# Clinical trial results:
# A Randomized, Double-Blind, Double Dummy, Comparative , Multicenter Study to Assess the Safety and Efficacy of Topical Retapamulin Ointment, 1%, versus Oral Linezolid in the Treatment of Secondarily-Infected Traumatic Lesions and Impetigo Due to Methicillin Resistant Staphylococcus aureus

## Summary

| | |
|---|---|
| EudraCT number | 2015-004886-98 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 27 September 2010 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 12 February 2017 |
| First version publication date | 12 February 2017 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 110978 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | GlaxoSmithKline |
| Sponsor organisation address | 980 Great West Road, Brentford, Middlesex, United Kingdom, |
| Public contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |
| Scientific contact | GSK Response Center, GlaxoSmithKline, 1 866-435-7343, |

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? | Yes |

Notes:

## Results analysis stage

| | |
|---|---|
| Analysis stage | Final |
| Date of interim/final analysis | 09 December 2010 |
| Is this the analysis of the primary completion data? | No |

| | |
|---|---|
| Global end of trial reached? | Yes |
| Global end of trial date | 27 September 2010 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study was to evaluate the clinical and bacteriological efficacy of topical retapamulin ointment, 1%, versus oral linezolid, in the treatment of subjects with secondarily-infected traumatic lesions (SITL: excluding abscesses) or impetigo due to methicillin-resistant Staphylococcus aureus (MRSA).

Protection of trial subjects:

Not applicable

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 27 April 2009 |
| 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 | United States: 404 |
| Worldwide total number of subjects | 404 |
| EEA total number of subjects | 0 |

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) | 14 |
| Children (2-11 years) | 68 |
| Adolescents (12-17 years) | 38 |
| Adults (18-64 years) | 256 |
| From 65 to 84 years | 24 |
| 85 years and over | 4 |

## Subject disposition

### Recruitment

Recruitment details:

In total, 410 participants were enrolled in the study, 267 received at least 1 dose of retapamulin arm and 137 received at least 1 dose of linezolid. Of these participants, 234 retapamulin participants and 122 linezolid participants completed the study.

### Pre-assignment

Screening details:

One participant was randomized to retapamulin but received linezolid. This participant is summarized in the linezolid group for all baseline and safety tables, but is summarized in the retapamulin group for all efficacy tables.

### Period 1

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

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | Retapamulin ointment, 1% (weight/weight) plus oral placebo |

Arm description:

Retapamulin ointment was administered topically twice daily (BID) for 5 days. The ointment formulation was to be applied to the infected lesion(s) at a dose of approximately 10 milligrams (mg) per centimeter squared (cm^2). Placebo was to be dosed, depending on participant age, either BID or three times a day (TID) for 10 days. Placebo oral suspension and oral tablet were formulated to appear identical to the linezolid formulations. Adolescent and adult participants (>=12 years of age) were dosed BID with 600 mg placebo tablets, pediatric participants 5 to 11 years of age were dosed with oral suspension at 0.5 milliliters (ml)/kilogram (kg) BID, and pediatric participants less than 5 years of age were dosed with oral suspension at 0.5 ml/kg TID.

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | Retapamulin |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Ointment |
| Routes of administration | Topical use |

Dosage and administration details:

1% (w/w) ointment, twice daily for 5 days

| | |
|---|---|
| **Arm title** | Linezolid plus placebo ointment |

Arm description:

Linezolid was to be dosed, depending on participant age, either BID or TID for 10 days. Adolescent and adult participants (>=12 years of age) were dosed BID with 600 mg tablets for 10 days. Pediatric participants who were 5-11 years of age were dosed with a 100 mg/5 ml oral suspension at a dose of 10 mg/kg BID for 10 days. Pediatric participants who were <5 years of age were dosed with a 100 mg/5 ml oral suspension at a dose of 10 mg/kg TID for 10 days. Placebo ointment was administered topically BID for 5 days.

| | |
|---|---|
| Arm type | Active comparator |
| Investigational medicinal product name | Linezolid |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Oral suspension, Tablet |
| Routes of administration | Oral use |

| | |
|---|---|
| Dosage and administration details: | |
| 600mg tablet, q12h for 10 days (>= 12 years of age) 100 mg/5 mL oral suspension; 10 mg/kg q12h for 10 days (5-11 years of age) 100 mg/5 mL oral suspension; 10 mg/kg q8h for 10 days (<5 years of age) | |
| Investigational medicinal product name | Placebo |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Ointment, Oral suspension, Tablet |
| Routes of administration | Oral use, Topical use |
| Dosage and administration details: | |
| Topical ointment, twice daily for 5 days. Tablet BID for 10 days (>= 12 years of age). Suspension BID for 10 days (5-11 years of age). Suspension TID for 10 days (<5 years of age). | |

| **Number of subjects in period 1** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment |
|---|---|---|
| Started | 267 | 137 |
| Completed | 234 | 122 |
| Not completed | 33 | 15 |
| Consent withdrawn by subject | 3 | 1 |
| Adverse event, non-fatal | 10 | 3 |
| Investigator Discretion | 2 | 3 |
| Lost to follow-up | 2 | 3 |
| Lack of efficacy | 15 | 3 |
| Protocol deviation | 1 | 2 |

## Baseline characteristics

### Reporting groups

| Reporting group title | Retapamulin ointment, 1% (weight/weight) plus oral placebo |
|---|---|

Reporting group description:

Retapamulin ointment was administered topically twice daily (BID) for 5 days. The ointment formulation was to be applied to the infected lesion(s) at a dose of approximately 10 milligrams (mg) per centimeter squared (cm^2). Placebo was to be dosed, depending on participant age, either BID or three times a day (TID) for 10 days. Placebo oral suspension and oral tablet were formulated to appear identical to the linezolid formulations. Adolescent and adult participants (>=12 years of age) were dosed BID with 600 mg placebo tablets, pediatric participants 5 to 11 years of age were dosed with oral suspension at 0.5 milliliters (ml)/kilogram (kg) BID, and pediatric participants less than 5 years of age were dosed with oral suspension at 0.5 ml/kg TID.

| Reporting group title | Linezolid plus placebo ointment |
|---|---|

Reporting group description:

Linezolid was to be dosed, depending on participant age, either BID or TID for 10 days. Adolescent and adult participants (>=12 years of age) were dosed BID with 600 mg tablets for 10 days. Pediatric participants who were 5-11 years of age were dosed with a 100 mg/5 ml oral suspension at a dose of 10 mg/kg BID for 10 days. Pediatric participants who were <5 years of age were dosed with a 100 mg/5 ml oral suspension at a dose of 10 mg/kg TID for 10 days. Placebo ointment was administered topically BID for 5 days.

| **Reporting group values** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | Total |
|---|---|---|---|
| Number of subjects | 267 | 137 | 404 |
| Age categorical | | | |
| Units: Subjects | | | |
| Age continuous | | | |
| Baseline characteristics were collected in all participants in the Intent-to-Treat Clinical (ITTC) Population, comprised of all randomized participants who took at least one dose of study medication. Three participants in both treatment groups were randomized but did not receive study medication. | | | |
| Units: years | | | |
| arithmetic mean | 34.6 | 33.8 | |
| standard deviation | ± 21.37 | ± 22.38 | - |
| Gender categorical | | | |
| Baseline characterisitcs were collected in all participants in the Intent-to-Treat Clinical (ITTC) Popluation, comprised of all randomized participants who took at least one dose of study medication. Three participants in both treatment groups were randomized but did not receive study medication. | | | |
| Units: Subjects | | | |
| Female | 108 | 49 | 157 |
| Male | 159 | 88 | 247 |
| Race/Ethnicity, Customized | | | |
| Baseline characterisitcs were collected in all participants in the Intent-to-Treat Clinical (ITTC) Popluation, comprised of all randomized participants who took at least one dose of study medication. Three participants in both treatment groups were randomized but did not receive study medication. | | | |
| Units: Subjects | | | |
| African American/African Heritage | 16 | 10 | 26 |
| American Indian or Alaska Native | 5 | 0 | 5 |
| Central/South Asian Heritage | 1 | 1 | 2 |
| East Asian Heritage | 0 | 1 | 1 |
| Japanese Heritage | 5 | 2 | 7 |

| | | | |
|---|---|---|---|
| South East Asian Heritage | 3 | 0 | 3 |
| Native Hawaiian or other Pacific Islander | 5 | 1 | 6 |
| Arabic/North African Heritage | 0 | 3 | 3 |
| White/Caucasian/European | 222 | 118 | 340 |
| White - Mixed Race | 10 | 1 | 11 |

## End points

### End points reporting groups

| Reporting group title | Retapamulin ointment, 1% (weight/weight) plus oral placebo |
|---|---|

Reporting group description:

Retapamulin ointment was administered topically twice daily (BID) for 5 days. The ointment formulation was to be applied to the infected lesion(s) at a dose of approximately 10 milligrams (mg) per centimeter squared (cm^2). Placebo was to be dosed, depending on participant age, either BID or three times a day (TID) for 10 days. Placebo oral suspension and oral tablet were formulated to appear identical to the linezolid formulations. Adolescent and adult participants (>=12 years of age) were dosed BID with 600 mg placebo tablets, pediatric participants 5 to 11 years of age were dosed with oral suspension at 0.5 milliliters (ml)/kilogram (kg) BID, and pediatric participants less than 5 years of age were dosed with oral suspension at 0.5 ml/kg TID.

| Reporting group title | Linezolid plus placebo ointment |
|---|---|

Reporting group description:

Linezolid was to be dosed, depending on participant age, either BID or TID for 10 days. Adolescent and adult participants (>=12 years of age) were dosed BID with 600 mg tablets for 10 days. Pediatric participants who were 5-11 years of age were dosed with a 100 mg/5 ml oral suspension at a dose of 10 mg/kg BID for 10 days. Pediatric participants who were <5 years of age were dosed with a 100 mg/5 ml oral suspension at a dose of 10 mg/kg TID for 10 days. Placebo ointment was administered topically BID for 5 days.

### Primary: Number of participants achieving clinical response at follow-up who had methicillin-resistant Staphylococcus aureus (MRSA) as a baseline pathogen

| End point title | Number of participants achieving clinical response at follow-up who had methicillin-resistant Staphylococcus aureus (MRSA) as a baseline pathogen |
|---|---|

End point description:

Follow-up is defined as 7-9 days post-therapy: Day 12-14 for retapamulin; Day 17-19 for linezolid. Clinical success at follow-up was defined as the resolution of clinically meaningful signs and symptoms of infection recorded at baseline, including a pus/exudate skin infection rating scale (SIRS) score of "0." The SIRS is used by the investigator to evaluate infected lesions. Scores on the SIRS range from 0 (absent) to 6 (severe). Intent-to-Treat MRSA (ITTMRSA) Population: all randomized participants who took at least one dose of study medication and who had an MRSA isolated at baseline.

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

End point timeframe:

7-9 days post-therapy; Day 12-14 for retapamulin and Day 17-19 for linezolid

| **End point values** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72[1] | 38[2] | | |
| Units: participants | 41 | 32 | | |

Notes:

[1] - Intent-to-Treat MRSA (ITTMRSA) Population.

[2] - Intent-to-Treat MRSA (ITTMRSA) Population.

### Statistical analyses

| **Statistical analysis title** | Statistical analysis 1 |
|---|---|
| Comparison groups | Linezolid plus placebo ointment v Retapamulin ointment, 1% (weight/weight) plus oral placebo |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | percentage of participants |
| Point estimate | 56.9 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 45.5 |
| upper limit | 68.4 |

| **Statistical analysis title** | Statistical analysis 2 |
|---|---|
| Comparison groups | Retapamulin ointment, 1% (weight/weight) plus oral placebo v Linezolid plus placebo ointment |
| Number of subjects included in analysis | 110 |
| Analysis specification | Pre-specified |
| Analysis type | |
| Parameter estimate | Percentage of participants |
| Point estimate | 84.2 |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| lower limit | 72.6 |
| upper limit | 95.8 |

## Secondary: Number of participants achieving microbiological response (MR) at follow-up (FU) who had MRSA as a baseline pathogen (BP)

| End point title | Number of participants achieving microbiological response (MR) at follow-up (FU) who had MRSA as a baseline pathogen (BP) |
|---|---|

End point description:

MR was defined as microbiological success if, (1) for participants (par.) whose clinical outcome at end of therapy (EOT) was "clinical success (CS)/improvement," the BP was eradicated/presumed to be eradicated at EOT, or the BP was present at EOT and absent at FU, or the BP was eradicated/presumed to be eradicated at EOT, or the BP was present at EOT and par. was a "CS" such that no culture was obtained due to lack of culturable material secondary to adequate clinical response; or (2) a pathogen not previously identified at baseline was isolated at FU in a par. identified at FU as a "CS." Intent-to-Treat MRSA (ITTMRSA) Population: all randomized participants who took at least one dose of study medication and who had an MRSA isolated at baseline.

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

End point timeframe:

7-9 days post-therapy; Day 12-14 for retapamulin and Day 17-19 for linezolid

| End point values | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72[3] | 38[4] | | |
| Units: participants | 41 | 32 | | |

Notes:

[3] - Intent-to-Treat MRSA (ITTMRSA) Population.

[4] - Intent-to-Treat MRSA (ITTMRSA) Population.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with clinical response at follow-up

| End point title | Number of participants with clinical response at follow-up |
|---|---|

End point description:

Follow-up is defined as 7-9 days post-therapy: Day 12-14 for retapamulin; Day 17-19 for linezolid. Clinical success at follow-up was defined as the resolution of clinically meaningful signs and symptoms of infection recorded at baseline, including a pus/exudate skin infection rating scale (SIRS) score of "0." The SIRS is used by the investigator to evaluate infected lesions. Scores on the SIRS range from 0 (absent) to 6 (severe). Intent-to-Treat Clinical (ITTC) Population: all randomized participants (par.) who took at least one dose of study medication. One par. was randomized to retapamulin but received linezolid. This par. is summarized in the linezolid group for all baseline and safety tables, but is summarized in the retapamulin group for all efficacy tables.

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

End point timeframe:

7-9 days post-therapy; Day 12-14 for retapamulin and Day 17-19 for linezolid

| End point values | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 267[5] | 137[6] | | |
| Units: participants | 161 | 112 | | |

Notes:

[5] - One par. was randomized to retapamulin but received linezolid; therefore, n=268.

[6] - One par. was randomized to retapamulin but received linezolid; therefore, n=136.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants who achieved microbiological response (MR) at follow-up (FU) who had a baseline pathogen (BP)

| End point title | Number of participants who achieved microbiological response (MR) at follow-up (FU) who had a baseline pathogen (BP) |
|---|---|

End point description:

MR was defined as microbiological success if, (1) for participants (par.) whose clinical outcome at end of therapy (EOT) was “clinical success (CS)/improvement,” the BP was eradicated/presumed to be

eradicated at EOT, or the BP was present at EOT and absent at FU, or the BP was eradicated/presumed to be eradicated at EOT, or the BP was present at EOT and par. was a "CS" such that no culture was obtained due to lack of culturable material secondary to adequate clinical response; or (2) a pathogen not previously identified at baseline was isolated at FU in a par. identified at FU as a "CS." Intent-to-Treat Bacteriology (ITTB) Population: all randomized participants who took at least one dose of study medication and who had a pathogen
isolated at base line .

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

End point timeframe:

7-9 days post-therapy; Day 12-14 for retapamulin and Day 17-19 for linezolid

| **End point values** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 177[7] | 78[8] | | |
| Units: participants | 100 | 65 | | |

Notes:

[7] - Intent-to-Treat Bacteriology (ITTB) Population.

[8] - Intent-to-Treat Bacteriology (ITTB) Population.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with the indicated clinical (clin.) outcome at the end of therapy (EOT) who had MRSA as a baseline (BL) pathogen

| End point title | Number of participants with the indicated clinical (clin.) outcome at the end of therapy (EOT) who had MRSA as a baseline (BL) pathogen |
|---|---|

End point description:

Clin. improvement (imp.)=imp. of signs/symptoms (S/S) of infection recorded at BL to such an extent that no further antimicrobial therapy is necessary. Clin. failure (CF)=insufficient imp./deterioration of S/S of the infection recorded at BL, such that additional antibiotic therapy is required. Clin. success at follow-up (FU)=resolution of clinically meaningful S/S of infection recorded at BL, including a pus/exudate SIRS score of "0." Unable to determine (UTD)=refusal to consent to a clin. examination, lost to FU. Participants who are "CF"/"UTD" at EOT are considered such at FU as well.

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

End point timeframe:

2-4 days post-therapy; Day 7-9 for retapamulin and Day 12-14 for linezolid

| **End point values** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72[9] | 38[10] | | |
| Units: participants | | | | |
| Clinical success | 20 | 28 | | |

| | | | | |
|---|---|---|---|---|
| Clinical improvement | 42 | 9 | | |
| Clinical failure | 8 | 1 | | |
| Unable to determine | 2 | 0 | | |

Notes:

[9] - ITTMRSA Population

[10] - ITTMRSA Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with the indicated microbiological outcome at the end of therapy who had MRSA as a baseline (BL) pathogen

| End point title | Number of participants with the indicated microbiological outcome at the end of therapy who had MRSA as a baseline (BL) pathogen |
|---|---|

End point description:

Eradication is the elimination of BL pathogens. Presumed eradication and presumed improvement are clinical outcomes of success or improvement, respectively, such that no culture was obtained due to lack of culturable material, secondary to adequate clinical response, and is documented in the electronic Case Report Form. Persistence is defined as BL pathogens still being present. Presumed persistence is defined as a participant that is a clinical failure with no obtained culture. "Unable to determine" was used if no determination of BL pathogen microbiological response could be made.

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

End point timeframe:

2-4 days post-therapy; Day 7-9 for retapamulin and Day 12-14 for linezolid

| **End point values** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 72[11] | 38[12] | | |
| Units: participants | | | | |
| Eradication | 1 | 0 | | |
| Presumed eradication | 20 | 28 | | |
| Presumed improvement | 42 | 9 | | |
| Persistence | 4 | 1 | | |
| Presumed persistence | 4 | 0 | | |
| Unable to determine | 1 | 0 | | |

Notes:

[11] - ITTMRSA Population

[12] - ITTMRSA Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with the indicated clinical (clin.) outcome at the end of therapy (EOT)

| End point title | Number of participants with the indicated clinical (clin.) outcome at the end of therapy (EOT) |
|---|---|

End point description:

Clin. improvement (imp.)=imp. of signs/symptoms (S/S) of infection recorded at BL to such an extent that no further antimicrobial therapy is necessary. Clin. failure (CF)=insufficient imp./deterioration of S/S of the infection recorded at BL, such that additional antibiotic therapy is required. Clin. success at follow-up (FU)=resolution of clinically meaningful S/S of infection recorded at BL, including a pus/exudate SIRS score of "0." Unable to determine (UTD)=refusal to consent to a clin. examination, lost to FU. Participants who are "CF"/"UTD" at EOT are considered such at FU as well. ITTC Population. One par. was randomized to retapamulin but received linezolid. This par. is summarized in the linezolid group for all baseline and safety tables, but is summarized in the retapamulin group for all efficacy tables.

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

End point timeframe:

2-4 days post-therapy; Day 7-9 for retapamulin and Day 12-14 for linezolid

| **End point values** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 267[13] | 137[14] | | |
| Units: participants | | | | |
| Clinical success | 92 | 96 | | |
| Clinical improvement | 155 | 34 | | |
| Clinical failure | 16 | 4 | | |
| Unable to determine | 5 | 2 | | |

Notes:

[13] - One par. was randomized to retapamulin but received linezolid; therefore, n=268.

[14] - One par. was randomized to retapamulin but received linezolid; therefore, n=136.

## Statistical analyses

No statistical analyses for this end point

## Secondary: Number of baseline pathogens with the indicated microbiological outcome at the end of therapy

| End point title | Number of baseline pathogens with the indicated microbiological outcome at the end of therapy |
|---|---|

End point description:

Eradication is the elimination of BL pathogens. Presumed eradication and presumed improvement are clinical outcomes of success or improvement, respectively, such that no culture was obtained due to lack of culturable material, secondary to adequate clinical response, and is documented in the electronic Case Report Form. Persistence is defined as BL pathogens still being present. Presumed persistence is defined as a participant that is a clinical failure with no obtained culture. "Unable to determine" was used if no determination of BL pathogen microbiological response could be made.

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

End point timeframe:

2-4 days post-therapy; Day 7-9 for retapamulin and Day 12-14 for linezolid

| End point values | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 177[15] | 78[16] | | |
| Units: pathogens | | | | |
| Eradication | 2 | 1 | | |
| Presumed eradication | 63 | 70 | | |
| Presumed improvement | 120 | 21 | | |
| Persistence | 7 | 1 | | |
| Presumed persistence | 9 | 1 | | |
| Unable to determine | 1 | 0 | | |

Notes:

[15] - ITTB Population

[16] - ITTB Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Number of participants with therapeutic response at follow-up

| End point title | Number of participants with therapeutic response at follow-up |
|---|---|

End point description:

Therapeutic response is defined as the combined clinical and microbiological response. Therapeutic response iss a measure of the overall efficacy response, and a therapeutic success refers to participants who had been deemed both a "clinical success" and a "microbiological success." All other combinations (other than "clinical success" + "microbiological success") were deemed failures for therapeutic response.

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

End point timeframe:

7-9 days post-therapy; Day 12-14 for retapamulin and Day 17-19 for linezolid

| End point values | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 177[17] | 78[18] | | |
| Units: participants | 100 | 65 | | |

Notes:

[17] - ITTB Population

[18] - ITTB Population

### Statistical analyses

No statistical analyses for this end point

## Secondary: Mean scores on the Skin Infection Rating Scale at Visits 1, 2, 3, 4, and 5

| End point title | Mean scores on the Skin Infection Rating Scale at Visits 1, 2, 3, 4, and 5 |
|---|---|

End point description:

The investigator evaluated skin infections by grading the infected lesion for exudate (a fluid that leaks out of blood vessels into surrounding tissue)/pus, crusting, erythema (redness of the skin)/ inflammation (E/I), tissue warmth, tissue edema (swelling), itching, and pain, according to the Skin Infection Rating Scale. All parameters were graded on a scale of 0 (absent) to 6 (severe). The total score is calculated by summing the individual scores from the 7 parameters; the total score ranges from 0 to 42. ITTC Population. Only participants with non-missing Skin Infection Rating Scale scores were included in this analysis. One par. was randomized to retapamulin but received linezolid. This par. is summarized in the linezolid group for all baseline and safety tables, but is summarized in the retapamulin group for all efficacy tables.

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

End point timeframe:

Visits 1 (Day 1), 2 (Day 3-4), 3 (Day 7-9), 4 (Day 12-14), and 5 (Day 17-19)

| **End point values** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 267[19] | 137[20] | | |
| Units: scores on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Pus/exudate, Visit 1, n=268, 136 | 3.6 (± 0.82) | 3.6 (± 0.8) | | |
| Pus/exudate, Visit 2, n=265, 135 | 1.7 (± 1.37) | 1.4 (± 1.25) | | |
| Pus/exudate, Visit 3, n=255, 130 | 0.6 (± 1.05) | 0.4 (± 0.74) | | |
| Pus/exudate, Visit 4, n=237, 125 | 0.2 (± 0.59) | 0.1 (± 0.34) | | |
| Pus/exudate, Visit 5, n=238, 122 | 0.1 (± 0.39) | 0 (± 0.29) | | |
| Crusting, Visit 1, n=268, 136 | 2.2 (± 1.48) | 2.1 (± 1.49) | | |
| Crusting, Visit 2, n=265, 135 | 1.3 (± 1.21) | 1.2 (± 1.15) | | |
| Crusting, Visit 3, n=255, 130 | 0.9 (± 1.08) | 0.8 (± 0.91) | | |
| Crusting, Visit 4, n=237, 125 | 0.6 (± 0.95) | 0.5 (± 0.83) | | |
| Crusting, Visit 5, n=238, 122 | 0.3 (± 0.59) | 0.3 (± 0.73) | | |
| E/I, Visit 1, n=268, 136 | 3.4 (± 1.09) | 3.4 (± 1.08) | | |
| E/I, Visit 2, n=265, 135 | 2.2 (± 1.19) | 2.2 (± 1.26) | | |
| E/I, Visit 3, n=255, 130 | 1.1 (± 1.15) | 1 (± 0.93) | | |
| E/I, Visit 4, n=237, 125 | 0.5 (± 0.69) | 0.5 (± 0.73) | | |
| E/I, Visit 5, n=238, 122 | 0.2 (± 0.54) | 0.2 (± 0.54) | | |
| Tissue warmth, Visit 1, n=268, 136 | 2.8 (± 1.33) | 2.6 (± 1.29) | | |
| Tissue warmth, Visit 2, n=265, 135 | 1.4 (± 1.22) | 1.3 (± 1.22) | | |
| Tissue warmth, Visit 3, n=255, 130 | 0.6 (± 0.97) | 0.4 (± 0.69) | | |
| Tissue warmth, Visit 4, n=237, 125 | 0.1 (± 0.41) | 0.1 (± 0.34) | | |
| Tissue warmth, Visit 5, n=238, 122 | 0.1 (± 0.38) | 0 (± 0.2) | | |
| Tissue edema, Visit 1, n=268, 136 | 2.8 (± 1.24) | 2.7 (± 1.3) | | |
| Tissue edema, Visit 2, n=265, 135 | 1.6 (± 1.23) | 1.5 (± 1.19) | | |
| Tissue edema, Visit 3, n=255, 130 | 0.7 (± 1.02) | 0.7 (± 0.86) | | |
| Tissue edema, Visit 4, n=237, 125 | 0.3 (± 0.6) | 0.2 (± 0.55) | | |
| Tissue edema, Visit 5, n=238, 122 | 0.1 (± 0.35) | 0.1 (± 0.36) | | |
| Itching, Visit 1, n=268, 136 | 1.6 (± 1.51) | 1.8 (± 1.51) | | |
| Itching, Visit 2, n=265, 135 | 1 (± 1.27) | 0.9 (± 1.11) | | |
| Itching, Visit 3, n=255, 130 | 0.7 (± 1.24) | 0.6 (± 1.08) | | |
| Itching, Visit 4, n=237, 125 | 0.3 (± 0.79) | 0.4 (± 0.76) | | |

| | | | | |
|---|---|---|---|---|
| Itching, Visit 5, n=238, 122 | 0.1 (± 0.42) | 0.2 (± 0.66) | | |
| Pain, Visit 1, n=268, 136 | 3.2 (± 1.57) | 3 (± 1.65) | | |
| Pain, Visit 2, n=265, 135 | 1.5 (± 1.56) | 1.2 (± 1.39) | | |
| Pain, Visit 3, n=255, 130 | 0.6 (± 1.14) | 0.4 (± 0.96) | | |
| Pain, Visit 4, n=237, 125 | 0.2 (± 0.6) | 0.1 (± 0.56) | | |
| Pain, Visit 5, n=238, 122 | 0.1 (± 0.39) | 0.1 (± 0.45) | | |
| Total score, Visit 1, n=268, 136 | 19.5 (± 5.69) | 19.2 (± 5.56) | | |
| Total score, Visit 2, n=265, 135 | 10.7 (± 6.78) | 9.7 (± 6.32) | | |
| Total score, Visit 3, n=255, 130 | 5.2 (± 5.83) | 4.1 (± 4.16) | | |
| Total score, Visit 4, n=237, 125 | 3.6 (± 6.13) | 2.5 (± 4.13) | | |
| Total score, Visit 5, n=238, 122 | 2.5 (± 6.14) | 1.6 (± 3.92) | | |

Notes:

[19] - One par. was randomized to retapamulin but received linezolid; therefore, n=268.

[20] - One par. was randomized to retapamulin but received linezolid; therefore, n=136.

### Statistical analyses

No statistical analyses for this end point

## Secondary: Mean wound size at Visits 1, 2, 3, 4, and 5

| End point title | Mean wound size at Visits 1, 2, 3, 4, and 5 |
|---|---|

End point description:

Lesion sized was measured in centimeters squared at Visits 1, 2, 3, 4, and 5. ITTC Population. Only participants with non-missing data were included in this analysis. One par. was randomized to retapamulin but received linezolid. This par. is summarized in the linezolid group for all baseline and safety tables, but is summarized in the retapamulin group for all efficacy tables.

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

End point timeframe:

Visits 1 (Day 1), 2 (Day 3-4), 3 (Day 7-9), 4 (Day 12-14), and 5 (Day 17-19)

| **End point values** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | | |
| Number of subjects analysed | 267[21] | 137[22] | | |
| Units: centimeters squared (cm^2) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Visit 1, n=268, 136 | 7.942 (± 13.3124) | 5.62 (± 9.6215) | | |
| Visit 2, n=265, 135 | 4.963 (± 8.5492) | 4.115 (± 9.4305) | | |
| Visit 3, n=255, 130 | 3.27 (± 10.8663) | 1.776 (± 6.7537) | | |
| Visit 4, n=237, 125 | 1.556 (± 5.2201) | 0.812 (± 3.4217) | | |
| Visit 5, n=237, 122 | 0.741 (± 3.5977) | 0.588 (± 3.3623) | | |

Notes:

[21] - One par. was randomized to retapamulin but received linezolid; therefore, n=268.

[22] - One par. was randomized to retapamulin but received linezolid; therefore, n=136

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

All on-treatment serious adverse events (SAEs) and non-serious AEs were collected from the start of study treatment day 1 and until the follow-up visit day 19.

Adverse event reporting additional description:

Serious adverse events and non-serious adverse events were collected in the Intent-to-Treat Clinical (ITTC) Population, comprised of all randomized participants who took at least one dose of study medication.

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

### Dictionary used

| | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 13.1 |

### Reporting groups

| | |
|---|---|
| Reporting group title | Retapamulin ointment, 1% (weight/weight) plus oral placebo |

Reporting group description:

Retapamulin ointment was administered topically twice daily (BID) for 5 days. The ointment formulation was to be applied to the infected lesion(s) at a dose of approximately 10 milligrams (mg) per centimeter squared (cm^2). Placebo was to be dosed, depending on participant age, either BID or three times a day (TID) for 10 days. Placebo oral suspension and oral tablet were formulated to appear identical to the linezolid formulations. Adolescent and adult participants (>=12 years of age) were dosed BID with 600 mg placebo tablets, pediatric participants 5 to 11 years of age were dosed with oral suspension at 0.5 milliliters (ml)/kilogram (kg) BID, and pediatric participants less than 5 years of age were dosed with oral suspension at 0.5 ml/kg TID.

| | |
|---|---|
| Reporting group title | Linezolid plus placebo ointment |

Reporting group description:

Linezolid was to be dosed, depending on participant age, either BID or TID for 10 days. Adolescent and adult participants (>=12 years of age) were dosed BID with 600 mg tablets for 10 days. Pediatric participants who were 5-11 years of age were dosed with a 100 mg/5 ml oral suspension at a dose of 10 mg/kg BID for 10 days. Pediatric participants who were <5 years of age were dosed with a 100 mg/5 ml oral suspension at a dose of 10 mg/kg TID for 10 days. Placebo ointment was administered topically BID for 5 days.

| **Serious adverse events** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 3 / 267 (1.12%) | 3 / 137 (2.19%) | |
| number of deaths (all causes) | 0 | 0 | |
| number of deaths resulting from adverse events | | | |
| Injury, poisoning and procedural complications | | | |
| Hip fracture | | | |
| subjects affected / exposed | 0 / 267 (0.00%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Infections and infestations | | | |

| | | | |
|---|---|---|---|
| Cellulitis | | | |
| subjects affected / exposed | 2 / 267 (0.75%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 2 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Staphylococcal infection | | | |
| subjects affected / exposed | 1 / 267 (0.37%) | 0 / 137 (0.00%) | |
| occurrences causally related to treatment / all | 0 / 1 | 0 / 0 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Metabolism and nutrition disorders | | | |
| Hypoglycaemia | | | |
| subjects affected / exposed | 0 / 267 (0.00%) | 1 / 137 (0.73%) | |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 1 | |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | |
| Hyponatraemia | | | |
| subjects affected / exposed | 0 / 267 (0.00%) | 1 / 137 (0.73%) | |
| 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: 5 %

| **Non-serious adverse events** | Retapamulin ointment, 1% (weight/weight) plus oral placebo | Linezolid plus placebo ointment | |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 13 / 267 (4.87%) | 22 / 137 (16.06%) | |
| Gastrointestinal disorders | | | |
| Diarrhea | | | |
| subjects affected / exposed | 8 / 267 (3.00%) | 16 / 137 (11.68%) | |
| occurrences (all) | 8 | 16 | |
| Nausea | | | |
| subjects affected / exposed | 6 / 267 (2.25%) | 10 / 137 (7.30%) | |
| occurrences (all) | 6 | 10 | |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported