Clinical trial results:
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 healthy volunteers with actinic keratosis

Summary

EudraCT number	2018-000034-36
Trial protocol	NL
Global end of trial date	31 October 2019

Results information

Result version number	v1 (current)
This version publication date	20 September 2022
First version publication date	20 September 2022
Summary attachment (see zip file)	M3. CHDR1734_CSR_Summary_15Jun2020 (M3. CHDR1734_CSR_Summary_15Jun2020.pdf)

Trial information

Trial identification

Sponsor protocol code	CHDR1734_CLS003-CO-PR-004

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	ToetsingOnline: NL6461 3.056.18

Notes:

Sponsors

Sponsor organisation name	Maruho Co., Ltd
Sponsor organisation address	93 Chudoji Awatacho , Kyoto, Japan, 600-8815
Public contact	Principal Investigator, Centre for Human Drug Research, +31 715246400, clintrials@chdr.nl
Scientific contact	Principal Investigator, Centre for Human Drug Research, +31 715246400, clintrials@chdr.nl

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	15 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2019
Global end of trial reached?	Yes
Global end of trial date	31 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

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 (dualagent), digoxin (single agent), furosemide (single agent).

Protection of trial subjects:

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.

Background therapy:

We hypothesized that topical ionic contra-viral therapy, comprised of digoxin (0.125%) and furosemide (0.125%), could serve as a potential treatment for HPV-mediated and associated diseases. 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.

Evidence for comparator:

Vehicle gel with identical appearance will serve as placebo.

Actual start date of recruitment	22 October 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 32
Worldwide total number of subjects	32
EEA total number of subjects	32

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	7
From 65 to 84 years	25
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Screenings started at 22-OCT-2018 and the last screening was at 18-JUN-2019 CHDR, Leiden, the Netherlands.

Pre-assignment

Screening details:

Male and female subjects ≥ 18 years with a condition of general good health (with the exception of AK). The health status was verified by absence of evidence of any clinically significant active or uncontrolled chronic disease other than AK.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	Active drugs

Arm description:

The patients were randomized 1:1:1:1 for the four treatment arms in blocks of 4. Per patient two AK fields were selected; one AK field was treated with the topical formulation and the other AK field was used as untreated comparator.

Arm type	Experimental
Investigational medicinal product name	Digoxin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subject received tubes of 5g. Once daily for 42 consecutive days, a drop in the form a small pea was applied on the treatment field of 25-35 cm2.

Investigational medicinal product name	Furosemide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subject received tubes of 5g. Once daily for 42 consecutive days, a drop in the form a small pea was applied on the treatment field of 25-35 cm2.

Investigational medicinal product name	ICVT
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subject received tubes of 5g. Once daily for 42 consecutive days, a drop in the form a small pea was applied on the treatment field of 25-35 cm2.

Arm title	Placebo

Arm description:

The patients were randomized 1:1:1:1 for the four treatment arms in blocks of 4. Per patient two AK fields were selected; one AK field was treated with the topical formulation and the other AK field was used as untreated comparator. less

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

Subject received tubes of 5g. Once daily for 42 consecutive days, a drop in the form a small pea was applied on the treatment field of 25-35 cm2.

Number of subjects in period 1	Active drugs	Placebo
Started	24	8
Completed	24	8

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	32	32	
Age categorical Units: Subjects			
Adults (18-64 years)	7	7	
From 65-84 years	25	25	
Gender categorical Units: Subjects			
Female	14	14	
Male	18	18	

End points

End points reporting groups

Reporting group title	Active drugs

Reporting group description:

The patients were randomized 1:1:1:1 for the four treatment arms in blocks of 4. Per patient two AK fields were selected; one AK field was treated with the topical formulation and the other AK field was used as untreated comparator.

Reporting group title	Placebo

Reporting group description:

The patients were randomized 1:1:1:1 for the four treatment arms in blocks of 4. Per patient two AK fields were selected; one AK field was treated with the topical formulation and the other AK field was used as untreated comparator. less

Primary: Total clearance present/absent at EOT and/or EOS

End point title	Total clearance present/absent at EOT and/or EOS[1]

End point description:

No total clearance was present at the end of study for any subject.

End point type	Primary

End point timeframe:

42 Days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: See attachment.

End point values	Active drugs	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	24	8		
Units: lesion	24	8		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Screening until end of study.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1
Reporting groups	
Reporting group title	Digoxin/Furosemide/ICVT/Placebo

Reporting group description: -

Serious adverse events	Digoxin/Furosemide/ICVT/Placebo		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 32 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Digoxin/Furosemide/ICVT/Placebo		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	25 / 32 (78.13%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Benign neoplasm of skin			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Cardiac disorders			
Palpitations			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 32 (15.63%)		
occurrences (all)	5		
Dizziness			

subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
General disorders and administration site conditions			
Administration site irritation			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Administration site reaction			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Application site irritation			
subjects affected / exposed	2 / 32 (6.25%)		
occurrences (all)	2		
Influenza like illness			
subjects affected / exposed	3 / 32 (9.38%)		
occurrences (all)	3		
Diarrhoea			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Gastrointestinal disorders			
Femoral hernia			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Toothache			
subjects affected / exposed	1 / 32 (3.13%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			

Cough subjects affected / exposed occurrences (all)	2 / 32 (6.25%) 3		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all) Skin exfoliation subjects affected / exposed occurrences (all)	 2 / 32 (6.25%) 2 3 / 32 (9.38%) 3		
Musculoskeletal and connective tissue disorders Bursitis subjects affected / exposed occurrences (all) Musculoskeletal pain subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1		
Infections and infestations Upper respiratory tract infection subjects affected / exposed occurrences (all) Helicobacter gastritis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1 1 / 32 (3.13%) 1		
Metabolism and nutrition disorders Gout subjects affected / exposed occurrences (all)	 1 / 32 (3.13%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2019	Change made in the protocol concerning the minimal amount of Actinic Keratosis (AK) lesions required to enroll into the study.
09 August 2019	Change of sponsor for this study from Cutanea Life Sciences to Maruho Co., Ltd. ln June 2019, Maruho acquired Cutanea Life Sciences as a wholly-owned subsidiar yand with that took over the R&D activities of Cutanea Life Sciences, including the current study.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported