A phase 2, randomized, double blind, vehicle controlled, parallel group study to explore the efficacy, pharmacodynamics and safety of topical ionic contra-viral therapy (ICVT), comprised of digoxin and furosemide in actinic keratosis

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Primary Objective* To explore the pharmacodynamics of ICVT comprised of digoxin and furosemide (dual agent), digoxin (single agent), furosemide (single agent) in patients with AK. * To evaluate clinical efficacy of ICVT comprised of digoxin and...

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

Summary

ID

NL-OMON48691

Source
ToetsingOnline

Brief title
Topical ionic contra-viral therapy in actinic keratosis

Condition

- Epidermal and dermal conditions

Synonym
Actinic keratosis

Research involving
Human

Sponsors and support

Primary sponsor: Maruho Co., Ltd.
Source(s) of monetary or material Support: Maruho Co.;Ltd.

Intervention

Keyword: Actinic keratosis, Digoxin, Furesemide, Topical ionic contra-viral therapy (ICVT)

Outcome measures

Primary outcome

* Complete clinical clearance (CCC) per field

* Change in AK-FAS (AK field assessment scale)

* Change in lesion count per field

* Investigator global score of each field (IGS, using a 7 point scale from -2 (significantly worse) to +4 (completely cured), according to Nelson et al. 2013)

* Evolution of one assigned target lesion in the field, assessed by dermoscopy (assessing erythema, scaling, pigmentation, and follicular plug, using a 5 point score)

* Standardized photography with Canfield VISIA or 2D photography (depending on the location of the field)

* Biopsy biomarkers (where validated assays available at the time of study completion: IFN-a. IFN-g, Ki-67, p53, MCM7 (minichromosome maintenance protein 7), putrescene, spermidine, beta HPV types 5,8,15,20,24,38)

* Skin swab markers (where validated assays available at the time of study

completion: beta HPV types 5,8,15,20,24,38 by luminex, qPCR for HPV DNA)

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 at screening and EOS. 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) as well as for treatment compliance and daily facial photography (*selfies*).

Study description

Background summary

Actinic keratosis (AK) are common skin lesions which appear clinically as erythematous, scaly plaques on sun-exposed skin. As UV radiation has been recognized the main risk factor, they are typically located on the face, scalp, neck and extremities. The prevalence of AK lesions in adults increases with age: less than 10 percent for 20- to 29-year-olds, approximately 80 percent for 60- to 69-year-olds, and more than 80 percent for 70-year-olds and older. On histology examination AK is a proliferation of neoplastic keratinocytes in the epidermis, characterized by architectural disorder, with features of abnormal shape and size of keratinocytes, nuclear atypia and hyperkeratosis. AK may enter spontaneous remission or remain stable. However, importantly, AK are also known as precursor lesions of squamous cell carcinoma (SCC). Furthermore, the annual burden for the treatment of AK has been estimated at around 900 million dollars in the USA alone. (Dodds A et al, 2014, Berlin JM, 2010).

Investigations have suggested a role for human papilloma virus (HPV) and the development of AK into SCC. In 2005, Weissenborn and colleagues determined viral DNA loads of six frequent HPV types (5, 8, 15, 20, 24 and 36) by qPCR in AK, NMSC and perilesional tissue. HPV viral load was highest in AK compared with non-melanoma skin cancer (NMSC) and perilesional tissue. It was suggested that active HPV replication and presumably enhanced gene expression may stimulate keratinocyte proliferation and contribute to carcinogenesis in early stages of NMSC development. (Weissenborn et. al. 2005).

In 2006 the association between HPV infection and SCC development was further explored. Presence of HPVL1 and E6 seroreactivity and viral DNA were determined for HPV types 5, 8, 15, 16, 20, 24, and 38 in three study groups: SCC patients, AK patients and controls without any history of skin tumors. After recruitment, the response rate was between 75% and 85% in all groups. Eyebrow hair was collected from 57 controls, 126 AK, and 63 SCC cases, and blood from 53 controls, 118 AK, and 55 SCC cases.HPV DNA positivity was most prevalent in the AK cases (54%) compared with the SCC (44%) or tumor-free controls (40%). (Struijk et. al 2006).
An additional study from 2009 published similar results for a long-term persistence of betapapillomavirus (betaHPV). Eyebrow hairs were collected from 171 participants and tested for 25 different betaHPV types in 1996 and 2003. Of the total betaHPV infections detected, 30% were found to persist. After accounting for AK at baseline, persistence of betaHPV DNA resulted in a 1.4 fold increase in risk of having AK on the face in 2007. (Plasmeijer E et. al. 2009)

Cutanea Life Sciences (CLS, former sponsor) is investigating ICVT, comprised of digoxin (0.125%) and furosemide (0.125%) as a potential treatment for HPV-mediated and associated diseases including cutaneous warts, anogentical warts (AGWs), and high-grade squamous intraepithelial neoplasion (HSIL), the later formerly referred to as usual type vulvar intraepithelial neoplasia (uVIN). This study will be the first study of ICVT in AK. The ionic properties of digoxin and furosemide interact with the cell membrane ion cotransporters Na+/K+-ATPase and Na+-K+-2Cl- co-transporter-1 and thereby inhibit the K+ influx on which DNA viruses rely for replication. In an in vitro study, published in 2006, digoxin and furosemide inhibited replication in DNA viruses, herpes simplex virus, varicella zoster virus, human cytomegalovirus and adenovirus. Both drugs prompted antiviral effects by extracellular K+; these effects were most potent when digoxin and furosemide were used in combination (Hartley C, 2006). In two exploratory clinical studies of CLS003 in patients with cutaneous warts tolerability and short-term safety was established as well as efficacy in terms of viral load reduction and dimensional changes of the lesions.

Based on the scientific literature on the potential association of HPV with AK, the study results to date with ICVT support the concept of an investigation of ICVT in the therapeutic management of AK. This study is intended to assess the clinical efficacy and pharmacodynamics of ICVT as a potential new treatment for AK. Clinical efficacy by means of clinical outcomes (i.e. clearance of the lesions, AK-FAS) and sub-clinical parameters / biomarkers on the skin and systemic ones will be assessed.

Study objective

Primary Objective
* To explore the pharmacodynamics of ICVT comprised of digoxin and furosemide

(dual agent), digoxin (single agent), furosemide (single agent) in patients with AK.
* To evaluate clinical efficacy of ICVT comprised of digoxin and furosemide (dual agent), digoxin (single agent), furosemide (single agent), and vehicle gel.
Secondary Objectives
* To evaluate the safety and tolerability of ICVT comprised of digoxin and furosemide (dual agent), digoxin (single agent), furosemide (single agent)

Study design

This study is a phase 2, double-blind, vehicle-controlled, parallel group, efficacy and pharmacodynamic study of ICVT in AK.

Intervention

Treatment
8 subjects : ICVT comprised of Digoxin and Furosemide (0.125%) QD during six weeks
8 subjects : Furosemide (0.125%) QD during six weeks.
8 subjects : Digoxin (0.125%) QD during six weeks.
8 subjects : Placebo (Vehicle Gel) QD daily during six weeks.

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 in a topical formulation.

Potential beneficial effects on AK are to be explored in this study. 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. Male and female subjects *18 years with a condition of general good health (with the exception of AK). The health status is verified by absence of evidence of any clinical significant active or uncontrolled chronic disease other than AK following a detailed medical history, a complete physical examination including vital signs, 12-lead ECG, hematology, blood chemistry, virology and urinalysis;
2. Confirmed clinical AK diagnosis by dermatologist (biopsy proven after end of study, in untreated part of the AK field)
3. At least 2 facial fields of at least 25 cm2 (but preferably >35 cm2) present at screening and baseline visit where at least 2 AK lesions are visible in each field (preferably the forehead, temple or cheek)
4. Able to participate and willing to give written informed consent and to comply with the study restrictions.
5. Ability to communicate well with the investigator in Dutch.
6. Willing to refrain from using other topical products in the treatment area, or prohibited medications for the duration of the study.
7. Willing to limit sun exposure of the involved skin to the extent

vocationally possible.
8. Subjects and their partners of childbearing potential must use effective contraception, for the duration of the study and for 3 months after the last dose.

Exclusion criteria

Eligible subjects must meet none of the following exclusion criteria:
1. Have used or received any treatment for AK in the treatment area within 28 days prior to enrollment (including topical medications, immunosuppressive or immunomodulating agents, phototherapy, oral retinoids, or other therapies for AKs)
2. Have any current pathologically relevant skin conditions in the field area other than AK (e.g. squamous cell carcinoma or basal cell carcinoma).
3. Have a known hypersensitivity to any of the investigational product ingredients, including digoxin and furosemide.
4. Current use of systemic digoxin or furosemide.
5. Participation in an investigational drug or device study within 3 months prior to screening or more than 4 times a year
6. Loss or donation of blood over 500 mL within three months (males) or four months (females) prior to screening or intention to donate blood or blood products during the study.
7. If a woman of childbearing potential, pregnant, or breast-feeding, or planning to become pregnant during the study.

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):	22-10-2018
Enrollment:	32
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Digoxin/Furosemide
Generic name:	NA

Ethics review

Approved WMO Date:	04-07-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	10-08-2018
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	04-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	05-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	13-08-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO Date:	26-08-2019
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

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2018-000034-36-NL
CCMO	NL64613.056.18

Study results