# Clinical trial results:
# Phase III, multicentre, randomised, double blind, parallel-group, clinical trial to evaluate the efficacy and safety of a new medicated nail lacquer for the treatment of toenail fungal infection

## Summary

| | |
|---|---|
| EudraCT number | 2016-003784-19 |
| Trial protocol | ES LV |
| Global end of trial date | 16 December 2019 |

### Results information

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 20 June 2021 |
| First version publication date | 20 June 2021 |

## Trial information

### Trial identification

| | |
|---|---|
| Sponsor protocol code | RJ-CPX01 |

### Additional study identifiers

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

Notes:

### Sponsors

| | |
|---|---|
| Sponsor organisation name | Laboratorio Reig Jofre, SA |
| Sponsor organisation address | C/Gran Capità, 10, San Joan Despí, Barcelona, Spain, 08970 |
| Public contact | Clinical R&D, Laboratorio Reig Jofre, SA, 0034 93 480 67 10 , Jordi.Picas@reigjofre.com |
| Scientific contact | Clinical R&D, Laboratorio Reig Jofre, SA, 0034 93 480 67 10 , Jordi.Picas@reigjofre.com |

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 | 21 December 2020 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 16 December 2019 |
| Global end of trial reached? | Yes |
| Global end of trial date | 16 December 2019 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective was to evaluate the efficacy of RJ-0265, in terms of complete cure (defined as complete replacement of the diseased nail by new healthy nail and conversion to negative on Dermatophyte Test Strip (DTS) and on culture), in comparison with placebo, for the treatment of toenail onychomycosis due to dermatophyte fungi, at week 52.

Protection of trial subjects:

The protocol and consent forms were submitted to a duly constituted Independent Ethics Committee (IEC) or Institutional Review Board (IRB) for review and approval before study initiation. All revisions to the consent forms (if applicable) after initial IEC/IRB approval were submitted to the IEC/IRB for review and approval before implementation in accordance with regulatory requirements. This study was conducted in accordance with recognized international scientific and ethical standards, including but not limited to the International Conference on Harmonization guideline for Good Clinical Practice (ICH GCP) and the original principles embodied in the Declaration of Helsinki. Local regulations at each participating country were also followed.

Background therapy:

None (not applicable)

Evidence for comparator:

Onytec is the active comparator. Onytec is a currently marketed ciclopirox nail lacquer 80mg/g. The invetigational product, RJ-0265, is a new ciclopirox nail lacquer 80 mg/g

| | |
|---|---|
| Actual start date of recruitment | 03 August 2017 |
| 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 | Spain: 201 |
| Country: Number of subjects enrolled | Latvia: 101 |
| Country: Number of subjects enrolled | Mexico: 79 |
| Worldwide total number of subjects | 381 |
| EEA total number of subjects | 302 |

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) | 285 |
| From 65 to 84 years | 96 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details:

Recruitment starte on 03-Aug-17 (first patient first visit) and finished on 16-Dec-19 (last patient last visit). The countries contributed recruiting patients for this clinical trial: Spain, Latvia and Mexico

### Pre-assignment

Screening details:

A total of 1430 subject were screened to reach 381 analysed for safety, 376 for efficacy and 255 completers

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | RJ-0265 |

Arm description:

RJ-0265 applied once daily (in the evening) as a thin layer, for a period of 48 weeks.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | RJ-0265 |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cutaneous liquid |
| Routes of administration | Cutaneous use |

Dosage and administration details:

Applied once daily (in the evening) as a thin layer

| | |
|---|---|
| **Arm title** | Active control (Ony-Tec) |

Arm description:

Ony-Tec applied once daily (in the evening) as a thin layer, for a period of 48 weeks.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Ony-Tec |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cutaneous liquid |
| Routes of administration | Cutaneous use |

Dosage and administration details:

Applied once daily (in the evening) as a thin layer

| | |
|---|---|
| **Arm title** | Placebo |

Arm description:

Applied once daily (in the evening) as a thin layer, for a period of 48 weeks.

| | |
|---|---|
| Arm type | Placebo |

| | |
|---|---|
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cutaneous liquid |
| Routes of administration | Cutaneous use |

Dosage and administration details:

Applied once daily (in the evening) as a thin layer

| **Number of subjects in period 1** | RJ-0265 | Active control (Ony-Tec) | Placebo |
|---|---|---|---|
| Started | 127 | 128 | 126 |
| Completed | 83 | 88 | 84 |
| Not completed | 44 | 40 | 42 |
| Physician decision | 5 | 4 | 5 |
| Consent withdrawn by subject | 5 | 2 | 6 |
| Adverse event, non-fatal | 1 | 2 | - |
| Subject's decision | 30 | 28 | 25 |
| undefined | 2 | - | 5 |
| undifined | - | 4 | - |
| Protocol deviation | 1 | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | RJ-0265 |
| Reporting group description: | |
| RJ-0265 applied once daily (in the evening) as a thin layer, for a period of 48 weeks. | |
| Reporting group title | Active control (Ony-Tec) |
| Reporting group description: | |
| Ony-Tec applied once daily (in the evening) as a thin layer, for a period of 48 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Applied once daily (in the evening) as a thin layer, for a period of 48 weeks. | |

| Reporting group values | RJ-0265 | Active control (Ony-Tec) | Placebo |
|---|---|---|---|
| Number of subjects | 127 | 128 | 126 |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | 0 |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | 0 |
| Newborns (0-27 days) | 0 | 0 | 0 |
| Infants and toddlers (28 days-23 months) | 0 | 0 | 0 |
| Children (2-11 years) | 0 | 0 | 0 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 99 | 93 | 93 |
| From 65-84 years | 28 | 35 | 33 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous<br>Units: years | | | |
| arithmetic mean | 56.3 | 55.6 | 54.9 |
| standard deviation | ± 11.1 | ± 12.7 | ± 12.7 |
| Gender categorical<br>Units: Subjects | | | |
| Female | 63 | 57 | 54 |
| Male | 64 | 71 | 72 |
| Race<br>Units: Subjects | | | |
| White | 105 | 105 | 107 |
| American Indian or Alaska Native | 22 | 22 | 19 |
| Black or African American | 0 | 1 | 0 |
| Etnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 91 | 90 | 90 |
| Not Hispanic or Latino | 36 | 38 | 36 |

| Reporting group values | Total | | |
|---|---|---|---|
| Number of subjects | 381 | | |

| | | | |
|---|---|---|---|
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | | |
| Preterm newborn infants (gestational age < 37 wks) | 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) | 285 | | |
| From 65-84 years | 96 | | |
| 85 years and over | 0 | | |
| Age continuous<br>Units: years | | | |
| arithmetic mean | | | |
| standard deviation | - | | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 174 | | |
| Male | 207 | | |
| Race<br>Units: Subjects | | | |
| White | 317 | | |
| American Indian or Alaska Native | 63 | | |
| Black or African American | 1 | | |
| Etnicity<br>Units: Subjects | | | |
| Hispanic or Latino | 271 | | |
| Not Hispanic or Latino | 110 | | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | RJ-0265 |
| Reporting group description: | |
| RJ-0265 applied once daily (in the evening) as a thin layer, for a period of 48 weeks. | |
| Reporting group title | Active control (Ony-Tec) |
| Reporting group description: | |
| Ony-Tec applied once daily (in the evening) as a thin layer, for a period of 48 weeks. | |
| Reporting group title | Placebo |
| Reporting group description: | |
| Applied once daily (in the evening) as a thin layer, for a period of 48 weeks. | |

### Primary: Rate of complete cure assessed by an independent evaluator at week 52 (comparison between RJ-0265 and placebo)

| | |
|---|---|
| End point title | Rate of complete cure assessed by an independent evaluator at week 52 (comparison between RJ-0265 and placebo) |
| End point description: | |
| The primary endpoint (complete cure rate) was evaluated testing the superiority contrast, RJ-0265 versus placebo. The primary analysis was done in the ITT population, using techniques of missing imputation.<br>The comparison between RJ-0265 and placebo emplyed Fisher´s exact test. Two-sided p- values were obtained and statistically significant results declared if $p < 0.05$. | |
| End point type | Primary |
| End point timeframe: | |
| Week 52 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 10.4 (9.99 to 12.46) | 11.1 (10.69 to 13.16) | 11.2 (10.79 to 13.26) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.839 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.7 |
| upper limit | 7.1 |

## Secondary: Complete cure rate (%) assessed by independent evaluator (W52)

| | |
|---|---|
| End point title | Complete cure rate (%) assessed by independent evaluator (W52) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Week 52

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 10.4 (9.92 to 12.82) | 11.1 (10.65 to 13.29) | 11.2 (10.79 to 13.26) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.839 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.8 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.7 |
| upper limit | 7.1 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.856 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.6 |
| upper limit | 7.2 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.982 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.1 |
| upper limit | 7.9 |

## Secondary: Complete cure rate (%) assessed by independent investigator (W52)

| End point title | Complete cure rate (%) assessed by independent investigator (W52) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Week 52

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 9.6 (9.13 to 12.11) | 10.3 (9.86 to 12.55) | 10.4 (10 to 12.5) | |

**Statistical analyses**

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.833 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.5 |
| upper limit | 6.9 |

| Statistical analysis title | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.849 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.4 |
| upper limit | 7 |

| Statistical analysis title | Ony-Tec vs. Placebo |
|---|---|

| | |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.983 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.9 |
| upper limit | 7.7 |

## Secondary: Complete cure rate (%) assessed by independent evaluator (W48)

| | |
|---|---|
| End point title | Complete cure rate (%) assessed by independent evaluator (W48) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Week 48 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 7.2 (6.65 to 10.64) | 9.5 (9.08 to 11.82) | 9.6 (9.31 to 11.39) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.493 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -2.4 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.7 |
| upper limit | 4.8 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.505 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -2.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.5 |
| upper limit | 4.8 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.984 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.6 |
| upper limit | 7.5 |

| **Secondary: Complete cure rate (%) assessed by investigator (W48)** | |
|---|---|
| End point title | Complete cure rate (%) assessed by investigator (W48) |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| Week 48 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 9.6 (9.13 to 12.11) | 10.3 (9.92 to 12.16) | 12 (11.66 to 13.74) | |

**Statistical analyses**

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.541 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -2.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.4 |
| upper limit | 5.5 |

| Statistical analysis title | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.849 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.4 |
| upper limit | 7 |

| Statistical analysis title | Ony-Tec vs. Placebo |
|---|---|

| | |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.672 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -1.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.7 |
| upper limit | 6.3 |

## Secondary: Responder’s rate (%) assessed by independent evaluator (W52)

| | |
|---|---|
| End point title | Responder’s rate (%) assessed by independent evaluator (W52) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Week 52 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 14.4 (14.2 to 16.07) | 11.9 (11.52 to 13.57) | 14.4 (13.91 to 16.44) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 0 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.8 |
| upper limit | 8.8 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.558 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6 |
| upper limit | 11 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.558 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 2.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6 |
| upper limit | 11 |

| **Secondary: Responder’s rate (%) assessed by investigator (W52)** | |
|---|---|
| End point title | Responder’s rate (%) assessed by investigator (W52) |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 17.6 (17.21 to 19.14) | 14.3 (13.75 to 16.66) | 12.8 (12.07 to 15.77) | |

**Statistical analyses**

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.29 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 4.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.2 |
| upper limit | 13.8 |

| Statistical analysis title | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.473 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 3.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.8 |
| upper limit | 12.5 |

| Statistical analysis title | Ony-Tec vs. Placebo |
|---|---|

| | |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.731 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.1 |
| upper limit | 10.1 |

## Secondary: Responder’s rate (%) assessed by independent evaluator (W48)

| | |
|---|---|
| End point title | Responder’s rate (%) assessed by independent evaluator (W48) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Week 48 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 10.4 (9.87 to 12.99) | 11.9 (11.47 to 13.86) | 12.8 (12.44 to 14.52) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.553 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -2.4 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.6 |
| upper limit | 5.7 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.705 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -1.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.5 |
| upper limit | 6.5 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.829 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.2 |
| upper limit | 7.4 |

## Secondary: Responder’s rate (%) assessed by investigator (W48)

| End point title | Responder’s rate (%) assessed by investigator (W48) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Week 48

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 16 (15.36 to 18.39) | 19 (18.28 to 21.76) | 14.4 (13.83 to 16.68) | |

**Statistical analyses**

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.725 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.4 |
| upper limit | 10.6 |

| Statistical analysis title | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.525 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.5 |
| upper limit | 6.4 |

| Statistical analysis title | Ony-Tec vs. Placebo |
|---|---|

| | |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.323 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -4.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.7 |
| upper limit | 13.9 |

## Secondary: Improvement rate (%) assessed by independent evaluator (W52)

| | |
|---|---|
| End point title | Improvement rate (%) assessed by independent evaluator (W52) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Week 52 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: percentage of participants | | | | |
| number (confidence interval 95%) | 27.2 (26.81 to 28.4) | 20.6 (20.09 to 22.33) | 21.6 (20.84 to 24.04) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.302 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 5.6 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.1 |
| upper limit | 16.1 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.222 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 6.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4 |
| upper limit | 17 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.851 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.1 |
| upper limit | 9.1 |

| **Secondary: Improvement rate (%) assessed by investigator W52)** | |
|---|---|
| End point title | Improvement rate (%) assessed by investigator W52) |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 25.6 (25.16 to 27.02) | 21.4 (20.81 to 23.43) | 20 (19.24 to 22.51) | |

**Statistical analyses**

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.291 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 5.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.8 |
| upper limit | 15.9 |

| Statistical analysis title | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.436 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 4.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.3 |
| upper limit | 14.6 |

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|

| | |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.78 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 1.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.6 |
| upper limit | 11.4 |

## Secondary: Improvement rate (%) assessed by independent evaluator W48)

| | |
|---|---|
| End point title | Improvement rate (%) assessed by independent evaluator W48) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Week 48 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 21.6 (20.94 to 23.74) | 24.6 (23.85 to 27.13) | 19.2 (18.57 to 21.36) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.638 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 2.4 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.6 |
| upper limit | 12.4 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.572 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -13.3 |
| upper limit | 7.4 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.3 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 5.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.9 |
| upper limit | 15.5 |

| **Secondary: Improvement rate (%) assessed by investigator (W48)** | |
|---|---|
| End point title | Improvement rate (%) assessed by investigator (W48) |
| End point description: | |

| End point type | Secondary |
|---|---|
| End point timeframe: | |
| Week 48 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 24 (23.15 to 26.58) | 31.7 (30.55 to 35.46) | 18.4 (17.64 to 21) | |

**Statistical analyses**

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.278 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 5.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -4.6 |
| upper limit | 15.6 |

| Statistical analysis title | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.171 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -7.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -18.6 |
| upper limit | 3.3 |

| Statistical analysis title | Ony-Tec vs. Placebo |
|---|---|

| | |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.014 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 13.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 2.6 |
| upper limit | 23.7 |

## Secondary: Decrease of disease nail area (%) to <10% of total assessed by independent evaluator (W52)

| | |
|---|---|
| End point title | Decrease of disease nail area (%) to <10% of total assessed by independent evaluator (W52) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Week 52

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 21.8 (21.37 to 23.31) | 18.4 (17.85 to 20.42) | 17.6 (16.9 to 20.06) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.407 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 4.2 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.7 |
| upper limit | 14 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.506 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 3.4 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.6 |
| upper limit | 13.3 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.869 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8.8 |
| upper limit | 10.4 |

## Secondary: Decrease of disease nail area (%) to <10% of total assessed by investigator (W52)

| End point title | Decrease of disease nail area (%) to <10% of total assessed by investigator (W52) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:
Week 52

| **End point values** | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 34.8 (34.32 to 36.35) | 22.2 (21.63 to 24.09) | 21.6 (20.94 to 23.77) | |

**Statistical analyses**

| **Statistical analysis title** | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.549 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 3.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.3 |
| upper limit | 13.6 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.63 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 2.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -7.9 |
| upper limit | 13 |

| Statistical analysis title | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.905 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.6 |
| upper limit | 10.8 |

**Secondary: Decrease of disease nail area (%) to <10% of total assessed by independent evaluator (W48)**

| End point title | Decrease of disease nail area (%) to <10% of total assessed by independent evaluator (W48) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Week 48

