Clinical trial results:
An Early Phase Development, Partly Blinded, Positive and Vehicle Controlled, Randomised, Non-inferiority Investigation of the Pharmacokinetics, Safety and Efficacy of BB2603 Cutaneous Hand-Pump Spray versus Lamisil® Spray and versus BB2603 Vehicle Hand-Pump Spray in Subjects with Onychomycosis and associated Tinea Pedis.

Summary

EudraCT number	2016-001242-25
Trial protocol	DE
Global end of trial date	13 August 2018

Results information

Result version number	v1 (current)
This version publication date	23 August 2019
First version publication date	23 August 2019

Trial information

Trial identification

Sponsor protocol code	BBT120126032001

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Blueberry Therapeutics Ltd
Sponsor organisation address	Mereside, Alderley Park, Congleton Road,Nether Alderley, Macclesfield, Cheshire, United Kingdom, SK10 4TG
Public contact	Medical Officer, Blueberry Therapeutics Ltd, +44 1625238776, info@blueberrytherapeutics.com
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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	13 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	13 August 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study was to assess the systemic exposure of the active pharmaceutical ingredient terbinafine after treatment with topical BB2603 cutaneous pump spray in subjects with onychomycosis (OM) and associated tinea pedis (TP) compared to Lamisil® Spray in Part 1 of the study and BB2603 vehicle control spray in Part 2 of the study.

Protection of trial subjects:

This study was performed in accordance with the ethical principles that have their origin in the Declaration of Helsinki 1996 and that are consistent with International Conference on Harmonisation/Good Clinical Practice as per commission directive 2005/28/EC, and in accordance with the national laws and regulations of Germany where this study was conducted.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0

Adults (18-64 years)	35
From 65 to 84 years	11
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This phase 1/2 prospective, partly blinded, positive and vehicle controlled, single site study in Germany included a two-part screening visit, a 28-day initial treatment period followed by a 14-day dose free period (Part 1). Eligible subjects then progressed to Part 2 of the study for long term dosing for up to a further 48 weeks.

Pre-assignment

Screening details:

The first screening visit included a clinical and polymerase chain reaction diagnosis of OM in at least one toenail with OM severity index (OSI) score of 1 to 15, and a clinical and potassium hydroxide wet mount microscopy (KOH) diagnosis of associated TP. Eligible subjects were invited to a second screening visit for all other assessments.

Period 1

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

Blinding implementation details:

This part of study was performed in a blinded manner for the BB2603 cutaneous pump spray and BB2603 vehicle spray groups. The study was open-label for Lamisil spray group.

Arms

Are arms mutually exclusive?	Yes
Arm title	BB2603 Cutaneous Pump Spray (Part 1)

Arm description:

BB2603 cutaneous pump spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (end of treatment [EOT] for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the Test of Cure [TOC] visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to 46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing).

Arm type	Experimental
Investigational medicinal product name	BB2603 cutaneous pump spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous spray, solution
Routes of administration	Topical use

Dosage and administration details:

BB2603 cutaneous pump spray contains 0.01% terbinafine, 0.03% polyhexanide, 20% ethanol and water. BB2603 cutaneous pump spray was applied as 10 sprays (1 millilitre [ml]) per foot/leg once daily giving a total daily dose of 100 microgram (µg) per foot/leg (a total of 200 µg terbinafine/day for the first 28 days). The footwear and inside the shoes were also sprayed.

Arm title	Lamisil Spray (Part 1)

Arm description:

Lamisil spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (EOT for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the TOC visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to

46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing) and were then assigned to the Part 2 BB2603 vehicle control spray group.

Arm type	Active comparator
Investigational medicinal product name	Lamisil spray
Investigational medicinal product code	
Other name	Terbinafine 1% Topical Spray
Pharmaceutical forms	Cutaneous spray, solution
Routes of administration	Topical use

Dosage and administration details:

Lamisil spray contains 1% terbinafine. Lamisil spray was applied as 10 sprays (1 ml) per foot/leg once daily giving a total daily dose of 20 milligrams (mg) terbinafine/day for the first 28 days.

Arm title	BB2603 Vehicle Control Spray (Part 1)

Arm description:

BB2603 vehicle control spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (EOT for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the TOC visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to 46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing).

Arm type	Experimental
Investigational medicinal product name	BB2603 vehicle control spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous spray, solution
Routes of administration	Topical use

Dosage and administration details:

BB2603 vehicle control spray contains 0.03% polyhexanide, 20% ethanol and water. BB2603 vehicle control spray was applied as 10 sprays (1 mL) per foot/leg once daily. The footwear and inside the shoes were also sprayed.

Number of subjects in period 1	BB2603 Cutaneous Pump Spray (Part 1)	Lamisil Spray (Part 1)	BB2603 Vehicle Control Spray (Part 1)
Started	31	10	5
Completed	31	10	5

Period 2

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

Arms

Are arms mutually exclusive?	Yes
Arm title	BB2603 Cutaneous Pump Spray (Part 2)

Arm description:

BB2603 cutaneous pump spray was applied once daily for up to 48 weeks. The final follow up (FFU) visit occurred at Week 52.

Arm type	Experimental
Investigational medicinal product name	BB2603 cutaneous pump spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous spray, solution
Routes of administration	Topical use

Dosage and administration details:

BB2603 cutaneous pump spray contains 0.01% terbinafine, 0.03% polyhexanide, 20% ethanol and water. BB2603 pump spray was applied as 5 sprays (0.5 ml) per foot once daily giving a total daily dose of 50 µg per foot (a total of 100 µg terbinafine per day for 48 weeks). The footwear and inside the shoes were also sprayed.

Arm title	BB2603 Vehicle Control Spray (Part 2)

Arm description:

Subjects from the Lamisil spray group in Part 1, joined the BB2603 vehicle control spray group for Part 2. BB2603 vehicle control spray was applied once daily for up to 48 weeks. The FFU visit occurred at Week 52.

Arm type	Experimental
Investigational medicinal product name	BB2603 vehicle control spray
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cutaneous spray, solution
Routes of administration	Topical use

Dosage and administration details:

BB2603 vehicle control spray contains 0.03% polyhexanide, 20% ethanol and water. BB2603 vehicle control spray was applied as 5 sprays (0.5 mL) per foot once daily. The footwear and inside the shoes were also sprayed.

Number of subjects in period 2	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)
Started	31	15
Completed	20	10
Not completed	11	5
No target nail to evaluate	1	-
OSI stopping criterion fulfilled	10	5

Baseline characteristics

Reporting groups

Reporting group title	BB2603 Cutaneous Pump Spray (Part 1)

Reporting group description:

BB2603 cutaneous pump spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (end of treatment [EOT] for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the Test of Cure [TOC] visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to 46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing).

Reporting group title	Lamisil Spray (Part 1)

Reporting group description:

Lamisil spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (EOT for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the TOC visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to 46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing) and were then assigned to the Part 2 BB2603 vehicle control spray group.

Reporting group title	BB2603 Vehicle Control Spray (Part 1)

Reporting group description:

BB2603 vehicle control spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (EOT for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the TOC visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to 46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing).

Reporting group values	BB2603 Cutaneous Pump Spray (Part 1)	Lamisil Spray (Part 1)	BB2603 Vehicle Control Spray (Part 1)
Number of subjects	31	10	5
Age categorical Units: Subjects			
18-45 years	10	2	1
46-64 years	14	7	1
65-74 years	5	1	3
75-90 years	2	0	0
Age continuous Units: years			
arithmetic mean	51.9	52.0	60.6
standard deviation	± 14.35	± 13.06	± 12.12
Gender categorical Units: Subjects			
Female	13	2	0
Male	18	8	5

Race Units: Subjects			
Asian	1	0	0
Mixed	1	0	0
White	29	10	5

Reporting group values	Total		
Number of subjects	46		
Age categorical Units: Subjects			
18-45 years	13		
46-64 years	22		
65-74 years	9		
75-90 years	2		
Age continuous Units: years arithmetic mean standard deviation	- -		
Gender categorical Units: Subjects			
Female	15		
Male	31		
Race Units: Subjects			
Asian	1		
Mixed	1		
White	44		

End points

End points reporting groups

Reporting group title	BB2603 Cutaneous Pump Spray (Part 1)

Reporting group description:

BB2603 cutaneous pump spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (end of treatment [EOT] for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the Test of Cure [TOC] visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to 46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing).

Reporting group title	Lamisil Spray (Part 1)

Reporting group description:

Lamisil spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (EOT for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the TOC visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to 46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing) and were then assigned to the Part 2 BB2603 vehicle control spray group.

Reporting group title	BB2603 Vehicle Control Spray (Part 1)

Reporting group description:

BB2603 vehicle control spray was applied once daily for 28 consecutive days. All OM and TP lesions on both feet were treated but each subject had target areas identified: the largest and worst nail for OM and the most severe lesion for TP.

At Day 28 (EOT for Part 1), subjects had a 14-day dosing break before returning on Day 42 (the TOC visit). Subjects who completed all assessments at TOC had a skin patch sensitisation test (Day 42 to 46). Subjects who completed Day 46 with no significant signs of sensitisation, local intolerability/irritation or significant systemic exposure or safety issues progressed to Part 2 of the study (re-start of dosing).

Reporting group title	BB2603 Cutaneous Pump Spray (Part 2)

Reporting group description:

BB2603 cutaneous pump spray was applied once daily for up to 48 weeks. The final follow up (FFU) visit occurred at Week 52.

Reporting group title	BB2603 Vehicle Control Spray (Part 2)

Reporting group description:

Subjects from the Lamisil spray group in Part 1, joined the BB2603 vehicle control spray group for Part 2. BB2603 vehicle control spray was applied once daily for up to 48 weeks. The FFU visit occurred at Week 52.

Primary: Concentration of Terbinafine in Plasma Over Time- Part 1

End point title	Concentration of Terbinafine in Plasma Over Time- Part 1[1]

End point description:

Blood samples were taken at Day 1 (baseline), at pre-dose (T0), 1 hour (hr), 2 hr, 4 hr, 8 hr, 12 hr post-dose and then each study visit to determine plasma terbinafine levels in all subjects. Where the level of terbinafine in plasma was below the level of quantification (LoQ), the LoQ of 500 nanograms/litre (ng/L), was reported. The concentration of terbinafine in plasma for all subjects in the pharmacokinetic (PK) analysis population is presented at each time point in Part 1. The PK analysis population consisted of all subjects who received at least one dose of treatment and had adequate sampling to calculate PK parameters.

End point type	Primary

End point timeframe:

Part 1: Day 1 (T0, 1 ,2 , 4 , 8 , 12 hr), followed by Days 2, 3, 4, 5, 6, 7, 14, 21, 28 and 42

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As so many of the results were below the LoQ, no comparative analyses were performed.

End point values	BB2603 Cutaneous Pump Spray (Part 1)	Lamisil Spray (Part 1)	BB2603 Vehicle Control Spray (Part 1)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	10	5	
Units: ng/L				
geometric mean (geometric coefficient of variation)				
Day 1/T0	500.0 (± 0.0)	647.9 (± 97.84)	500.0 (± 0.0)	
Day 1/1 hr	500.0 (± 0.0)	629.1 (± 83.32)	500.0 (± 0.0)	
Day 1/2 hr	500.0 (± 0.0)	647.1 (± 97.16)	500.0 (± 0.0)	
Day 1/4 hr	500.0 (± 0.0)	655.0 (± 103.62)	500.0 (± 0.0)	
Day 1/8 hr	500.0 (± 0.0)	673.3 (± 87.92)	500.0 (± 0.0)	
Day 1/12 hr	500.0 (± 0.0)	691.4 (± 101.00)	500.0 (± 0.0)	
Day 2	500.0 (± 0.0)	705.6 (± 96.55)	500.0 (± 0.0)	
Day 3	500.0 (± 0.0)	758.0 (± 91.93)	500.0 (± 0.0)	
Day 4	500.0 (± 0.0)	766.6 (± 97.28)	500.0 (± 0.0)	
Day 5	500.0 (± 0.0)	810.7 (± 95.14)	500.0 (± 0.0)	
Day 6	500.0 (± 0.0)	832.4 (± 97.72)	500.0 (± 0.0)	
Day 7	500.0 (± 0.0)	876.8 (± 102.12)	500.0 (± 0.0)	
Day 14	500.0 (± 0.0)	802.7 (± 102.50)	500.0 (± 0.0)	
Day 21	500.0 (± 0.0)	858.9 (± 81.07)	500.0 (± 0.0)	
Day 28	500.0 (± 0.0)	820.2 (± 60.64)	500.0 (± 0.0)	
Day 42	500.0 (± 0.0)	587.5 (± 54.47)	500.0 (± 0.0)	

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of Terbinafine in Plasma Over Time- Part 2

End point title	Concentration of Terbinafine in Plasma Over Time- Part 2[2]

End point description:

Blood samples were taken at each study visit in Part 2 to determine plasma terbinafine levels in all subjects. Where the level of terbinafine in plasma was below the LoQ, the LoQ of 500 ng/L, was reported. The concentration of terbinafine in plasma for all subjects in the PK analysis population is presented at each time point in Part 2. The PK analysis population consisted of all subjects who received at least one dose of treatment and had adequate sampling to calculate PK parameters.

End point type	Primary

End point timeframe:

Part 2: Day 46/Week 0, Weeks 4, 8, 12, 16, 20, 24, 36, 48 and 52

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As so many of the results were below the LoQ, no comparative analyses were performed.

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	31[3]	15[4]		
Units: ng/L				
geometric mean (geometric coefficient of variation)				
Week 0	500.0 (± 0.0)	537.1 (± 28.26)		
Week 4	500.0 (± 0.0)	517.2 (± 13.17)		
Week 8	500.0 (± 0.0)	500.0 (± 0.0)		
Week 12	500.0 (± 0.0)	500.0 (± 0.0)		
Week 16	500.0 (± 0.0)	500.0 (± 0.0)		
Week 20	500.0 (± 0.0)	500.0 (± 0.0)		
Week 24	500.0 (± 0.0)	500.0 (± 0.0)		
Week 36	500.0 (± 0.0)	500.0 (± 0.0)		
Week 48	500.0 (± 0.0)	500.0 (± 0.0)		
Week 52	500.0 (± 0.0)	500.0 (± 0.0)		

Notes:

[3] - Except: Weeks 4-8, n=30; Week 16, n=29; Week 20, n=27; Week 24, n=26; Week 36, n=24; Week 48, n=20
[4] - Except: Week 24, n=14; Week 36, n=12; Week 48, n=10

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of Terbinafine in Nail Samples Over Time - Part 1

End point title	Concentration of Terbinafine in Nail Samples Over Time - Part

End point description:

Nail clippings and scrapings were collected from the target OM lesions to assess localised terbinafine exposure. Samples were collected from subjects at baseline (Day 1/T0) and Day 28 from Part 1 of the study and analysed for terbinafine concentration. Where the level of terbinafine was below the LoQ, the LoQ of 0.0040 mg/L, was reported. The concentration of terabinafine in nail samples for all subjects in the PK analysis population is presented at each time point in Part 1. The PK analysis population consisted of all subjects who received at least one dose of treatment and had adequate sampling to calculate PK parameters.

End point type	Primary

End point timeframe:

Part 1: Day 1 (T0) and Day 28

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As so many of the results were below the LoQ, no comparative analyses were performed.

End point values	BB2603 Cutaneous Pump Spray (Part 1)	Lamisil Spray (Part 1)	BB2603 Vehicle Control Spray (Part 1)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	31	10	5	
Units: mg/L				
geometric mean (geometric coefficient of variation)				
Clippings Day 1	0.0040 (± 0.00000)	0.0135 (± 2229.01504)	0.0040 (± 0.00000)	
Clippings Day 28	0.0500 (± 203.11839)	5.3477 (± 219.81286)	0.0040 (± 0.00000)	
Scrapings Day 1	0.0044 (± 54.06850)	0.0135 (± 1555.46873)	0.0040 (± 0.00000)	
Scrapings Day 28	0.0333 (± 128.45942)	3.4480 (± 531.94940)	0.0040 (± 0.00000)	

Statistical analyses

No statistical analyses for this end point

Primary: Concentration of Terbinafine in Nail Samples Over Time - Part 2

End point title	Concentration of Terbinafine in Nail Samples Over Time - Part

End point description:

Nail clippings and scrapings were collected from the target OM lesions to assess localised terbinafine exposure. Samples were collected from subjects at Day 46/Week 0, Weeks 12, 24, 36, 48 and 52 in Part 2 of the study and analysed for terbinafine concentration. Where the level of terbinafine was below the LoQ, the LoQ of 0.0040 mg/L, was reported. The concentration of terbinafine in nail samples for all subjects in the PK analysis population is presented at each time point in Part 2. The PK analysis population consisted of all subjects who received at least one dose of treatment and had adequate sampling to calculate PK parameters.

End point type	Primary

End point timeframe:

Part 2: Day 46/Week 0, Weeks 12, 24, 36, 48 and 52

Notes:

[6] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: As so many of the results were below the LoQ, no comparative analyses were performed.

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30[7]	15[8]		
Units: mg/L				
geometric mean (geometric coefficient of variation)				

Clippings Week 0	0.0079 (± 68.93527)	0.0901 (± 3818.58840)		
Clippings Week 12	0.1595 (± 205.04130)	0.0089 (± 751.13565)		
Clippings Week 24	0.2031 (± 138.84601)	0.0068 (± 278.81358)		
Clippings Week 36	0.2271 (± 218.27985)	0.0066 (± 444.83859)		
Clippings Week 48	0.1293 (± 203.63449)	0.0061 (± 219.43656)		
Clippings Week 52	0.0184 (± 472.95252)	0.0051 (± 103.85511)		
Scrapings Week 0	0.0085 (± 88.76985)	0.1019 (± 13858.77514)		
Scrapings Week 12	0.1383 (± 208.66846)	0.0156 (± 920.60044)		
Scrapings Week 24	0.1724 (± 151.96280)	0.0077 (± 499.25629)		
Scrapings Week 36	0.2072 (± 173.65924)	0.0072 (± 363.22453)		
Scrapings Week 48	0.0977 (± 171.84931)	0.0060 (± 196.66150)		
Scrapings Week 52	0.0191 (± 395.25603)	0.0052 (± 96.91706)		

Notes:

[7] - Except: Week 12, n=30/29 (clippings/scrapings); Week 24, n=25/26; Week 36, n=23/24 Week 48, n=20/20

[8] - Except:Week 24, n=14/14 (clippings/scrapings); Week 36, n=12/12; Week 48, n=10/10

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a Clinical TP Cure - Part 1

End point title	Percentage of Subjects with a Clinical TP Cure - Part 1

End point description:

A target TP area on one foot was identified as the most severe TP lesion and evaluated at the baseline visit and at each subsequent visit in Part 1 of the study. Each of the clinical signs (fissuring/cracking, erythema, maceration and scaling) and symptoms (pruritus and burning/stinging) of TP were scored and documented with photographs. Each score was objectively defined on a 0-3 scale where 0 = none - complete absence of any signs or symptoms, 1 = mild - slight, 2 = moderate definitely present, 3 = severe - marked, intense.

The percentage of subjects from the modified intent-to-treat (mITT) population with a clinical TP cure (i.e. no clinical signs or symptoms of TP) at Days 1, 28 and 42 during Part 1 of the study is presented. The mITT population included all randomised subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

Part 1: Days 1, 28 and 42

End point values	BB2603 Cutaneous Pump Spray (Part 1)	Lamisil Spray (Part 1)	BB2603 Vehicle Control Spray (Part 1)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	1	4	
Units: Percentage of subjects				
number (not applicable)				
Day 1	0.0	0.0	0.0	
Day 28	5.6	0.0	25.0	
Day 42	11.1	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a Complete TP Cure - Part 1

End point title	Percentage of Subjects with a Complete TP Cure - Part 1

End point description:

Subjects with no clinical symptoms or signs, a negative KOH wet mount microscopy and a negative culture for dermatophytes were classed as having a complete TP cure. The percentage of subjects in the mITT population with a complete TP cure is presented for Days 1, 28 and 42 in Part 1 of the study. The mITT population included all subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

Part1: Days 1, 28 and 42

End point values	BB2603 Cutaneous Pump Spray (Part 1)	Lamisil Spray (Part 1)	BB2603 Vehicle Control Spray (Part 1)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	18	1	4	
Units: Percentage of subjects				
number (not applicable)				
Day 1	0.0	0.0	0.0	
Day 28	5.6	0.0	0.0	
Day 42	0.0	0.0	0.0	

Statistical analyses

No statistical analyses for this end point

Secondary: Median Time to Total Mycological Cure Day - Part 1

End point title	Median Time to Total Mycological Cure Day - Part 1

End point description:

Skin scrapings for KOH assessment were taken from the target lesion (and other visible lesions) at baseline (Day 1) and each study visit up to Day 42 in Part 1 of the study. Total mycological cure day was defined as the study day on which ≥ 60% of subjects have a negative KOH and time to total mycological cure day was computed using the Kaplan-Meier estimate. Subjects who did not achieve negative KOH were censored on day of last TP assessment. The median time to total mycological cure day is reported for subjects in the mITT population in the BB2603 Cutaneous Pump Spray and Lamisil Spray groups only. The mITT population included all subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

From Day 1 to Day 42

End point values	BB2603 Cutaneous Pump Spray (Part 1)	Lamisil Spray (Part 1)	BB2603 Vehicle Control Spray (Part 1)	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	17	1	0[9]	
Units: Days				
median (inter-quartile range (Q1-Q3))	42.0 (15.0 to 70.0)	46.0 (46.0 to 46.0)	(to)	

Notes:

[9] - Total mycological cure day was not reached for this group as <60% of subjects had a negative KOH.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with TP Recurrence - Part 2

End point title	Percentage of Subjects with TP Recurrence - Part 2

End point description:

Recurrence of TP after improvement was defined as some clinical symptoms or signs of TP, assessed using documented photographs, scored on a scale of 0-3 and from skin scrapings (KOH). Recurrence of TP was assessed at the FFU visit in Part 2 and the percentage of subjects (calculated based on the number of subjects with clinical TP cure at Day 28 in Part 1 of the study) is presented.

End point type	Secondary

End point timeframe:

Week 52 in Part 2

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1[10]	1[11]		
Units: Percentage of Subjects				
number (not applicable)	100.0	0.0		

Notes:

[10] - Number of subjects with clinical TP cure at Day 28 in Part 1.

[11] - Number of subjects with clinical TP cure at Day 28 in Part 1.

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with an OM Negative Culture - Part 2

End point title	Percentage of Subjects with an OM Negative Culture - Part 2

End point description:

OM culture for dermatophytes was assessed at each study visit in Part 2 of the study. The percentage of subjects in the mITT population with no dermatophyte growth in the OM cultures (i.e. OM negative culture) is presented for Weeks 0, 48 and 52 in Part 2 of the study. The mITT population included all subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

Part 2: Day 46/Week 0, Weeks 48 and 52

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Percentage of Subjects				
number (not applicable)				
Week 0	77.8	80.0		
Week 48	33.3	40.0		
Week 52	72.2	40.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean OSI Total Score - Part 2

End point title	Mean OSI Total Score - Part 2

End point description:

Clinical OM assessment was made using the OSI at each study visit in Part 2 of the study. The OSI was obtained by multiplying the score for the area of involvement (range, 0-5) by the score for the proximity of disease to the matrix (range, 1-5). Ten points were added for the presence of a longitudinal streak or a patch (dermatophytoma) or for greater than 2mm of subungual hyperkeratosis. Mild OM corresponds to a score of 1-5; moderate OM to a score of 6-15; and severe OM to a score of 16-35. The mean OSI total score is presented for subjects in the mITT population at Weeks 0, 48 and 52 in Part 2 of the study. The mITT population included all subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

Part 2: Day 46/Week 0, Weeks 48 and 52

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18[12]	5[13]		
Units: OSI score				
arithmetic mean (standard deviation)				
Week 0	8.1 (± 4.39)	4.6 (± 2.97)		
Week 48	6.0 (± 3.20)	5.3 (± 2.99)		
Week 52	8.7 (± 5.12)	5.4 (± 2.61)		

Notes:

[12] - Except: Week 48, n=9; Week 52, n=17

[13] - Except: Week 48, n=4

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with an OM Negative Culture for Dermatophytes and an OSI of Zero - Part 2

End point title	Percentage of Subjects with an OM Negative Culture for Dermatophytes and an OSI of Zero - Part 2

End point description:

The percentage of subjects in the mITT population with an OM negative culture for dermatophytes, combined with an OSI score of zero, is presented for subjects at Weeks 0, 48 and 52 in Part 2 of the study. The mITT population included all subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

Part 2: Day 46/Week 0, Weeks 48 and 52

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Percentage of Subjects				
number (not applicable)				
Week 0	0.0	0.0		
Week 48	0.0	0.0		
Week 52	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with a Partial Cure of OM - Part 2

End point title	Percentage of Subjects with a Partial Cure of OM - Part 2

End point description:

Partial cure of OM was defined as eradication of dermatophyte infection on cultures from nail scrapings and with less than or equal to 10% of the target nail still with a clinical diagnosis of OM. The percentage of subjects in the mITT population with a partial OM cure at Weeks 0, 48 and 52 of Part 2 of the study is presented. The mITT population included all subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

Part 2: Day 46/Week 0, Weeks 48 and 52

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Percentage of Subjects				
number (not applicable)				
Week 0	5.6	0.0		
Week 48	0.0	0.0		
Week 52	0.0	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with OM Improvement - Part 2

End point title	Percentage of Subjects with OM Improvement - Part 2

End point description:

OM improvement was defined as eradication of dermatophyte infection on culture from nail scrapings and with a reduction in OSI score by at least 40% from baseline (Day 1). The percentage of subjects in the mITT population with OM improvement at Weeks 0, 48 and 52 in Part 2 of the study is presented. The mITT population included all subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

Part 2: Day 46/Week 0, Weeks 48 and 52

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	18	5		
Units: Percentage of Subjects				
number (not applicable)				
Week 0	0.0	0.0		
Week 48	11.1	0.0		
Week 52	5.6	0.0		

Statistical analyses

No statistical analyses for this end point

Secondary: Mean Change from Baseline in OSI Score - Part 2

End point title	Mean Change from Baseline in OSI Score - Part 2

End point description:

The OSI is obtained by multiplying the score for the area of involvement (range, 0-5) by the score for the proximity of disease to the matrix (range, 1-5). Ten points are added for the presence of a longitudinal streak or a patch (dermatophytoma) or for greater than 2mm of subungual hyperkeratosis. Mild OM corresponds to a score of 1-5; moderate OM to a score of 6-15; and severe OM to a score of 16-35. The mean change from baseline (Day 1 in Part 1) in OSI total score at Weeks 0, 48 and 52 in Part 2 of the study is presented for subjects in the mITT population. The mITT population included all subjects who met the important inclusion/exclusion criteria, and, for the TP analysis, had a dermatophyte infection.

End point type	Secondary

End point timeframe:

Part 1: Day 1 and Part 2: Day 46/Week 0, Weeks 48 and 52

End point values	BB2603 Cutaneous Pump Spray (Part 2)	BB2603 Vehicle Control Spray (Part 2)		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16[14]	4[15]		
Units: OSI score				
arithmetic mean (standard deviation)				
Week 0	1.3 (± 3.13)	0.0 (± 0.00)		
Week 48	-0.8 (± 2.77)	0.0 (± 0.00)		
Week 52	1.1 (± 2.89)	1.0 (± 2.00)		

Notes:

[14] - Except: Week 48, n=9; Week 52, n=15

[15] - Except: Week 48, n=3

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Treatment emergent adverse events (TEAEs) were recorded from baseline (Day 1 in Part 1) until Week 52 (FFU visit in Part 2).

Adverse event reporting additional description:

TEAEs are reported for the safety population which included all subjects who had at least one dose of study treatment and one subsequent contact with the Investigator.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups

Reporting group title	Part 1: BB2603 Cutaneous Pump Spray

Reporting group description:

All subjects assigned to the BB2603 Cutaneous Pump Spray group in Part 1 who have had at least one dose of study treatment and one subsequent contact with the Investigator.

Reporting group title	Part 1: Lamisil Spray

Reporting group description:

All subjects assigned to the Lamisil Spray group in Part 1 who have had at least one dose of study treatment and one subsequent contact with the Investigator.

Reporting group title	Part 1: BB2603 Vehicle Control Spray

Reporting group description:

All subjects assigned to the BB2603 Vehicle Control Spray group in Part 1 who have had at least one dose of study treatment and one subsequent contact with the Investigator.

Reporting group title	Part 2: BB2603 Cutaneous Pump Spray

Reporting group description:

All subjects assigned to the BB2603 Cutaneous Pump Spray group in Part 2 who have had at least one dose of study treatment and one subsequent contact with the Investigator.

Reporting group title	Part 2: BB2603 Vehicle Control Spray

Reporting group description:

All subjects assigned to the BB2603 Vehicle Control Spray group in Part 2 who have had at least one dose of study treatment and one subsequent contact with the Investigator.

Serious adverse events	Part 1: BB2603 Cutaneous Pump Spray	Part 1: Lamisil Spray	Part 1: BB2603 Vehicle Control Spray
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Part 2: BB2603 Cutaneous Pump Spray	Part 2: BB2603 Vehicle Control Spray	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 31 (3.23%)	1 / 15 (6.67%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Gastric haemorrhage			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Diverticulitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Part 1: BB2603 Cutaneous Pump Spray	Part 1: Lamisil Spray	Part 1: BB2603 Vehicle Control Spray
Total subjects affected by non-serious adverse events			
subjects affected / exposed	17 / 31 (54.84%)	4 / 10 (40.00%)	2 / 5 (40.00%)
Vascular disorders			
Angiodysplasia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Haematoma			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypertension			

subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Hypertensive crisis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Surgical and medical procedures			
Dental care			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Elective surgery			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Endometrial ablation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Tooth repair			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
General disorders and administration site conditions			
Catheter site related reaction			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Reproductive system and breast disorders			
Dysmenorrhoea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Asthma			

subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	0 / 31 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Limb injury			
subjects affected / exposed	2 / 31 (6.45%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Sunburn			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Foot fracture			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Joint injury			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Scratch			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Nervous system disorders			
Headache			
subjects affected / exposed	5 / 31 (16.13%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	6	1	0
Migraine			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Somnolence			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Toothache			
subjects affected / exposed	2 / 31 (6.45%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Abdominal pain upper			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Diarrhoea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Gastritis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Vomiting			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Skin and subcutaneous tissue disorders			
Skin irritation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rash erythematous			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Pain in extremity			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Back pain			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Musculoskeletal pain			

subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Myalgia			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Folliculitis			
subjects affected / exposed	0 / 31 (0.00%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0
Nasopharyngitis			
subjects affected / exposed	2 / 31 (6.45%)	1 / 10 (10.00%)	0 / 5 (0.00%)
occurrences (all)	2	1	0
Oral herpes			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Rash pustular			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	2	0	0
Tooth abscess			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Borrelia infection			
subjects affected / exposed	0 / 31 (0.00%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 31 (3.23%)	0 / 10 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0

Non-serious adverse events	Part 2: BB2603 Cutaneous Pump Spray	Part 2: BB2603 Vehicle Control Spray	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 31 (58.06%)	9 / 15 (60.00%)	

Vascular disorders			
Angiodysplasia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Hypertensive crisis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Surgical and medical procedures			
Dental care			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Elective surgery			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Endometrial ablation			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Tooth repair			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Catheter site related reaction			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			

Dysmenorrhoea			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Respiratory, thoracic and mediastinal disorders			
Rhinitis allergic			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Asthma			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Oropharyngeal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Injury, poisoning and procedural complications			
Ligament sprain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Limb injury			
subjects affected / exposed	2 / 31 (6.45%)	2 / 15 (13.33%)	
occurrences (all)	2	2	
Sunburn			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Foot fracture			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Joint injury			
subjects affected / exposed	0 / 31 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Scratch			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Headache			
subjects affected / exposed	4 / 31 (12.90%)	0 / 15 (0.00%)	
occurrences (all)	19	0	

Migraine			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Somnolence			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Toothache			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	4	0	
Abdominal pain upper			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	1 / 31 (3.23%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Gastritis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Vomiting			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Skin irritation			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Rash erythematous			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 31 (3.23%)	3 / 15 (20.00%)	
occurrences (all)	1	3	

Pain in extremity			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Back pain			
subjects affected / exposed	1 / 31 (3.23%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Musculoskeletal pain			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Folliculitis			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Nasopharyngitis			
subjects affected / exposed	4 / 31 (12.90%)	1 / 15 (6.67%)	
occurrences (all)	4	1	
Oral herpes			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Rash pustular			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Tooth abscess			
subjects affected / exposed	0 / 31 (0.00%)	0 / 15 (0.00%)	
occurrences (all)	0	0	
Borrelia infection			
subjects affected / exposed	1 / 31 (3.23%)	0 / 15 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			

Decreased appetite subjects affected / exposed occurrences (all)	0 / 31 (0.00%) 0	0 / 15 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 January 2017	Amendment 1 (03 Jan 17) was in response to the deficiency letter to the ethics committee to confirm that safety and PK analyses were to be performed and that both must not have shown any harm to the subjects before Part 2 commenced. It also included confirmation that the data and safety monitoring board must assess the data and confirm that it was safe for the subjects to proceed and confirmation that significant disease progression/tolerability resulted in the subject leaving the study and being given standard medical treatment. This was triggered by the subject or the increase of OSI score ≥2.
08 January 2018	Amendment 2 (08 January 2018). Clarification that only systemic PK data was to be used during Part 1 for safety review. OSI score was developed and validated to define the severity of OM in 4 categories.The OSI score numerical values were not validated as a staging or prognostic score. In addition, analysis of ongoing data suggested that the OSI score increase of ≥2 was too sensitive to identify clinical worsening. Clarification that the individual subject data was to be reviewed for concomitant medication during the study that might impact safety or efficacy assessment. Clarification added that clinical site team and sponsor remained blinded on a per subject level and that the pharmacy was responsible for keeping all code break envelopes. Sample size for this study was corrected to reflect that sample size is appropriate for testing of the efficacy endpoint of complete TP cure at Day 42 and mycological OM cure at 52 weeks. Statistical section 'efficacy analyses' was updated to allow for further sensitivity analysis. Sample collection procedures were updated and micro lab procedures deleted to reconcile with standard procedures used by the study laboratory.
13 August 2018	Amendment 3 (23 August 2018). Mycological OM cure definition clarified to what is measured in the study and hence revised to 'OM negative culture'. Clarification of the term 'complete OM cure' was revised to 'combined endpoint of negative culture for dermatophytes and an OSI of zero' since OM KOH was not assessed in Part 2 of the study. Clarification of what was measured at baseline for 'Change from Baseline OSI' endpoint. The photometric OSI score and planimetric assessment were made an exploratory endpoint since the OSI score was not validated to measure and assess treatment response. OSI score used for early withdrawal was to be based on photographic OSI assessment. Clarification that Trichophyton mentagrophytes is also known as Trichophyton mentagrophytes var. interdigitale or Trichophyton interdigitale. Clarification of when the adverse events were to be collected (i.e., the data cut-off date) for the safety analysis. Clarification that OM of the target nail would be assessed clinically using OSI, and also by independent photographic assessment. Inclusion of the Occupational, Environmental and Lifestyle risk factor questionnaire. Stratification by dermatophyte group was replaced with classification by dermatophyte group for clarification.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported