A phase I/IIa open-label First-in-Human study to assess safety and pharmacokinetics and explore biomarker effects of topical ionic contra-viral therapy (ICVT) comprised of digoxin and furosemide in subjects with cutaneous warts.

Published: 04-02-2014
Last updated: 20-04-2024

Primary objectives• To evaluate the systemic exposure of digoxin and furosemide after repeated topical CLS003 application in otherwise healthy subjects with multiple cutaneous warts;• To assess the safety/tolerability profile of CLS003.Secondary…

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

Summary

ID

NL-OMON41213

Source
ToetsingOnline

Brief title
Safety, PK and biomarker effects of ICVT in subjects with warts

Condition

- Epidermal and dermal conditions

Synonym
cutaneous warts

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cutaneous warts, First-in-Human, Ionic contra-viral therapy (ICVT), Safety

Outcome measures

Primary outcome

Tolerability / safety endpoints

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 (protocol, table 1).

Pharmacokinetic endpoints

Samples for pharmacokinetic determination of plasma digoxin and furosemide concentrations will be collected according to the Visit and Assessment Schedule (protocol, table 1). Samples will be tested by validated HPLC/MS/MS with a lower limit of quantification (LLOQ) of 0.05 ng/mL.

Secondary outcome

Efficacy / pharmacodynamic endpoints

Pharmacodynamic effects of CLS003 will be assessed at the time points indicated in the Visit and Assessment Schedule (protocol, table 1) by

• Morphological wart assessment on-site;

• Wart size and morphology assessment by standardized clinical photography;

• HPV viral load assessment of target lesions by quantitative PCR (exploratory biomarker).

Study description

Background summary

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. The anti-viral activity of digoxin and furosemide has been demonstrated in several in-vitro studies conducted by CLS. Both drugs prompted antiviral effects by extracellular K+; these effects were most potent when digoxin and furosemide were used in combination.
This new approach, described as Ionic Contra-Viral Therapy (ICVT), is suggested to be most effective via local application. One potential viral target of ICVT is human papillomavirus (HPV) in associated cutaneous and mucosal lesions. While there are multiple potential clinical indications, this first study will focus on cutaneous warts.
Current clinical treatments for HPV infections mainly involve lesion destruction. The usual first line treatments are wart paints containing salicylic acid and / or lactic acid and cryotherapy, usually with liquid nitrogen. However, current available treatments are considered unsatisfactory and there is an unmet need to develop drugs with greater efficacy and specificity.
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-1. This controlled depletion of cellular K+ has the potential to broaden the spectrum of antiviral activity.
This study is intended to utilize an efficient biomarker and pharmacokinetic study design to assess safety and to evaluate ICVT as a potential treatment for HPV-associated conditions in a small group of healthy subjects as a pilot study. Because clinical outcomes (i.e. clearance of the lesion) often require lengthy treatment / observation periods the study design will utilize measurements of HPV viral load as a biomarker of anti-viral effect.

Study objective

Primary objectives
• To evaluate the systemic exposure of digoxin and furosemide after repeated topical CLS003 application in otherwise healthy subjects with multiple

cutaneous warts;
• To assess the safety/tolerability profile of CLS003.

Secondary objectives
• To explore the pharmacodynamic effects of topically applied CLS003 on wart morphology and HPV viral load;
• To apply HPV viral load quantitative PCR (qPCR) on relevant clinical material as preparation for subsequent studies.

Study design

This phase I/IIa study has an open-label, First-in-Human (FIH), single center design to assess the safety, pharmacokinetics (PK) and pharmacodynamics (PD) of multiple doses of topically applied CLS003 in healthy subjects with cutaneous warts.

Intervention

A fixed dose of 1000 mg of CLS003 will be applied topically once daily on 7 consecutive days; 980 mg on healthy skin of the lower back on an area of 98 cm2; 10 mg CLS003 to each of the two treated target warts, equivalent to a daily dose of 12.5 µg digoxin and 12.5 µg furosemide per wart. The total applied dose will equal 1250 µg per day for digoxin and furosemide, respectively.

Study burden and risks

Of investigational products that have not been administered to humans before such as CLS003, not all adverse events are known
and unexpected adverse events could occur.
In general, the sub-therapeutic doses administered in this study are considered safe. Nevertheless, we have implemented the following precautionary measures;

• The use of medication that could interact with digoxin or furosemide is prohibited;
• Subjects who have any current and / or recurrent pathologically relevant skin infections in the treatment area other than common warts (with the exception of herpes simplex virus labialis) are excluded from study participation;
• Subjects who have any current uncontrolled infection will be excluded from study participation;
• Subjects are excluded from study participation if they have atopic dermatitis or any other skin diseases involving chronic inflammation or reducing the skin barrier function;
• Subjects with a known sensitivity to any of the investigational product ingredients, including digoxin and furosemide are excluded from study participation;

Thus, in this study the subjects will only receive sub-therapeutic doses of test product and the subjects will be screened thoroughly prior to study enrolment. The subjects will be closely monitored on vital signs, safety laboratory, ECG and for any adverse signs during the course of the study to minimize the risks.

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 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 30 kg/m2, inclusive;

3. Fitzpatrick skin type I-II-III-IV;
4. At least 4 cutaneous warts on the hands, separated by at least 1 cm of skin;

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. For women: a positive pregnancy test and/or nursing at screening;
3. A positive test for drugs of abuse at screening;
4. Have used salicylic acid or any other over-the-counter wart-removing product in the treatment area within 30 days prior to enrolment;
5. Have received cryotherapy in the treatment area within 60 days prior to enrolment;
6. Have required systemic intake of immunosuppressive or immunomodulatory medication (including oral or parenteral corticosteroids) within 30 days prior to enrolment or during the course of the study. Routine use of inhaled or intranasal corticosteroids during the study is allowed;
7. Subjects currently using systemic digoxin or furosemide or any of the following prohibited medications (Note: exceptions will only be made if the rationale is discussed and clearly documented between the investigator and the sponsor):;Potential drug interactions with furosemide:
Aminoglycoside antibiotics
Ethacrynic acid
Salicylates
Cisplatin
Tubocurarine
Suyccinlycholine
Lithium
ACE inhibitors
Chloral hydrate
Phenytoin
Methotrexate
Cephalosporins
Cyclosporine;Potential drug interactions with digoxin:
Potassium-depleting diuretics
Quinidine
Verapamil
Amiodarone
Propafenone
Indomethacin
Intraconazole
Alprazolam
Spironolactone
Beta-adrenergic blocking agents
Calcium channel blockers;8. Have any current and / or recurrent pathologically relevant skin

infections in the treatment area other than common warts (with the exception of herpes simplex virus labialis);
9. Have any current uncontrolled infection;
10. Atopic dermatitis or any other skin diseases involving chronic inflammation or reducing the skin barrier function;
11. Have a known sensitivity to any of the investigational product ingredients, including digoxin and furosemide.

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	18-03-2014
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	digoxin / furosemide
Generic name:	NA

Ethics review

Approved WMO

Date:	04-02-2014
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	17-02-2014
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	EUCTR2013-005569-38-NL
CCMO	NL47819.056.14