



## Clinical trial results:

### Tolerance of virucidal alcohol-based hand rubs - healthy volunteer trial Summary

|                          |                 |
|--------------------------|-----------------|
| EudraCT number           | 2010-018624-20  |
| Trial protocol           | DE              |
| Global end of trial date | 17 January 2011 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 04 October 2019 |
| First version publication date | 04 October 2019 |

#### Trial information

##### Trial identification

|                       |                  |
|-----------------------|------------------|
| Sponsor protocol code | OPM-CIC-G-H-0902 |
|-----------------------|------------------|

##### Additional study identifiers

|                                    |   |
|------------------------------------|---|
| ISRCTN number                      | - |
| ClinicalTrials.gov id (NCT number) | - |
| WHO universal trial number (UTN)   | - |

Notes:

#### Sponsors

|                              |                                                                                                                                  |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Medical Center - University of Freiburg                                                                                          |
| Sponsor organisation address | Breisacherstr. 153, Freiburg, Germany, 79110                                                                                     |
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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                       | 22 December 2011 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 13 August 2010   |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 17 January 2011  |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

Uncoated viruses such as adenovirus or norovirus are a challenge for infection control strategies since these pathogens are highly resistant to disinfectants. Hand hygiene is accepted to be an essential measure to prevent infections caused by adeno- or norovirus. In case of an adeno- or norovirus infection within the clinical setting it is strongly recommended to use a virucidal hand rub and to exchange conventional hand disinfectants by virucidal ones (German recommendation by the Robert Koch-Institute; [www.rki.de](http://www.rki.de)). Disadvantage of virucidal hand rubs, however, might be limited skin-tolerability compared to conventional products. This in turn may impair hand hygiene compliance. The aim of this trial is to compare the tolerability of three different virucidal hand rubs and a reference conventional product. This is a cross-over trial with 4 periods.

Protection of trial subjects:

The safety, tolerability and acceptance of hand hygiene preparations impacts on compliance. In Germany, hand rub is classified as a drug, approval of which includes evaluation for efficacy, safety and tolerability. Nonetheless, few systematic scientific trials are available on the safety and tolerability of hand rubs. In particular, comparative data are missing for different preparations and their composition. The results obtained in this work on the safety and tolerability of four different virucidal hand rubs should provide important information to optimize their safety and tolerability.

Background therapy:

none

Evidence for comparator: -

|                                                           |              |
|-----------------------------------------------------------|--------------|
| Actual start date of recruitment                          | 21 June 2010 |
| Long term follow-up planned                               | No           |
| Independent data monitoring committee (IDMC) involvement? | No           |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |             |
|--------------------------------------|-------------|
| Country: Number of subjects enrolled | Germany: 22 |
| Worldwide total number of subjects   | 22          |
| EEA total number of subjects         | 22          |

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)                     | 22 |
| From 65 to 84 years                      | 0  |
| 85 years and over                        | 0  |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were recruited from students of the Medical Center, University of Freiburg, and nursing students of the Freiburg Academy of Medical Professions. Inclusion criteria were subject's written informed consent, age > 18 years; legal capacity; healthy in body and mind and not under medical treatment at the time of inclusion.

### Pre-assignment

Screening details:

healthy volunteers

### Period 1

|                              |                                              |
|------------------------------|----------------------------------------------|
| Period 1 title               | Intervention 1                               |
| Is this the baseline period? | Yes                                          |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

### Arms

|                              |                             |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes                         |
| <b>Arm title</b>             | R - P1 - P3 - P2 / Period 1 |

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 1 received R in period 1.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Softa-Man® pure    |
| Investigational medicinal product code | 60998.00.00        |
| Other name                             |                    |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Cutaneous use      |

Dosage and administration details:

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (=total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P1 - P2 - R - P3 / Period 1 |
|------------------|-----------------------------|

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 2 received P1 in period 1.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Softa-Man(R) acute |
| Investigational medicinal product code | 61000.00.00        |
| Other name                             |                    |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Cutaneous use      |

Dosage and administration details:

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (= total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P2 - P3 - P1 - R / Period 1 |
|------------------|-----------------------------|

**Arm description:**

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 3 received P2 in period 1.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Sterillium(R) virugard |
| Investigational medicinal product code | 13814.00.00            |
| Other name                             |                        |
| Pharmaceutical forms                   | Cutaneous solution     |
| Routes of administration               | Cutaneous use          |

**Dosage and administration details:**

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (= total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P3 - R - P2 - P1 / Period 1 |
|------------------|-----------------------------|

**Arm description:**

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 4 received P3 in period 4.

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Active comparator    |
| Investigational medicinal product name | Manorapid(R) Synergy |
| Investigational medicinal product code | 57801.00.00          |
| Other name                             |                      |
| Pharmaceutical forms                   | Cutaneous solution   |
| Routes of administration               | Cutaneous use        |

**Dosage and administration details:**

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (=total application of 90 mL per day).

| <b>Number of subjects in period 1</b> | R - P1 - P3 - P2 /<br>Period 1 | P1 - P2 - R - P3 /<br>Period 1 | P2 - P3 - P1 - R /<br>Period 1 |
|---------------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Started                               | 5                              | 6                              | 6                              |
| Completed                             | 5                              | 6                              | 6                              |
| Not completed                         | 0                              | 0                              | 0                              |
| Consent withdrawn by subject          | -                              | -                              | -                              |

| <b>Number of subjects in period 1</b> | P3 - R - P2 - P1 /<br>Period 1 |
|---------------------------------------|--------------------------------|
| Started                               | 5                              |
| Completed                             | 4                              |
| Not completed                         | 1                              |
| Consent withdrawn by subject          | 1                              |

**Period 2**

|                              |                                              |
|------------------------------|----------------------------------------------|
| Period 2 title               | Intervention 2                               |
| Is this the baseline period? | No                                           |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

Blinding of products were done by the pharmacy using a working bench.

**Arms**

|                              |                             |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes                         |
| <b>Arm title</b>             | R - P1 - P3 - P2 / Period 2 |

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 1 received P1 in period 2.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Softa-Man(R) acute |
| Investigational medicinal product code | 61000.00.00        |
| Other name                             |                    |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Cutaneous use      |

Dosage and administration details:

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (= total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P1 - P2 - R - P3 / Period 2 |
|------------------|-----------------------------|

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 2 received P2 in period 2.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Sterillium(R) virugard |
| Investigational medicinal product code | 13814.00.00            |
| Other name                             |                        |
| Pharmaceutical forms                   | Cutaneous solution     |
| Routes of administration               | Cutaneous use          |

Dosage and administration details:

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (= total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P2 - P3 - P1 - R / Period 2 |
|------------------|-----------------------------|

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 3 received P3 in period 2.

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Active comparator    |
| Investigational medicinal product name | Manorapid(R) Synergy |
| Investigational medicinal product code | 57801.00.00          |
| Other name                             |                      |
| Pharmaceutical forms                   | Cutaneous solution   |
| Routes of administration               | Cutaneous use        |

**Dosage and administration details:**

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (=total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P3 - R - P2 - P1 / Period 2 |
|------------------|-----------------------------|

**Arm description:**

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 4 received R in period 2.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Softa-Man® pure    |
| Investigational medicinal product code | 60998.00.00        |
| Other name                             |                    |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Cutaneous use      |

**Dosage and administration details:**

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (=total application of 90 mL per day).

| <b>Number of subjects in period 2</b> | R - P1 - P3 - P2 /<br>Period 2 | P1 - P2 - R - P3 /<br>Period 2 | P2 - P3 - P1 - R /<br>Period 2 |
|---------------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Started                               | 5                              | 6                              | 6                              |
| Completed                             | 5                              | 5                              | 6                              |
| Not completed                         | 0                              | 1                              | 0                              |
| Consent withdrawn by subject          | -                              | 1                              | -                              |
| Joined                                | 0                              | 0                              | 0                              |
| Restarting                            | -                              | -                              | -                              |

| <b>Number of subjects in period 2</b> | P3 - R - P2 - P1 /<br>Period 2 |
|---------------------------------------|--------------------------------|
| Started                               | 4                              |
| Completed                             | 4                              |
| Not completed                         | 1                              |
| Consent withdrawn by subject          | 1                              |
| Joined                                | 1                              |
| Restarting                            | 1                              |

**Period 3**

|                              |                                              |
|------------------------------|----------------------------------------------|
| Period 3 title               | Intervention 3                               |
| Is this the baseline period? | No                                           |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

Blinding of products were done by the pharmacy using a working bench.

**Arms**

|                              |                             |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes                         |
| <b>Arm title</b>             | R - P1 - P3 - P2 / Period 3 |

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 1 received P3 in period 3.

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Active comparator    |
| Investigational medicinal product name | Manorapid(R) Synergy |
| Investigational medicinal product code | 57801.00.00          |
| Other name                             |                      |
| Pharmaceutical forms                   | Cutaneous solution   |
| Routes of administration               | Cutaneous use        |

Dosage and administration details:

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (=total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P1 - P2 - R - P3 / Period 3 |
|------------------|-----------------------------|

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 2 received R in period 3.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Softa-Man® pure    |
| Investigational medicinal product code | 60998.00.00        |
| Other name                             |                    |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Cutaneous use      |

Dosage and administration details:

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (=total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P2 - P3 - P1 - R / Period 3 |
|------------------|-----------------------------|

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 3 received P1 in period 3.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Softa-Man(R) acute |
| Investigational medicinal product code | 61000.00.00        |
| Other name                             |                    |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Cutaneous use      |



**Dosage and administration details:**

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (= total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P3 - R - P2 - P1 / Period 3 |
|------------------|-----------------------------|

**Arm description:**

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 4 received P2 in period 3.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Active comparator      |
| Investigational medicinal product name | Sterillium(R) virugard |
| Investigational medicinal product code | 13814.00.00            |
| Other name                             |                        |
| Pharmaceutical forms                   | Cutaneous solution     |
| Routes of administration               | Cutaneous use          |

**Dosage and administration details:**

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (= total application of 90 mL per day).

| <b>Number of subjects in period 3</b> | R - P1 - P3 - P2 /<br>Period 3 | P1 - P2 - R - P3 /<br>Period 3 | P2 - P3 - P1 - R /<br>Period 3 |
|---------------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Started                               | 5                              | 5                              | 6                              |
| Completed                             | 3                              | 5                              | 5                              |
| Not completed                         | 2                              | 1                              | 1                              |
| Consent withdrawn by subject          | 2                              | 1                              | 1                              |
| Joined                                | 0                              | 1                              | 0                              |
| Restarted                             | -                              | 1                              | -                              |
| Restarting                            | -                              | -                              | -                              |

| <b>Number of subjects in period 3</b> | P3 - R - P2 - P1 /<br>Period 3 |
|---------------------------------------|--------------------------------|
| Started                               | 4                              |
| Completed                             | 4                              |
| Not completed                         | 1                              |
| Consent withdrawn by subject          | 1                              |
| Joined                                | 1                              |
| Restarted                             | -                              |
| Restarting                            | 1                              |

**Period 4**

|                              |                                              |
|------------------------------|----------------------------------------------|
| Period 4 title               | Intervention 4                               |
| Is this the baseline period? | No                                           |
| Allocation method            | Randomised - controlled                      |
| Blinding used                | Double blind                                 |
| Roles blinded                | Subject, Investigator, Monitor, Data analyst |

Blinding implementation details:

Blinding procedure took place within the pharmacy.

**Arms**

|                              |                             |
|------------------------------|-----------------------------|
| Are arms mutually exclusive? | Yes                         |
| <b>Arm title</b>             | R - P1 - P3 - P2 / Period 4 |

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 1 received P2 in period 4.

|                                        |                        |
|----------------------------------------|------------------------|
| Arm type                               | Experimental           |
| Investigational medicinal product name | Sterillium(R) virugard |
| Investigational medicinal product code | 13814.00.00            |
| Other name                             |                        |
| Pharmaceutical forms                   | Cutaneous solution     |
| Routes of administration               | Cutaneous use          |

Dosage and administration details:

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (= total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P1 - P2 - R - P3 / Period 4 |
|------------------|-----------------------------|

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 2 received P3 in period 4.

|                                        |                      |
|----------------------------------------|----------------------|
| Arm type                               | Experimental         |
| Investigational medicinal product name | Manorapid(R) Synergy |
| Investigational medicinal product code | 57801.00.00          |
| Other name                             |                      |
| Pharmaceutical forms                   | Cutaneous solution   |
| Routes of administration               | Cutaneous use        |

Dosage and administration details:

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (=total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P2 - P3 - P1 - R / Period 4 |
|------------------|-----------------------------|

Arm description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 3 received R in period 4.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Experimental       |
| Investigational medicinal product name | Softa-Man® pure    |
| Investigational medicinal product code | 60998.00.00        |
| Other name                             |                    |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Cutaneous use      |

**Dosage and administration details:**

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (=total application of 90 mL per day).

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | P3 - R - P2 - P1 / Period 4 |
|------------------|-----------------------------|

**Arm description:**

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 4 received P1 in period 4.

|                                        |                    |
|----------------------------------------|--------------------|
| Arm type                               | Active comparator  |
| Investigational medicinal product name | Softa-Man(R) acute |
| Investigational medicinal product code | 61000.00.00        |
| Other name                             |                    |
| Pharmaceutical forms                   | Cutaneous solution |
| Routes of administration               | Cutaneous use      |

**Dosage and administration details:**

4 days with 30 hand disinfections each day; 3 mL per hand disinfection (= total application of 90 mL per day).

| <b>Number of subjects in period 4</b> | R - P1 - P3 - P2 /<br>Period 4 | P1 - P2 - R - P3 /<br>Period 4 | P2 - P3 - P1 - R /<br>Period 4 |
|---------------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Started                               | 3                              | 5                              | 5                              |
| Completed                             | 5                              | 5                              | 4                              |
| Not completed                         | 0                              | 1                              | 2                              |
| Consent withdrawn by subject          | -                              | 1                              | 2                              |
| Joined                                | 2                              | 1                              | 1                              |
| Restarted                             | 2                              | 1                              | 1                              |

| <b>Number of subjects in period 4</b> | P3 - R - P2 - P1 /<br>Period 4 |
|---------------------------------------|--------------------------------|
| Started                               | 4                              |
| Completed                             | 5                              |
| Not completed                         | 0                              |
| Consent withdrawn by subject          | -                              |
| Joined                                | 1                              |
| Restarted                             | 1                              |

## Baseline characteristics

### Reporting groups

|                                                                                                                                                                                                                                                     |                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Reporting group title                                                                                                                                                                                                                               | R - P1 - P3 - P2 / Period 1 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 1 received R in period 1.  |                             |
| Reporting group title                                                                                                                                                                                                                               | P1 - P2 - R - P3 / Period 1 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 2 received P1 in period 1. |                             |
| Reporting group title                                                                                                                                                                                                                               | P2 - P3 - P1 - R / Period 1 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 3 received P2 in period 1. |                             |
| Reporting group title                                                                                                                                                                                                                               | P3 - R - P2 - P1 / Period 1 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 4 received P3 in period 4. |                             |

| Reporting group values                                | R - P1 - P3 - P2 /<br>Period 1 | P1 - P2 - R - P3 /<br>Period 1 | P2 - P3 - P1 - R /<br>Period 1 |
|-------------------------------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Number of subjects                                    | 5                              | 6                              | 6                              |
| Age categorical<br>Units: Subjects                    |                                |                                |                                |
| In utero                                              | 0                              | 0                              | 0                              |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0                              | 0                              | 0                              |
| Newborns (0-27 days)                                  | 0                              | 0                              | 0                              |
| Infants and toddlers (28 days-23<br>months)           | 0                              | 0                              | 0                              |
| Children (2-11 years)                                 | 0                              | 0                              | 0                              |
| Adolescents (12-17 years)                             | 0                              | 0                              | 0                              |
| Adults (18-64 years)                                  | 5                              | 6                              | 6                              |
| From 65-84 years                                      | 0                              | 0                              | 0                              |
| 85 years and over                                     | 0                              | 0                              | 0                              |
| Age continuous<br>Units: years                        |                                |                                |                                |
| median                                                | 23                             | 26.5                           | 24.5                           |
| inter-quartile range (Q1-Q3)                          | 23 to 24                       | 23.5 to 31                     | 23.25 to 25.75                 |
| Gender categorical<br>Units: Subjects                 |                                |                                |                                |
| Female                                                | 3                              | 5                              | 3                              |
| Male                                                  | 2                              | 1                              | 3                              |

|                        |                    |       |  |
|------------------------|--------------------|-------|--|
| Reporting group values | P3 - R - P2 - P1 / | Total |  |
|------------------------|--------------------|-------|--|

Period 1

|                                                       |          |    |  |
|-------------------------------------------------------|----------|----|--|
| Number of subjects                                    | 5        | 22 |  |
| Age categorical                                       |          |    |  |
| Units: Subjects                                       |          |    |  |
| In utero                                              | 0        | 0  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0        | 0  |  |
| Newborns (0-27 days)                                  | 0        | 0  |  |
| Infants and toddlers (28 days-23<br>months)           | 0        | 0  |  |
| Children (2-11 years)                                 | 0        | 0  |  |
| Adolescents (12-17 years)                             | 0        | 0  |  |
| Adults (18-64 years)                                  | 5        | 22 |  |
| From 65-84 years                                      | 0        | 0  |  |
| 85 years and over                                     | 0        | 0  |  |
| Age continuous                                        |          |    |  |
| Units: years                                          |          |    |  |
| median                                                | 25       |    |  |
| inter-quartile range (Q1-Q3)                          | 22 to 26 | -  |  |
| Gender categorical                                    |          |    |  |
| Units: Subjects                                       |          |    |  |
| Female                                                | 4        | 15 |  |
| Male                                                  | 1        | 7  |  |

### Subject analysis sets

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Safety analysis |
| Subject analysis set type  | Safety analysis |

Subject analysis set description:

All the analyses were performed in the safety population, including subjects who had started treatment in at least one period.

| Reporting group values                                | Safety analysis |  |  |
|-------------------------------------------------------|-----------------|--|--|
| Number of subjects                                    | 22              |  |  |
| Age categorical                                       |                 |  |  |
| Units: Subjects                                       |                 |  |  |
| In utero                                              | 0               |  |  |
| Preterm newborn infants<br>(gestational age < 37 wks) | 0               |  |  |
| Newborns (0-27 days)                                  | 0               |  |  |
| Infants and toddlers (28 days-23<br>months)           | 0               |  |  |
| Children (2-11 years)                                 | 0               |  |  |
| Adolescents (12-17 years)                             | 0               |  |  |
| Adults (18-64 years)                                  | 22              |  |  |
| From 65-84 years                                      | 0               |  |  |
| 85 years and over                                     | 0               |  |  |
| Age continuous                                        |                 |  |  |
| Units: years                                          |                 |  |  |
| median                                                | 25              |  |  |
| inter-quartile range (Q1-Q3)                          | 23 to 26        |  |  |

|                    |    |  |  |
|--------------------|----|--|--|
| Gender categorical |    |  |  |
| Units: Subjects    |    |  |  |
| Female             | 15 |  |  |
| Male               | 7  |  |  |

---

## End points

### End points reporting groups

|                                                                                                                                                                                                                                                     |                             |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------|
| Reporting group title                                                                                                                                                                                                                               | R - P1 - P3 - P2 / Period 1 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 1 received R in period 1.  |                             |
| Reporting group title                                                                                                                                                                                                                               | P1 - P2 - R - P3 / Period 1 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 2 received P1 in period 1. |                             |
| Reporting group title                                                                                                                                                                                                                               | P2 - P3 - P1 - R / Period 1 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 3 received P2 in period 1. |                             |
| Reporting group title                                                                                                                                                                                                                               | P3 - R - P2 - P1 / Period 1 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 4 received P3 in period 4. |                             |
| Reporting group title                                                                                                                                                                                                                               | R - P1 - P3 - P2 / Period 2 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 1 received P1 in period 2. |                             |
| Reporting group title                                                                                                                                                                                                                               | P1 - P2 - R - P3 / Period 2 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 2 received P2 in period 2. |                             |
| Reporting group title                                                                                                                                                                                                                               | P2 - P3 - P1 - R / Period 2 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 3 received P3 in period 2. |                             |
| Reporting group title                                                                                                                                                                                                                               | P3 - R - P2 - P1 / Period 2 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 4 received R in period 2.  |                             |
| Reporting group title                                                                                                                                                                                                                               | R - P1 - P3 - P2 / Period 3 |
| Reporting group description:<br>Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.<br>Arm 1 received P3 in period 3. |                             |
| Reporting group title                                                                                                                                                                                                                               | P1 - P2 - R - P3 / Period 3 |

Reporting group description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 2 received R in period 3.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | P2 - P3 - P1 - R / Period 3 |
|-----------------------|-----------------------------|

Reporting group description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 3 received P1 in period 3.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | P3 - R - P2 - P1 / Period 3 |
|-----------------------|-----------------------------|

Reporting group description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 4 received P2 in period 3.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | R - P1 - P3 - P2 / Period 4 |
|-----------------------|-----------------------------|

Reporting group description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 1 received P2 in period 4.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | P1 - P2 - R - P3 / Period 4 |
|-----------------------|-----------------------------|

Reporting group description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 2 received P3 in period 4.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | P2 - P3 - P1 - R / Period 4 |
|-----------------------|-----------------------------|

Reporting group description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 3 received R in period 4.

|                       |                             |
|-----------------------|-----------------------------|
| Reporting group title | P3 - R - P2 - P1 / Period 4 |
|-----------------------|-----------------------------|

Reporting group description:

Healthy volunteers received three different virucidal hand rubs (P1-P3) and a reference product (R) in randomized sequence over a period of four days each with a washout period.

Arm 4 received P1 in period 4.

|                            |                 |
|----------------------------|-----------------|
| Subject analysis set title | Safety analysis |
|----------------------------|-----------------|

|                           |                 |
|---------------------------|-----------------|
| Subject analysis set type | Safety analysis |
|---------------------------|-----------------|

Subject analysis set description:

All the analyses were performed in the safety population, including subjects who had started treatment in at least one period.

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## Primary: Transepidermal water loss (TEWL)

|                 |                                  |
|-----------------|----------------------------------|
| End point title | Transepidermal water loss (TEWL) |
|-----------------|----------------------------------|

End point description:

The primary endpoint was skin barrier function measured by transepidermal water loss (TEWL) in g/hm<sup>2</sup> at the end of the 4-day application period.

|                |         |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Measured at the end of the 4-day application period



| <b>End point values</b>              | R - P1 - P3 - P2<br>/ Period 1 | P1 - P2 - R - P3<br>/ Period 1 | P2 - P3 - P1 - R<br>/ Period 1 | P3 - R - P2 - P1<br>/ Period 1 |
|--------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Subject group type                   | Reporting group                | Reporting group                | Reporting group                | Reporting group                |
| Number of subjects analysed          | 4                              | 5                              | 6                              | 4                              |
| Units: g/hm2                         |                                |                                |                                |                                |
| arithmetic mean (standard deviation) | 26.93 (± 5.07)                 | 21.26 (± 4.92)                 | 19.25 (± 6.17)                 | 13.93 (± 3.39)                 |

| <b>End point values</b>              | R - P1 - P3 - P2<br>/ Period 2 | P1 - P2 - R - P3<br>/ Period 2 | P2 - P3 - P1 - R<br>/ Period 2 | P3 - R - P2 - P1<br>/ Period 2 |
|--------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Subject group type                   | Reporting group                | Reporting group                | Reporting group                | Reporting group                |
| Number of subjects analysed          | 5                              | 5                              | 6                              | 4                              |
| Units: g/hm2                         |                                |                                |                                |                                |
| arithmetic mean (standard deviation) | 17.92 (± 2.63)                 | 19.94 (± 9.41)                 | 15.48 (± 3.08)                 | 23.98 (± 6.39)                 |

| <b>End point values</b>              | R - P1 - P3 - P2<br>/ Period 4 | P1 - P2 - R - P3<br>/ Period 4 | P2 - P3 - P1 - R<br>/ Period 4 | P3 - R - P2 - P1<br>/ Period 4 |
|--------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Subject group type                   | Reporting group                | Reporting group                | Reporting group                | Reporting group                |
| Number of subjects analysed          | 3                              | 5                              | 3                              | 4                              |
| Units: g/hm2                         |                                |                                |                                |                                |
| arithmetic mean (standard deviation) | 13.40 (± 2.72)                 | 20.67 (± 1.33)                 | 23.74 (± 8.20)                 | 28.03 (± 12.99)                |

| <b>End point values</b>              | R - P1 - P3 - P2<br>/ Period 3 | P1 - P2 - R - P3<br>/ Period 3 | P2 - P3 - P1 - R<br>/ Period 3 | P3 - R - P2 - P1<br>/ Period 3 |
|--------------------------------------|--------------------------------|--------------------------------|--------------------------------|--------------------------------|
| Subject group type                   | Reporting group                | Reporting group                | Reporting group                | Reporting group                |
| Number of subjects analysed          | 5                              | 5                              | 4                              | 5                              |
| Units: g/hm2                         |                                |                                |                                |                                |
| arithmetic mean (standard deviation) | 17.08 (± 5.09)                 | 21.50 (± 6.95)                 | 24.08 (± 3.26)                 | 13.02 (± 2.11)                 |

## Statistical analyses

| <b>Statistical analysis title</b>                                                                                                                                                                              | Analysis of TEWL in SAF, P1 vs R                                                                                                                                                                                                                                                                                                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Statistical analysis description:                                                                                                                                                                              |                                                                                                                                                                                                                                                                                                                                                                       |
| This is a cross-over trial with 4 periods in 22 patients. The analysis was performed in the safety population (SAF) including all patients who started treatment in at least one of the 4 intervention period. |                                                                                                                                                                                                                                                                                                                                                                       |
| Comparison groups                                                                                                                                                                                              | R - P1 - P3 - P2 / Period 1 v P1 - P2 - R - P3 / Period 1 v P2 - P3 - P1 - R / Period 1 v P3 - R - P2 - P1 / Period 1 v R - P1 - P3 - P2 / Period 2 v P1 - P2 - R - P3 / Period 2 v P2 - P3 - P1 - R / Period 2 v P3 - R - P2 - P1 / Period 2 v R - P1 - P3 - P2 / Period 4 v P1 - P2 - R - P3 / Period 4 v P2 - P3 - P1 - R / Period 4 v P3 - R - P2 - P1 / Period 4 |

|                                         |                                                                                                                                                  |
|-----------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------|
|                                         | - R - P2 - P1 / Period 4 v R - P1 - P3 - P2 / Period 3 v P1 - P2 - R - P3 / Period 3 v P2 - P3 - P1 - R / Period 3 v P3 - R - P2 - P1 / Period 3 |
| Number of subjects included in analysis | 73                                                                                                                                               |
| Analysis specification                  | Pre-specified                                                                                                                                    |
| Analysis type                           | superiority <sup>[1]</sup>                                                                                                                       |
| P-value                                 | = 0.42                                                                                                                                           |
| Method                                  | ANCOVA                                                                                                                                           |
| Parameter estimate                      | Mean difference (final values)                                                                                                                   |
| Point estimate                          | -1.54                                                                                                                                            |
| Confidence interval                     |                                                                                                                                                  |
| level                                   | 95 %                                                                                                                                             |
| sides                                   | 2-sided                                                                                                                                          |
| lower limit                             | -5.33                                                                                                                                            |
| upper limit                             | 2.26                                                                                                                                             |

Notes:

[1] - The effects of the different agents on TEWL were analyzed in linear models including 'agent', 'period', 'randomized sequence' and baseline measurement as fixed effects, and 'subject within sequence' as random effect. Differences between mean results per agent were estimated with 95% confidence intervals. This is the analysis of P1 vs R.

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Analysis of TEWL in SAF, P2 vs R |
|-----------------------------------|----------------------------------|

Statistical analysis description:

This is a cross-over trial with 4 periods in 22 patients. The analysis was performed in the safety population (SAF) including all patients who started treatment in at least one of the 4 intervention period.

|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison groups                       | R - P1 - P3 - P2 / Period 1 v P1 - P2 - R - P3 / Period 1 v P2 - P3 - P1 - R / Period 1 v P3 - R - P2 - P1 / Period 1 v R - P1 - P3 - P2 / Period 2 v P1 - P2 - R - P3 / Period 2 v P2 - P3 - P1 - R / Period 2 v P3 - R - P2 - P1 / Period 2 v R - P1 - P3 - P2 / Period 4 v P1 - P2 - R - P3 / Period 4 v P2 - P3 - P1 - R / Period 4 v P3 - R - P2 - P1 / Period 4 v R - P1 - P3 - P2 / Period 3 v P1 - P2 - R - P3 / Period 3 v P2 - P3 - P1 - R / Period 3 v P3 - R - P2 - P1 / Period 3 |
| Number of subjects included in analysis | 73                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Analysis type                           | superiority <sup>[2]</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| P-value                                 | < 0.0001                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Method                                  | ANCOVA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Point estimate                          | -7.7                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Confidence interval                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| level                                   | 95 %                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| sides                                   | 2-sided                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| lower limit                             | -11.45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| upper limit                             | -3.96                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |

Notes:

[2] - The effects of the different agents on TEWL were analyzed in linear models including 'agent', 'period', 'randomized sequence' and baseline measurement as fixed effects, and 'subject within sequence' as random effect. Differences between mean results per agent were estimated with 95% confidence intervals. This is the analysis of P2 vs R.

|                                   |                                  |
|-----------------------------------|----------------------------------|
| <b>Statistical analysis title</b> | Analysis of TEWL in SAF, P3 vs R |
|-----------------------------------|----------------------------------|

Statistical analysis description:

This is a cross-over trial with 4 periods in 22 patients. The analysis was performed in the safety population (SAF) including all patients who started treatment in at least one of the 4 intervention period.

|                   |                                                                    |
|-------------------|--------------------------------------------------------------------|
| Comparison groups | P1 - P2 - R - P3 / Period 1 v P2 - P3 - P1 - R / Period 1 v R - P1 |
|-------------------|--------------------------------------------------------------------|

|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                            |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                         | - P3 - P2 / Period 1 v P3 - R - P2 - P1 / Period 1 v R - P1 - P3 - P2 / Period 2 v P1 - P2 - R - P3 / Period 2 v P2 - P3 - P1 - R / Period 2 v P3 - R - P2 - P1 / Period 2 v R - P1 - P3 - P2 / Period 4 v P1 - P2 - R - P3 / Period 4 v P2 - P3 - P1 - R / Period 4 v P3 - R - P2 - P1 / Period 4 v R - P1 - P3 - P2 / Period 3 v P1 - P2 - R - P3 / Period 3 v P2 - P3 - P1 - R / Period 3 v P3 - R - P2 - P1 / Period 3 |
| Number of subjects included in analysis | 73                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                                                                                                                                                                                                              |
| Analysis type                           | superiority <sup>[3]</sup>                                                                                                                                                                                                                                                                                                                                                                                                 |
| P-value                                 | = 0.0002                                                                                                                                                                                                                                                                                                                                                                                                                   |
| Method                                  | ANCOVA                                                                                                                                                                                                                                                                                                                                                                                                                     |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                                                                             |
| Point estimate                          | -7.67                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Confidence interval                     |                                                                                                                                                                                                                                                                                                                                                                                                                            |
| level                                   | 95 %                                                                                                                                                                                                                                                                                                                                                                                                                       |
| sides                                   | 2-sided                                                                                                                                                                                                                                                                                                                                                                                                                    |
| lower limit                             | -11.45                                                                                                                                                                                                                                                                                                                                                                                                                     |
| upper limit                             | -3.9                                                                                                                                                                                                                                                                                                                                                                                                                       |

Notes:

[3] - The effects of the different agents on TEWL were analyzed in linear models including 'agent', 'period', 'randomized sequence' and baseline measurement as fixed effects, and 'subject within sequence' as random effect. Differences between mean results per agent were estimated with 95% confidence intervals. This is the analysis of P3 vs R.

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Analysis of TEWL in SAF, P1 vs P2 |
|-----------------------------------|-----------------------------------|

Statistical analysis description:

This is a cross-over trial with 4 periods in 22 patients. The analysis was performed in the safety population (SAF) including all patients who started treatment in at least one of the 4 intervention period.

|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison groups                       | R - P1 - P3 - P2 / Period 1 v P1 - P2 - R - P3 / Period 1 v P2 - P3 - P1 - R / Period 1 v P3 - R - P2 - P1 / Period 1 v R - P1 - P3 - P2 / Period 2 v P1 - P2 - R - P3 / Period 2 v P2 - P3 - P1 - R / Period 2 v P3 - R - P2 - P1 / Period 2 v R - P1 - P3 - P2 / Period 4 v P1 - P2 - R - P3 / Period 4 v P2 - P3 - P1 - R / Period 4 v P3 - R - P2 - P1 / Period 4 v R - P1 - P3 - P2 / Period 3 v P1 - P2 - R - P3 / Period 3 v P2 - P3 - P1 - R / Period 3 v P3 - R - P2 - P1 / Period 3 |
| Number of subjects included in analysis | 73                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Analysis type                           | superiority <sup>[4]</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| P-value                                 | = 0.0013                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| Method                                  | ANCOVA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Point estimate                          | 6.16                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Confidence interval                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| level                                   | 95 %                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| sides                                   | 2-sided                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| lower limit                             | 2.54                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| upper limit                             | 9.79                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

Notes:

[4] - The effects of the different agents on TEWL were analyzed in linear models including 'agent', 'period', 'randomized sequence' and baseline measurement as fixed effects, and 'subject within sequence' as random effect. Differences between mean results per agent were estimated with 95% confidence intervals. This is the analysis of P1 vs P2.

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Analysis of TEWL in SAF, P1 vs P3 |
|-----------------------------------|-----------------------------------|

**Statistical analysis description:**

This is a cross-over trial with 4 periods in 22 patients. The analysis was performed in the safety population (SAF) including all patients who started treatment in at least one of the 4 intervention period.

|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison groups                       | R - P1 - P3 - P2 / Period 1 v P1 - P2 - R - P3 / Period 1 v P2 - P3 - P1 - R / Period 1 v P3 - R - P2 - P1 / Period 1 v R - P1 - P3 - P2 / Period 2 v P1 - P2 - R - P3 / Period 2 v P2 - P3 - P1 - R / Period 2 v P3 - R - P2 - P1 / Period 2 v R - P1 - P3 - P2 / Period 4 v P1 - P2 - R - P3 / Period 4 v P2 - P3 - P1 - R / Period 4 v P3 - R - P2 - P1 / Period 4 v R - P1 - P3 - P2 / Period 3 v P1 - P2 - R - P3 / Period 3 v P2 - P3 - P1 - R / Period 3 v P3 - R - P2 - P1 / Period 3 |
| Number of subjects included in analysis | 73                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Analysis type                           | superiority <sup>[5]</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| P-value                                 | = 0.002                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| Method                                  | ANCOVA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Point estimate                          | 6.14                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| Confidence interval                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| level                                   | 95 %                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| sides                                   | 2-sided                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| lower limit                             | 2.38                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| upper limit                             | 9.89                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

Notes:

[5] - The effects of the different agents on TEWL were analyzed in linear models including 'agent', 'period', 'randomized sequence' and baseline measurement as fixed effects, and 'subject within sequence' as random effect. Differences between mean results per agent were estimated with 95% confidence intervals. This is the analysis of P1 vs P3.

|                                   |                                   |
|-----------------------------------|-----------------------------------|
| <b>Statistical analysis title</b> | Analysis of TEWL in SAF, P2 vs P3 |
|-----------------------------------|-----------------------------------|

**Statistical analysis description:**

This is a cross-over trial with 4 periods in 22 patients. The analysis was performed in the safety population (SAF) including all patients who started treatment in at least one of the 4 intervention period.

|                                         |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|-----------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Comparison groups                       | R - P1 - P3 - P2 / Period 1 v P1 - P2 - R - P3 / Period 1 v P2 - P3 - P1 - R / Period 1 v P3 - R - P2 - P1 / Period 1 v R - P1 - P3 - P2 / Period 2 v P1 - P2 - R - P3 / Period 2 v P2 - P3 - P1 - R / Period 2 v P3 - R - P2 - P1 / Period 2 v R - P1 - P3 - P2 / Period 4 v P1 - P2 - R - P3 / Period 4 v P2 - P3 - P1 - R / Period 4 v P3 - R - P2 - P1 / Period 4 v R - P1 - P3 - P2 / Period 3 v P1 - P2 - R - P3 / Period 3 v P2 - P3 - P1 - R / Period 3 v P3 - R - P2 - P1 / Period 3 |
| Number of subjects included in analysis | 73                                                                                                                                                                                                                                                                                                                                                                                                                                                                                            |
| Analysis specification                  | Pre-specified                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| Analysis type                           | superiority <sup>[6]</sup>                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| P-value                                 | = 0.99                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Method                                  | ANCOVA                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| Parameter estimate                      | Mean difference (final values)                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| Point estimate                          | -0.03                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| Confidence interval                     |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| level                                   | 95 %                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| sides                                   | 2-sided                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| lower limit                             | -3.69                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| upper limit                             | 3.64                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

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Notes:

[6] - The effects of the different agents on TEWL were analyzed in linear models including 'agent', 'period', 'randomized sequence' and baseline measurement as fixed effects, and 'subject within sequence' as random effect. Differences between mean results per agent were estimated with 95% confidence intervals. This is the analysis of P2 vs P3.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

Each day during the intervention period the volunteer was questioned about adverse events.

Adverse event reporting additional description:

The percentage of subjects experiencing at least one adverse event

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |    |
|--------------------|----|
| Dictionary version | 13 |
|--------------------|----|

### Reporting groups

|                       |          |
|-----------------------|----------|
| Reporting group title | P1 Group |
|-----------------------|----------|

Reporting group description:

P1 = Investigational Product 1: Softa-Man® acute

|                       |          |
|-----------------------|----------|
| Reporting group title | P2 Group |
|-----------------------|----------|

Reporting group description:

P2 = Investigational Product 2: Sterillium® virugard

|                       |          |
|-----------------------|----------|
| Reporting group title | P3 Group |
|-----------------------|----------|

Reporting group description:

P3 = Investigational Product 3: Manorapid® Synergy

|                       |             |
|-----------------------|-------------|
| Reporting group title | R Reference |
|-----------------------|-------------|

Reporting group description:

R = Reference: Softa-Man® pure

| Serious adverse events                            | P1 Group       | P2 Group       | P3 Group       |
|---------------------------------------------------|----------------|----------------|----------------|
| Total subjects affected by serious adverse events |                |                |                |
| subjects affected / exposed                       | 0 / 21 (0.00%) | 0 / 20 (0.00%) | 0 / 18 (0.00%) |
| number of deaths (all causes)                     | 0              | 0              | 0              |
| number of deaths resulting from adverse events    | 0              | 0              | 0              |

| Serious adverse events                            | R Reference    |  |  |
|---------------------------------------------------|----------------|--|--|
| Total subjects affected by serious adverse events |                |  |  |
| subjects affected / exposed                       | 0 / 18 (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 %

| <b>Non-serious adverse events</b>                                                                                                                                                                                                                                                                                                                 | P1 Group                                                                                                | P2 Group                                                                                              | P3 Group                                                                                                |
|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------|
| Total subjects affected by non-serious adverse events<br>subjects affected / exposed                                                                                                                                                                                                                                                              | 18 / 21 (85.71%)                                                                                        | 5 / 20 (25.00%)                                                                                       | 16 / 18 (88.89%)                                                                                        |
| Injury, poisoning and procedural complications<br>Skin injury<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                 | 0 / 21 (0.00%)<br>0                                                                                     | 0 / 20 (0.00%)<br>0                                                                                   | 0 / 18 (0.00%)<br>0                                                                                     |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                         | 0 / 21 (0.00%)<br>0                                                                                     | 0 / 20 (0.00%)<br>0                                                                                   | 0 / 18 (0.00%)<br>0                                                                                     |
| General disorders and administration site conditions<br>Influenza like illness<br>subjects affected / exposed<br>occurrences (all)<br><br>Application site pruritus<br>subjects affected / exposed<br>occurrences (all)                                                                                                                           | 0 / 21 (0.00%)<br>0<br><br>1 / 21 (4.76%)<br>1                                                          | 0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0                                                        | 0 / 18 (0.00%)<br>0<br><br>1 / 18 (5.56%)<br>1                                                          |
| Gastrointestinal disorders<br>Nausea<br>subjects affected / exposed<br>occurrences (all)                                                                                                                                                                                                                                                          | 0 / 21 (0.00%)<br>0                                                                                     | 0 / 20 (0.00%)<br>0                                                                                   | 0 / 18 (0.00%)<br>0                                                                                     |
| Skin and subcutaneous tissue disorders<br>Dermatitis<br>subjects affected / exposed<br>occurrences (all)<br><br>Erythema<br>subjects affected / exposed<br>occurrences (all)<br><br>Pruritus<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin exfoliation<br>subjects affected / exposed<br>occurrences (all)<br><br>Skin reaction | 0 / 21 (0.00%)<br>0<br><br>1 / 21 (4.76%)<br>1<br><br>0 / 21 (0.00%)<br>0<br><br>13 / 21 (61.90%)<br>13 | 0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0<br><br>0 / 20 (0.00%)<br>0<br><br>5 / 20 (25.00%)<br>5 | 1 / 18 (5.56%)<br>1<br><br>1 / 18 (5.56%)<br>1<br><br>1 / 18 (5.56%)<br>1<br><br>14 / 18 (77.78%)<br>14 |

|                             |                |                |                |
|-----------------------------|----------------|----------------|----------------|
| subjects affected / exposed | 0 / 21 (0.00%) | 0 / 20 (0.00%) | 1 / 18 (5.56%) |
| occurrences (all)           | 0              | 0              | 1              |

| <b>Non-serious adverse events</b>                     | R Reference      |  |  |
|-------------------------------------------------------|------------------|--|--|
| Total subjects affected by non-serious adverse events |                  |  |  |
| subjects affected / exposed                           | 10 / 18 (55.56%) |  |  |
| Injury, poisoning and procedural complications        |                  |  |  |
| Skin injury                                           |                  |  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Nervous system disorders                              |                  |  |  |
| Dizziness                                             |                  |  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| General disorders and administration site conditions  |                  |  |  |
| Influenza like illness                                |                  |  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Application site pruritus                             |                  |  |  |
| subjects affected / exposed                           | 0 / 18 (0.00%)   |  |  |
| occurrences (all)                                     | 0                |  |  |
| Gastrointestinal disorders                            |                  |  |  |
| Nausea                                                |                  |  |  |
| subjects affected / exposed                           | 1 / 18 (5.56%)   |  |  |
| occurrences (all)                                     | 1                |  |  |
| Skin and subcutaneous tissue disorders                |                  |  |  |
| Dermatitis                                            |                  |  |  |
| subjects affected / exposed                           | 0 / 18 (0.00%)   |  |  |
| occurrences (all)                                     | 0                |  |  |
| Erythema                                              |                  |  |  |
| subjects affected / exposed                           | 0 / 18 (0.00%)   |  |  |
| occurrences (all)                                     | 0                |  |  |
| Pruritus                                              |                  |  |  |
| subjects affected / exposed                           | 0 / 18 (0.00%)   |  |  |
| occurrences (all)                                     | 0                |  |  |
| Skin exfoliation                                      |                  |  |  |



|                             |                 |  |  |
|-----------------------------|-----------------|--|--|
| subjects affected / exposed | 8 / 18 (44.44%) |  |  |
| occurrences (all)           | 8               |  |  |
| Skin reaction               |                 |  |  |
| subjects affected / exposed | 0 / 18 (0.00%)  |  |  |
| occurrences (all)           | 0               |  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

|      |
|------|
| none |
|------|

Notes:

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26448861>