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 15.3 (14.84 to 17.17) | 14.4 (13.96 to 16.17) | 16 (15.52 to 17.89) | |

**Statistical analyses**

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.883 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.7 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.8 |
| upper limit | 8.5 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.838 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 0.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -8 |
| upper limit | 9.9 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.725 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -1.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10.6 |
| upper limit | 7.4 |

**Secondary: Decrease of disease nail area (%) to <10% of total assessed by**

| investigator (W48) | |
|---|---|
| End point title | Decrease of disease nail area (%) to <10% of total assessed by investigator (W48) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: Week 48 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 21.6 (21.06 to 23.41) | 21.4 (20.83 to 23.31) | 20.8 (20.23 to 22.73) | |

**Statistical analyses**

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.887 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 0.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.93 |
| upper limit | 10.9 |

| Statistical analysis title | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.974 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 0.2 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -10 |
| upper limit | 10.3 |

| | |
|---|---|
| **Statistical analysis title** | Ony-Tec vs. Placebo |
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.903 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 0.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -9.5 |
| upper limit | 10.7 |

| **Secondary: Conversion to negative KOH/DTS rate (W52)** | |
|---|---|
| End point title | Conversion to negative KOH/DTS rate (W52) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| **End point values** | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 40 (39.38 to 41.69) | 40.5 (39.57 to 43.13) | 30.4 (29.49 to 32.98) | |

**Statistical analyses**

| **Statistical analysis title** | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.112 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 9.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 21.1 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.939 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -0.5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -12.4 |
| upper limit | 11.5 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.095 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 10.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -1.7 |
| upper limit | 21.5 |

## Secondary: Conversion to negative KOH/DTS rate (W48)

| End point title | Conversion to negative KOH/DTS rate (W48) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Week 48

| **End point values** | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 34.4 (33.62 to 36.57) | 40.5 (39.72 to 42.67) | 34.4 (33.81 to 36.09) | |

**Statistical analyses**

| **Statistical analysis title** | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 1 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 0 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11.6 |
| upper limit | 11.6 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -6.1 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -17.7 |
| upper limit | 5.8 |

| | |
|---|---|
| **Statistical analysis title** | Ony-Tec vs. Placebo |
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.32 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 6.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -5.8 |
| upper limit | 17.7 |

**Secondary: Conversion to negative to dermatophyte by culture rate (W52)**

| | |
|---|---|
| End point title | Conversion to negative to dermatophyte by culture rate (W52) |
| End point description: | |

| | |
|---|---|
| End point type | Secondary |
| End point timeframe: | |
| Week 52 | |

| **End point values** | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 47.2 (46.62 to 48.77) | 46 (45.02 to 48.72) | 34.4 (33.37 to 37.25) | |

**Statistical analyses**

| | |
|---|---|
| **Statistical analysis title** | RJ-0265 vs. Placebo |
| Comparison groups | RJ-0265 v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.039 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 12.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 0.6 |
| upper limit | 24.5 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.853 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 1.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -11 |
| upper limit | 13.3 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.06 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 11.6 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -0.5 |
| upper limit | 23.3 |

## Secondary: Conversion to negative to dermatophyte by culture rate (W48)

| End point title | Conversion to negative to dermatophyte by culture rate (W48) |
|---|---|

End point description:

| End point type | Secondary |
|---|---|

End point timeframe:

Week 48

| **End point values** | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 59.2 (57.35 to 64.41) | 69 (68.08 to 71.59) | 32 (29.2 to 40.15) | |

**Statistical analyses**

| **Statistical analysis title** | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 27.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 14.9 |
| upper limit | 38.3 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.103 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -9.8 |

| | |
|---|---|
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -21.3 |
| upper limit | 2 |

| | |
|---|---|
| **Statistical analysis title** | Ony-Tec vs. Placebo |
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | < 0.001 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 37 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 24.9 |
| upper limit | 47.6 |

**Secondary: Conversion to negative to dermatophyte by culture and negative to KOH/DTS rate (%) (W52)**

| | |
|---|---|
| End point title | Conversion to negative to dermatophyte by culture and negative to KOH/DTS rate (%) (W52) |

End point description:

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

Week 52

| **End point values** | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 32 (31.55 to 33.35) | 27 (26.31 to 29.18) | 23.2 (22.31 to 25.94) | |

**Statistical analyses**

| **Statistical analysis title** | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.119 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 8.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.3 |
| upper limit | 19.6 |

| **Statistical analysis title** | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.383 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 5 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.2 |
| upper limit | 16.1 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.489 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 3.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -6.9 |
| upper limit | 14.4 |

## Secondary: nConversion to negative to dermatophyte by culture and negative to KOH/DTS rate (%) (48)

| | |
|---|---|
| End point title | nConversion to negative to dermatophyte by culture and negative to KOH/DTS rate (%) (48) |
| End point description: | |
| End point type | Secondary |
| End point timeframe: | |
| Week 48 | |

| End point values | RJ-0265 | Active control (Ony-Tec) | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 125 | 126 | 125 | |
| Units: Percentage of participants | | | | |
| number (confidence interval 95%) | 31.2 (30.31 to 33.73) | 40.5 (39.13 to 44.62) | 22.4 (21.5 to 25.18) | |

### Statistical analyses

| Statistical analysis title | RJ-0265 vs. Placebo |
|---|---|
| Comparison groups | RJ-0265 v Placebo |
| Number of subjects included in analysis | 250 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.116 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 8.8 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -2.2 |
| upper limit | 19.5 |

| Statistical analysis title | RJ-0265 vs. Ony-Tec |
|---|---|
| Comparison groups | RJ-0265 v Active control (Ony-Tec) |

| | |
|---|---|
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.125 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | -9.3 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | -20.8 |
| upper limit | 2.6 |

| **Statistical analysis title** | Ony-Tec vs. Placebo |
|---|---|
| Comparison groups | Active control (Ony-Tec) v Placebo |
| Number of subjects included in analysis | 251 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | = 0.002 |
| Method | Fisher exact |
| Parameter estimate | Percentage Difference |
| Point estimate | 18.1 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 6.6 |
| upper limit | 28.9 |

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From writen informed consent to the end of the study (whaterver the reason is) [maximum 1 year and 6 weeks]

Adverse event reporting additional description:

The Safety Analysis Set included all randomized participants

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 21.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | RJ-0265 |

Reporting group description:

RJ-0265 applied once daily (in the evening) as a thin layer, for a period of 48 weeks.

| | |
|---|---|
| Reporting group title | Active control (Ony-Tec) |

Reporting group description:

Ony-Tec applied once daily (in the evening) as a thin layer, for a period of 48 weeks.

| | |
|---|---|
| Reporting group title | Placebo |

Reporting group description:

Applied once daily (in the evening) as a thin layer, for a period of 48 weeks.

| Serious adverse events | RJ-0265 | Active control (Ony-Tec) | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 127 (2.36%) | 6 / 128 (4.69%) | 2 / 126 (1.59%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Uterine leiomyoma | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Gastric cancer | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Pancreatic cancer | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 1 / 1 |
| Bladder cancer | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Injury, poisoning and procedural complications | | | |
| ankle fracture | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cardiac disorders | | | |
| Acute myocardial infarction | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Pneumonitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Infections and infestations | | | |
| Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| post surgical infection | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Dengue fever | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | 0 / 0 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

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

| **Non-serious adverse events** | RJ-0265 | Active control (Ony-Tec) | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 22 / 127 (17.32%) | 24 / 128 (18.75%) | 23 / 126 (18.25%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) | | | |
| Infected neoplasm | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Phlebitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Surgical and medical procedures | | | |
| Dental implantation | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 2 | 0 | 1 |
| Cataract operation | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Inguinal hernia repair | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 2 |
| Knee operation | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 2 |
| Tooth extraction | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Wisdom teeth removal | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| General disorders and administration site conditions | | | |
| Malaise | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 2 / 128 (1.56%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Pain | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Immune system disorders | | | |
| Hypersensitivity | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 1 | 2 |
| Reproductive system and breast disorders | | | |
| Dysmenorrhoea | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory, thoracic and mediastinal disorders | | | |
| Oropharyngeal pain | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 1 | 0 | 1 |
| Asthma | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cough | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rhinitis allergic | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| Psychiatric disorders | | | |

| | | | |
|---|---|---|---|
| Anxiety | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 2 / 128 (1.56%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 2 | 1 |
| Depression | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Insomnia | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Injury, poisoning and procedural complications | | | |
| Contusion | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 1 | 0 | 1 |
| Dental restoration failure | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Ligament sprain | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 2 |
| Limb injury | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Meniscus injury | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Traumatic haematoma | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Cardiac disorders | | | |
| Arrhythmia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 3 / 127 (2.36%) | 1 / 128 (0.78%) | 2 / 126 (1.59%) |
| occurrences (all) | 5 | 2 | 7 |

| | | | |
|---|---|---|---|
| Sciatica | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 128 (0.78%) | 1 / 126 (0.79%) |
| occurrences (all) | 1 | 1 | 1 |
| Perineurial cyst | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| Ear and labyrinth disorders | | | |
| Vertigo | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Dyspepsia | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Gastrooesophageal reflux disease | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| Intestinal congestion | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| Toothache | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Skin and subcutaneous tissue disorders | | | |
| Onychalgia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 2 / 126 (1.59%) |
| occurrences (all) | 0 | 1 | 3 |
| Nail discolouration | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 2 | 0 | 1 |
| Dermatitis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Dermatitis allergic | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Rash | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Rosacea | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Renal and urinary disorders | | | |
| Nephrolithiasis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| Musculoskeletal and connective tissue disorders | | | |
| Myalgia | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 2 / 128 (1.56%) | 2 / 126 (1.59%) |
| occurrences (all) | 0 | 3 | 2 |
| back pain | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |
| Arthralgia | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Intervertebral disc protrusion | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Musculoskeletal pain | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| neck pain | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| Periarthritis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Periostitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Rotator cuff syndrome | | | |

| | | | |
|---|---|---|---|
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Tendonitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 2 | 0 |
| Infections and infestations | | | |
| Influenza | | | |
| subjects affected / exposed | 4 / 127 (3.15%) | 4 / 128 (3.13%) | 4 / 126 (3.17%) |
| occurrences (all) | 4 | 4 | 4 |
| Nasopharyngitis | | | |
| subjects affected / exposed | 4 / 127 (3.15%) | 2 / 128 (1.56%) | 3 / 126 (2.38%) |
| occurrences (all) | 4 | 3 | 4 |
| Ear infection | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 3 / 128 (2.34%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 3 | 0 |
| Bronchitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 1 | 1 |
| Cellulitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Dengue | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| Gastroenteritis viral | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 1 | 0 | 1 |
| Gingivitis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 1 | 1 |
| Pharyngitis | | | |
| subjects affected / exposed | 2 / 127 (1.57%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |
| Tonsillitis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 1 | 0 |

| | | | |
|---|---|---|---|
| Conjunctivitis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| Cystitis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Fungal skin infection | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| gastroenteritis | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |
| Helicobacter infection | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Infection | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 1 / 128 (0.78%) | 0 / 126 (0.00%) |
| occurrences (all) | 0 | 1 | 0 |
| Oral candidiasis | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Respiratory syncytial virus infection | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vulvovaginal mycotic infection | | | |
| subjects affected / exposed | 1 / 127 (0.79%) | 0 / 128 (0.00%) | 0 / 126 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Metabolism and nutrition disorders | | | |
| Vitamin D deficiency | | | |
| subjects affected / exposed | 0 / 127 (0.00%) | 0 / 128 (0.00%) | 1 / 126 (0.79%) |
| occurrences (all) | 0 | 0 | 1 |

## More information

## Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|---|---|
| 19 October 2017 | The amendment consisted of the following changes:<br>- Change of one of the protocol's diagnostic test (from KOH-based microscopic examination to Diafactory Tinea Unguium commercial test kit) to increase the sensitivity and reduce examiner subjectivity. It also provided an immediate diagnostic.<br>- Participant's age extended from 70 to 75 years.<br>- Change in the number and distribution of participating centres (from 30 to 31).<br>Taking advantage of this amendment, the study calendar was updated, and typographic errors of the<br>previous version were corrected. |

Notes:

## 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.

Elevated number of screening failures (90.8%) due to lack of a positive culture at screening before randomization

Notes: