A randomized, placebo-controlled, double-blind phase I study to explore safety, tolerability and pharmacodynamics of Cypep-1 in subjects with cutaneous warts

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* To evaluate the safety and tolerability of CyPep-1 when applied on healthy skin for up to one week. * To evaluate the safety and tolerability of CyPep-1 when applied to cutaneous warts for up to four weeks.* To evaluate the activity of the CyPep-1…

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

Summary

ID

NL-OMON48409

Source
ToetsingOnline

Brief title
A Phase 1 Safety and PD Study of CyPep-1 in Subjects with Cutaneous Warts

Condition

- Epidermal and dermal conditions

Synonym
Cutaneous warts, warts

Research involving
Human

Sponsors and support

Primary sponsor: Cytovation AS
Source(s) of monetary or material Support: Cytovation AS

Intervention

Keyword: Cutaneous Warts, CyPep-1, Pharmacodynamics, Safety

Outcome measures

Primary outcome

Pharmacodynamic / efficacy endpoints

Pharmacodynamic effects of CyPep-1 will be assessed at the time points

indicated in the Visit and

Assessment Schedule (Table 1) by

o Changes in morphology on-site;

o Change in total wart count;

o HPV viral load assessment of target lesions by quantitative PCR including HPV

genotyping in swabs and biopsies;

o Absolute reduction in wart size (diameter and volume) at Week 4 as compared

to baseline, measured by calliper and 3D photography;

o Absolute reduction in wart size (diameter and volume) at follow-up (week 10

and 16) as compared to baseline, measured by calliper and 3D photography;

o Change in the HPV viral load (nominal, natural log transformed, and natural

log of viral load per DNA copies) as determined by qPCR at Weeks 1, 2,3,4, 10

and 16 as compared to baseline

o Mean HPV viral load (nominal, natural log transformed, and natural log of

viral load per DNA copies) at treatment weeks and overall

o Percent reduction and clearance of warts

o If considered applicable, cellular and immune response in biopsies (inlcuding

H&E, HPV E4, Ki67)

Pharmacokinetic endpoints

Following PK samples will be analyzed:

Part 2: Day 28 (EOT) to determine if there is systemic exposure to CyPep-1.

Tolerability / safety endpoints

Adverse events (AE) will be collected throughout the study, at every study

visit. Vital signs and ECGs will performed at several timepoints as represented

in the Visit and Assessment schedules (table 1).

Secondary outcome

Exploratory endpoints

o Changes in morphology

o Changes in morphology by optical coherence tomography

Study description

Background summary

Human papillomavirus (HPV) refers to a group of DNA viruses that can induce neoplastic growth of human epithelial cells. In the skin, these neoplastic tumors are commonly known as warts. Cutaneous wart diagnosis is generally based on clinical examination, but it can also be determined by specific histological criteria. Some warts persist for many years and untreated warts represent a pool of HPV cross infection within the community. Many people find warts either

unsightly or painful and there is considerable social stigma associated with visible warts. Current clinical treatments for HPV-induced warts mainly involve mechanical or chemical destruction. The usual first line treatments are wart paints containing salicylic acid and / or trichloroacetic acid and cryotherapy with liquid nitrogen. However, current available treatments are considered painful, unsatisfactory and there is an unmet need to develop drugs with greater efficacy and specificity.
Normal mammalian cells are known for their asymmetric distribution of electrostatically neutral zwitterionic phospholipids within their membrane bilayer. Their outer membrane leaflets consist mainly of cholinophospholipids with neutral polar head-groups, while the aminophospholipids with negatively charged headgroups, such as phosphatidylethanolamine (PE) and phosphatidylserine (PS) are mainly found in their inner membrane leaflets. This asymmetrical lipid arrangement is thought to promote mechanical membrane stability, whereby especially interactions between the PS on the inner leaflet and skeletal proteins seem to entail membrane modulatory effects. In contrast, neoplastic cells often overexpress PS in the outer leaflet of their cell membranes, resulting in a slightly more negatively charged membrane than normal cells. As such, the electrochemical differences between normal and tumor cells represent a largely unexplored therapeutic opportunity.
Based on this observation, Cytovation has developed CyPep-1, a chemically synthesized, positively charged peptide consisting of 27-D amino acids. Cytovation is investigating various formulations with CyPep-1 as a potential treatment for HPV infections of skin and other tissues. CyPep-1s mode of action selectively targets- and lyses HPV-infected cells by inducing pyroptosis (necrosis) of infected keratinocytes by removing the surrounding cell membrane. This releases viral particles, potentially providing in-situ immunization. The described mode of action of this broad-spectrum product has been validated through extensive preclinical testing and applies to all HPV strains.

This Phase 1 study is intended to explore the safety, tolerability, pharmacodynamics and efficacy of topical CyPep-1 as a potential treatment for HPV-associated conditions. Since this is a first-on-human study of a topical formulation, the first subjects will be monitored more frequently in order to establish the safety profile. Because clinical outcomes (i.e. reduction/clearance of the lesion) often require lengthy treatment / observation periods, the study design will primarily utilize clinical measurements of wart dimensions, along with HPV viral load as a biomarker of anti-viral effect.

Study objective

* To evaluate the safety and tolerability of CyPep-1 when applied on healthy skin for up to one week.
* To evaluate the safety and tolerability of CyPep-1 when applied to cutaneous warts for up to four weeks.

* To evaluate the activity of the CyPep-1, after four weeks of treatment, and after six and twelve weeks of post-treatment follow-up, when applied to cutaneous common warts, as assessed by:
o Changes from pretreatment in wart size
o Clinical assessments of the wart morphology
o Changes from pre-treatment in the HPV load

Study design

This study has a phase 1, randomized, vehicle-controlled, double-blind, single center design to explore the safety, tolerability and pharmacodynamics (PD) of topically applied CyPep-1 in otherwise healthy patients with cutaneous warts. The study will entail two parts. Part 1 will follow a target area of 5x5 cm healthy skin to study tolerability and safety of the formulation. During this study part also a maximum of 3 common warts, preferably at the dorsal side of the hand / finger(s), will be treated. Several assessments will be done to determine pharmacodynamics and (possible) efficacy after a treatment period of 1 week.
Part 2 will evaluate the pharmacodynamics and efficacy of CyPep-1 after a treatment period of 4 weeks. Study part 2 will commence after an interim analysis, e.g. a blind data review, of study part 1 has been conducted.

Intervention

o CyPep-1 topical formulation 1% (w/w)
o Vehicle topical formulation (placebo)

Study burden and risks

The nonclinical studies to date conducted on CyPep-1 indicate that there were no unexpected adverse events following administration to dogs, rats or mini-pigs. The risks associated with the topical administration of CyPep-1 to humans have not yet been identified in man. Due to the topical administration of CyPep-1 only limited systemic exposure can be expected. To mitigate the risk a dense monitoring period is implemented after administration in Part 1. In general the risk can be evaluated as acceptable.

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. Healthy subjects (male, non-pregnant female), 18 to 65 years of age, inclusive. (Healthy status is defined by absence of evidence of any clinical significant/uncontrolled active or chronic disease following a detailed medical and surgical history, a complete physical examination including vital signs,12-lead ECG, haematology, blood chemistry, and urinalysis);
2. Body mass index (BMI) between 18 and 35 kg/m2, inclusive;
3. Free of clinically significant systemic or dermatologic disorders, which, in the opinion of the investigator, will interfere with the study results or increase the risk of Adverse Events;
4. Have at least 1 (non- peri / subungual) common wart on the, preferably, dorsal side of the hand /fingers which is 3-10 mm (inclusive) in diameter in its longest dimension on the plane of the skin;
5. If female of childbearing potential, have a negative urine pregnancy test at Screening/Day 0, and is willing to use effective contraception during the study (i.e. oral, implanted, injectable, IUD, diaphragm, condom, tubal ligation, abstinence, or are in a monogamous relationship with a partner who has had a vasectomy);
6. Able to participate and willing to give written informed consent and to comply with the study restrictions;
7. Ability to communicate well with the investigator in the Dutch language;
8. Willing to refrain from using cosmetics or other topical products in the treatment area for the duration of the study;
9. Agree not to use wart-removing products (prescription or over-the-counter) in the target

area or prohibited medications other than the study medication during the course of the study.

Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria:
1. Any clinically significant abnormality as determined by medical history taking and physical examinations obtained during the screening visit that in the opinion of the investigator would interfere with the study objectives or compromise subject safety;
2. Not willing to use effective (double barrier) contraception until at least 3 months after last study drug application;
3. For women: a positive pregnancy test and/or breastfeeding at screening or women who plan to become pregnant;
4. A positive test for drugs of abuse at screening;
5. History of alcohol or illicit drug abuse (alcohol abuse defined as alcohol consumption > 21 units/week);
6. Positive test results for Hepatitis B, Hepatitis C or HIV;
7. Have used salicylic acid or any other over-the-counter wart-removing product including cryo-therapy in the treatment area within 28 days prior to first study drug application;
8. Have required systemic intake of immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 60 days prior to first study drug application or during the course of the study. Routine use of inhaled or intranasal corticosteroids during the study is allowed;
9. Have any current and / or recurrent clinical significant skin infection in the treatment area other than common warts;
10. Have a known sensitivity to any of the investigational product ingredients;
11. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times in the past year;
12. Donation of blood or blood loss of >500 mL within 3 months prior to screening or donation of plasma within 14 days
13. Not having a general practitioner;
14. Not willing to give permission to have the general practitioner to be notified upon participation in this study;
15. Any condition that in the opinion of the investigator would complicate or compromise the study or the well-being of the subject.;Part 2 only:
16. Have treatment resistant / persistent warts as defined as one of the following:
a. More than 5 different failed treatments including topical formulations and cryotherapy
b. Longer than 6 years presence of the target wart
c. Having received active treatment in a clinical trial with an experimental drug for cutaneous warts.

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):	15-02-2019
Enrollment:	58
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	CyPep-1
Generic name:	N.A.

Ethics review

Approved WMO Date:	09-01-2019
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	23-01-2019
Application type:	First submission
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-002733-38-NL
CCMO	NL67664.056.18

Study results

Date completed: 20-12-2019

Results posted: 21-12-2020

First publication
25-09-2020