

**Clinical trial results:****A Multicenter, Randomized, Double-Blind, Parallel, Vehicle-Controlled Study to Evaluate the Efficacy And Safety of P-3058 10% Nail Solution in the Treatment of Onychomycosis****Summary**

|                          |                                     |
|--------------------------|-------------------------------------|
| EudraCT number           | 2015-000561-31                      |
| Trial protocol           | HU LV BG SE DE SK BE PL CZ LT GR IS |
| Global end of trial date | 17 September 2018                   |

**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 | PM1331 |
|-----------------------|--------|

**Additional study identifiers**

|                                    |             |
|------------------------------------|-------------|
| ISRCTN number                      | -           |
| ClinicalTrials.gov id (NCT number) | NCT02549001 |
| WHO universal trial number (UTN)   | -           |

Notes:

**Sponsors**

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Almirall S.A.  |
| Sponsor organisation address | Via Senago 42D, Lugano, Switzerland, CH-6912   |
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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                       | 02 July 2019      |
| Is this the analysis of the primary completion data? | No                |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 17 September 2018 |
| Was the trial ended prematurely?                     | No                |

Notes:

## General information about the trial

Main objective of the trial:

To establish the efficacy and safety of P-3058 (terbinafine 10 percent [%] nail solution) administered once daily for the first 4 weeks and once weekly for the remaining 44 weeks for an overall period of 48 weeks, in comparison to its vehicle in a double-blinded manner. With amendment 1 of the protocol, implemented prior to the randomization of any patient, an open label third arm was added to descriptively compare the efficacy of P-3058 also to that of an active comparator (amorolfine 5%) applied topically once weekly for 48 weeks.

Protection of trial subjects:

The subjects were informed by the Investigator of all the aspects including nature and purpose, participation conditions, and the risks and benefits of study, before undertaking any study-related procedure. This study was conducted in compliance with the study protocol, the recommendations on biomedical research on human subjects of the Declaration of Helsinki, International Conference of Harmonization – Good Clinical Practice (ICH-GCP) Guidelines, and all applicable national laws and regulations. Signed written informed consent form and privacy authorizations were obtained from all subjects. The subjects were also informed that complete confidentiality would be maintained concerning their identity.

Background therapy: -

Evidence for comparator: -

|   |                |
|---|----------------|
| Actual start date of recruitment                          | 20 August 2015 |
| Long term follow-up planned                               | No             |
| Independent data monitoring committee (IDMC) involvement? | Yes            |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                        |
|--------------------------------------|------------------------|
| Country: Number of subjects enrolled | Poland: 123            |
| Country: Number of subjects enrolled | Slovakia: 17           |
| Country: Number of subjects enrolled | Sweden: 127            |
| Country: Number of subjects enrolled | Belgium: 5             |
| Country: Number of subjects enrolled | Bulgaria: 89           |
| Country: Number of subjects enrolled | Czech Republic: 105    |
| Country: Number of subjects enrolled | Germany: 197           |
| Country: Number of subjects enrolled | Greece: 3              |
| Country: Number of subjects enrolled | Hungary: 41            |
| Country: Number of subjects enrolled | Iceland: 8             |
| Country: Number of subjects enrolled | Latvia: 157            |
| Country: Number of subjects enrolled | Lithuania: 33          |
| Country: Number of subjects enrolled | Russian Federation: 48 |

|                                    |     |
|------------------------------------|-----|
| Worldwide total number of subjects | 953 |
| EEA total number of subjects       | 905 |

Notes:

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**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)                 | 1   |
| Adults (18-64 years)                      | 603 |
| From 65 to 84 years                       | 342 |
| 85 years and over                         | 7   |

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted from 20 August 2015 to 17 September 2018 at 114 sites in 13 countries. A total of 953 subjects who met all of the inclusion criteria and none of the exclusion criteria were enrolled and randomised in three arms to receive treatment with P-3058 10%, Vehicle, and Amorolfine, in a ratio of 3:3:1.

### Pre-assignment

Screening details:

Screening and randomisation were performed based on positive potassium hydroxide (KOH) microscopy and mycology results (percentage of the affected target nail area and positive culture for dermatophyte[s] or positive mixed dermatophyte[s]/Candida).

### Period 1

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

Blinding implementation details:

This study was conducted with a double-blind, vehicle-controlled design for P-3058 and Vehicle as the vehicle was identical in appearance and indistinguishable from the active treatment to minimize any potential bias. However, Amorolfine was applied in an open label manner due to difference in its product characteristics when compared to P-3058 and Vehicle. Unblinding was performed only in an emergency situation when a medical treatment was required or to assure the safety of the trial subjects.

### Arms

|                              |            |
|------------------------------|------------|
| Are arms mutually exclusive? | Yes        |
| <b>Arm title</b>             | P-3058 10% |

Arm description:

Subjects applied P-3058 10% nail solution topically, once daily for first 4 weeks and then once weekly for the remaining 44 weeks on all dry nails with suspected onychomycosis.

|  |   |
|--|---|
| Arm type                               | Experimental                              |
| Investigational medicinal product name | P-3058 10% nail solution                  |
| Investigational medicinal product code |   |
| Other name                             | P-3058 nail solution with 10% terbinafine |
| Pharmaceutical forms                   | Medicated nail lacquer                    |
| Routes of administration               | Topical use                               |

Dosage and administration details:

Subjects administered topical nail solution on dry nails, once daily for the first 4 weeks, then once weekly for an additional 44 weeks.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | Vehicle |
|------------------|---------|

Arm description:

Subjects applied Vehicle of the P-3058 10% nail solution topically, once daily for the first 4 weeks and then once weekly for the remaining 44 weeks on all dry nails with suspected onychomycosis.

|  |                        |
|--|------------------------|
| Arm type                               | Placebo                |
| Investigational medicinal product name | Vehicle                |
| Investigational medicinal product code |                        |
| Other name                             |                        |
| Pharmaceutical forms                   | Medicated nail lacquer |
| Routes of administration               | Topical use            |

Dosage and administration details:

Subjects administered topical nail solution (identical in appearance and indistinguishable from P-3058)

on dry nails, once daily for the first 4 weeks, then once weekly for an additional 44 weeks.

|  |                                 |
|--|---------------------------------|
| <b>Arm title</b>   | Amorolfine                      |
| Arm description:<br>Subjects applied Amorolfine topically, once weekly for 48 weeks on all dry nails with suspected onychomycosis. |                                 |
| Arm type   | Active comparator               |
| Investigational medicinal product name   | Amorolfine nail lacquer 50mg/ml |
| Investigational medicinal product code   |                                 |
| Other name   | Loceryl®                        |
| Pharmaceutical forms   | Medicated nail lacquer          |
| Routes of administration   | Topical use                     |

Dosage and administration details:

Subjects administered topical nail lacquer on dry nails, once weekly for 48 weeks.

| <b>Number of subjects in period 1</b>   | P-3058 10% | Vehicle | Amorolfine |
|---|------------|---------|------------|
| Started                                 | 406        | 410     | 137        |
| Completed                               | 349        | 353     | 120        |
| Not completed                           | 57         | 57      | 17         |
| Consent withdrawn by subject            | 25         | 32      | 9          |
| Adverse event, non-fatal                | 4          | 1       | -          |
| Protocol violation                      | 4          | 2       | -          |
| Non-compliant                           | 4          | 1       | -          |
| Other                                   | -          | 2       | -          |
| Lost to follow-up                       | 19         | 17      | 8          |
| Relevant deterioration of treated nails | 1          | 2       | -          |

## Baseline characteristics

### Reporting groups

|   |            |
|---|------------|
| Reporting group title   | P-3058 10% |
| Reporting group description:  |            |
| Subjects applied P-3058 10% nail solution topically, once daily for first 4 weeks and then once weekly for the remaining 44 weeks on all dry nails with suspected onychomycosis.                    |            |
| Reporting group title   | Vehicle    |
| Reporting group description:  |            |
| Subjects applied Vehicle of the P-3058 10% nail solution topically, once daily for the first 4 weeks and then once weekly for the remaining 44 weeks on all dry nails with suspected onychomycosis. |            |
| Reporting group title   | Amorolfine |
| Reporting group description:  |            |
| Subjects applied Amorolfine topically, once weekly for 48 weeks on all dry nails with suspected onychomycosis.  |            |

| Reporting group values | P-3058 10% | Vehicle | Amorolfine |
|------------------------|------------|---------|------------|
| Number of subjects     | 406        | 410     | 137        |
| Age categorical        |            |         |            |
| Units: Subjects        |            |         |            |

|  |         |         |         |
|--|---------|---------|---------|
| Age continuous                         |         |         |         |
| Units: years                           |         |         |         |
| arithmetic mean                        | 58.99   | 59.19   | 58.19   |
| standard deviation                     | ± 12.65 | ± 13.06 | ± 12.72 |
| Gender categorical                     |         |         |         |
| Units: Subjects                        |         |         |         |
| Female                                 | 180     | 157     | 52      |
| Male                                   | 226     | 253     | 85      |
| Race                                   |         |         |         |
| Units: Subjects                        |         |         |         |
| White                                  | 405     | 407     | 137     |
| Black or African American              | 0       | 1       | 0       |
| Asian                                  | 0       | 1       | 0       |
| American Indian or Alaska Native       | 0       | 1       | 0       |
| Other                                  | 1       | 0       | 0       |
| Percent of affected target big toenail |         |         |         |
| Units: Percentage                      |         |         |         |
| arithmetic mean                        | 34.72   | 34.82   | 35.23   |
| standard deviation                     | ± 9.92  | ± 10.14 | ± 10.11 |
| Total number of affected toenails      |         |         |         |
| Units: number                          |         |         |         |
| arithmetic mean                        | 4.81    | 4.65    | 4.96    |
| standard deviation                     | ± 2.90  | ± 2.81  | ± 2.73  |

| Reporting group values | Total |  |  |
|------------------------|-------|--|--|
| Number of subjects     | 953   |  |  |

|  |     |   |  |
|--|-----|---|--|
| Age categorical<br>Units: Subjects   |     |   |  |
| Age continuous<br>Units: years<br>arithmetic mean<br>standard deviation                              |     | - |  |
| Gender categorical<br>Units: Subjects  |     |   |  |
| Female   | 389 |   |  |
| Male   | 564 |   |  |
| Race<br>Units: Subjects  |     |   |  |
| White  | 949 |   |  |
| Black or African American  | 1   |   |  |
| Asian  | 1   |   |  |
| American Indian or Alaska Native   | 1   |   |  |
| Other  | 1   |   |  |
| Percent of affected target big toenail<br>Units: Percentage<br>arithmetic mean<br>standard deviation |     | - |  |
| Total number of affected toenails<br>Units: number<br>arithmetic mean<br>standard deviation          |     | - |  |

## End points

### End points reporting groups

|   |            |
|---|------------|
| Reporting group title   | P-3058 10% |
| Reporting group description:<br>Subjects applied P-3058 10% nail solution topically, once daily for first 4 weeks and then once weekly for the remaining 44 weeks on all dry nails with suspected onychomycosis.                    |            |
| Reporting group title   | Vehicle    |
| Reporting group description:<br>Subjects applied Vehicle of the P-3058 10% nail solution topically, once daily for the first 4 weeks and then once weekly for the remaining 44 weeks on all dry nails with suspected onychomycosis. |            |
| Reporting group title   | Amorolfine |
| Reporting group description:<br>Subjects applied Amorolfine topically, once weekly for 48 weeks on all dry nails with suspected onychomycosis.  |            |

### Primary: Percentage of Subjects With Complete Cure Rate of Onychomycosis Disease at Week 60

|  |  |
|--|--|
| End point title  | Percentage of Subjects With Complete Cure Rate of Onychomycosis Disease at Week 60 |
| End point description:<br>Complete cure rate at week 60, was defined as a composite of negative potassium hydroxide (KOH) microscopy, negative culture for dermatophytes, and no residual clinical involvement (nail totally clear) of the target big toenail. The complete cure rate was analysed using the logistic regression models with factor for treatment. Analysis was performed on intention-to-treat (ITT) population which included all subjects randomised and dispensed study medication, using the last observation carried forward (LOCF) approach for missing values (i.e., missing values were replaced by the last non-missing, post-baseline value). |  |
| End point type   | Primary  |
| End point timeframe:<br>Week 60  |  |

| End point values              | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 406             | 410             | 137             |  |
| Units: percentage of subjects |                 |                 |                 |  |
| number (not applicable)       |                 |                 |                 |  |
| Success rate                  | 5.67            | 2.20            | 2.92            |  |
| Failure rate                  | 94.33           | 97.80           | 97.08           |  |

### Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | P-3058 10% versus Vehicle |
| Comparison groups          | Vehicle v P-3058 10%      |

|   |                         |
|---|-------------------------|
| Number of subjects included in analysis | 816                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.0138 <sup>[1]</sup> |
| Method                                  | Regression, Logistic    |
| Parameter estimate                      | Odds ratio (OR)         |
| Point estimate                          | 2.68                    |
| Confidence interval                     |                         |
| level                                   | 95 %                    |
| sides                                   | 2-sided                 |
| lower limit                             | 1.22                    |
| upper limit                             | 5.86                    |

Notes:

[1] - p-value less than (<) 0.05 was considered statistically significant.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | P-3058 10% versus Amorolfine |
| Comparison groups                       | P-3058 10% v Amorolfine      |
| Number of subjects included in analysis | 543                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.2095 <sup>[2]</sup>      |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Odds ratio (OR)              |
| Point estimate                          | 2                            |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.68                         |
| upper limit                             | 5.88                         |

Notes:

[2] - p-value <0.05 was considered statistically significant.

### **Secondary: Percentage of Subjects With Responder Rate of Onychomycosis at Week 60**

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Responder Rate of Onychomycosis at Week 60 |
|-----------------|--|

End point description:

Responder rate at Week 60, was defined as a composite of negative KOH microscopy and negative culture for dermatophytes and less than equal to ( $\leq$ ) 10% residual involvement of the target toenail. The responder rate was analysed using the logistic regression models with factor for treatment and missing values for the components were replaced by the last non-missing value. Analysis was performed on ITT population.

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

End point timeframe:

Week 60

| <b>End point values</b>       | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 406             | 410             | 137             |  |
| Units: Percentage of subjects |                 |                 |                 |  |
| number (not applicable)       |                 |                 |                 |  |
| Success rate                  | 6.65            | 3.41            | 3.65            |  |
| Failure rate                  | 93.35           | 96.59           | 96.35           |  |

### Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | P-3058 10% versus Vehicle |
| Comparison groups                       | P-3058 10% v Vehicle      |
| Number of subjects included in analysis | 816                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.0377 [3]              |
| Method                                  | Regression, Logistic      |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 2.02                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 1.04                      |
| upper limit                             | 3.9                       |

Notes:

[3] - p-value <0.05 was considered statistically significant.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | P-3058 10% versus Amorolfine |
| Comparison groups                       | P-3058 10% v Amorolfine      |
| Number of subjects included in analysis | 543                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.204 [4]                  |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Odds ratio (OR)              |
| Point estimate                          | 1.88                         |
| Confidence interval                     |                              |
| level                                   | 95 %                         |
| sides                                   | 2-sided                      |
| lower limit                             | 0.71                         |
| upper limit                             | 4.98                         |

Notes:

[4] - p-value <0.05 was considered statistically significant.

### Secondary: Percentage of Subjects With Mycological Cure Rate of Onychomycosis at Week 60

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Mycological Cure Rate of Onychomycosis at Week 60 |
|-----------------|---|

End point description:

Mycological cure rate at Week 60, was defined as a composite of negative KOH microscopy and negative culture for dermatophytes of the target toenail. The mycological Cure rate was analysed using the logistic regression models with factor for treatment and missing values for the components were replaced by the last non-missing value. Analysis was performed on ITT population.

End point type Secondary

End point timeframe:

Week 60

| <b>End point values</b>       | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 406             | 410             | 137             |  |
| Units: percentage of subjects |                 |                 |                 |  |
| number (not applicable)       |                 |                 |                 |  |
| Success rate                  | 20.44           | 12.20           | 18.98           |  |
| Failure rate                  | 79.56           | 87.80           | 81.02           |  |

### Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | P-3058 10% versus Vehicle |
| Comparison groups                       | P-3058 10% v Vehicle      |
| Number of subjects included in analysis | 816                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.0016 [5]              |
| Method                                  | Regression, Logistic      |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 1.85                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 1.26                      |
| upper limit                             | 2.71                      |

Notes:

[5] - p-value <0.05 was considered statistically significant.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | P-3058 10% versus Amorolfine |
| Comparison groups                       | P-3058 10% v Amorolfine      |
| Number of subjects included in analysis | 543                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.7113 [6]                 |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Odds ratio (OR)              |
| Point estimate                          | 1.1                          |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.67    |
| upper limit         | 1.79    |

Notes:

[6] - p-value <0.05 was considered statistically significant.

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**Secondary: Number of Subjects With Any Adverse Events (AEs) From Baseline (Week 0) to Week 60/Discontinuation Visit**

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Any Adverse Events (AEs) From Baseline (Week 0) to Week 60/Discontinuation Visit |
|-----------------|--|

End point description:

An AE is defined as "any untoward medical event in a patient or clinical investigation subject administered any dose of a pharmaceutical product and which does not necessarily have to have a causal relationship with the use of the product. Number of subjects with treatment-emergent adverse events (TEAEs), i.e. those AEs with an onset date after at least treatment initiation) and the non-treatment emergent adverse events (non-TEAEs), i.e. AEs with onset date between signed informed consent form and treatment initiation) that occurred during the study were assessed for safety of study drug. Analysis was done on safety population which included all randomised subjects who receive at least one dose of the study drug.

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

End point timeframe:

Baseline (Week 0) to Week 60/Discontinuation Visit

| End point values                               | P-3058 10%      | Vehicle         | Amorolfine      |  |
|--|-----------------|-----------------|-----------------|--|
| Subject group type                             | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed                    | 406             | 407             | 137             |  |
| Units: number of subjects                      |                 |                 |                 |  |
| Subjects with any non-TEAEs                    | 21              | 29              | 7               |  |
| Subjects with any TEAEs                        | 170             | 190             | 63              |  |
| Subjects with serious TEAEs                    | 21              | 22              | 9               |  |
| Subjects with TEAEs leading to discontinuation | 4               | 1               | 0               |  |
| Subjects with fatal AEs                        | 2               | 0               | 0               |  |

**Statistical analyses**

No statistical analyses for this end point

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**Secondary: Number of Subjects With Local Tolerability From Baseline (Week 0) to Week 60/Discontinuation visit**

|                 |  |
|-----------------|--|
| End point title | Number of Subjects With Local Tolerability From Baseline (Week 0) to Week 60/Discontinuation visit |
|-----------------|--|

End point description:

The overall safety of study drug from Baseline to Week 60/Discontinuation visit was assessed through local tolerability score. Local tolerability at the application site was assessed to rate the severity of any periungual irritation from Week 4 to Week 60 (study end-point), or at discontinuation visit, through a severity score for skin irritation. The dermal response score ranges from 0 (no evidence of irritation) to 7 (strong reaction spreading beyond test site), and the score of other effects ranges from A (slight

glazed appearance) to G (small petechial erosions or scabs); where higher scores (7 and G) indicated more severe condition. Here, "Discont." represents 'Discontinuation visit'. Analysis was done of safety population.

|   |           |
|---|-----------|
| End point type                                      | Secondary |
| End point timeframe:                                |           |
| Baseline (Week 0) to Week 60; Discontinuation visit |           |

| End point values                                  | P-3058 10%         | Vehicle            | Amorolfine         |  |
|---|--------------------|--------------------|--------------------|--|
| Subject group type                                | Reporting group    | Reporting group    | Reporting group    |  |
| Number of subjects analysed                       | 406 <sup>[7]</sup> | 407 <sup>[8]</sup> | 137 <sup>[9]</sup> |  |
| Units: number of subjects                         |                    |                    |                    |  |
| Week 4, Skin irritation evidence- No              | 386                | 395                | 129                |  |
| Week 4, Skin irritation evidence- Yes             | 16                 | 8                  | 7                  |  |
| Week 12, Skin irritation evidence- No             | 380                | 383                | 126                |  |
| Week 12, Skin irritation evidence- Yes            | 7                  | 12                 | 6                  |  |
| Week 12, Skin irritation evidence- Missing        | 0                  | 0                  | 1                  |  |
| Week 24, Skin irritation evidence- No             | 368                | 378                | 128                |  |
| Week 24, Skin irritation evidence- Yes            | 6                  | 6                  | 3                  |  |
| Week 24, Skin irritation evidence- Missing        | 1                  | 0                  | 0                  |  |
| Week 36, Skin irritation evidence- No             | 364                | 368                | 127                |  |
| Week 36, Skin irritation evidence- Yes            | 4                  | 3                  | 1                  |  |
| Week 36, Skin irritation evidence- Missing        | 0                  | 1                  | 0                  |  |
| Week 48, Skin irritation evidence- No             | 358                | 356                | 123                |  |
| Week 48, Skin irritation evidence- Yes            | 1                  | 5                  | 2                  |  |
| Week 48, Skin irritation evidence- Missing        | 0                  | 1                  | 1                  |  |
| Week 60, Skin irritation evidence- No             | 350                | 349                | 118                |  |
| Week 60, Skin irritation evidence- Yes            | 1                  | 1                  | 2                  |  |
| Week 60, Skin irritation evidence- Missing        | 0                  | 1                  | 0                  |  |
| Discont. Visit, Skin irritation evidence- No      | 21                 | 19                 | 7                  |  |
| Discont. Visit, Skin irritation evidence- Yes     | 1                  | 0                  | 0                  |  |
| Discont. Visit, Skin irritation evidence- Missing | 3                  | 8                  | 1                  |  |

Notes:

[7] - No. of subjects analysed-Weeks4,12,24,36,48,60,Discont. were 402,387,375,368,359,351,25; respectively

[8] - No. of subjects analysed-Weeks4,12,24,36,48,60,Discont. were 403,395,384,372,362,351,27; respectively

[9] - No. of subjects analysed- Weeks4,12,24,36,48,60,Discont. were 136,133,131,128,126,120,8; respectively

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Percentage of Subjects With Modified Cure Rate of Onychomycosis at Week 60

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Modified Cure Rate of |
|-----------------|---|

## End point description:

Modified cure rate at Week 60, was defined as negative culture for dermatophytes and no residual clinical involvement (nail totally clear) of the target toenail. The modified Cure rate was analysed using the logistic regression models with factor for treatment and missing values for the components were replaced by the last non-missing value. Analysis was performed on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

|                      |  |
|----------------------|--|
| End point timeframe: |  |
|----------------------|--|

|         |  |
|---------|--|
| Week 60 |  |
|---------|--|

| End point values              | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 406             | 410             | 137             |  |
| Units: percentage of subjects |                 |                 |                 |  |
| number (not applicable)       |                 |                 |                 |  |
| Success rate                  | 10.34           | 6.83            | 3.65            |  |
| Failure rate                  | 89.66           | 93.17           | 96.35           |  |

### Statistical analyses

|   |                           |
|---|---------------------------|
| <b>Statistical analysis title</b>       | P-3058 10% versus Vehicle |
| Comparison groups                       | P-3058 10% v Vehicle      |
| Number of subjects included in analysis | 816                       |
| Analysis specification                  | Pre-specified             |
| Analysis type                           | superiority               |
| P-value                                 | = 0.0749 <sup>[10]</sup>  |
| Method                                  | Regression, Logistic      |
| Parameter estimate                      | Odds ratio (OR)           |
| Point estimate                          | 1.57                      |
| Confidence interval                     |                           |
| level                                   | 95 %                      |
| sides                                   | 2-sided                   |
| lower limit                             | 0.96                      |
| upper limit                             | 2.59                      |

Notes:

[10] - p-value <0.05 was considered statistically significant.

|   |                              |
|---|------------------------------|
| <b>Statistical analysis title</b>       | P-3058 10% versus Amorolfine |
| Comparison groups                       | P-3058 10% v Amorolfine      |
| Number of subjects included in analysis | 543                          |
| Analysis specification                  | Pre-specified                |
| Analysis type                           | superiority                  |
| P-value                                 | = 0.0213 <sup>[11]</sup>     |
| Method                                  | Regression, Logistic         |
| Parameter estimate                      | Odds ratio (OR)              |
| Point estimate                          | 3.05                         |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 1.18    |
| upper limit         | 7.86    |

Notes:

[11] - p-value <0.05 was considered statistically significant.

### Other pre-specified: Percentage of Subjects With Modified Responder Rate of Onychomycosis at Week 60

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With Modified Responder Rate of Onychomycosis at Week 60 |
|-----------------|---|

End point description:

Modified responder rate at Week 60, was defined as composite of negative culture for dermatophytes and ≤10% residual involvement of the target big toenail. This rate was analysed using the logistic regression models with factor for treatment and missing values for the components were replaced by the last non-missing value. Analysis was done on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Week 60

| End point values              | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 406             | 410             | 137             |  |
| Units: percentage of subjects |                 |                 |                 |  |
| number (not applicable)       |                 |                 |                 |  |
| Success rate                  | 14.04           | 9.76            | 5.11            |  |
| Failure rate                  | 85.96           | 90.24           | 94.89           |  |

### Statistical analyses

|                            |                           |
|----------------------------|---------------------------|
| Statistical analysis title | P-3058 10% versus Vehicle |
|----------------------------|---------------------------|

Statistical analysis description:

The comparisons between treatment groups at Week 60 were based on odds ratio calculated from a logistic model with factor for treatment. Missing values for the components were replaced by the last non-missing value (LOCF) and the Modified responder rate is computed on the LOCF values.

|   |                        |
|---|------------------------|
| Comparison groups                       | Vehicle v P-3058 10%   |
| Number of subjects included in analysis | 816                    |
| Analysis specification                  | Pre-specified          |
| Analysis type                           | superiority            |
| P-value                                 | = 0.06 <sup>[12]</sup> |
| Method                                  | Regression, Logistic   |
| Parameter estimate                      | Odds ratio (OR)        |
| Point estimate                          | 1.51                   |

|                     |         |
|---------------------|---------|
| Confidence interval |         |
| level               | 95 %    |
| sides               | 2-sided |
| lower limit         | 0.98    |
| upper limit         | 2.32    |

Notes:

[12] - p-value <0.05 was considered statistically significant.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | P-3058 10% versus Amorolfine |
|-----------------------------------|------------------------------|

Statistical analysis description:

The comparisons between treatment groups at Week 60 were based on odds ratio calculated from a logistic model with factor for treatment. Missing values for the components were replaced by the last non-missing value (LOCF) and the Modified responder rate is computed on the LOCF values.

|   |                          |
|---|--------------------------|
| Comparison groups                       | P-3058 10% v Amorolfine  |
| Number of subjects included in analysis | 543                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.0073 <sup>[13]</sup> |
| Method                                  | Regression, Logistic     |
| Parameter estimate                      | Odds ratio (OR)          |
| Point estimate                          | 3.03                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 1.35                     |
| upper limit                             | 6.82                     |

Notes:

[13] - p-value <0.05 was considered statistically significant.

### Other pre-specified: Percentage of Subjects With Negative Culture for Dermatophyte at Weeks 4, 12, 24, 36, 48, and 60

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects With Negative Culture for Dermatophyte at Weeks 4, 12, 24, 36, 48, and 60 |
|-----------------|--|

End point description:

Rate of negative culture for dermatophytes of the target toenail at each visit. The number and percentage of subjects with negative or positive culture for dermatophytes were assessed using the LOCF approach . The rate of negative culture was analysed using the logistic regression models with factor for treatment. Analysis was done on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Weeks 4, 12, 24, 36, 48, 60

| End point values              | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 406             | 410             | 137             |  |
| Units: percentage of subjects |                 |                 |                 |  |
| number (not applicable)       |                 |                 |                 |  |
| Week 4                        | 96.80           | 47.07           | 97.08           |  |

|         |       |       |       |  |
|---------|-------|-------|-------|--|
| Week 12 | 98.03 | 48.78 | 99.27 |  |
| Week 24 | 97.78 | 45.37 | 98.54 |  |
| Week 36 | 97.29 | 46.10 | 97.08 |  |
| Week 48 | 96.06 | 51.46 | 95.62 |  |
| Week 60 | 86.70 | 51.46 | 67.15 |  |

## Statistical analyses

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | P-3058 10% versus Vehicle |
|-----------------------------------|---------------------------|

Statistical analysis description:

The comparisons between treatment groups at Week 60 were based on odds ratio calculated from a logistic model with factor for treatment, since the model with factors for treatment, study site, and treatment-by-site interaction did not converge. Missing values were replaced by the last non-missing value (LOCF).

|   |                          |
|---|--------------------------|
| Comparison groups                       | P-3058 10% v Vehicle     |
| Number of subjects included in analysis | 816                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.0001 <sup>[14]</sup> |
| Method                                  | Regression, Logistic     |
| Parameter estimate                      | Odds ratio (OR)          |
| Point estimate                          | 6.15                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 4.35                     |
| upper limit                             | 8.69                     |

Notes:

[14] - p-value <0.05 was considered statistically significant.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | P-3058 10% versus Amorolfine |
|-----------------------------------|------------------------------|

Statistical analysis description:

The comparisons between treatment groups at Week 60 were based on odds ratio calculated from a logistic model with factor for treatment, since the model with factors for treatment, study site, and treatment-by-site interaction did not converge. Missing values were replaced by the last non-missing value (LOCF).

|   |                          |
|---|--------------------------|
| Comparison groups                       | P-3058 10% v Amorolfine  |
| Number of subjects included in analysis | 543                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | < 0.0001 <sup>[15]</sup> |
| Method                                  | Regression, Logistic     |
| Parameter estimate                      | Odds ratio (OR)          |
| Point estimate                          | 3.19                     |
| Confidence interval                     |                          |
| level                                   | 95 %                     |
| sides                                   | 2-sided                  |
| lower limit                             | 2.02                     |
| upper limit                             | 5.04                     |

Notes:

[15] - p-value <0.05 was considered statistically significant.

### Other pre-specified: Change From Baseline (Week 0) of Domain Scores of Onychomycosis Quality of Life Questionnaire For Toenails at Week 60

|                 |   |
|-----------------|---|
| End point title | Change From Baseline (Week 0) of Domain Scores of Onychomycosis Quality of Life Questionnaire For Toenails at Week 60 |
|-----------------|---|

End point description:

The Onychomycosis quality of life (ONYCHO) questionnaire consists of 17 questions, assessing social problems, emotional state, and the burden of symptoms. There are 5 possible responses to each question, which are rated as follows: 1 point - 'Not at all'; 2 points - 'Yes, but this is not bothersome'; 3 points - 'Yes, this is somewhat bothersome'; 4 points - 'Yes, this is very bothersome'; 5 points - 'Yes, this is extremely bothersome'. These raw scores to items within each problem group were added to a total and a mean was calculated. All scores were transformed into a 0-100 scale where 0 represented worst score and 100 best score, that is, 0 representing 5 points - (Yes, this is extremely bothersome) (worst), 25 representing 4 points (Yes, this is very bothersome), 50 representing 3 points (Yes, this is somewhat bothersome), 75 representing 2 points (Yes, but this is not bothersome), and 100 represent 1 point (Not at all) (best). Analysis was done on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (Week 0); Week 60

| End point values                    | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type                  | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed         | 406             | 410             | 137             |  |
| Units: score on a scale             |                 |                 |                 |  |
| least squares mean (standard error) |                 |                 |                 |  |
| Social problems                     | 4.97 (± 1.31)   | 5.15 (± 1.30)   | 5.23 (± 2.31)   |  |
| Emotional state                     | 6.27 (± 0.99)   | 6.04 (± 0.99)   | 8.96 (± 1.75)   |  |
| Burden of symptoms                  | 6.79 (± 1.08)   | 6.34 (± 1.08)   | 12.68 (± 1.91)  |  |

### Statistical analyses

|                            |  |
|----------------------------|--|
| Statistical analysis title | Social problems: P-3058 10% versus Vehicle |
|----------------------------|--|

Statistical analysis description:

Statistical analysis of the ONYCHO questionnaire by domain change from baseline was reported at Week 60 and were based on ANCOVA model with baseline value as covariate, treatment group, site and treatment-by-site interaction as factors.

|   |                          |
|---|--------------------------|
| Comparison groups                       | P-3058 10% v Vehicle     |
| Number of subjects included in analysis | 816                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.9947 <sup>[16]</sup> |
| Method                                  | ANCOVA                   |

Notes:

[16] - p-value <0.05 was considered statistically significant.

|                            |   |
|----------------------------|---|
| Statistical analysis title | Social problems: P-3058 10% versus Amorolfine |
|----------------------------|---|

Statistical analysis description:

Statistical analysis of the ONYCHO questionnaire by domain change from baseline was reported at Week 60 and were based on ANCOVA model with baseline value as covariate, treatment group, site and treatment-by-site interaction as factors.

|   |                          |
|---|--------------------------|
| Comparison groups                       | P-3058 10% v Amorolfine  |
| Number of subjects included in analysis | 543                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.9948 <sup>[17]</sup> |
| Method                                  | ANCOVA                   |

Notes:

[17] - p-value <0.05 was considered statistically significant.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Emotional state: P-3058 10% versus Vehicle |
|-----------------------------------|--|

Statistical analysis description:

Statistical analysis of the ONYCHO questionnaire by domain change from baseline was reported at Week 60 and were based on ANCOVA model with baseline value as covariate, treatment group, site and treatment-by-site interaction as factors.

|   |                          |
|---|--------------------------|
| Comparison groups                       | P-3058 10% v Vehicle     |
| Number of subjects included in analysis | 816                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.9862 <sup>[18]</sup> |
| Method                                  | ANCOVA                   |

Notes:

[18] - p-value <0.05 was considered statistically significant.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Emotional state: P-3058 10% versus Amorolfine |
|-----------------------------------|---|

Statistical analysis description:

Statistical analysis of the ONYCHO questionnaire by domain change from baseline was reported at Week 60 and were based on ANCOVA model with baseline value as covariate, treatment group, site and treatment-by-site interaction as factors.

|   |                          |
|---|--------------------------|
| Comparison groups                       | P-3058 10% v Amorolfine  |
| Number of subjects included in analysis | 543                      |
| Analysis specification                  | Pre-specified            |
| Analysis type                           | superiority              |
| P-value                                 | = 0.3736 <sup>[19]</sup> |
| Method                                  | ANCOVA                   |

Notes:

[19] - p-value <0.05 was considered statistically significant.

|                                   |   |
|-----------------------------------|---|
| <b>Statistical analysis title</b> | Burden of symptoms: P-3058 10% versus Vehicle |
|-----------------------------------|---|

Statistical analysis description:

Statistical analysis of the ONYCHO questionnaire by domain change from baseline was reported at Week 60 and were based on ANCOVA model with baseline value as covariate, treatment group, site and treatment-by-site interaction as factors.

|                   |                      |
|-------------------|----------------------|
| Comparison groups | P-3058 10% v Vehicle |
|-------------------|----------------------|

|   |               |
|---|---------------|
| Number of subjects included in analysis | 816           |
| Analysis specification                  | Pre-specified |
| Analysis type                           | superiority   |
| P-value                                 | = 0.9528 [20] |
| Method                                  | ANCOVA        |

Notes:

[20] - p-value <0.05 was considered statistically significant.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | Burden of symptoms: P-3058 10% versus Amorolfine |
|-----------------------------------|--|

Statistical analysis description:

Statistical analysis of the ONYCHO questionnaire by domain change from baseline was reported at Week 60 and were based on ANCOVA model with baseline value as covariate, treatment group, site and treatment-by-site interaction as factors.

|   |                         |
|---|-------------------------|
| Comparison groups                       | P-3058 10% v Amorolfine |
| Number of subjects included in analysis | 543                     |
| Analysis specification                  | Pre-specified           |
| Analysis type                           | superiority             |
| P-value                                 | = 0.02 [21]             |
| Method                                  | ANCOVA                  |

Notes:

[21] - p-value <0.05 was considered statistically significant.

### Other pre-specified: Percentage of Subjects Who Represent Therapy Acceptability at Week 48 - Observed Data

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects Who Represent Therapy Acceptability at Week 48 - Observed Data |
|-----------------|---|

End point description:

Therapy acceptability was reported at different level of acceptability of therapy which were classified into 1 - poor, 2 - moderate, 3 - good, 4 - very good, and 5 - not evaluated, summarized at Week 48 by treatment, considering the observed data approach. Analysis was done on ITT population. Here, 'number of subjects analysed' = subjects with the available data for the specified treatment arm.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Week 48 (End of treatment)

| End point values              | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 383             | 389             | 132             |  |
| Units: percentage of subjects |                 |                 |                 |  |
| number (not applicable)       |                 |                 |                 |  |
| Score 1 - Poor                | 15.14           | 20.05           | 16.67           |  |
| Score 2 - Moderate            | 27.42           | 23.65           | 25.00           |  |
| Score 3 - Good                | 27.94           | 31.62           | 28.79           |  |
| Score 4 - Very Good           | 27.68           | 23.14           | 29.55           |  |
| Score 5 - Not Evaluated       | 1.83            | 1.54            | 0.00            |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percentage of Subjects Who Represent Therapy Acceptability at Week 48 - Worst Case

|                 |  |
|-----------------|--|
| End point title | Percentage of Subjects Who Represent Therapy Acceptability at Week 48 - Worst Case |
|-----------------|--|

End point description:

Therapy acceptability according to a worst-case approach (i.e. missing values/not evaluated scores were replaced with the worst score) where summarized at Week 48, by treatment and were classified according to subjects acceptance of study therapy as 1 - poor, 2 - moderate, 3 - good, and 4 - very good. Analysis was done on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Week 48

| End point values              | P-3058 10%      | Vehicle         | Amorolfine      |  |
|-------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type            | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed   | 406             | 410             | 137             |  |
| Units: percentage of subjects |                 |                 |                 |  |
| number (not applicable)       |                 |                 |                 |  |
| Score 1 - Poor                | 21.67           | 25.61           | 19.71           |  |
| Score 2 - Moderate            | 25.86           | 22.44           | 24.09           |  |
| Score 3 - Good                | 26.35           | 30.00           | 27.74           |  |
| Score 4 - Very good           | 26.11           | 21.95           | 28.47           |  |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percent Change From Baseline (Week 0) in Involved Target Nail Area to Week 60 - Observed Data

|                 |   |
|-----------------|---|
| End point title | Percent Change From Baseline (Week 0) in Involved Target Nail Area to Week 60 - Observed Data |
|-----------------|---|

End point description:

The affected area of the target big toenail (%) as measured on the digital photographs by the imaging company was classified into three categories, i.e. 0%,  $\leq 10\%$  but greater than ( $>$ ) 0%, and  $> 10\%$  at each post screening visit. Analysis was done on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Baseline (Week 0); Weeks 12, 24, 36, 48, 60

| End point values                     | P-3058 10%      | Vehicle         | Amorolfine       |  |
|--------------------------------------|-----------------|-----------------|------------------|--|
| Subject group type                   | Reporting group | Reporting group | Reporting group  |  |
| Number of subjects analysed          | 406             | 410             | 137              |  |
| Units: Involved Target nail Area (%) |                 |                 |                  |  |
| arithmetic mean (standard deviation) |                 |                 |                  |  |
| Week 12 (n=368, 381, 125)            | -4.38 (± 13.81) | -4.72 (± 12.48) | -3.96 (± 12.85)  |  |
| Week 24 (n=353, 366, 129)            | -4.91 (± 15.52) | -4.32 (± 14.37) | -5.79 (± 14.51)  |  |
| Week 36 (n=353, 356, 126)            | -5.97 (± 17.43) | -4.83 (± 15.38) | -6.50 (± 14.94)  |  |
| Week 48 (n=350, 350, 123)            | -5.95 (± 18.34) | -5.67 (± 15.57) | -5.86 (± 15.89)  |  |
| Week 60 (n=326, 339, 114)            | -5.31 (± 18.61) | -5.20 (± 17.58) | -4.91 (± 17.85)  |  |
| Discontinued visit (n=20, 15, 7)     | -0.24 (± 16.89) | 3.83 (± 18.88)  | -13.74 (± 16.21) |  |

### Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Percentage of Subjects With No Residual Clinical Involvement (Nail Totally Clear) of the Target Toenail at Weeks 12, 24, 36, 48, and 60

|                 |   |
|-----------------|---|
| End point title | Percentage of Subjects With No Residual Clinical Involvement (Nail Totally Clear) of the Target Toenail at Weeks 12, 24, 36, 48, and 60 |
|-----------------|---|

End point description:

Rates of no residual clinical involvement (nail totally clear) of the target toenail assessment ensured that the diseased target nail area equal to (=) 0%. This rate was analysed using the logistic regression models with factor for treatment and LOCF approach, by visit. Analysis was done on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Weeks 12, 24, 36, 48, 60

| End point values              | P-3058 10%          | Vehicle             | Amorolfine          |  |
|-------------------------------|---------------------|---------------------|---------------------|--|
| Subject group type            | Reporting group     | Reporting group     | Reporting group     |  |
| Number of subjects analysed   | 406 <sup>[22]</sup> | 410 <sup>[23]</sup> | 137 <sup>[24]</sup> |  |
| Units: percentage of subjects |                     |                     |                     |  |
| number (not applicable)       |                     |                     |                     |  |
| Week 12 - No                  | 97.54               | 98.29               | 100.00              |  |
| Week 12 - Yes                 | 2.46                | 1.71                | 0.00                |  |
| Week 24 - No                  | 95.57               | 96.83               | 97.81               |  |
| Week 24 - Yes                 | 4.43                | 3.17                | 2.19                |  |
| Week 36 - No                  | 91.63               | 95.37               | 97.81               |  |
| Week 36 - Yes                 | 8.37                | 4.63                | 2.19                |  |
| Week 48 - No                  | 90.15               | 91.95               | 94.89               |  |
| Week 48 - Yes                 | 9.85                | 8.05                | 5.11                |  |

|               |       |       |       |  |
|---------------|-------|-------|-------|--|
| Week 60 - No  | 89.66 | 91.46 | 95.62 |  |
| Week 60 - Yes | 10.34 | 8.54  | 4.38  |  |

Notes:

[22] - Subjects evaluable at Weeks 12, 24, 36, 48, and 60 were 396, 388, 372, 366, and 364; respectively.

[23] - Subjects evaluable at Weeks 12, 24, 36, 48, and 60 were 403, 397, 391, 377, and 375; respectively.

[24] - Subjects evaluable at Weeks 12, 24, 36, 48, and 60 were 137, 134, 134, 130, and 131; respectively.

## Statistical analyses

|                                   |                           |
|-----------------------------------|---------------------------|
| <b>Statistical analysis title</b> | P-3058 10% versus Vehicle |
|-----------------------------------|---------------------------|

Statistical analysis description:

The comparisons between treatment groups at Week 60 were based on odds ratio calculated from a logistic model with factor for treatment, since the model with factors for treatment, study site, and treatment-by-site interaction did not converge. Missing values were replaced by the LOCF.

|   |                      |
|---|----------------------|
| Comparison groups                       | P-3058 10% v Vehicle |
| Number of subjects included in analysis | 816                  |
| Analysis specification                  | Pre-specified        |
| Analysis type                           | superiority          |
| P-value                                 | = 0.3777 [25]        |
| Method                                  | Wald Chi-square      |
| Parameter estimate                      | Odds ratio (OR)      |
| Point estimate                          | 1.24                 |
| Confidence interval                     |                      |
| level                                   | 95 %                 |
| sides                                   | 2-sided              |
| lower limit                             | 0.77                 |
| upper limit                             | 1.98                 |

Notes:

[25] - p-value <0.05 was considered statistically significant.

|                                   |                              |
|-----------------------------------|------------------------------|
| <b>Statistical analysis title</b> | P-3058 10% versus Amorolfine |
|-----------------------------------|------------------------------|

Statistical analysis description:

The comparisons between treatment groups at Week 60 were based on odds ratio calculated from a logistic model with factor for treatment, since the model with factors for treatment, study site, and treatment-by-site interaction did not converge. Missing values were replaced by the last non-missing value (LOCF).

|   |                             |
|---|-----------------------------|
| Comparison groups                       | P-3058 10% v Amorolfine     |
| Number of subjects included in analysis | 543                         |
| Analysis specification                  | Pre-specified               |
| Analysis type                           | superiority <sup>[26]</sup> |
| P-value                                 | = 0.0393                    |
| Method                                  | Wald Chi-square             |
| Parameter estimate                      | Odds ratio (OR)             |
| Point estimate                          | 2.52                        |
| Confidence interval                     |                             |
| level                                   | 95 %                        |
| sides                                   | 2-sided                     |
| lower limit                             | 1.05                        |
| upper limit                             | 6.06                        |

Notes:

[26] - p-value <0.05 was considered statistically significant.

**Other pre-specified: Dermatological Assessment - Percentage of Subjects With Number of Toenails (5,8,9,&10) and Fingernails (6,7,9,&10) Present at Weeks 4, 12, 36, 48, and 60 - Observed Data**

|                 |   |
|-----------------|---|
| End point title | Dermatological Assessment - Percentage of Subjects With Number of Toenails (5,8,9,&10) and Fingernails (6,7,9,&10) Present at Weeks 4, 12, 36, 48, and 60 - Observed Data |
|-----------------|---|

End point description:

Dermatological assessments was defined to be assessed through percentage of subjects with right or left target big toenail, percentage of affected area of the target big toenail (according to the Investigator's clinical evaluation), number of toenails/fingernails present per subject (as categorical term), number of toenails/fingernails with suspected onychomycosis per subject (as categorical term) and location of toenails with suspected onychomycosis are summarized by treatment. The data for this end point reported number of toenails present per subject. Analysis was done on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Weeks 4, 12, 36, 48, 60; Discontinuation visit

| End point values               | P-3058 10%      | Vehicle         | Amorolfine      |  |
|--------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type             | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed    | 406             | 410             | 137             |  |
| Units: percentage of subjects  |                 |                 |                 |  |
| number (not applicable)        |                 |                 |                 |  |
| Week 4, Number of toenails=5   | 0.00            | 0.25            | 0.00            |  |
| Week 4, Number of toenails=8   | 0.00            | 0.25            | 0.00            |  |
| Week 4, Number of toenails=9   | 0.00            | 0.25            | 0.00            |  |
| Week 4, Number of toenails=10  | 100.00          | 99.26           | 100.00          |  |
| Week 12, Number of toenails=5  | 0.00            | 0.25            | 0.00            |  |
| Week 12, Number of toenails=8  | 0.00            | 0.25            | 0.00            |  |
| Week 12, Number of toenails=9  | 0.00            | 0.51            | 0.00            |  |
| Week 12, Number of toenails=10 | 100.00          | 98.99           | 100.00          |  |
| Week 24, Number of toenails=5  | 0.00            | 0.26            | 0.00            |  |
| Week 24, Number of toenails=8  | 0.00            | 0.26            | 0.00            |  |
| Week 24, Number of toenails=9  | 0.00            | 0.26            | 0.00            |  |
| Week 24, Number of toenails=10 | 100.00          | 99.22           | 100.00          |  |
| Week 36, Number of toenails=5  | 0.00            | 0.27            | 0.00            |  |
| Week 36, Number of toenails=8  | 0.00            | 0.27            | 0.00            |  |
| Week 36, Number of toenails=9  | 0.00            | 0.27            | 0.00            |  |
| Week 36, Number of toenails=10 | 100.00          | 99.20           | 100.00          |  |
| Week 48, Number of toenails=5  | 0.00            | 0.28            | 0.00            |  |
| Week 48, Number of toenails=8  | 0.00            | 0.28            | 0.00            |  |
| Week 48, Number of toenails=9  | 0.00            | 0.28            | 0.00            |  |
| Week 48, Number of toenails=10 | 100.00          | 99.17           | 100.00          |  |
| Week 60, Number of toenails=5  | 0.00            | 0.28            | 0.00            |  |
| Week 60, Number of toenails=8  | 0.00            | 0.28            | 0.00            |  |
| Week 60, Number of toenails=9  | 0.00            | 0.28            | 0.00            |  |
| Week 60, Number of toenails=10 | 100.00          | 99.15           | 100.00          |  |

|   |        |        |        |
|---|--------|--------|--------|
| Discontinuation Visit, Number of toenails=9     | 0.00   | 5.26   | 0.00   |
| Discontinuation Visit, Number of toenails=10    | 100.00 | 94.74  | 100.00 |
| Week 4, Number of fingernails=6                 | 0.00   | 0.00   | 0.74   |
| Week 4, Number of fingernails=7                 | 0.00   | 0.00   | 0.74   |
| Week 4, Number of fingernails=9                 | 0.50   | 0.49   | 0.00   |
| Week 4, Number of fingernails=10                | 99.50  | 99.51  | 98.53  |
| Week 12, Number of fingernails=6                | 0.00   | 0.00   | 0.76   |
| Week 12, Number of fingernails=7                | 0.00   | 0.00   | 0.76   |
| Week 12, Number of fingernails=9                | 0.52   | 0.51   | 0.00   |
| Week 12, Number of fingernails=10               | 99.48  | 99.49  | 98.48  |
| Week 24, Number of fingernails=6                | 0.00   | 0.00   | 0.76   |
| Week 24, Number of fingernails=7                | 0.00   | 0.00   | 0.76   |
| Week 24, Number of fingernails=9                | 0.54   | 0.52   | 0.00   |
| Week 24, Number of fingernails=10               | 99.46  | 99.48  | 98.47  |
| Week 36, Number of fingernails=6                | 0.00   | 0.00   | 0.78   |
| Week 36, Number of fingernails=7                | 0.00   | 0.00   | 0.78   |
| Week 36, Number of fingernails=9                | 0.55   | 0.54   | 0.00   |
| Week 36, Number of fingernails=10               | 99.45  | 99.46  | 98.44  |
| Week 48, Number of fingernails=6                | 0.00   | 0.00   | 0.80   |
| Week 48, Number of fingernails=7                | 0.00   | 0.00   | 0.80   |
| Week 48, Number of fingernails=9                | 0.56   | 0.55   | 0.00   |
| Week 48, Number of fingernails=10               | 99.44  | 99.45  | 98.40  |
| Week 60, Number of fingernails=6                | 0.00   | 0.00   | 0.83   |
| Week 60, Number of fingernails=7                | 0.00   | 0.00   | 0.83   |
| Week 60, Number of fingernails=9                | 0.57   | 0.57   | 0.00   |
| Week 60, Number of fingernails=10               | 99.43  | 99.43  | 98.33  |
| Discontinuation Visit, Number of fingernails=10 | 100.00 | 100.00 | 100.00 |

## Statistical analyses

No statistical analyses for this end point

### Other pre-specified: Dermatological Assessment - Percentage of Subjects With Number of Nails With Suspected Onychomycosis (0 to 10) Present at Weeks 4, 12, 36, 48, 60, and Discontinuation Visit - Observed Data

|                 |  |
|-----------------|--|
| End point title | Dermatological Assessment - Percentage of Subjects With Number of Nails With Suspected Onychomycosis (0 to 10) Present at Weeks 4, 12, 36, 48, 60, and Discontinuation Visit - Observed Data |
|-----------------|--|

End point description:

Dermatological assessments was defined to be assessed through percentage of subjects with right or left target big toenail, percentage of affected area of the target big toenail (according to the Investigator's clinical evaluation), number of toenails/fingernails present per subject (as categorical term), number of toenails/fingernails with suspected onychomycosis per subject (as categorical term) and location of toenails/fingernails with suspected onychomycosis are summarized by treatment. The data for this end point reported total number of toenails with suspected onychomycosis. Here, 'Discont.Visit' represents Discontinuation Visit. Analysis was done on ITT population.

|                |                     |
|----------------|---------------------|
| End point type | Other pre-specified |
|----------------|---------------------|

End point timeframe:

Weeks 4, 12, 36, 48, 60; Discontinuation visit

| <b>End point values</b>                        | P-3058 10%      | Vehicle         | Amorolfine      |  |
|--|-----------------|-----------------|-----------------|--|
| Subject group type                             | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed                    | 406             | 410             | 137             |  |
| Units: percentage of subjects                  |                 |                 |                 |  |
| number (not applicable)                        |                 |                 |                 |  |
| Week 4, Total number of suspected toenails=1   | 9.00            | 8.64            | 5.88            |  |
| Week 4, Total number of suspected toenails=2   | 22.00           | 22.22           | 21.32           |  |
| Week 4, Total number of suspected toenails=3   | 12.00           | 8.89            | 8.09            |  |
| Week 4, Total number of suspected toenails=4   | 7.25            | 14.32           | 17.65           |  |
| Week 4, Total number of suspected toenails=5   | 10.50           | 9.88            | 7.35            |  |
| Week 4, Total number of suspected toenails=6   | 9.50            | 9.63            | 13.97           |  |
| Week 4, Total number of suspected toenails=7   | 7.00            | 6.42            | 5.88            |  |
| Week 4, Total number of suspected toenails=8   | 7.75            | 6.91            | 7.35            |  |
| Week 4, Total number of suspected toenails=9   | 4.25            | 2.47            | 2.94            |  |
| Week 4, Total number of suspected toenails=10  | 10.75           | 10.62           | 9.56            |  |
| Week 12, Total number of suspected toenails=0  | 1.04            | 0.76            | 0.76            |  |
| Week 12, Total number of suspected toenails=1  | 8.83            | 8.84            | 4.55            |  |
| Week 12, Total number of suspected toenails=2  | 21.82           | 22.47           | 21.21           |  |
| Week 12, Total number of suspected toenails=3  | 11.69           | 8.08            | 9.85            |  |
| Week 12, Total number of suspected toenails=4  | 8.31            | 14.39           | 18.18           |  |
| Week 12, Total number of suspected toenails=5  | 8.83            | 9.85            | 6.82            |  |
| Week 12, Total number of suspected toenails=6  | 9.87            | 9.34            | 12.12           |  |
| Week 12, Total number of suspected toenails=7  | 6.75            | 6.31            | 6.06            |  |
| Week 12, Total number of suspected toenails=8  | 7.01            | 7.58            | 7.58            |  |
| Week 12, Total number of suspected toenails=9  | 5.19            | 2.27            | 3.79            |  |
| Week 12, Total number of suspected toenails=10 | 10.65           | 10.10           | 9.09            |  |
| Week 24, Total number of suspected toenails=0  | 1.88            | 1.55            | 1.53            |  |
| Week 24, Total number of suspected toenails=1  | 11.29           | 9.84            | 5.34            |  |
| Week 24, Total number of suspected toenails=2  | 19.35           | 20.98           | 20.61           |  |
| Week 24, Total number of suspected toenails=3  | 11.29           | 10.88           | 10.69           |  |

|  |       |       |       |  |
|--|-------|-------|-------|--|
| Week 24, Total number of suspected toenails=4  | 8.60  | 14.77 | 16.79 |  |
| Week 24, Total number of suspected toenails=5  | 8.87  | 9.07  | 5.34  |  |
| Week 24, Total number of suspected toenails=6  | 9.68  | 8.03  | 15.27 |  |
| Week 24, Total number of suspected toenails=7  | 6.72  | 5.70  | 5.34  |  |
| Week 24, Total number of suspected toenails=8  | 7.53  | 8.03  | 9.16  |  |
| Week 24, Total number of suspected toenails=9  | 2.69  | 2.07  | 2.29  |  |
| Week 24, Total number of suspected toenails=10 | 12.10 | 9.07  | 7.63  |  |
| Week 36, Total number of suspected toenails=0  | 4.10  | 2.95  | 2.34  |  |
| Week 36, Total number of suspected toenails=1  | 10.66 | 10.72 | 6.25  |  |
| Week 36, Total number of suspected toenails=2  | 18.31 | 21.18 | 18.75 |  |
| Week 36, Total number of suspected toenails=3  | 11.75 | 10.19 | 10.16 |  |
| Week 36, Total number of suspected toenails=4  | 9.56  | 12.87 | 19.53 |  |
| Week 36, Total number of suspected toenails=5  | 9.02  | 9.92  | 7.81  |  |
| Week 36, Total number of suspected toenails=6  | 8.74  | 7.51  | 10.16 |  |
| Week 36, Total number of suspected toenails=7  | 5.46  | 5.63  | 3.91  |  |
| Week 36, Total number of suspected toenails=8  | 7.38  | 7.51  | 10.16 |  |
| Week 36, Total number of suspected toenails=9  | 3.28  | 2.68  | 2.34  |  |
| Week 36, Total number of suspected toenails=10 | 11.75 | 8.85  | 8.59  |  |
| Week 48, Total number of suspected toenails=0  | 5.88  | 4.68  | 2.40  |  |
| Week 48, Total number of suspected toenails=1  | 10.36 | 11.57 | 8.00  |  |
| Week 48, Total number of suspected toenails=2  | 21.57 | 19.28 | 24.00 |  |
| Week 48, Total number of suspected toenails=3  | 9.80  | 10.74 | 10.40 |  |
| Week 48, Total number of suspected toenails=4  | 10.08 | 13.22 | 17.60 |  |
| Week 48, Total number of suspected toenails=5  | 8.40  | 9.64  | 4.00  |  |
| Week 48, Total number of suspected toenails=6  | 9.24  | 7.71  | 8.80  |  |
| Week 48, Total number of suspected toenails=7  | 6.44  | 5.51  | 6.40  |  |
| Week 48, Total number of suspected toenails=8  | 5.04  | 7.16  | 8.80  |  |
| Week 48, Total number of suspected toenails=9  | 2.52  | 1.93  | 2.40  |  |
| Week 48, Total number of suspected toenails=10 | 10.64 | 8.54  | 7.20  |  |
| Week 60, Total number of suspected toenails=0  | 8.31  | 5.70  | 2.50  |  |
| Week 60, Total number of suspected toenails=1  | 12.32 | 12.54 | 9.17  |  |

|  |       |       |       |  |
|--|-------|-------|-------|--|
| Week 60, Total number of suspected toenails=2      | 20.06 | 19.37 | 25.83 |  |
| Week 60, Total number of suspected toenails=3      | 9.46  | 9.69  | 5.00  |  |
| Week 60, Total number of suspected toenails=4      | 11.46 | 13.96 | 20.83 |  |
| Week 60, Total number of suspected toenails=5      | 6.88  | 7.41  | 9.17  |  |
| Week 60, Total number of suspected toenails=6      | 8.88  | 9.12  | 7.50  |  |
| Week 60, Total number of suspected toenails=7      | 4.87  | 7.98  | 2.50  |  |
| Week 60, Total number of suspected toenails=8      | 5.16  | 4.84  | 8.33  |  |
| Week 60, Total number of suspected toenails=9      | 2.58  | 1.42  | 1.67  |  |
| Week 60, Total number of suspected toenails=10     | 10.03 | 7.98  | 7.50  |  |
| Discont.Visit,Total number of suspected toenails=0 | 0.00  | 0.00  | 14.29 |  |
| Discont.Visit,Total number of suspected toenails=1 | 9.09  | 5.26  | 0.00  |  |
| Discont.Visit,Total number of suspected toenails=2 | 22.73 | 10.53 | 14.29 |  |
| Discont.Visit,Total number of suspected toenails=3 | 18.18 | 21.05 | 14.29 |  |
| Discont.Visit,Total number of suspected toenails=4 | 4.55  | 10.53 | 14.29 |  |
| Discont.Visit,Total number of suspected toenails=5 | 4.55  | 21.05 | 0.00  |  |
| Discont.Visit,Total number of suspected toenails=7 | 9.09  | 5.26  | 28.57 |  |
| Discont.Visit,Total number of suspected toenails=8 | 18.18 | 5.26  | 14.29 |  |
| Discont.Visit,Total number of suspected toenails=9 | 4.55  | 10.53 | 0.00  |  |
| Discont.Visit,Total number of suspected toenail=10 | 9.09  | 10.53 | 0.00  |  |
| Week 4, Total number of suspected fingernails=0    | 94.00 | 91.60 | 93.38 |  |
| Week 4, Total number of suspected fingernails=1    | 3.75  | 5.19  | 2.94  |  |
| Week 4, Total number of suspected fingernails=2    | 2.00  | 2.72  | 2.94  |  |
| Week 4, Total number of suspected fingernails=3    | 0.00  | 0.00  | 0.74  |  |
| Week 4, Total number of suspected fingernails=4    | 0.00  | 0.25  | 0.00  |  |
| Week 4, Total number of suspected fingernails=5    | 0.25  | 0.25  | 0.00  |  |
| Week 12, Total number of suspected fingernails=0   | 94.03 | 92.17 | 93.18 |  |
| Week 12, Total number of suspected fingernails=1   | 3.64  | 5.05  | 3.79  |  |
| Week 12, Total number of suspected fingernails=2   | 2.08  | 2.53  | 2.27  |  |
| Week 12, Total number of suspected fingernails=3   | 0.00  | 0.00  | 0.76  |  |
| Week 12, Total number of suspected fingernails=5   | 0.26  | 0.25  | 0.00  |  |
| Week 24, Total number of suspected fingernails=0   | 94.35 | 92.75 | 93.13 |  |

|  |       |        |        |  |
|--|-------|--------|--------|--|
| Week 24, Total number of suspected fingernails=1   | 3.49  | 4.15   | 3.82   |  |
| Week 24, Total number of suspected fingernails=2   | 1.88  | 2.59   | 2.29   |  |
| Week 24, Total number of suspected fingernails=3   | 0.00  | 0.26   | 0.76   |  |
| Week 24, Total number of suspected fingernails=5   | 0.27  | 0.26   | 0.00   |  |
| Week 36, Total number of suspected fingernails=0   | 96.17 | 93.57  | 94.53  |  |
| Week 36, Total number of suspected fingernails=1   | 2.46  | 3.49   | 3.13   |  |
| Week 36, Total number of suspected fingernails=2   | 1.09  | 2.41   | 1.56   |  |
| Week 36, Total number of suspected fingernails=3   | 0.00  | 0.27   | 0.78   |  |
| Week 36, Total number of suspected fingernails=5   | 0.27  | 0.27   | 0.00   |  |
| Week 48, Total number of suspected fingernails=0   | 97.20 | 93.94  | 95.20  |  |
| Week 48, Total number of suspected fingernails=1   | 1.96  | 3.86   | 4.00   |  |
| Week 48, Total number of suspected fingernails=2   | 0.56  | 1.65   | 0.80   |  |
| Week 48, Total number of suspected fingernails=3   | 0.00  | 0.28   | 0.00   |  |
| Week 48, Total number of suspected fingernails=5   | 0.28  | 0.28   | 0.00   |  |
| Week 60, Total number of suspected fingernails=0   | 98.85 | 96.58  | 98.33  |  |
| Week 60, Total number of suspected fingernails=1   | 0.57  | 2.28   | 1.67   |  |
| Week 60, Total number of suspected fingernails=2   | 0.29  | 1.14   | 0.00   |  |
| Week 60, Total number of suspected fingernails=5   | 0.29  | 0.00   | 0.00   |  |
| Discont.Visit,Total number suspected fingernails=0 | 95.45 | 100.00 | 100.00 |  |
| Discont.Visit,Total number suspected fingernails=3 | 4.55  | 0.00   | 0.00   |  |

## Statistical analyses

No statistical analyses for this end point

## Other pre-specified: Dermatological Assessment - Percentage of Subjects With Location of Toenails (Right and Left Foot) and Fingernails (Right and Left Hand) With Suspected Onychomycosis, Present at Weeks 4, 12, 36, 48, 60, and Discontinuation Visit - Observed Data

|                 |  |
|-----------------|--|
| End point title | Dermatological Assessment - Percentage of Subjects With Location of Toenails (Right and Left Foot) and Fingernails (Right and Left Hand) With Suspected Onychomycosis, Present at Weeks 4, 12, 36, 48, 60, and Discontinuation Visit - Observed Data |
|-----------------|--|

End point description:

Dermatological assessments was defined to be assessed through percentage of subjects with right or left target big toenail, percentage of affected area of the target big toenail (according to the Investigator's clinical evaluation), number of toenails/fingernails present per subject (as categorical

term), number of toenails/fingernails with suspected onychomycosis per subject (as categorical term) and location of toenails/fingernails with suspected onychomycosis are summarized by treatment. The data for this end point reported location of toenails in right and left foot and fingernails in right and left hand, with suspected onychomycosis. Analysis was done on ITT population.

|  |                     |
|--|---------------------|
| End point type                                 | Other pre-specified |
| End point timeframe:                           |                     |
| Weeks 4, 12, 36, 48, 60; Discontinuation Visit |                     |

| <b>End point values</b>          | P-3058 10%      | Vehicle         | Amorolfine      |  |
|----------------------------------|-----------------|-----------------|-----------------|--|
| Subject group type               | Reporting group | Reporting group | Reporting group |  |
| Number of subjects analysed      | 406             | 410             | 137             |  |
| Units: percentage of subjects    |                 |                 |                 |  |
| number (not applicable)          |                 |                 |                 |  |
| Week 4, Right foot- 1st toenail  | 88.50           | 90.62           | 87.50           |  |
| Week 4, Right foot- 2nd toenail  | 35.50           | 33.58           | 39.71           |  |
| Week 4, Right foot- 3rd toenail  | 30.00           | 32.35           | 32.35           |  |
| Week 4, Right foot- 4th toenail  | 35.00           | 35.31           | 37.50           |  |
| Week 4, Right foot- 5th toenail  | 50.25           | 48.64           | 52.94           |  |
| Week 4, Left foot- 1st toenail   | 90.00           | 88.64           | 88.24           |  |
| Week 4, Left foot- 2nd toenail   | 35.50           | 33.58           | 33.82           |  |
| Week 4, Left foot- 3rd toenail   | 35.00           | 30.37           | 32.35           |  |
| Week 4, Left foot- 4th toenail   | 35.00           | 32.35           | 30.88           |  |
| Week 4, Left foot- 5th toenail   | 49.50           | 47.41           | 50.74           |  |
| Week 12, Right foot- 1st toenail | 87.53           | 89.17           | 88.72           |  |
| Week 12, Right foot- 2nd toenail | 36.36           | 33.50           | 37.59           |  |
| Week 12, Right foot- 3rd toenail | 29.61           | 32.24           | 32.33           |  |
| Week 12, Right foot- 4th toenail | 34.29           | 35.26           | 37.59           |  |
| Week 12, Right foot- 5th toenail | 50.65           | 48.61           | 49.62           |  |
| Week 12, Left foot- 1st toenail  | 87.79           | 87.91           | 87.22           |  |
| Week 12, Left foot- 2nd toenail  | 35.84           | 30.73           | 31.58           |  |
| Week 12, Left foot- 3rd toenail  | 33.51           | 30.48           | 32.33           |  |
| Week 12, Left foot- 4th toenail  | 35.58           | 31.99           | 33.08           |  |
| Week 12, Left foot- 5th toenail  | 49.61           | 46.10           | 50.38           |  |
| Week 24, Right foot- 1st toenail | 85.25           | 88.08           | 89.31           |  |
| Week 24, Right foot- 2nd toenail | 35.39           | 31.09           | 32.82           |  |
| Week 24, Right foot- 3rd toenail | 29.49           | 30.57           | 32.82           |  |
| Week 24, Right foot- 4th toenail | 35.39           | 32.64           | 41.22           |  |
| Week 24, Right foot- 5th toenail | 49.06           | 47.67           | 49.62           |  |
| Week 24, Left foot- 1st toenail  | 86.86           | 87.31           | 86.26           |  |
| Week 24, Left foot- 2nd toenail  | 34.58           | 29.02           | 28.24           |  |
| Week 24, Left foot- 3rd toenail  | 32.98           | 27.98           | 31.30           |  |
| Week 24, Left foot- 4th toenail  | 35.12           | 31.61           | 31.30           |  |
| Week 24, Left foot- 5th toenail  | 47.72           | 44.56           | 48.85           |  |
| Week 36, Right foot- 1st toenail | 83.88           | 85.29           | 89.06           |  |
| Week 36, Right foot- 2nd toenail | 34.43           | 31.28           | 33.59           |  |
| Week 36, Right foot- 3rd toenail | 28.69           | 29.95           | 30.47           |  |
| Week 36, Right foot- 4th toenail | 34.70           | 32.35           | 39.84           |  |
| Week 36, Right foot- 5th toenail | 47.27           | 45.72           | 50.00           |  |
| Week 36, Left foot- 1st toenail  | 85.25           | 86.36           | 84.38           |  |

|  |       |       |       |  |
|--|-------|-------|-------|--|
| Week 36, Left foot- 2nd toenail                | 33.88 | 29.14 | 27.34 |  |
| Week 36, Left foot- 3rd toenail                | 30.87 | 25.94 | 32.81 |  |
| Week 36, Left foot- 4th toenail                | 36.61 | 29.68 | 33.59 |  |
| Week 36, Left foot- 5th toenail                | 46.99 | 44.92 | 46.88 |  |
| Week 48, Right foot- 1st toenail               | 82.63 | 84.07 | 86.51 |  |
| Week 48, Right foot- 2nd toenail               | 31.65 | 31.32 | 32.54 |  |
| Week 48, Right foot- 3rd toenail               | 27.17 | 27.20 | 26.19 |  |
| Week 48, Right foot- 4th toenail               | 30.81 | 29.95 | 35.71 |  |
| Week 48, Right foot- 5th toenail               | 45.38 | 45.05 | 43.65 |  |
| Week 48, Left foot- 1st toenail                | 82.91 | 83.24 | 83.33 |  |
| Week 48, Left foot- 2nd toenail                | 30.53 | 29.12 | 25.40 |  |
| Week 48, Left foot- 3rd toenail                | 27.17 | 23.90 | 27.78 |  |
| Week 48, Left foot- 4th toenail                | 32.77 | 28.30 | 31.75 |  |
| Week 48, Left foot- 5th toenail                | 44.26 | 45.05 | 42.86 |  |
| Week 60, Right foot- 1st toenail               | 78.51 | 82.72 | 85.83 |  |
| Week 60, Right foot- 2nd toenail               | 30.09 | 29.18 | 30.83 |  |
| Week 60, Right foot- 3rd toenail               | 26.36 | 24.08 | 25.00 |  |
| Week 60, Right foot- 4th toenail               | 29.80 | 29.75 | 36.67 |  |
| Week 60, Right foot- 5th toenail               | 41.83 | 45.04 | 46.67 |  |
| Week 60, Left foot- 1st toenail                | 78.80 | 81.30 | 81.67 |  |
| Week 60, Left foot- 2nd toenail                | 28.37 | 27.48 | 23.33 |  |
| Week 60, Left foot- 3rd toenail                | 26.65 | 22.38 | 23.33 |  |
| Week 60, Left foot- 4th toenail                | 30.09 | 26.63 | 30.00 |  |
| Week 60, Left foot- 5th toenail                | 42.69 | 44.19 | 40.83 |  |
| Discontinuation Visit, Right foot- 1st toenail | 74.07 | 57.14 | 50.00 |  |
| Discontinuation Visit, Right foot- 2nd toenail | 25.93 | 25.00 | 12.50 |  |
| Discontinuation Visit, Right foot- 3rd toenail | 22.22 | 28.57 | 37.50 |  |
| Discontinuation Visit, Right foot- 4th toenail | 33.33 | 32.14 | 37.50 |  |
| Discontinuation Visit, Right foot- 5th toenail | 44.44 | 39.29 | 50.00 |  |
| Discontinuation Visit, Left foot- 1st toenail  | 77.78 | 57.14 | 75.00 |  |
| Discontinuation Visit, Left foot- 2nd toenail  | 22.22 | 21.43 | 25.00 |  |
| Discontinuation Visit, Left foot- 3rd toenail  | 22.22 | 32.14 | 37.50 |  |
| Discontinuation Visit, Left foot- 4th toenail  | 33.33 | 25.00 | 25.00 |  |
| Discontinuation Visit, Left foot- 5th toenail  | 44.44 | 32.14 | 37.50 |  |
| Week 4, Right hand- 1st fingernail             | 1.75  | 4.94  | 2.94  |  |
| Week 4, Right hand- 2nd fingernail             | 1.50  | 1.48  | 0.74  |  |
| Week 4, Right hand- 3rd fingernail             | 0.50  | 1.23  | 1.47  |  |
| Week 4, Right hand- 4th fingernail             | 0.00  | 0.49  | 1.47  |  |
| Week 4, Right hand- 5th fingernail             | 0.00  | 0.74  | 0.00  |  |
| Week 4, Left hand- 1st fingernail              | 2.25  | 1.48  | 3.68  |  |
| Week 4, Left hand- 2nd fingernail              | 0.75  | 0.99  | 0.00  |  |
| Week 4, Left hand- 3rd fingernail              | 0.50  | 0.99  | 0.74  |  |
| Week 4, Left hand- 4th fingernail              | 1.25  | 0.25  | 0.00  |  |
| Week 4, Left hand- 5th fingernail              | 0.50  | 0.25  | 0.00  |  |
| Week 12, Right hand- 1st fingernail            | 1.82  | 4.53  | 3.76  |  |

|   |      |      |      |  |
|---|------|------|------|--|
| Week 12, Right hand- 2nd fingernail               | 1.30 | 1.51 | 0.75 |  |
| Week 12, Right hand- 3rd fingernail               | 0.52 | 1.01 | 0.75 |  |
| Week 12, Right hand- 4th fingernail               | 0.00 | 0.50 | 0.00 |  |
| Week 12, Right hand- 5th fingernail               | 0.00 | 0.50 | 0.00 |  |
| Week 12, Left hand- 1st fingernail                | 2.08 | 1.51 | 3.76 |  |
| Week 12, Left hand- 2nd fingernail                | 0.78 | 1.01 | 0.00 |  |
| Week 12, Left hand- 3rd fingernail                | 0.52 | 0.76 | 0.75 |  |
| Week 12, Left hand- 4th fingernail                | 1.30 | 0.00 | 0.75 |  |
| Week 12, Left hand- 5th fingernail                | 0.78 | 0.00 | 0.00 |  |
| Week 24, Right hand- 1st fingernail               | 1.61 | 4.40 | 3.82 |  |
| Week 24, Right hand- 2nd fingernail               | 1.34 | 1.30 | 0.76 |  |
| Week 24, Right hand- 3rd fingernail               | 0.54 | 1.04 | 0.76 |  |
| Week 24, Right hand- 4th fingernail               | 0.00 | 0.52 | 0.76 |  |
| Week 24, Right hand- 5th fingernail               | 0.00 | 0.78 | 0.00 |  |
| Week 24, Left hand- 1st fingernail                | 2.14 | 1.55 | 3.82 |  |
| Week 24, Left hand- 2nd fingernail                | 0.80 | 1.30 | 0.00 |  |
| Week 24, Left hand- 3rd fingernail                | 0.54 | 0.52 | 0.76 |  |
| Week 24, Left hand- 4th fingernail                | 1.07 | 0.00 | 0.00 |  |
| Week 24, Left hand- 5th fingernail                | 0.54 | 0.00 | 0.00 |  |
| Week 36, Right hand- 1st fingernail               | 0.82 | 4.01 | 2.34 |  |
| Week 36, Right hand- 2nd fingernail               | 1.09 | 1.07 | 0.78 |  |
| Week 36, Right hand- 3rd fingernail               | 0.55 | 0.80 | 0.78 |  |
| Week 36, Right hand- 4th fingernail               | 0.00 | 0.53 | 0.78 |  |
| Week 36, Right hand- 5th fingernail               | 0.00 | 0.80 | 0.00 |  |
| Week 36, Left hand- 1st fingernail                | 1.09 | 1.87 | 3.13 |  |
| Week 36, Left hand- 2nd fingernail                | 0.55 | 0.80 | 0.00 |  |
| Week 36, Left hand- 3rd fingernail                | 0.27 | 0.53 | 0.78 |  |
| Week 36, Left hand- 4th fingernail                | 1.09 | 0.00 | 0.00 |  |
| Week 36, Left hand- 5th fingernail                | 0.55 | 0.00 | 0.00 |  |
| Week 48, Right hand- 1st fingernail               | 0.00 | 3.57 | 1.59 |  |
| Week 48, Right hand- 2nd fingernail               | 1.12 | 1.65 | 0.79 |  |
| Week 48, Right hand- 3rd fingernail               | 0.28 | 0.82 | 0.79 |  |
| Week 48, Right hand- 4th fingernail               | 0.00 | 0.55 | 0.00 |  |
| Week 48, Right hand- 5th fingernail               | 0.00 | 0.82 | 0.00 |  |
| Week 48, Left hand- 1st fingernail                | 1.12 | 1.37 | 2.38 |  |
| Week 48, Left hand- 2nd fingernail                | 0.28 | 0.27 | 0.00 |  |
| Week 48, Left hand- 3rd fingernail                | 0.28 | 0.27 | 0.00 |  |
| Week 48, Left hand- 4th fingernail                | 0.84 | 0.00 | 0.00 |  |
| Week 48, Left hand- 5th fingernail                | 0.56 | 0.00 | 0.00 |  |
| Week 60, Right hand- 1st fingernail               | 0.00 | 2.55 | 0.83 |  |
| Week 60, Right hand- 2nd fingernail               | 0.29 | 0.57 | 0.00 |  |
| Week 60, Right hand- 5th fingernail               | 0.00 | 0.28 | 0.00 |  |
| Week 60, Left hand- 1st fingernail                | 0.29 | 0.28 | 0.83 |  |
| Week 60, Left hand- 2nd fingernail                | 0.29 | 0.57 | 0.00 |  |
| Week 60, Left hand- 3rd fingernail                | 0.29 | 0.28 | 0.00 |  |
| Week 60, Left hand- 4th fingernail                | 0.86 | 0.00 | 0.00 |  |
| Week 60, Left hand- 5th fingernail                | 0.57 | 0.00 | 0.00 |  |
| Discontinuation Visit, Right hand- 1st fingernail | 3.70 | 0.00 | 0.00 |  |
| Discontinuation Visit, Left hand- 1st fingernail  | 3.70 | 0.00 | 0.00 |  |
| Discontinuation Visit, Left hand- 2nd fingernail  | 3.70 | 0.00 | 0.00 |  |

## **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From Baseline (Week 0) up to Week 60/Discontinuation visit

Adverse event reporting additional description:

All AEs (TEAEs, non-TEAEs, and serious AEs) which occurred during the study period were recorded. TEAE was defined as those AE with an onset date after at least treatment initiation and non-TEAE was defined as AE with onset date between signed informed consent form and treatment initiation, during study. Analysis was performed on Safety population.

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |            |
|-----------------------|------------|
| Reporting group title | P-3058 10% |
|-----------------------|------------|

Reporting group description:

Subjects applied P-3058 10% nail solution topically, once daily for first 4 weeks and then once weekly for the remaining 44 weeks on all dry nails with suspected onychomycosis.

|                       |         |
|-----------------------|---------|
| Reporting group title | Vehicle |
|-----------------------|---------|

Reporting group description:

Subjects applied Vehicle of the P-3058 10% nail solution topically, once daily for the first 4 weeks and then once weekly for the remaining 44 weeks on all dry nails with suspected onychomycosis.

|                       |            |
|-----------------------|------------|
| Reporting group title | Amorolfine |
|-----------------------|------------|

Reporting group description:

Subjects applied Amorolfine topically, once weekly for 48 weeks on all dry nails with suspected onychomycosis.

| <b>Serious adverse events</b>                                       | P-3058 10%       | Vehicle          | Amorolfine      |
|---|------------------|------------------|-----------------|
| Total subjects affected by serious adverse events                   |                  |                  |                 |
| subjects affected / exposed   | 21 / 406 (5.17%) | 22 / 407 (5.41%) | 9 / 137 (6.57%) |
| number of deaths (all causes)                                       | 2                | 0                | 0               |
| number of deaths resulting from adverse events                      | 0                | 0                | 0               |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                  |                  |                 |
| Basal cell carcinoma  |                  |                  |                 |
| subjects affected / exposed   | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (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           |
| Breast cancer   |                  |                  |                 |
| subjects affected / exposed   | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (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           |
| Gastric cancer  |                  |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Malignant melanoma</b>                       |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Pancreatic carcinoma</b>                     |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Prostate cancer</b>                          |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Prostate cancer recurrent</b>                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Surgical and medical procedures</b>          |                 |                 |                 |
| <b>Catheter management</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Hysterectomy</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Knee arthroplasty</b>                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Nasal septal operation</b>                   |                 |                 |                 |

|  |                 |                 |                 |
|--|-----------------|-----------------|-----------------|
| subjects affected / exposed                            | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Oophorectomy</b>                                    |                 |                 |                 |
| subjects affected / exposed                            | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Pelvic floor repair</b>                             |                 |                 |                 |
| subjects affected / exposed                            | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Tonsillectomy</b>                                   |                 |                 |                 |
| subjects affected / exposed                            | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Vitrectomy</b>                                      |                 |                 |                 |
| subjects affected / exposed                            | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Reproductive system and breast disorders</b>        |                 |                 |                 |
| <b>Ovarian disorder</b>                                |                 |                 |                 |
| subjects affected / exposed                            | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Respiratory, thoracic and mediastinal disorders</b> |                 |                 |                 |
| <b>Sleep apnoea syndrome</b>                           |                 |                 |                 |
| subjects affected / exposed                            | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Investigations</b>                                  |                 |                 |                 |
| Prostatic specific antigen increased                   |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                           | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Injury, poisoning and procedural complications</b> |                 |                 |                 |
| <b>Ankle fracture</b>                                 |                 |                 |                 |
| subjects affected / exposed                           | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Cervical vertebral fracture</b>                    |                 |                 |                 |
| subjects affected / exposed                           | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Humerus fracture</b>                               |                 |                 |                 |
| subjects affected / exposed                           | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Intestinal anastomosis complication</b>            |                 |                 |                 |
| subjects affected / exposed                           | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Joint dislocation</b>                              |                 |                 |                 |
| subjects affected / exposed                           | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Joint injury</b>                                   |                 |                 |                 |
| subjects affected / exposed                           | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Ligament rupture</b>                               |                 |                 |                 |
| subjects affected / exposed                           | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Lumbar vertebral fracture</b>                      |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Tendon rupture</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Thermal burn</b>                             |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Wound</b>                                    |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Cardiac disorders</b>                        |                 |                 |                 |
| <b>Arrhythmia</b>                               |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Atrial fibrillation</b>                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 2 / 137 (1.46%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           | 0 / 2           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Coronary artery disease</b>                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Nervous system disorders</b>                 |                 |                 |                 |
| <b>Cerebrovascular accident</b>                 |                 |                 |                 |
| subjects affected / exposed                     | 2 / 406 (0.49%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           | 0 / 0           |
| <b>Encephalopathy</b>                           |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Neuropathy peripheral</b>                    |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Polyneuropathy chronic</b>                   |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Transient ischaemic attack</b>               |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastrointestinal disorders</b>               |                 |                 |                 |
| <b>Colitis</b>                                  |                 |                 |                 |
| subjects affected / exposed                     | 2 / 406 (0.49%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Food poisoning</b>                           |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| <b>Gastric ulcer haemorrhage</b>                |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| <b>Gastrointestinal inflammation</b>            |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| <b>Pancreatitis acute</b>                       |                 |                 |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| Peptic ulcer perforation                        |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| Renal and urinary disorders                     |                 |                 |                 |
| Chronic kidney disease                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| Haematuria                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| Nephrolithiasis                                 |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| Musculoskeletal and connective tissue disorders |                 |                 |                 |
| Intervertebral disc protrusion                  |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Lumbar spinal stenosis                          |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| Osteoarthritis                                  |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| Spinal pain                                     |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           | 0 / 0           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Infections and infestations                     |                 |                 |                 |
| Erysipelas                                      |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (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           |
| Pneumonia                                       |                 |                 |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 0           | 0 / 1           |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           | 0 / 0           |
| Viral rash                                      |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |
| Metabolism and nutrition disorders              |                 |                 |                 |
| Type 2 diabetes mellitus                        |                 |                 |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (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           |

Frequency threshold for reporting non-serious adverse events: 0 %

| <b>Non-serious adverse events</b>                                   | P-3058 10%         | Vehicle            | Amorolfine        |
|---|--------------------|--------------------|-------------------|
| Total subjects affected by non-serious adverse events               |                    |                    |                   |
| subjects affected / exposed   | 166 / 406 (40.89%) | 187 / 407 (45.95%) | 62 / 137 (45.26%) |
| Neoplasms benign, malignant and unspecified (incl cysts and polyps) |                    |                    |                   |
| Basal cell carcinoma  |                    |                    |                   |
| subjects affected / exposed   | 0 / 406 (0.00%)    | 3 / 407 (0.74%)    | 0 / 137 (0.00%)   |
| occurrences (all)   | 0                  | 3                  | 0                 |
| Breast cancer   |                    |                    |                   |
| subjects affected / exposed   | 1 / 406 (0.25%)    | 0 / 407 (0.00%)    | 0 / 137 (0.00%)   |
| occurrences (all)   | 1                  | 0                  | 0                 |

|                             |                 |                  |                 |
|-----------------------------|-----------------|------------------|-----------------|
| Haemangioma                 |                 |                  |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1                | 0               |
| Haemangioma of liver        |                 |                  |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1                | 0               |
| Malignant melanoma          |                 |                  |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%)  | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0                | 1               |
| Pancreatic carcinoma        |                 |                  |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1                | 0               |
| Prostate cancer             |                 |                  |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%)  | 2 / 137 (1.46%) |
| occurrences (all)           | 0               | 0                | 2               |
| Skin papilloma              |                 |                  |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 1 / 407 (0.25%)  | 2 / 137 (1.46%) |
| occurrences (all)           | 3               | 1                | 2               |
| Thyroid neoplasm            |                 |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0                | 0               |
| Vascular disorders          |                 |                  |                 |
| Haematoma                   |                 |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 1                | 0               |
| Haemorrhage                 |                 |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0                | 0               |
| Hot flush                   |                 |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0                | 0               |
| Hypertension                |                 |                  |                 |
| subjects affected / exposed | 8 / 406 (1.97%) | 14 / 407 (3.44%) | 4 / 137 (2.92%) |
| occurrences (all)           | 8               | 14               | 4               |
| Hypertensive crisis         |                 |                  |                 |

|                                 |                 |                 |                 |
|---------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed     | 1 / 406 (0.25%) | 3 / 407 (0.74%) | 0 / 137 (0.00%) |
| occurrences (all)               | 1               | 3               | 0               |
| Peripheral venous disease       |                 |                 |                 |
| subjects affected / exposed     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)               | 1               | 0               | 0               |
| Phlebitis                       |                 |                 |                 |
| subjects affected / exposed     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)               | 0               | 0               | 1               |
| Phlebitis superficial           |                 |                 |                 |
| subjects affected / exposed     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Thrombosis                      |                 |                 |                 |
| subjects affected / exposed     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Varicose vein                   |                 |                 |                 |
| subjects affected / exposed     | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)               | 1               | 1               | 0               |
| Surgical and medical procedures |                 |                 |                 |
| Blepharoplasty                  |                 |                 |                 |
| subjects affected / exposed     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Cataract operation              |                 |                 |                 |
| subjects affected / exposed     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)               | 2               | 0               | 0               |
| Cholecystectomy                 |                 |                 |                 |
| subjects affected / exposed     | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)               | 0               | 1               | 0               |
| Neoplasm prophylaxis            |                 |                 |                 |
| subjects affected / exposed     | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)               | 1               | 0               | 0               |
| Shoulder operation              |                 |                 |                 |
| subjects affected / exposed     | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)               | 0               | 0               | 1               |
| Skin neoplasm excision          |                 |                 |                 |
| subjects affected / exposed     | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences (all)               | 1               | 1               | 1               |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| Toe operation<br>subjects affected / exposed<br>occurrences (all)   | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Tooth extraction<br>subjects affected / exposed<br>occurrences (all)  | 1 / 406 (0.25%)<br>1 | 1 / 407 (0.25%)<br>1 | 1 / 137 (0.73%)<br>1 |
| Tooth repair<br>subjects affected / exposed<br>occurrences (all)  | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Varicose vein operation<br>subjects affected / exposed<br>occurrences (all)   | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Pregnancy, puerperium and perinatal conditions<br>Pregnancy<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| General disorders and administration site conditions<br>Application site pain<br>subjects affected / exposed<br>occurrences (all) | 2 / 406 (0.49%)<br>2 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Asthenia<br>subjects affected / exposed<br>occurrences (all)  | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Chest discomfort<br>subjects affected / exposed<br>occurrences (all)  | 1 / 406 (0.25%)<br>1 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>3 | 0 / 137 (0.00%)<br>0 |
| Chills<br>subjects affected / exposed<br>occurrences (all)  | 1 / 406 (0.25%)<br>3 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)   | 5 / 406 (1.23%)<br>8 | 5 / 407 (1.23%)<br>5 | 0 / 137 (0.00%)<br>0 |
| Impaired healing  |                      |                      |                      |

|   |                      |                      |                      |
|---|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)  | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Influenza like illness<br>subjects affected / exposed<br>occurrences (all)  | 0 / 406 (0.00%)<br>0 | 2 / 407 (0.49%)<br>2 | 1 / 137 (0.73%)<br>1 |
| Malaise<br>subjects affected / exposed<br>occurrences (all)   | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)   | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Pain<br>subjects affected / exposed<br>occurrences (all)  | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Pyrexia<br>subjects affected / exposed<br>occurrences (all)   | 3 / 406 (0.74%)<br>4 | 2 / 407 (0.49%)<br>2 | 1 / 137 (0.73%)<br>1 |
| Immune system disorders<br>Seasonal allergy<br>subjects affected / exposed<br>occurrences (all)                                 | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Social circumstances<br>Family stress<br>subjects affected / exposed<br>occurrences (all)                                       | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Reproductive system and breast<br>disorders<br>Benign prostatic hyperplasia<br>subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 1 / 407 (0.25%)<br>1 | 1 / 137 (0.73%)<br>1 |
| Dysmenorrhoea<br>subjects affected / exposed<br>occurrences (all)   | 2 / 406 (0.49%)<br>6 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Uterine disorder<br>subjects affected / exposed<br>occurrences (all)  | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Uterine polyp   |                      |                      |                      |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)   | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| <b>Respiratory, thoracic and mediastinal disorders</b>                                   |                      |                      |                      |
| Acute respiratory failure<br>subjects affected / exposed<br>occurrences (all)            | 1 / 406 (0.25%)<br>2 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Asthma<br>subjects affected / exposed<br>occurrences (all)                               | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 1 / 137 (0.73%)<br>1 |
| Cough<br>subjects affected / exposed<br>occurrences (all)                                | 2 / 406 (0.49%)<br>2 | 5 / 407 (1.23%)<br>5 | 2 / 137 (1.46%)<br>2 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)                             | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Oropharyngeal pain<br>subjects affected / exposed<br>occurrences (all)                   | 1 / 406 (0.25%)<br>2 | 3 / 407 (0.74%)<br>3 | 2 / 137 (1.46%)<br>2 |
| Rhinitis allergic<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 406 (0.25%)<br>1 | 2 / 407 (0.49%)<br>2 | 0 / 137 (0.00%)<br>0 |
| Rhinorrhoea<br>subjects affected / exposed<br>occurrences (all)                          | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Sleep apnoea syndrome<br>subjects affected / exposed<br>occurrences (all)                | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Upper respiratory tract inflammation<br>subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| <b>Psychiatric disorders</b>   |                      |                      |                      |
| Anxiety<br>subjects affected / exposed<br>occurrences (all)                              | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Depressed mood   |                      |                      |                      |

|                                    |                 |                 |                 |
|------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed        | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)                  | 0               | 0               | 1               |
| Depression                         |                 |                 |                 |
| subjects affected / exposed        | 3 / 406 (0.74%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                  | 4               | 0               | 0               |
| Drug dependence                    |                 |                 |                 |
| subjects affected / exposed        | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                  | 0               | 1               | 0               |
| Insomnia                           |                 |                 |                 |
| subjects affected / exposed        | 2 / 406 (0.49%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences (all)                  | 2               | 2               | 1               |
| Loss of libido                     |                 |                 |                 |
| subjects affected / exposed        | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                  | 0               | 1               | 0               |
| Sleep disorder                     |                 |                 |                 |
| subjects affected / exposed        | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Hepatobiliary disorders            |                 |                 |                 |
| Cholecystitis                      |                 |                 |                 |
| subjects affected / exposed        | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Gallbladder polyp                  |                 |                 |                 |
| subjects affected / exposed        | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Hepatic function abnormal          |                 |                 |                 |
| subjects affected / exposed        | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)                  | 0               | 0               | 1               |
| Hepatic steatosis                  |                 |                 |                 |
| subjects affected / exposed        | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                  | 1               | 0               | 0               |
| Hyperbilirubinaemia                |                 |                 |                 |
| subjects affected / exposed        | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                  | 1               | 1               | 0               |
| Investigations                     |                 |                 |                 |
| Alanine aminotransferase increased |                 |                 |                 |

|                                      |                 |                 |                 |
|--------------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed          | 5 / 406 (1.23%) | 4 / 407 (0.98%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 5               | 4               | 0               |
| Aspartate aminotransferase increased |                 |                 |                 |
| subjects affected / exposed          | 4 / 406 (0.99%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 4               | 0               | 0               |
| Bilirubin conjugated increased       |                 |                 |                 |
| subjects affected / exposed          | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Blood cholesterol increased          |                 |                 |                 |
| subjects affected / exposed          | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 1               | 1               | 0               |
| Blood creatinine increased           |                 |                 |                 |
| subjects affected / exposed          | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 1               | 1               | 0               |
| Blood glucose abnormal               |                 |                 |                 |
| subjects affected / exposed          | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)                    | 0               | 0               | 1               |
| Blood glucose increased              |                 |                 |                 |
| subjects affected / exposed          | 6 / 406 (1.48%) | 5 / 407 (1.23%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 7               | 5               | 0               |
| Blood potassium increased            |                 |                 |                 |
| subjects affected / exposed          | 1 / 406 (0.25%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 1               | 2               | 0               |
| Blood pressure increased             |                 |                 |                 |
| subjects affected / exposed          | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences (all)                    | 0               | 2               | 1               |
| Blood uric acid increased            |                 |                 |                 |
| subjects affected / exposed          | 1 / 406 (0.25%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 1               | 2               | 0               |
| Cardiac murmur                       |                 |                 |                 |
| subjects affected / exposed          | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |
| Crystal urine present                |                 |                 |                 |
| subjects affected / exposed          | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                    | 1               | 0               | 0               |

|   |                        |                      |                      |
|---|------------------------|----------------------|----------------------|
| Eosinophil count increased<br>subjects affected / exposed<br>occurrences (all)          | 1 / 406 (0.25%)<br>1   | 2 / 407 (0.49%)<br>2 | 0 / 137 (0.00%)<br>0 |
| Gamma-glutamyltransferase increased<br>subjects affected / exposed<br>occurrences (all) | 10 / 406 (2.46%)<br>12 | 4 / 407 (0.98%)<br>4 | 1 / 137 (0.73%)<br>1 |
| Haemoglobin urine<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 406 (0.49%)<br>2   | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Haemoglobin urine present<br>subjects affected / exposed<br>occurrences (all)           | 1 / 406 (0.25%)<br>1   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Hepatic enzyme increased<br>subjects affected / exposed<br>occurrences (all)            | 1 / 406 (0.25%)<br>1   | 4 / 407 (0.98%)<br>4 | 1 / 137 (0.73%)<br>1 |
| Liver function test abnormal<br>subjects affected / exposed<br>occurrences (all)        | 1 / 406 (0.25%)<br>1   | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Lymphocyte count decreased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 406 (0.00%)<br>0   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Monocyte count increased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 406 (0.00%)<br>0   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Neutrophil count increased<br>subjects affected / exposed<br>occurrences (all)          | 0 / 406 (0.00%)<br>0   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Platelet count decreased<br>subjects affected / exposed<br>occurrences (all)            | 0 / 406 (0.00%)<br>0   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Protein urine present<br>subjects affected / exposed<br>occurrences (all)               | 1 / 406 (0.25%)<br>1   | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Red blood cells urine positive  |                        |                      |                      |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                                     | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Urine analysis abnormal<br>subjects affected / exposed<br>occurrences (all)          | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Weight decreased<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| White blood cell count decreased<br>subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| White blood cell count increased<br>subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| White blood cells urine positive<br>subjects affected / exposed<br>occurrences (all) | 2 / 406 (0.49%)<br>2 | 1 / 407 (0.25%)<br>1 | 1 / 137 (0.73%)<br>1 |
| Injury, poisoning and procedural complications                                       |                      |                      |                      |
| Arthropod bite<br>subjects affected / exposed<br>occurrences (all)                   | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Arthropod sting<br>subjects affected / exposed<br>occurrences (all)                  | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Contusion<br>subjects affected / exposed<br>occurrences (all)                        | 2 / 406 (0.49%)<br>2 | 2 / 407 (0.49%)<br>2 | 0 / 137 (0.00%)<br>0 |
| Epicondylitis<br>subjects affected / exposed<br>occurrences (all)                    | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Face injury<br>subjects affected / exposed<br>occurrences (all)                      | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Fall   |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 406 (0.25%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 2               | 0               |
| Frostbite                   |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hand fracture               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Joint dislocation           |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 1               | 0               | 1               |
| Joint injury                |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 1               | 1               |
| Laceration                  |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Ligament rupture            |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Limb injury                 |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)           | 2               | 2               | 0               |
| Muscle rupture              |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Muscle strain               |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 2 / 407 (0.49%) | 1 / 137 (0.73%) |
| occurrences (all)           | 1               | 2               | 1               |
| Nail injury                 |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 6 / 407 (1.47%) | 1 / 137 (0.73%) |
| occurrences (all)           | 2               | 7               | 1               |
| Procedural pain             |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Rib fracture                |                 |                 |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Sunburn  |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Traumatic haematoma                              |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 1 / 407 (0.25%)<br>1 | 1 / 137 (0.73%)<br>1 |
| Cardiac disorders                                |                      |                      |                      |
| Angina pectoris                                  |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Arrhythmia                                       |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0 | 2 / 407 (0.49%)<br>2 | 0 / 137 (0.00%)<br>0 |
| Atrial fibrillation                              |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Cardiac failure                                  |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Cardiac failure chronic                          |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Extrasystoles                                    |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Hypertensive cardiomyopathy                      |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Ventricular extrasystoles                        |                      |                      |                      |
| subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Nervous system disorders                         |                      |                      |                      |
| Cerebral arteriosclerosis                        |                      |                      |                      |

|                             |                  |                  |                 |
|-----------------------------|------------------|------------------|-----------------|
| subjects affected / exposed | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1                | 0                | 0               |
| Cerebral ischaemia          |                  |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1                | 0                | 0               |
| Cervical radiculopathy      |                  |                  |                 |
| subjects affected / exposed | 0 / 406 (0.00%)  | 2 / 407 (0.49%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 0                | 2                | 0               |
| Dizziness                   |                  |                  |                 |
| subjects affected / exposed | 2 / 406 (0.49%)  | 6 / 407 (1.47%)  | 1 / 137 (0.73%) |
| occurrences (all)           | 2                | 6                | 1               |
| Dysgeusia                   |                  |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%)  | 2 / 407 (0.49%)  | 1 / 137 (0.73%) |
| occurrences (all)           | 1                | 2                | 1               |
| Epilepsy                    |                  |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1                | 0                | 0               |
| Essential tremor            |                  |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1                | 0                | 0               |
| Headache                    |                  |                  |                 |
| subjects affected / exposed | 19 / 406 (4.68%) | 18 / 407 (4.42%) | 5 / 137 (3.65%) |
| occurrences (all)           | 28               | 31               | 6               |
| Migraine                    |                  |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 2                | 2                | 0               |
| Migraine with aura          |                  |                  |                 |
| subjects affected / exposed | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 0                | 1                | 0               |
| Neuralgia                   |                  |                  |                 |
| subjects affected / exposed | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 0                | 1                | 0               |
| Neuritis                    |                  |                  |                 |
| subjects affected / exposed | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)           | 1                | 0                | 0               |
| Parkinsonism                |                  |                  |                 |

|   |                 |                 |                 |
|---|-----------------|-----------------|-----------------|
| subjects affected / exposed                 | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 1               | 0               | 0               |
| <b>Polyneuropathy</b>                       |                 |                 |                 |
| subjects affected / exposed                 | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 0               | 1               | 0               |
| <b>Radiculitis</b>                          |                 |                 |                 |
| subjects affected / exposed                 | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)                           | 0               | 0               | 1               |
| <b>Restless legs syndrome</b>               |                 |                 |                 |
| subjects affected / exposed                 | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 1               | 0               | 0               |
| <b>Sciatica</b>                             |                 |                 |                 |
| subjects affected / exposed                 | 1 / 406 (0.25%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 1               | 2               | 0               |
| <b>Transient ischaemic attack</b>           |                 |                 |                 |
| subjects affected / exposed                 | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 0               | 1               | 0               |
| <b>Tremor</b>                               |                 |                 |                 |
| subjects affected / exposed                 | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 1               | 1               | 0               |
| <b>Blood and lymphatic system disorders</b> |                 |                 |                 |
| <b>Anaemia</b>                              |                 |                 |                 |
| subjects affected / exposed                 | 1 / 406 (0.25%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 1               | 2               | 0               |
| <b>Eosinophilia</b>                         |                 |                 |                 |
| subjects affected / exposed                 | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 2               | 0               | 0               |
| <b>Haemorrhagic anaemia</b>                 |                 |                 |                 |
| subjects affected / exposed                 | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 0               | 1               | 0               |
| <b>Leukocytosis</b>                         |                 |                 |                 |
| subjects affected / exposed                 | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 0               | 1               | 0               |
| <b>Leukopenia</b>                           |                 |                 |                 |
| subjects affected / exposed                 | 1 / 406 (0.25%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)                           | 1               | 2               | 0               |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Lymph node pain             |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Lymphadenopathy             |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Lymphopenia                 |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Neutropenia                 |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Polycythaemia               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Thrombocytosis              |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Ear and labyrinth disorders |                 |                 |                 |
| Ear pain                    |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Ear pruritus                |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Hypoacusis                  |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Tinnitus                    |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 2               | 1               | 0               |
| Vertigo positional          |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Eye disorders               |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Cataract                    |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Chalazion                   |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Conjunctivitis allergic     |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Erythema of eyelid          |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 1               | 0               | 1               |
| Eye oedema                  |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Eye pruritus                |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Eyelid oedema               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Eyelid rash                 |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Retinal haemorrhage         |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Vision blurred              |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Gastrointestinal disorders  |                 |                 |                 |
| Abdominal discomfort        |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Abdominal distension        |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Abdominal pain              |                 |                 |                 |
| subjects affected / exposed | 3 / 406 (0.74%) | 2 / 407 (0.49%) | 1 / 137 (0.73%) |
| occurrences (all)           | 3               | 2               | 1               |
| Abdominal pain lower        |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Abdominal pain upper        |                 |                 |                 |
| subjects affected / exposed | 7 / 406 (1.72%) | 1 / 407 (0.25%) | 2 / 137 (1.46%) |
| occurrences (all)           | 7               | 1               | 2               |
| Abdominal tenderness        |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Cheilitis                   |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Constipation                |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Dental caries               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Diarrhoea                   |                 |                 |                 |
| subjects affected / exposed | 5 / 406 (1.23%) | 5 / 407 (1.23%) | 1 / 137 (0.73%) |
| occurrences (all)           | 5               | 6               | 1               |
| Diverticulum                |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Diverticulum intestinal     |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Dyspepsia                   |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 2               | 0               | 1               |
| Dysphagia                   |                 |                 |                 |

|                                  |                 |                 |                 |
|----------------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed      | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Faecal incontinence              |                 |                 |                 |
| subjects affected / exposed      | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Faeces discoloured               |                 |                 |                 |
| subjects affected / exposed      | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                | 2               | 0               | 0               |
| Faeces pale                      |                 |                 |                 |
| subjects affected / exposed      | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Flatulence                       |                 |                 |                 |
| subjects affected / exposed      | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Frequent bowel movements         |                 |                 |                 |
| subjects affected / exposed      | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                | 0               | 1               | 0               |
| Gastric disorder                 |                 |                 |                 |
| subjects affected / exposed      | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Gastritis                        |                 |                 |                 |
| subjects affected / exposed      | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Gastrooesophageal reflux disease |                 |                 |                 |
| subjects affected / exposed      | 2 / 406 (0.49%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)                | 2               | 0               | 1               |
| Haematochezia                    |                 |                 |                 |
| subjects affected / exposed      | 2 / 406 (0.49%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                | 2               | 0               | 0               |
| Haemorrhoids                     |                 |                 |                 |
| subjects affected / exposed      | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)                | 1               | 0               | 0               |
| Hyperchlorhydria                 |                 |                 |                 |
| subjects affected / exposed      | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                | 0               | 3               | 0               |
| Inguinal hernia                  |                 |                 |                 |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                             | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Irritable bowel syndrome<br>subjects affected / exposed<br>occurrences (all) | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)                   | 2 / 406 (0.49%)<br>2 | 1 / 407 (0.25%)<br>1 | 1 / 137 (0.73%)<br>1 |
| Pancreatitis chronic<br>subjects affected / exposed<br>occurrences (all)     | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Periodontal disease<br>subjects affected / exposed<br>occurrences (all)      | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Proctitis<br>subjects affected / exposed<br>occurrences (all)                | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Toothache<br>subjects affected / exposed<br>occurrences (all)                | 2 / 406 (0.49%)<br>2 | 4 / 407 (0.98%)<br>7 | 2 / 137 (1.46%)<br>3 |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)                 | 2 / 406 (0.49%)<br>2 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| <b>Skin and subcutaneous tissue disorders</b>                                |                      |                      |                      |
| Actinic keratosis<br>subjects affected / exposed<br>occurrences (all)        | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Dermatitis contact<br>subjects affected / exposed<br>occurrences (all)       | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 1 / 137 (0.73%)<br>1 |
| Diabetic ulcer<br>subjects affected / exposed<br>occurrences (all)           | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>2 | 0 / 137 (0.00%)<br>0 |
| Dry skin<br>subjects affected / exposed<br>occurrences (all)                 | 0 / 406 (0.00%)<br>0 | 2 / 407 (0.49%)<br>2 | 0 / 137 (0.00%)<br>0 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Dyshidrotic eczema          |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Eczema                      |                 |                 |                 |
| subjects affected / exposed | 4 / 406 (0.99%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)           | 4               | 2               | 0               |
| Eczema nummular             |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Erythema                    |                 |                 |                 |
| subjects affected / exposed | 4 / 406 (0.99%) | 4 / 407 (0.98%) | 1 / 137 (0.73%) |
| occurrences (all)           | 5               | 4               | 1               |
| Hyperkeratosis              |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Nail bed bleeding           |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Nail disorder               |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 3 / 407 (0.74%) | 1 / 137 (0.73%) |
| occurrences (all)           | 2               | 3               | 2               |
| Onychalgia                  |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Onychoclasia                |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Onychomadesis               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Pityriasis rosea            |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Pruritus                    |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 3 / 407 (0.74%) | 1 / 137 (0.73%) |
| occurrences (all)           | 1               | 3               | 1               |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Psoriasis                   |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Rash                        |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 2 / 407 (0.49%) | 2 / 137 (1.46%) |
| occurrences (all)           | 2               | 4               | 2               |
| Seborrhoeic dermatitis      |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Skin burning sensation      |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Skin disorder               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Skin exfoliation            |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Skin irritation             |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 2               | 2               | 0               |
| Skin lesion                 |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Urticaria                   |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 1               | 1               |
| Renal and urinary disorders |                 |                 |                 |
| Bladder discomfort          |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Calculus urinary            |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 2               | 0               |
| Chromaturia                 |                 |                 |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Chronic kidney disease      |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Glycosuria                  |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Haematuria                  |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Haemoglobinuria             |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Hyperoxaluria               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Micturition urgency         |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Nephrolithiasis             |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Proteinuria                 |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Renal cyst                  |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Urinary tract inflammation  |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 2               |
| Endocrine disorders         |                 |                 |                 |
| Androgen deficiency         |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |

|   |                  |                  |                 |
|---|------------------|------------------|-----------------|
| Musculoskeletal and connective tissue disorders |                  |                  |                 |
| Acquired foramen magnum stenosis                |                  |                  |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)                               | 1                | 0                | 0               |
| Arthralgia                                      |                  |                  |                 |
| subjects affected / exposed                     | 8 / 406 (1.97%)  | 4 / 407 (0.98%)  | 2 / 137 (1.46%) |
| occurrences (all)                               | 8                | 5                | 3               |
| Arthritis                                       |                  |                  |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%) |
| occurrences (all)                               | 2                | 0                | 0               |
| Back pain                                       |                  |                  |                 |
| subjects affected / exposed                     | 10 / 406 (2.46%) | 13 / 407 (3.19%) | 5 / 137 (3.65%) |
| occurrences (all)                               | 16               | 13               | 6               |
| Bursitis  |                  |                  |                 |
| subjects affected / exposed                     | 3 / 406 (0.74%)  | 0 / 407 (0.00%)  | 1 / 137 (0.73%) |
| occurrences (all)                               | 4                | 0                | 1               |
| Chondropathy                                    |                  |                  |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)                               | 0                | 1                | 0               |
| Exostosis                                       |                  |                  |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%)  | 0 / 407 (0.00%)  | 1 / 137 (0.73%) |
| occurrences (all)                               | 0                | 0                | 1               |
| Fibromyalgia                                    |                  |                  |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)                               | 0                | 1                | 0               |
| Gouty arthritis                                 |                  |                  |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)                               | 0                | 1                | 0               |
| Intervertebral disc protrusion                  |                  |                  |                 |
| subjects affected / exposed                     | 0 / 406 (0.00%)  | 3 / 407 (0.74%)  | 0 / 137 (0.00%) |
| occurrences (all)                               | 0                | 3                | 0               |
| Muscle spasms                                   |                  |                  |                 |
| subjects affected / exposed                     | 1 / 406 (0.25%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%) |
| occurrences (all)                               | 1                | 1                | 0               |
| Musculoskeletal pain                            |                  |                  |                 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 4 / 406 (0.99%) | 1 / 407 (0.25%) | 2 / 137 (1.46%) |
| occurrences (all)           | 5               | 3               | 2               |
| Musculoskeletal stiffness   |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Myositis                    |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Neck pain                   |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Osteoarthritis              |                 |                 |                 |
| subjects affected / exposed | 3 / 406 (0.74%) | 1 / 407 (0.25%) | 2 / 137 (1.46%) |
| occurrences (all)           | 3               | 1               | 2               |
| Pain in extremity           |                 |                 |                 |
| subjects affected / exposed | 5 / 406 (1.23%) | 3 / 407 (0.74%) | 0 / 137 (0.00%) |
| occurrences (all)           | 8               | 3               | 0               |
| Periarthritis               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Plantar fasciitis           |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Scoliosis                   |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 0               | 0               |
| Spinal osteoarthritis       |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)           | 2               | 2               | 0               |
| Spinal pain                 |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Tendonitis                  |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 2               | 1               | 0               |
| Torticollis                 |                 |                 |                 |

|   |                        |                      |                      |
|---|------------------------|----------------------|----------------------|
| subjects affected / exposed<br>occurrences (all)                        | 0 / 406 (0.00%)<br>0   | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Trigger finger<br>subjects affected / exposed<br>occurrences (all)      | 1 / 406 (0.25%)<br>1   | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| <b>Infections and infestations</b>                                      |                        |                      |                      |
| Abscess jaw<br>subjects affected / exposed<br>occurrences (all)         | 0 / 406 (0.00%)<br>0   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Acute tonsillitis<br>subjects affected / exposed<br>occurrences (all)   | 1 / 406 (0.25%)<br>1   | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Borrelia infection<br>subjects affected / exposed<br>occurrences (all)  | 2 / 406 (0.49%)<br>2   | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Bronchitis<br>subjects affected / exposed<br>occurrences (all)          | 11 / 406 (2.71%)<br>11 | 8 / 407 (1.97%)<br>8 | 4 / 137 (2.92%)<br>4 |
| Cellulitis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 406 (0.00%)<br>0   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Conjunctivitis<br>subjects affected / exposed<br>occurrences (all)      | 0 / 406 (0.00%)<br>0   | 3 / 407 (0.74%)<br>3 | 1 / 137 (0.73%)<br>1 |
| Cystitis<br>subjects affected / exposed<br>occurrences (all)            | 2 / 406 (0.49%)<br>2   | 4 / 407 (0.98%)<br>4 | 0 / 137 (0.00%)<br>0 |
| Dacryocanaliculitis<br>subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Diverticulitis<br>subjects affected / exposed<br>occurrences (all)      | 1 / 406 (0.25%)<br>1   | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Ear infection<br>subjects affected / exposed<br>occurrences (all)       | 1 / 406 (0.25%)<br>1   | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| Erysipelas                  |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Gastroenteritis             |                 |                 |                 |
| subjects affected / exposed | 4 / 406 (0.99%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)           | 4               | 2               | 0               |
| Gastroenteritis norovirus   |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Gastroenteritis viral       |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 1               | 0               |
| Gastrointestinal infection  |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Helicobacter infection      |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Herpes simplex              |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 2 / 137 (1.46%) |
| occurrences (all)           | 0               | 1               | 2               |
| Herpes zoster               |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 2               | 0               | 1               |
| Hordeolum                   |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Impetigo                    |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Infected bites              |                 |                 |                 |
| subjects affected / exposed | 1 / 406 (0.25%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 1               | 0               | 0               |
| Infection                   |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 1               | 1               |

|                             |                  |                  |                  |
|-----------------------------|------------------|------------------|------------------|
| Influenza                   |                  |                  |                  |
| subjects affected / exposed | 5 / 406 (1.23%)  | 11 / 407 (2.70%) | 1 / 137 (0.73%)  |
| occurrences (all)           | 5                | 13               | 1                |
| Laryngitis                  |                  |                  |                  |
| subjects affected / exposed | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0                |
| Nasopharyngitis             |                  |                  |                  |
| subjects affected / exposed | 39 / 406 (9.61%) | 38 / 407 (9.34%) | 13 / 137 (9.49%) |
| occurrences (all)           | 48               | 49               | 15               |
| Onychomycosis               |                  |                  |                  |
| subjects affected / exposed | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 0                | 1                | 0                |
| Oral herpes                 |                  |                  |                  |
| subjects affected / exposed | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0                |
| Oral infection              |                  |                  |                  |
| subjects affected / exposed | 1 / 406 (0.25%)  | 0 / 407 (0.00%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 1                | 0                | 0                |
| Paronychia                  |                  |                  |                  |
| subjects affected / exposed | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 0                | 1                | 0                |
| Peritonsillitis             |                  |                  |                  |
| subjects affected / exposed | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 0                | 1                | 0                |
| Pharyngitis                 |                  |                  |                  |
| subjects affected / exposed | 4 / 406 (0.99%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 4                | 1                | 0                |
| Pneumonia                   |                  |                  |                  |
| subjects affected / exposed | 0 / 406 (0.00%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 0                | 1                | 0                |
| Pulpitis dental             |                  |                  |                  |
| subjects affected / exposed | 1 / 406 (0.25%)  | 1 / 407 (0.25%)  | 0 / 137 (0.00%)  |
| occurrences (all)           | 1                | 1                | 0                |
| Respiratory tract infection |                  |                  |                  |
| subjects affected / exposed | 1 / 406 (0.25%)  | 1 / 407 (0.25%)  | 1 / 137 (0.73%)  |
| occurrences (all)           | 1                | 1                | 1                |

|                                   |                 |                 |                 |
|-----------------------------------|-----------------|-----------------|-----------------|
| Rhinitis                          |                 |                 |                 |
| subjects affected / exposed       | 3 / 406 (0.74%) | 0 / 407 (0.00%) | 2 / 137 (1.46%) |
| occurrences (all)                 | 4               | 0               | 2               |
| Sepsis                            |                 |                 |                 |
| subjects affected / exposed       | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)                 | 0               | 0               | 1               |
| Sinusitis                         |                 |                 |                 |
| subjects affected / exposed       | 3 / 406 (0.74%) | 3 / 407 (0.74%) | 0 / 137 (0.00%) |
| occurrences (all)                 | 3               | 4               | 0               |
| Skin candida                      |                 |                 |                 |
| subjects affected / exposed       | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                 | 0               | 1               | 0               |
| Tinea cruris                      |                 |                 |                 |
| subjects affected / exposed       | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                 | 0               | 1               | 0               |
| Tinea infection                   |                 |                 |                 |
| subjects affected / exposed       | 0 / 406 (0.00%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)                 | 0               | 2               | 0               |
| Tinea pedis                       |                 |                 |                 |
| subjects affected / exposed       | 0 / 406 (0.00%) | 8 / 407 (1.97%) | 0 / 137 (0.00%) |
| occurrences (all)                 | 0               | 8               | 0               |
| Tinea versicolour                 |                 |                 |                 |
| subjects affected / exposed       | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)                 | 0               | 0               | 1               |
| Tonsillitis                       |                 |                 |                 |
| subjects affected / exposed       | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                 | 0               | 1               | 0               |
| Tooth infection                   |                 |                 |                 |
| subjects affected / exposed       | 1 / 406 (0.25%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)                 | 1               | 1               | 0               |
| Tracheitis                        |                 |                 |                 |
| subjects affected / exposed       | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)                 | 0               | 0               | 1               |
| Upper respiratory tract infection |                 |                 |                 |
| subjects affected / exposed       | 4 / 406 (0.99%) | 3 / 407 (0.74%) | 1 / 137 (0.73%) |
| occurrences (all)                 | 4               | 3               | 1               |

|  |                      |                      |                      |
|--|----------------------|----------------------|----------------------|
| Urinary tract infection<br>subjects affected / exposed<br>occurrences (all)    | 5 / 406 (1.23%)<br>6 | 3 / 407 (0.74%)<br>4 | 1 / 137 (0.73%)<br>2 |
| Vaginal infection<br>subjects affected / exposed<br>occurrences (all)          | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Viral infection<br>subjects affected / exposed<br>occurrences (all)            | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Viral pharyngitis<br>subjects affected / exposed<br>occurrences (all)          | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Vulvovaginal candidiasis<br>subjects affected / exposed<br>occurrences (all)   | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Metabolism and nutrition disorders   |                      |                      |                      |
| Appetite disorder<br>subjects affected / exposed<br>occurrences (all)          | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Dehydration<br>subjects affected / exposed<br>occurrences (all)                | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 0 / 137 (0.00%)<br>0 |
| Diabetes mellitus<br>subjects affected / exposed<br>occurrences (all)          | 0 / 406 (0.00%)<br>0 | 1 / 407 (0.25%)<br>1 | 1 / 137 (0.73%)<br>1 |
| Folate deficiency<br>subjects affected / exposed<br>occurrences (all)          | 1 / 406 (0.25%)<br>1 | 0 / 407 (0.00%)<br>0 | 0 / 137 (0.00%)<br>0 |
| Glucose tolerance impaired<br>subjects affected / exposed<br>occurrences (all) | 0 / 406 (0.00%)<br>0 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Gout<br>subjects affected / exposed<br>occurrences (all)                       | 2 / 406 (0.49%)<br>2 | 0 / 407 (0.00%)<br>0 | 1 / 137 (0.73%)<br>1 |
| Hypercholesterolaemia  |                      |                      |                      |

|                             |                 |                 |                 |
|-----------------------------|-----------------|-----------------|-----------------|
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |
| Hyperglycaemia              |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 2               | 1               |
| Hyperkalaemia               |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 1               | 1               |
| Hyperlipidaemia             |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 0 / 407 (0.00%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 0               | 1               |
| Hyperuricaemia              |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Hypokalaemia                |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 2 / 407 (0.49%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 2               | 0               |
| Type 2 diabetes mellitus    |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 4 / 407 (0.98%) | 1 / 137 (0.73%) |
| occurrences (all)           | 0               | 4               | 1               |
| Vitamin B12 deficiency      |                 |                 |                 |
| subjects affected / exposed | 2 / 406 (0.49%) | 0 / 407 (0.00%) | 0 / 137 (0.00%) |
| occurrences (all)           | 2               | 0               | 0               |
| Vitamin D deficiency        |                 |                 |                 |
| subjects affected / exposed | 0 / 406 (0.00%) | 1 / 407 (0.25%) | 0 / 137 (0.00%) |
| occurrences (all)           | 0               | 1               | 0               |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 26 May 2015      | Amendment 2 presented change in the study design with the addition of the open-label amorolfine arm.   |
| 18 November 2015 | Amendment 3 presented inclusion criteria (age) no longer presents an upper age limit: "Subjects aged 12 years and older of any race."  |
| 11 April 2016    | Amendment 4 presented the addition of re-screening procedures. The wording of the analysis populations and serious adverse event sections were also improved.  |
| 22 March 2017    | <p>Amendment 5 presented the removal of sample drawing intended to assess the presence of terbinafine in plasma.</p> <p>Additional details about the sensitivity analyses for handling missing data, the combination of small centres for the analysis of primary and secondary efficacy endpoints, the trial termination and data collection and validation were included. The negative culture rate for dermatophytes of the target nail at Week 60 was reclassified as a supportive efficacy endpoint, instead of a key secondary efficacy endpoint, the inclusion of a multiplicity adjustment among the key secondary endpoints using the Holm-Bonferroni method, an additional week (from 1 to 2 weeks) for repeating mycology tests at screening, a timeframe for study documents retention and a Quality Assurance section.</p> <p>Unblinding procedures and subjects numbering were specified as detailed in separate documents archived in the Trial Master File.</p> <p>The following changes were applied prior to database lock:</p> <ol style="list-style-type: none"><li>1) Negative culture rate for dermatophytes of the target toenail was displayed at all study visits.</li><li>2) Additional supportive efficacy endpoints: -Since the initial definition of complete cure was considered too stringent to reflect the true benefit of onychomycosis treatment in general practice, particularly since hyphae seen on microscopy may in reality no longer be viable, and may therefore limit the use of newer topical agents in mild-to moderate disease, the absence of clinical signs following an adequate washout period, coupled with negative culture, with or without negative microscopy, was considered a suitable indicator of onychomycosis cure. For this reason, two additional modified supportive endpoints were added:- Modified cure rate at Week 60 and Modified responder rate at Week 60.</li></ol> |

Notes:

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported