A phase 2, randomized, vehicle-controlled, double-blind study to explore the efficacy, pharmacodynamics and safety of topical ionic contra-viral therapy (ICVT) comprised of digoxin and furosemide in HPV-induced genital lesions of immunocompromised and immunocompetent patients.

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Primary Objective• To explore the pharmacodynamics of the ionic contra-viral therapy CLS003 in immunocompromised and immunocompetent patients with benign and premalignant HPV-induced genital lesions.• To evaluate clinical efficacy of CLS003 compared...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Vulvovaginal disorders (excl infections and inflammations)
Study type	Interventional

Summary

ID

NL-OMON46258

Source
ToetsingOnline

Brief title
ICVT in HPVinduced genital lesions of immunocompromised/-competent patients

Condition

- Vulvovaginal disorders (excl infections and inflammations)

- Cutaneous neoplasms benign

Synonym
genital warts / vulva dysplasia

Research involving
Human

Sponsors and support

Primary sponsor: Cutanea Life Sciences
Source(s) of monetary or material Support: Cutanea

Intervention

Keyword: digoxin/furosemide, Genital, HPV-induced, Immunocompromised

Outcome measures

Primary outcome

Pharmacodynamic / efficacy endpoints

- For both cohorts:

• Lesion (vulvar HSIL or wart) size reduction as absolute and percent reduction

in lesion diameter as measured by caliper and 3D photography

• Change in patient-reported outcomes (QoL and patient-reported clearance)

• HPV viral load assessment (quantitative PCR including HPV genotyping in swabs

and biopsies)

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

log of viral load per DNA copies) as determined by qPCR in swabs and biopsies

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

viral load per DNA copies) in swabs and biopsies

• Histology (regression of vulvar HSIL or AGWs, HPV genotyping)

• Local immunity status (Histological changes in immune cells in the

mucosa/submucosa)

- For vulvar HSIL cohort

• Vulvar HSIL, size and reduction in lesion size (clinical assessment of lesions by RECIST, absolute reduction in lesion size, lesion size reduction (percentage) as measured by caliper and 3D photograpy

• Percentage clearance of vulvar HSIL lesions

• Proportion of subjects with all vulvar HSIL lesions cleared

• Histology (regression of high grade dysplasia to no dysplasia)

• Histological recurrence (progression of no dysplasia to high grade dysplasia) in the Part 1 follow-up period

- For genital wart cohort:

• Wart size and reduction in wart size of the target wart (absolute reduction in lesion size, lesion size reduction (percentage)) as measured by caliper and 3D photography

• Percentage clearance of genital warts

• Proportion of subjects with all genital warts cleared

• Clinical recurrence in the Part 1 follow-up period

Secondary outcome

Adverse events (AE) will be collected throughout the study, at every study visit. Laboratory safety testing, 12-Lead ECGs and vital signs will be performed and measured multiple times during the course the study according to the Visit and Assessment Schedule. Plasma digoxin levels will be determined by therapeutic drug monitoring (TDM) at the end week 3 (day 21) and 6 (day 42). Patients will fill in a daily questionnaire (numeric rating scale pain/itch)

about local tolerance (e-diary).

Study description

Background summary

Human papillomavirus (HPV) infection is the most common sexually transmitted disease worldwide and can result in benign, premalignant and malignant lesions of the genital skin and genital mucosal surfaces. Among immunosuppressed patients, the prevalence of low as well as high risk HPV-infections is higher than in the immune competent population, and therefore HPV-induced genital lesions are more common in this group of patients[1;2].

Current surgical therapies for HPV-induced genital lesions are not directed at clearance of the HPV infection, but at physical removal of the lesions and stimulating the host immune system. Recurrence rate is high and often the currently available treatments cause a high physical and psychosocial burden [2;3].

Cutanea Life Sciences (CLS) is investigating various formulations with digoxin and furosemide as a potential treatment for HPV infections of skin and other similar tissue. In a published in vitro study in 2006 [4], the cardiac glycoside digoxin and loop diuretic furosemide inhibited replication in DNA viruses, herpes simplex virus, varicella zoster virus, human cytomegalovirus and adenovirus. The effects were most potent when digoxin and furosemide were used in combination as the topical formulation CLS003. This new approach, described as Ionic Contra-Viral Therapy (ICVT), is suggested to be most effective via topical application.

One potential viral target of ICVT is human papillomavirus (HPV) in associated cutaneous and mucosal lesions. Specifically, the ionic properties of digoxin and furosemide were noted to inhibit the K+ influx on which DNA viruses rely for replication. These drugs interact with the cell membrane ion co-transporters Na+/K+-ATPase and Na+-K+-2Cl- co-transporter. A previous study was conducted with a group of 80 patients with cutaneous warts, which demonstrated ICVT to be effective, safe and well tolerated.

Study objective

Primary Objective
• To explore the pharmacodynamics of the ionic contra-viral therapy CLS003 in immunocompromised and immunocompetent patients with benign and premalignant HPV-induced genital lesions.
• To evaluate clinical efficacy of CLS003 compared to vehicle in

immunocompromised and immunocompetent patients with benign and premalignant HPV-induced genital lesions

Secondary Objectives
• To evaluate the safety and tolerability of CLS003 in immunocompromised and immunocompetent patients with benign and premalignant HPV-induced genital lesions

Study design

A phase 2 efficacy and pharmacodynamic study of digoxin / furosemide ICVT in immunocompromised and immunocompetent patients with benign and premalignant HPV-induced genital lesions.

Intervention

Investigational drug
- CLS003: topical formulation (gel) containing digoxin (0.125% w/w) and furosemide (0.125%).
Comparative treatment
- Vehicle topical formulation (placebo)
During the treatment period topical formulation will be applied once daily.

Study burden and risks

CLS003 consists of a combination of the active substances digoxin and furosemide. The cardiac glycoside digoxin and the loop diuretic furosemide are currently market registered drugs for various indications e.g. heart failure / atrium fibrillation and hypertension, respectively. The formulations on the market comprise oral and parenteral route of administration leading to high systemic exposure to both drugs. Consequently, there is a vast amount of pre-clinical and clinical experience with these mechanisms of action. Therefore, drugs of this class can be administered safely to healthy volunteers and patients with a topical formulation.

Potential beneficial effects on AGWs and vulvar HSIL are to be explored in this study. Therefore, providing the protocol is adhered to, careful observation and medical management will minimize any associated risk in this study.

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

For enrollment of subjects the following criteria must be met:
1. Vulvar HSIL or AGW patients, >= 18 years of age, in general, stable good health (with the exception of the immunocompromised disorder) as per judgment of the investigator based upon the results of a medical history, physical examination, ECG, chemistry, hematology.
2. In case of the immunocompromised patient group(s): having an immunosuppressive disease or receiving immunosuppressive therapy for any reason including but not limited to; patients with auto-immune disease, HIV patients, transplantation patients
3. In case of genital warts: have at least 3 genital warts (only applicable for study part 1)
4. In case of vulvar HSIL: at least one lesion that can be accurately measured (using RECIST criteria) in at least one dimension with longest diameter >=20 mm OR in 2 perpendicular dimensions that when multiplied together give a surface area >=120 mm^2 (only applicable for study part 1)
5. If female of childbearing potential, have a negative urine pregnancy test at Screening and Day 0, and is willing to use effective contraception during the study and 3 months afterwards (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 other topical products in the treatment area, or prohibited medications for the duration of the study

Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria:
1. Significant, uncontrolled or unstable disease in any organ system as per judgment of the investigator (regardless of association with the immunosuppressing disorder/therapy), including but not limited to: psychiatric, neurologic, cardiovascular, pulmonary, gastrointestinal, hepatic, renal, endocrine, hematologic or respiratory disease
2. Have used or received any topical genital wart treatment, cryotherapy, electrocoagulation, surgery in the treatment area within 28 days prior to enrolment
3. Have used or received any topical vulvar HSIL treatment, laser therapy or surgery in the treatment area within 28 days prior to enrolment
4. Have any current relevant skin infections in the treatment area other than genital warts (inclusively, but not limited to atopic dermatitis, lichen sclerosis, lichen planus or psoriasis)
5. Have a known sensitivity to any of the investigational product ingredients, including digoxin and furosemide
6. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times in the past year
7. Loss or donation of blood over 500 mL within three months prior to screening.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL
Recruitment status: Recruitment stopped

Start date (anticipated):	04-09-2017
Enrollment:	48
Type:	Actual

Ethics review

Approved WMO Date:	09-08-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	21-08-2017
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	EUCTR2016-000870-39-NL
CCMO	NL57025.056.17