Clinical trial results:
A randomized, double-blind, multicenter, superiority Phase III study to assess the safety and efficacy of Topical Retapamulin Ointment 1%, applied twice daily versus Placebo Ointment in Adults and Children in the treatment of Secondarily- Infected Traumatic Lesions

Summary

EudraCT number	2015-004903-22
Trial protocol	Outside EU/EEA
Global end of trial date	02 October 2009

Results information

Result version number	v1 (current)
This version publication date	29 December 2016
First version publication date	29 December 2016

Trial information

Trial identification

Sponsor protocol code	TOC110977

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	23 December 2009
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	02 October 2009
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

TBD

Protection of trial subjects:

Not Applicable

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 May 2008
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	Argentina: 21
Country: Number of subjects enrolled	Brazil: 4
Country: Number of subjects enrolled	India: 42
Country: Number of subjects enrolled	South Africa: 236
Country: Number of subjects enrolled	United States: 204
Worldwide total number of subjects	507
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)	6
Children (2-11 years)	82
Adolescents (12-17 years)	34
Adults (18-64 years)	362
From 65 to 84 years	21

85 years and over	2

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

A total of 508 participants were randomized. One participant did not receive treatment; thus, no data were collected for this participant. Only 507 participants were included in the analysis.

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

Arm description:

Topical retapamulin ointment, 1% twice daily for 5 days

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:

This was provided as approximately 10 grams of an off-white smooth ointment and was applied to the infected lesion(s) at a dose of approximately 10 mg per cm2 twice daily for 5 days; the maximum amount applied per application was to be approximately 1 gram

Arm title	Placebo

Arm description:

Matching placebo

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Ointment
Routes of administration	Topical use

Dosage and administration details:

This was provided as approximately 10 grams of an off-white smooth ointment and was applied to the infected lesion(s) at a dose of approximately 10 mg per cm2 twice daily for 5 days; the maximum amount applied per application was to be approximately 1 gram

Number of subjects in period 1	Retapamulin	Placebo
Started	343	164
Completed	322	141
Not completed	21	23
Physician decision	2	-
Consent withdrawn by subject	1	2
Adverse event, non-fatal	4	3
Unknown	1	2
Lost to follow-up	2	1
Lack of efficacy	10	15
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Retapamulin
Reporting group description:	
Topical retapamulin ointment, 1% twice daily for 5 days	
Reporting group title	Placebo
Reporting group description:	
Matching placebo	

Reporting group values	Retapamulin	Placebo	Total
Number of subjects	343	164	507
Age categorical			
Units: Subjects			

Age continuous			
Age continuous description			
Units: years			
arithmetic mean	32.6	28.6	
standard deviation	± 18.77	± 18.32	-
Gender categorical			
Gender categorical description			
Units: Subjects			
Female	144	63	207
Male	199	101	300
Race/Ethnicity, Customized			
Units: Subjects			
African American/African Heritage	144	71	215
American Indian or Alaskan Native	9	3	12
Asian - Central / South Asian Heritage	0	1	1
Asian - East Asian Heritage	4	2	6
Asian - South East Asian Heritage	33	15	48
Native Hawaiian or Other Pacific Islander	1	2	3
White - Arabic/North African Heritage	1	0	1
White - White/Caucasian/European Heritage	132	61	193
Mixed Race	19	9	28

End points

End points reporting groups

Reporting group title	Retapamulin
Reporting group description:	
Topical retapamulin ointment, 1% twice daily for 5 days	
Reporting group title	Placebo
Reporting group description:	
Matching placebo	

Primary: Number of Participants with Clinical Success and Failure at Follow-up (7-9 days post therapy) for the Primary Efficacy Population

End point title	Number of Participants with Clinical Success and Failure at Follow-up (7-9 days post therapy) for the Primary Efficacy Population

End point description:

"Clinical Success" at follow-up was defined as "Resolution of clinically meaningful signs and symptoms of infection recorded at baseline including a pus/exudate Skin Infection Rating Scale (SIRS) score of "0". Clinical response at follow-up was classified as "Clinical Failure" for all other cases. The SIRS consists of seven items (pus/exudates, crusting, erythema/inflammation, tissue warmth, tissue edema, itching and pain). Each item has a score ranging from 0 to 6 (0=absent, 6=severe). The SIRS total score was calculated as the sum of the scores of all 7 SIRS items. Primary Efficacy Population:ITTC participants with base line pus/exudate >=3 who were enrolled under the original protocol with data captured under eCRF V1 and who were enrolled under protocol amendments with data captured under eCRF V2; ITTC (Intent-to-treat Clinical): all randomized par. who received at least one dose of study medication.

End point type	Primary

End point timeframe:

Days 12-14

End point values	Retapamulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[1]	113		
Units: participants				
Clinical Success	184	75		
Clinical Failure	62	38		

Notes:

[1] - Primary Efficacy Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Retapamulin v Placebo

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.098
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	8.4
Confidence interval	
level	95 %
sides	2-sided
lower limit	-1.6
upper limit	18.4

Secondary: Number of Participants with Clinical Success and Failure at Follow-up (7-9 days post therapy) for the Intent-to-Treat Bacteriology (ITTB) subset of the Primary Efficacy Population

End point title	Number of Participants with Clinical Success and Failure at Follow-up (7-9 days post therapy) for the Intent-to-Treat Bacteriology (ITTB) subset of the Primary Efficacy Population

End point description:

"Clinical Success" at follow-up was defined as "Resolution of clinically meaningful signs and symptoms of infection recorded at baseline including a pus/exudate Skin Infection Rating Scale (SIRS) score of "0". Clinical response at follow-up was classified as "Clinical Failure" for all other cases. The SIRS consists of seven items (pus/exudates, crusting, erythema/inflammation, tissue warmth, tissue edema, itching and pain). Each item has a score ranging from 0 to 6 (0=absent, 6=severe). The SIRS total score was calculated as the sum of the scores of all 7 SIRS items. ITTB subset of Primary Efficacy Population: participants in the Primary Efficacy Population (see analysis population description in the Primary Outcome
section) who had at least one pathogen isolated at the base line visit.

End point type	Secondary

End point timeframe:

Days 12-14

End point values	Retapamulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182[2]	84		
Units: participants				
Clinical Success	139	54		
Clinical Failure	43	30		

Notes:

[2] - ITTB subset of Primary Efficacy Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Retapamulin

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	23.6

Secondary: Number of Participants with Microbiological Success and Failure at Follow-up (7-9 days post therapy)

End point title	Number of Participants with Microbiological Success and Failure at Follow-up (7-9 days post therapy)

End point description:

The "by pathogen" microbiological outcome was determined by comparing the baseline culture results to those at follow-up. The "by subject" microbiological response was "Microbiological Success" if the microbiological outcomes for all baseline pathogens (bps) belong to "Eradication" (elimination of bps), "Presumed Eradication" (clinical outcome was success; no culture was obtained due to lack of culturable material), or "Colonization" (previously unidentified pathogen is identified at end of therapy in participant who is resolved/improved); otherwise, response was "Microbiological Failure".

End point type	Secondary

End point timeframe:

Days 12-14

End point values	Retapamulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182[3]	84		
Units: participants				
Microbiological Success	139	54		
Microbiological Failure	43	30		

Notes:

[3] - ITTB subset of Primary Efficacy Population

Statistical analyses

Statistical analysis title	Statistical analysis 1
Comparison groups	Placebo v Retapamulin

Number of subjects included in analysis	266
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.04
Method	Chi-squared
Parameter estimate	Risk difference (RD)
Point estimate	12.1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.6
upper limit	23.6

Secondary: Number of Participants with the Indicated Clinical Outcome at End of Therapy (2-4 days post therapy)

End point title	Number of Participants with the Indicated Clinical Outcome at End of Therapy (2-4 days post therapy)

End point description:

Clinical outcome is determined by the investigator based on signs and symptoms (S/S) at the end of therapy evaluation. The 4 clincal outcome categories are: clinical success, resolution of clinically meaningful S/S of infection recorded at baseline (BL), including a pus/exudates score of 0; clinical improvement, improvement of S/S of infection recorded at BL to such an extent that no further antimicrobial therapy is necessary; clinical failure, insufficient improvement of deterioration of S/S of infection recorded at BL such that additional antibiotic therapy is required; unable to determine.

End point type	Secondary

End point timeframe:

Days 7-9

End point values	Retapamulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	246[4]	113		
Units: participants				
Clinical Success	130	52		
Clinical Improvement	102	45		
Clinical Failure	11	14		
Unable to Determine	3	2		

Notes:

[4] - Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Baseline Pathogens with the Indicated Microbiological Outcome at End of Therapy (2-4 days post therapy)

End point title	Number of Baseline Pathogens with the Indicated Microbiological Outcome at End of Therapy (2-4 days post therapy)

End point description:

The "by pathogen" microbiological outcome was determined by comparing the baseline culture results to those at follow-up. The results presented below pooled all baseline pathogens (bps). Eradication: elimination of bps. Presumed Eradication: clinical outcome was success; no culture was obtained due to lack of culturable material. Presumed Improvement: clinical outcome was improvement such that no culture was obtained due to lack of culturable material. Persistence: bps still present. Presumed persistence: clinical failure and no culture was obtained.

End point type	Secondary

End point timeframe:

Days 7-9

End point values	Retapamulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	243[5]	110		
Units: baseline pathogens				
Eradication	4	5		
Presumed Eradication	137	49		
Presumed Improvement	94	35		
Persistence	3	13		
Presumed Persistence	5	8		

Notes:

[5] - ITTB subset of Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants with Therapeutic Success and Failure at Follow-up (7-9 days post therapy)

End point title	Number of Participants with Therapeutic Success and Failure at Follow-up (7-9 days post therapy)

End point description:

"Therapeutic Success (Succ)" was referred to as both "Clinical Succ" and "Microbiological (Micro) Succ" at Follow-up. "Clinical Succ" was the "Resolution of baseline signs/symptoms of infection with a pus score of "0." A participant was "Micro Succ" if the micro outcome for all baseline pathogens (bps) belonged to "Eradication" (elimination of bps), "Presumed Eradication" (clinical outcome is success; no culturable material), or "Colonization" (new pathogen is identified at end of therapy in participants who are resolved/improved). All other combinations were deemed "Therapeutic Failures."

End point type	Secondary

End point timeframe:

Follow-up (Days 12-14)

End point values	Retapamulin	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	182[6]	84		
Units: participants				
Success	139	54		
Failure	43	30		

Notes:
[6] - ITTB subset of Primary Efficacy Population

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events (AEs) were recorded from the first dose of study medication until study completion. Serious AEs (SAEs) were collected from the time of consent and continued until study completion (including the Follow-up Period).

Adverse event reporting additional description:

AEs were collected for all randomized participants (par.) who received at least one dose of study medications (i.e., ITTC Population). Safety data were analyzed based on the actual treatment received. One par. who was randomized to retapamulin treatment but actually received placebo was included in the placebo arm for the safety analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	12.1

Reporting groups

Reporting group title	Retapamulin

Reporting group description:

Topical retapamulin ointment, 1% twice daily for 5 days

Reporting group title	Placebo

Reporting group description:

Matching placebo

Serious adverse events	Retapamulin	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 342 (0.29%)	1 / 165 (0.61%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Cardiac disorders			
Myocardial infarction			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (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			
Pneumococcal pneumonia			
subjects affected / exposed	0 / 342 (0.00%)	1 / 165 (0.61%)	
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	Retapamulin	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 342 (2.34%)	4 / 165 (2.42%)	
Injury, poisoning and procedural complications			
Wound secretion			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Tension headache			
subjects affected / exposed	0 / 342 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Application site pain			
subjects affected / exposed	5 / 342 (1.46%)	0 / 165 (0.00%)	
occurrences (all)	5	0	
Condition aggravated			
subjects affected / exposed	3 / 342 (0.88%)	1 / 165 (0.61%)	
occurrences (all)	3	1	
Pyrexia			
subjects affected / exposed	0 / 342 (0.00%)	3 / 165 (1.82%)	
occurrences (all)	0	3	
Application site paraesthesia			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Application site pruritus			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Eye pruritus			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Ocular hyperaemia			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Nausea			
subjects affected / exposed	0 / 342 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Dermatitis			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Abscess			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Cellulitis			
subjects affected / exposed	0 / 342 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	1 / 342 (0.29%)	0 / 165 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	0 / 342 (0.00%)	1 / 165 (0.61%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
25 November 2008	This amendment was conducted to: make a change to the entry criterion regarding minimum pus/exudate SIRS score; revise the exclusion criterion regarding surgical intervention and other investigational drug use; amend information provided in the introduction; and, re-define and re-classify clinical and microbiological outcomes at the end of therapy and follow-up visits.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported