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:

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
Arm title	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.

Arm title	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.

Arm title	Amorolfine
Arm description:	
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.	

Number of subjects in period 1	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 Units: Subjects			

Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	389		
Male	564		
Race 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 Units: Percentage arithmetic mean standard deviation	- -		
Total number of affected toenails Units: number arithmetic mean standard deviation	- -		

End points

End points 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.	

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:	
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:	
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 [1]
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.

Statistical analysis title	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 [2]
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 (<=) 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

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	6.65	3.41	3.65	
Failure rate	93.35	96.59	96.35	

Statistical analyses

Statistical analysis title	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.

Statistical analysis title	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

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	20.44	12.20	18.98	
Failure rate	79.56	87.80	81.02	

Statistical analyses

Statistical analysis title	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.

Statistical analysis title	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.

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

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[7]	407[8]	137[9]	
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

	Onychomycosis at Week 60

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

Statistical analysis title	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 [10]
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.

Statistical analysis title	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 [11]
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 [12]
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.

Statistical analysis title	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 [13]
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

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, 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 [14]
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.

Statistical analysis title	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 [15]
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 [16]
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 [17]
Method	ANCOVA

Notes:

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

Statistical analysis title	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 [18]
Method	ANCOVA

Notes:

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

Statistical analysis title	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 [19]
Method	ANCOVA

Notes:

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

Statistical analysis title	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.

Statistical analysis title	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%, <=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[22]	410[23]	137[24]	
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

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, 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.

Statistical analysis title	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[26]
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

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, 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

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, 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

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.

Serious adverse events	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
Malignant melanoma			
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
Pancreatic carcinoma			
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
Prostate 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
Prostate cancer recurrent			
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
Surgical and medical procedures			
Catheter management			
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
Hysterectomy			
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
Knee arthroplasty			
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
Nasal septal operation			

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
Oophorectomy			
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
Pelvic floor repair			
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
Tonsillectomy			
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
Vitrectomy			
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
Reproductive system and breast disorders			
Ovarian disorder			
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
Respiratory, thoracic and mediastinal disorders			
Sleep apnoea syndrome			
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
Investigations			
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
Injury, poisoning and procedural complications			
Ankle fracture			
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
Cervical vertebral fracture			
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
Humerus fracture			
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
Intestinal anastomosis complication			
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
Joint dislocation			
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
Joint injury			
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
Ligament rupture			
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
Lumbar vertebral fracture			

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
Tendon rupture			
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
Thermal burn			
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
Wound			
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
Cardiac disorders			
Arrhythmia			
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
Atrial fibrillation			
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
Coronary artery disease			
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
Nervous system disorders			
Cerebrovascular accident			
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
Encephalopathy			

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
Neuropathy peripheral			
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
Polyneuropathy chronic			
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
Transient ischaemic attack			
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
Gastrointestinal disorders			
Colitis			
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
Food poisoning			
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
Gastric ulcer haemorrhage			
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
Gastrointestinal inflammation			
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
Pancreatitis acute			

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 %

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

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

subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	2	0	0
Asthma			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	1 / 137 (0.73%)
occurrences (all)	0	1	1
Cough			
subjects affected / exposed	2 / 406 (0.49%)	5 / 407 (1.23%)	2 / 137 (1.46%)
occurrences (all)	2	5	2
Dyspnoea			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Oropharyngeal pain			
subjects affected / exposed	1 / 406 (0.25%)	3 / 407 (0.74%)	2 / 137 (1.46%)
occurrences (all)	2	3	2
Rhinitis allergic			
subjects affected / exposed	1 / 406 (0.25%)	2 / 407 (0.49%)	0 / 137 (0.00%)
occurrences (all)	1	2	0
Rhinorrhoea			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Sleep apnoea syndrome			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Upper respiratory tract inflammation			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	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			
subjects affected / exposed	1 / 406 (0.25%)	2 / 407 (0.49%)	0 / 137 (0.00%)
occurrences (all)	1	2	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	10 / 406 (2.46%)	4 / 407 (0.98%)	1 / 137 (0.73%)
occurrences (all)	12	4	1
Haemoglobin urine			
subjects affected / exposed	2 / 406 (0.49%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	2	0	0
Haemoglobin urine present			
subjects affected / exposed	1 / 406 (0.25%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	1	1	0
Hepatic enzyme increased			
subjects affected / exposed	1 / 406 (0.25%)	4 / 407 (0.98%)	1 / 137 (0.73%)
occurrences (all)	1	4	1
Liver function test abnormal			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Lymphocyte count decreased			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Monocyte count increased			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Neutrophil count increased			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Platelet count decreased			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Protein urine present			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Red blood cells urine positive			

subjects affected / exposed	0 / 406 (0.00%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	0	0	1
Urine analysis abnormal			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Weight decreased			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
White blood cell count decreased			
subjects affected / exposed	0 / 406 (0.00%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	0	0	1
White blood cell count increased			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
White blood cells urine positive			
subjects affected / exposed	2 / 406 (0.49%)	1 / 407 (0.25%)	1 / 137 (0.73%)
occurrences (all)	2	1	1
Injury, poisoning and procedural complications			
Arthropod bite			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Arthropod sting			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Contusion			
subjects affected / exposed	2 / 406 (0.49%)	2 / 407 (0.49%)	0 / 137 (0.00%)
occurrences (all)	2	2	0
Epicondylitis			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Face injury			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	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	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Sunburn			
subjects affected / exposed	0 / 406 (0.00%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	0	0	1
Traumatic haematoma			
subjects affected / exposed	1 / 406 (0.25%)	1 / 407 (0.25%)	1 / 137 (0.73%)
occurrences (all)	1	1	1
Cardiac disorders			
Angina pectoris			
subjects affected / exposed	0 / 406 (0.00%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	0	0	1
Arrhythmia			
subjects affected / exposed	0 / 406 (0.00%)	2 / 407 (0.49%)	0 / 137 (0.00%)
occurrences (all)	0	2	0
Atrial fibrillation			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Cardiac failure			
subjects affected / exposed	1 / 406 (0.25%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	1	1	0
Cardiac failure chronic			
subjects affected / exposed	0 / 406 (0.00%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	0	0	1
Extrasystoles			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Hypertensive cardiomyopathy			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Ventricular extrasystoles			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	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
Polyneuropathy			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Radiculitis			
subjects affected / exposed	0 / 406 (0.00%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	0	0	1
Restless legs syndrome			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Sciatica			
subjects affected / exposed	1 / 406 (0.25%)	2 / 407 (0.49%)	0 / 137 (0.00%)
occurrences (all)	1	2	0
Transient ischaemic attack			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Tremor			
subjects affected / exposed	1 / 406 (0.25%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	1	1	0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 406 (0.25%)	2 / 407 (0.49%)	0 / 137 (0.00%)
occurrences (all)	1	2	0
Eosinophilia			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	2	0	0
Haemorrhagic anaemia			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Leukocytosis			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Leukopenia			
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	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Irritable bowel syndrome			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Nausea			
subjects affected / exposed	2 / 406 (0.49%)	1 / 407 (0.25%)	1 / 137 (0.73%)
occurrences (all)	2	1	1
Pancreatitis chronic			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Periodontal disease			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Proctitis			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Toothache			
subjects affected / exposed	2 / 406 (0.49%)	4 / 407 (0.98%)	2 / 137 (1.46%)
occurrences (all)	2	7	3
Vomiting			
subjects affected / exposed	2 / 406 (0.49%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	2	1	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Dermatitis contact			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	1 / 137 (0.73%)
occurrences (all)	0	1	1
Diabetic ulcer			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	2	0
Dry skin			
subjects affected / exposed	0 / 406 (0.00%)	2 / 407 (0.49%)	0 / 137 (0.00%)
occurrences (all)	0	2	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
Onychoclasis			
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	0 / 406 (0.00%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	0	0	1
Trigger finger			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Infections and infestations			
Abscess jaw			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Acute tonsillitis			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Borrelia infection			
subjects affected / exposed	2 / 406 (0.49%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	2	0	0
Bronchitis			
subjects affected / exposed	11 / 406 (2.71%)	8 / 407 (1.97%)	4 / 137 (2.92%)
occurrences (all)	11	8	4
Cellulitis			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Conjunctivitis			
subjects affected / exposed	0 / 406 (0.00%)	3 / 407 (0.74%)	1 / 137 (0.73%)
occurrences (all)	0	3	1
Cystitis			
subjects affected / exposed	2 / 406 (0.49%)	4 / 407 (0.98%)	0 / 137 (0.00%)
occurrences (all)	2	4	0
Dacryocanaliculitis			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Diverticulitis			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Ear infection			
subjects affected / exposed	1 / 406 (0.25%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	1	1	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			
subjects affected / exposed	5 / 406 (1.23%)	3 / 407 (0.74%)	1 / 137 (0.73%)
occurrences (all)	6	4	2
Vaginal infection			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Viral infection			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Viral pharyngitis			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Metabolism and nutrition disorders			
Appetite disorder			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Dehydration			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	0 / 137 (0.00%)
occurrences (all)	0	1	0
Diabetes mellitus			
subjects affected / exposed	0 / 406 (0.00%)	1 / 407 (0.25%)	1 / 137 (0.73%)
occurrences (all)	0	1	1
Folate deficiency			
subjects affected / exposed	1 / 406 (0.25%)	0 / 407 (0.00%)	0 / 137 (0.00%)
occurrences (all)	1	0	0
Glucose tolerance impaired			
subjects affected / exposed	0 / 406 (0.00%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	0	0	1
Gout			
subjects affected / exposed	2 / 406 (0.49%)	0 / 407 (0.00%)	1 / 137 (0.73%)
occurrences (all)	2	0	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	Amendment 5 presented the removal of sample drawing intended to assess the presence of terbinafine in plasma. 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. Unblinding procedures and subjects numbering were specified as detailed in separate documents archived in the Trial Master File. The following changes were applied prior to database lock: 1) Negative culture rate for dermatophytes of the target toenail was displayed at all study visits. 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported