A Randomized, Double-Blind, Vehicle-Controlled, Phase I Study to Evaluate the Safety and Tolerability of Topically Applied INM-755 Cream on Epidermal Wounds in Healthy Volunteers

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Primary Objective• To evaluate the local safety and tolerability of INM-755 cream following repeated once-daily topical applications for 14 consecutive days on wounded skin of healthy volunteers. Secondary Objectives• To evaluate the systemic safety…

Ethical review	Approved WMO
Status	Completed
Health condition type	Epidermal and dermal conditions
Study type	Interventional

Summary

ID

NL-OMON49368

Source
ToetsingOnline

Brief title
INM-755 Cream on Epidermal Wounds

Condition

- Epidermal and dermal conditions

Synonym
Epidermolysis Bullosa, spontaneaous blistering

Research involving
Human

Sponsors and support

Primary sponsor: InMed Pharmaceuticals Inc.
Source(s) of monetary or material Support: InMed Pharmaceuticals Inc.

Intervention

Keyword: Healthy volunteers, INM-755, Tolerability, Wounds

Outcome measures

Primary outcome

Tolerability / safety endpoints

• Incidence of local and systemic treatment-emergent adverse events (TEAEs)

• Changes in vital signs, ECG, safety laboratory tests, and local tolerability

assessments

Wound healing endpoints

• Wound characteristics by LSCI, OCT, TEWL, multispectral and 3D photography

• Status of wound closure over time

Secondary outcome

N.A.

Study description

Background summary

Epidermolysis Bullosa (EB) is a rare inherited disorder characterized by mechanical stress-induced blistering of the skin and mucous membranes. EB is classified into four major types, namely, EB simplex (EBS), junctional EB (JEB), dystrophic EB (DEB), and Kindler syndrome. Tissue separation occurs in the epidermis, lamina lucida, or in the sublamina densa (1). The overall incidence and prevalence of EB is estimated to be 19 per million live births and approximately 11 per million, respectively (2).
Cutaneous wound healing is a complex process with four main phases: inflammation, re-epithelialization, tissue formation, and tissue remodeling. In

EB wounds, all four phases of cutaneous wound healing can be impaired, leading to chronic non-healing wounds. Persistent inflammatory activity, which may occur with infection or re-injury (e.g., from ongoing friction with clothing or due to pressure from sitting, and leaning back in chairs), often interferes with healing of EB wounds (3).
In addition to a persistent inflammatory response, half of the EBS patients suffer from a mutation in the K14 gene. Basal keratin 14 forms a complex with keratin 5 providing strength and flexibility to basal keratinocytes and helps in the formation of hemidesmosomes (4). A desirable outcome for a treatment for all subtypes of EB would be enhanced skin integrity to prevent new wounds from forming in combination with anti-inflammatory properties.
INM-755 is being developed for dermal application and treatment of medical indications characterized by inflammation, pain, and itching. The first clinical indication under development is EB. INM-755 is a cream containing cannabinol (CBN) as the active substance. CBN occurs naturally as a trace component of cannabis, or as a degradation product of Δ9-tetrahydrocannabinol (THC). CBN is a weak agonist for the Cannabinoid-1 (CB1) and Cannabinoid-2 receptor (CB2) (5).
Pre-clinical studies indicate that INM-755 reduces expression of MMP-9 and IL-8 (after challenging with TNFα and IFN*) which are upregulated in blisters of EB patients and are suspected to contribute to blister formation (6). After treatment with CBN, an upregulation in basal keratin 15 (K15) was observed. Upregulation of K15 might substitute K14 in forming a construct with K5, which could lead to strengthening of skin in EBS patients with a K14 mutation (7).
Pre-clinical safety studies show that CBN can be safely administered systemically by subcutaneous injection and topically on the skin using the intended clinical formulation. Previous clinical research showed no adverse effects of INM-755 application in humans.
A first-on-human clinical trial showed that INM-755 was well tolerated and safe after repeated once-daily topical applications for 14 consecutive days on healthy skin. Based on blinded interim safety analysis, no significant changes in vital signs, ECG, or laboratory tests were observed. Only low levels of erythema, oedema, and scaling were observed, probably caused by the semi-occlusive dressing application. Successful blisters were drawn on 12 subjects and completely re-epithelialized within 10-12 days after blister formation. This substantiates the design in the current study to follow-up on wound healing for a period of 3 weeks. No safety concerns were raised in this procedure.
However, no human experience with topical INM-755 applied to epidermal wounds is available to date. Therefore, this study will investigate the local safety and tolerability of topically applied INM-755 on epidermal wounds of healthy volunteers.

Study objective

Primary Objective
• To evaluate the local safety and tolerability of INM-755 cream following

repeated once-daily topical applications for 14 consecutive days on wounded skin of healthy volunteers.
Secondary Objectives
• To evaluate the systemic safety and tolerability of INM-755 cream following repeated once-daily topical applications for 14 consecutive days on wounded skin of healthy volunteers.
• To assess wound healing with INM-755 cream following repeated once-daily topical applications for 14 consecutive days on wounded skin of healthy volunteers.
Exploratory Objectives
• To quantify pharmacodynamic biomarker levels in epidermal wounds using FibroTx Patch analyses following repeated once-daily topical applications of INM-755 for 14 consecutive days.

Study design

This study is a Phase I, Double-Blind, Randomized, Vehicle-Controlled, Single-Center Study in Healthy Volunteers. A total of 8 subjects, in whom 4 successful blisters can be drawn on Day 1, will be included.

Intervention

INM-755 cream (high concentration, 0.3%), INM-755 cream (low concentration, 0.03%), or matching
vehicle.

Study burden and risks

Benefit
There are no anticipated benefits for subjects participating in the Phase 1 study, other than the benefit of medical evaluation at screening and throughout the study.

Risk
In all volunteers, 4 suction blisters will be induced on the untreated skin. The suction blister device (NP-4, Electric Diversities, Maryland, USA) is widely used in dermatological research settings. This device does not qualify as a medical device according to the Medical Devices Act, see the CCMO website (*An instrument intended by the manufacturer to be used specifically for diagnostic or therapeutic purposes*). By using negative pressure (up to 8 in/Hg), the device induces a 10mm diameter blister in approximately 60 to 90 minutes. The blister formation process is not painful. In the untreated subjects, the roof of the formed blister is pierced with a needle and the blister fluid is aspirated. Then the blister roof, i.e., epidermal sheet will be harvested. Treatment will be randomized on blister wound location. Treatment will be applied to occlusive bandages and applied to the blister wounds. All

blister wounds will be covered with occlusive bandages.

Complications of the blister include infection (rare) and post inflammatory hyperpigmentation. To minimize the risk of hypertrophic scaring, volunteers with a positive medical history will be excluded. In addition, to mitigate the risk of post inflammatory hyperpigmentation Fitzpatrick skin types 4-6 are excluded (see Appendix A for explanation of Fitzpatrick types).
All other quality, pharmacology and toxicology data, and satisfactory safety and tolerability data demonstrated in nonclinical studies are considered sufficient to initiate this study.
The risk to subjects in this trial will be minimized by compliance with the eligibility criteria, proper study design, and close monitoring.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female subject between 18 and 45 years of age inclusive at the time of consent.
2. Body mass index (BMI) between 18 and 30 kg/m2, inclusive, and with a minimum weight of 50 kg.
3. Subject is in good general health, according to the investigator*s judgement based on vital signs, medical history, physical examination, and laboratory tests performed.
4. Contraception:
a. Male participants:
i. A male participant who agrees to follow the contraceptive guidance during their participation in this study from Day 1 until at least 90 days after the last treatment administration. Effective contraceptive methods are described in Section 4.5.1.
b. Female participants:
i. A female participant is eligible to participate if she is not pregnant, does not plan to become pregnant during the study, not breastfeeding, and at least 1 of the following conditions applies:
1. Not a women of child-bearing potential (WOCBP)

OR

2. A WOCBP who agrees to follow the contraceptive guidance during their participation in this study from at least 90 days before Day 1 until at least 90 days after the last treatment administration. Effective contraceptive methods are described in Section 4.5.1.
5. Female subject has had a negative urine pregnancy test at screening and at Day 1 before dosing.
6. Subject is willing to participate and is capable of giving informed consent.
7. Subjects must be willing to comply with all study procedures, have the ability to communicate well with the investigator in Dutch language and must be available for the duration of the study.
8. Subject has sufficient application area of healthy intact skin of the back (>100 cm2).

Exclusion criteria

A subject who meets any of the following criteria and at Day 1 before dosing, unless specified otherwise, will be excluded from participation in this study.
1. Subject is a female who is breastfeeding, pregnant, or who is planning to become pregnant during the study.
2. Subject has a history of skin disease or presence of skin condition that, in the opinion of the investigator, would interfere with the study assessments.

3. Subject has presence of or has a history of atopic dermatitis or psoriasis.
4. Any known allergy or hypersensitivity to medical adhesives used in this study or any component of the study product (e.g., Poloxamers, Lecithin, Isopropyl Palmitate).
5. Subject has a positive reaction to skin marker test and/or dermographism test.
6. Subject has presence of any tattoos, scratches, open sores, excessive hair, or skin damages in the target treatment area(s) that, in the opinion of the investigator, may interfere with study evaluations.
7. Subject has a Fitzpatrick*s Skin Phototype >=4.
8. Subject is known to have immune deficiency or is immunocompromised.
9. Subject has a known history of chronic infectious disease (e.g., hepatitis B, hepatitis C, or infection with human immunodeficiency virus).
10. Subject has a history of cancer or lymphoproliferative disease within 5 years prior to Day 1. Subjects with successfully treated nonmetastatic cutaneous squamous cell or basal cell carcinoma and/or localized carcinoma in situ of the cervix are not to be excluded.
11. Subject had a major surgery within 8 weeks prior to Day 1 or has a major surgery planned during the study.
12. Subject has any clinically significant medical condition or physical, laboratory, ECG, or vital signs abnormality that would, in the opinion of the investigator, put the subject at undue risk or interfere with interpretation of study results.
13. Subject has used any systemic treatment that could be immunosuppressive (including oral corticosteroids, oral retinoids, immunosuppressive medication, methotrexate, cyclosporine, or apremilast) within 4 weeks prior to Day 1. Note: Intranasal corticosteroids and inhaled corticosteroids are allowed. Eye and ear drops containing corticosteroids are also allowed.
14. Subject has had excessive sun exposure, is planning a trip to a sunny climate, or has used tanning booths within 4 weeks prior to Day 1 or is not willing to minimize natural and artificial sunlight exposure during the study. Use of sunscreen products (except on application areas) and protective apparel are recommended when sun exposure cannot be avoided.
15. Subject has received laser treatment, electrolysis on the application areas within 4 weeks prior to Day 1 or is planning to during the study period.
16. Subject has shaved the application area 72 hours prior to Day 1 or is planning to do so during the study period.
17. Subject has used cannabis or any cannabinoid products within 12 weeks prior to Day 1.
18. Subject has used any medication known to impair alertness and/or ability to detect discomfort within 1 week prior to Day 1.
19. Subject has used a topical applied treatment on the targeted application area(s) within 1 week prior to Day 1.
20. Subject has a known history of clinically significant drug or alcohol abuse in the last year prior to Day 1.
21. Subject has a positive screen result for drug of abuse at screening and at Day 1 before dosing.

22. Subject is unwilling to avoid contact with water on the treatment condition area(s) during the treatment period.
23. Subject is requiring frequent use of pain medication (e.g., acetaminophen or NSAIDs) to relieve chronic pain (e.g., frequent headaches, migraines, dysmenorrhea, arthritis).
24. Subject has a history of hypertrophic scarring or keloid formation in scars or suture sites.
25. Subject has taken anticoagulant medication, such as heparin, low molecular weight (LMW)-heparin, warfarin, antiplatelets (except low-dose aspirin <=81 mg which will be allowed), within 2 weeks prior to Day 1, or has a contraindication to skin biopsies.
26. Loss or donation of blood over 500 mL within 12 weeks prior to screening.
27. Participation in any marketed or investigational drug or device study within 3 months or 5 half-lives (whichever is longer) prior to first dosing
28. Subject has a body temperature of >38 °C at any visit.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	01-07-2020
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	INM-755

Generic name:	N.a.

Ethics review

Approved WMO Date:	06-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	17-04-2020
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	11-06-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

ID: 28723
Source: NTR
Title:

In other registers

Register	ID
EudraCT	EUCTR2020-000425-65-NL
CCMO	NL72831.056.20

Study results

Date completed:	30-09-2020
Results posted:	24-03-2022

First publication
17-12-2021