subject had received phototherapy, oral corticosteroids, oral retinoid, oral immunosuppressive / immune modulative drugs, cytostatic / cytotoxic drugs, cyclosporine, or methotrexate within 30 days prior to the first application of the study product.
5. Subject was currently using any medications including biologics or undergoing treatment known to affect skin conditions.
6. Subject had any other clinically significant laboratory abnormalities, co-morbidities or psychiatric conditions that would place the subject at increased risk or confound the objectives of the study.
7. Subject had used any investigational drugs or biologics and/or participated in any clinical trial within the last 60 days before the day of the first dose of the study drug or was taking part in a non-medication study that would interfere with study compliance or outcome assessments.

Dosage

MSC exosome ointment (70 µg MSC exosomes/g ointment) was the study intervention to be administered. It was administered as a topical intervention of one FTU per one hand area on the forearm (average hand area was 160-200 cm^2), thrice a day for 20 days.

Safety Assessment

Safety assessment included vital signs, clinical safety laboratory tests, inflammatory blood examinations, assessment of area of application and incidence and severity of AEs.

Vital signs

Vital signs including blood pressure (both systolic and diastolic), heart rate, respiratory rate, and body temperature were assessed on Day 1 (pre-treatment) and Day 21 (+3 days)

Clinical safety laboratory tests

Clinical safety laboratory tests including hematology panel, renal panel, and liver function test were assessed on Day 1 (pre-treatment) and Day 21 (+3 days)

Inflammatory blood examinations

Inflammatory blood examinations including CRP and ESR were performed on Day 1 (pre-treatment) and Day 21 (+3 days).

Assessment of area of application

The area of application was assessed by a dermatologist for parameters adapted from the SCORAD scale as shown in the next paragraph. The patient graded the subjective symptoms including itch and sleeplessness using an SCORAD scale.

This scale assessed the following:

- Intensity of reaction: The identified area of application was assessed for the intensity of signs including redness, swelling, oozing/crusting, scratch marks, skin thickening, and dryness and graded as none (0), mild (1), moderate (2) or severe (3).

- Subjective symptoms: The identified area of application was assessed for the subjective symptoms including itch and sleeplessness and graded from 0 (no itch or no sleeplessness) to 10 (worst imaginable itch or sleeplessness).

Adverse events

All through the treatment period, the subjects completed the Subject Diary to capture the frequency of TEAEs.

Statistical Analysis

The analysis was conducted on all subject data at the time the study ended. Data collected in this study were presented using summary tables and subject data listings. Continuous variables were summarized using descriptive statistics, including the number of subjects (n), mean, median, standard deviation (SD), and minimum and maximum values. Categorical variables were summarized as frequencies and percentages. No formal statistical assessment, in terms of sample size, was conducted. A sample size of 10 subjects was considered a feasible sample size to provide sufficient safety data for a topical formulation study.

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