



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 (dual agent), 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 occurrences (all) | 1 / 32 (3.13%) 1 | | |
| General disorders and administration site conditions | | | |
| Administration site irritation subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | | |
| Administration site reaction subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | | |
| Application site irritation subjects affected / exposed occurrences (all) | 2 / 32 (6.25%) 2 | | |
| Influenza like illness subjects affected / exposed occurrences (all) | 3 / 32 (9.38%) 3 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | | |
| Chills subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | | |
| Immune system disorders | | | |
| Seasonal allergy subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | | |
| Gastrointestinal disorders | | | |
| Femoral hernia subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 1 | | |
| Toothache subjects affected / exposed occurrences (all) | 1 / 32 (3.13%) 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. In June 2019, Maruho acquired Cutanea Life Sciences as a wholly-owned subsidiary and 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