Clinical trial results:
SINCERE: A single-centre, assessor blind, randomised pilot study to evaluate the safety, tolerability and acceptability of RB Lotion compared to standard-of-care for Radiation Induced SkIN ReaCtions (RISR), in subjEcts undergoing palliative external beam RadiothErapy (RT).

Summary

EudraCT number	2015-002258-10
Trial protocol	GB
Global end of trial date	10 August 2018

Results information

Result version number	v1 (current)
This version publication date	25 August 2019
First version publication date	25 August 2019

Trial information

Trial identification

Sponsor protocol code	IBRB-02

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Dermal Laboratories Ltd
Sponsor organisation address	Tatmore Place, Gosmore, Hitchin, Hertfordshire, England, United Kingdom, SG4 7QR
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Scientific contact	Jennine Walker, Dermal Laboratories Ltd, +44 1462458866, clinical@dermal.co.uk

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	29 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 August 2018
Global end of trial reached?	Yes
Global end of trial date	10 August 2018
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To investigate the safety and tolerability of the daily topical application of RB Lotion to the radiation treatment field compared to the standard of care, Diprobase Cream, when used by subjects during their Radiotherapy treatment period.

Protection of trial subjects:

RB Lotion contains ibuprofen, therefore it is plausible that it may be effective in relieving RISR related pain. Topically applied ibuprofen is a very well established licensed treatment for painful musculoskeletal conditions and injuries. RB Lotion has unknown effectiveness for this particular indication, however is licensed for pain associated with mild to moderate sunburn in adults and children over the age of 12 years. Diprobase Cream was chosen as the comparator.

The study design was such that subjects' participation did not affect their standard of care or their ongoing RT treatment. The study visits were in accordance with current RT treatment local practice/standard of care, therefore no additional study visits were required.

Subjects had the option to provide specific informed consent for two exploratory biomarker samples to be taken. Subjects also had the option to provide separate informed consent for clinical photograph(s) of the treatment field to be taken by a medical photographer.

Subjects performed a skin patch test with each study medication the evening prior to Visit 2. This skin patch test was essential for the review of the skin for any reactions or visible changes, which could prevent the subject from continuing in the study.

Subjects were required to provide additional laboratory safety tests, if these were not performed within the past 6 weeks before commencement in the study.

The cohort selected for this study was subjects receiving RT treatment with palliative intent only, as the RT dose and duration of treatment is usually less, in comparison to the dose administered to non-palliative subjects and also a potential cure is not impacted in any way. Consequently RT induced reactions are less severe, allowing any reaction due to the study medication to be more discernible. It was anticipated that this study would not have any significant pain reported and it was expected that a low RTOG score would be reported for subjects.

Background therapy: -

Evidence for comparator:

The use of the comparator, Diprobase Cream, was chosen because at the time of the study, it was the standard of care used at a number of clinics in the UK (and in particular the investigative site). Other comparators were considered, in particular aqueous cream, which is commonly used, however this was not chosen due to increasing concerns about possible skin irritants within its formulation. The option to compare against no treatment was not considered acceptable, as this was less than standard of care.

Actual start date of recruitment	18 September 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	United Kingdom: 10
Worldwide total number of subjects	10
EEA total number of subjects	10

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)	0
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The recruitment rate was very slow, with only 10 subjects randomised in 12 months compared to the target in the study protocol of 35 randomised subjects. First subject was enrolled on 18 Sep 2017 and the last subject last visit was 02 Aug 2018. The study was terminated early as of 10 Aug 2018.

Pre-assignment

Screening details:

Study population was subjects with advanced cancer receiving external beam Radiotherapy with palliative intent who are 18 years or older of age. 10 subjects attended screening, all of which met the eligibility criteria and were randomised. 3 subjects were withdrawn during the conduct of the study.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind[1]
Roles blinded	Investigator, Assessor[2]

Blinding implementation details:

The monitor was unblinded and performed all monitoring responsibilities without compromising the assessor blind status. All subjects and some of the investigative site team were unblinded, due to the different viscosities of the study medications and were aware of which study medication was being administered to each treatment site side. RTOG was only assessed by a blinded assessor (Investigator or Treatment Radiographer). The sealed opaque code break envelopes were stored in the Pharmacy File.

Arms

Arm title	Active and Comparator

Arm description:

RB Lotion (Ibuprofen 1% w/w, Isopropyl Myristate 10% w/w) and comparator product Diprobase Cream (PL00010/0658) applied to the left and right side of the treatment field.

Arm type	Active and Comparator
Investigational medicinal product name	RB Lotion
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

RB Lotion is a white aqueous cutaneous emulsion containing ibuprofen 1% weight for weight (w/w) (an analgesic and anti-inflammatory NSAID) and isopropyl myristate 10% w/w. Subjects, their relative or carer, were required to apply RB Lotion to the treatment area, four times daily (QID) during the RT treatment phase of the study (Visits 2-6). All applications were to be at approximately the same time each day: morning, lunch-time, dinner-time and before bed for RB Lotion. After RT was complete, subjects (or if required their relative or carer) were to apply as required (PRN) up to a maximum of eight times daily for RB Lotion. RB Lotion was to be used until RTOG 0 on both sides was confirmed, otherwise until the final study follow up visit (Visit 13) on day 54+/-3 days. Subjects were instructed on how to only apply RB Lotion to the left or right hand side of the treatment site.

Investigational medicinal product name	Diprobase Cream
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Cream
Routes of administration	Topical use

Dosage and administration details:

Diprobase Cream is the standard of care in a number of clinics in the UK (in particular the Investigative Site).
Subjects, their relative or carer, were required to apply Diprobase Cream to the treatment area, twice

daily (BD) during the RT treatment phase of the study (Visits 2-6). All applications were to be at approximately the same time each day: in the morning and before bed for Diprobase Cream. After RT was complete, subjects (or if required their relative or carer) were to apply as required (PRN) up to four times daily for Diprobase Cream. Diprobase Cream was to be used until RTOG 0 on both sides was confirmed, otherwise until the final study follow up visit (Visit 13) on day 54+/-3 days. Subjects were instructed on how to only apply Diprobase to the left or right hand side of the treatment site.

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: In this study both the Investigator and Treatment Radiographers were blinded as they both completed skin assessments related to RISR.

[2] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: In this study both the Investigator and Treatment Radiographers were blinded as they both completed skin assessments related to RISR.

Number of subjects in period 1	Active and Comparator
Started	10
Completed	7
Not completed	3
Adverse event, serious fatal	1
Adverse event, non-fatal	1
Protocol deviation	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description:	
All randomised subjects.	

Reporting group values	Overall trial	Total	
Number of subjects	10	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	10	10	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	3	3	
Male	7	7	
Race Units: Subjects			
Caucasian	10	10	
Black	0	0	
Asian	0	0	
Other	0	0	
Unknown	0	0	

Subject analysis sets	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Defined as all randomised subjects who applied at least one administration of the study medication (RB Lotion/Diprobase Cream).	
Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description:	
Defined as all randomised subjects who applied at least one administration of both RB Lotion and Diprobase Cream.	
Subject analysis set title	Per-Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
Defined as all randomised subjects included in the Full Analysis Set who are not defined as major	

protocol deviators.

Subject analysis set title	Plasma Ibuprofen Population
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Defined as all randomised subjects in the Full Analysis Set for whom an evaluable post-dose plasma Ibuprofen analysis is completed (Visit 6 and Visit 7 [Visit 7 only if the subject used the IMP beyond Visit 6]) and there are no major protocol deviations that could affect the plasma levels of Ibuprofen.

Subject analysis set title	Randomised Population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Defined as all randomised subjects.

Reporting group values	Safety Population	Full Analysis Population	Per-Protocol Population
Number of subjects	9	9	8
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	0	0	0
From 65-84 years	9	9	8
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	3	3	3
Male	6	6	5
Race Units: Subjects			
Caucasian	9	9	8
Black	0	0	0
Asian	0	0	0
Other	0	0	0
Unknown	0	0	0

Reporting group values	Plasma Ibuprofen Population	Randomised Population	
Number of subjects	7	10	
Age categorical Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	7	10	

85 years and over	0	0	

Gender categorical Units: Subjects			
Female	2	3	
Male	5	7	
Race Units: Subjects			
Caucasian	7	10	
Black	0	0	
Asian	0	0	
Other	0	0	
Unknown	0	0	

End points

End points reporting groups

Reporting group title	Active and Comparator
Reporting group description: RB Lotion (Ibuprofen 1% w/w, Isopropyl Myristate 10% w/w) and comparator product Diprobase Cream (PL00010/0658) applied to the left and right side of the treatment field.	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description: Defined as all randomised subjects who applied at least one administration of the study medication (RB Lotion/Diprobase Cream).	
Subject analysis set title	Full Analysis Population
Subject analysis set type	Full analysis
Subject analysis set description: Defined as all randomised subjects who applied at least one administration of both RB Lotion and Diprobase Cream.	
Subject analysis set title	Per-Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description: Defined as all randomised subjects included in the Full Analysis Set who are not defined as major protocol deviators.	
Subject analysis set title	Plasma Ibuprofen Population
Subject analysis set type	Sub-group analysis
Subject analysis set description: Defined as all randomised subjects in the Full Analysis Set for whom an evaluable post-dose plasma Ibuprofen analysis is completed (Visit 6 and Visit 7 [Visit 7 only if the subject used the IMP beyond Visit 6]) and there are no major protocol deviations that could affect the plasma levels of Ibuprofen.	
Subject analysis set title	Randomised Population
Subject analysis set type	Intention-to-treat
Subject analysis set description: Defined as all randomised subjects.	

Primary: Safety evaluated by differential in the grade of skin reaction between the RB Lotion and Diprobase Cream treated skin surfaces as measured by the Radiation Therapy Oncology Group (RTOG) skin reaction scale

End point title	Safety evaluated by differential in the grade of skin reaction between the RB Lotion and Diprobase Cream treated skin surfaces as measured by the Radiation Therapy Oncology Group (RTOG) skin reaction scale[1]

End point description:

Refer to tables attached. Majority of the treatment site reviews were recorded as RTOG 0 (normal) for both RB Lotion and Diprobase Cream.

Three of nine subjects (within Full Analysis Set and Safety Populations) reported RTOG 1 (faint or full erythema) at Visit 7, for both RB Lotion and Diprobase Cream. These results indicate that there was no difference between treatments.

For one subject, RTOG 0 (normal) was reported on the RB Lotion treatment site, however RTOG 1 (faint or dull erythema) was reported on the Diprobase treatment site, during Visit 6. This was the only variation reported between the treatment sites and indicates that RB Lotion has maintained a normal RTOG at the treatment site longer than Diprobase.

End point type	Primary

End point timeframe:

RTOG scores at Visit 1 (study day -4±3), 3, 4, 5, 6 (study day 2 to 10), 7 (study day 12 ±2) and if applicable, Visits 8, 9, 10, 11, 12, 13 (study day 54 ±3).

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: Only descriptive analysis completed.

End point values	Active and Comparator	Safety Population	Full Analysis Population	Per-Protocol Population
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10[2]	9	9	8
Units: RTOG Score	10	9	9	8

Notes:

[2] - All randomised subjects

Attachments (see zip file)	Table 14.3.4-1.1 Primary Safety Analysis of RTOG Scores - Table 14.3.4-1.2 Primary Safety Analysis of RTOG Scores - Full Table 14.3.4-1.3 Primary Safety Analysis of RTOG Scores - Per

Statistical analyses

No statistical analyses for this end point

Secondary: Differential in the duration (measured in days) of each grade of skin reaction between the RB Lotion and Diprobase Cream treated skin surfaces as measured by the RTOG skin reaction scale

End point title	Differential in the duration (measured in days) of each grade of skin reaction between the RB Lotion and Diprobase Cream treated skin surfaces as measured by the RTOG skin reaction scale

End point description:

Refer to tables attached. RTOG 1 (faint or dull erythema) was confirmed for three of nine subjects (Full Analysis Set and Safety Populations) on both RB Lotion and Diprobase Cream treatment sites, with a mean of 9.3 days and 12.3 days, respectively. All subjects had a RTOG score of 0 (normal) at randomisation.

The maximum period of RTOG 1 observed on the RB Lotion treatment site was 12 days and 17 days on the Diprobase Cream treatment site (Full Analysis Set and Safety Populations).

End point type	Secondary

End point timeframe:

The duration of the RTOG score is defined as the number of days in which a subject had that score from Visit 3 to Visit 13.

End point values	Active and Comparator	Safety Population	Full Analysis Population	Per-Protocol Population
Subject group type	Reporting group	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	10[3]	9	9	8
Units: Days	10	9	9	8

Notes:

[3] - All randomised subjects

Attachments (see zip file)	Table 14.2-1.1 Efficacy Analysis of Duration of RTOG Scores - Table 14.2-1.2 Efficacy Analysis of Duration of RTOG Scores - Table 14.2-1.3 Efficacy Analysis of Duration of RTOG Scores -

Statistical analyses

No statistical analyses for this end point

Secondary: Subject compliance with the study medication

End point title	Subject compliance with the study medication

End point description:

Measure compliance up to Visit 6 during RT phase only. Subjects expected to apply 28 doses of Diprobase and 14 doses of RB Lotion.

Refer to table attached. Treatment duration for the eight treated subjects (Safety Population) who returned the patient diary in the study ranged from 5 to 8 days for both RB Lotion and Diprobase Cream. The total number of applications ranged from 17 to 28 for RB Lotion and from 9 to 15 for Diprobase Cream. Mean compliance was 79.0% (range 59.4% to 89.3%) with RB Lotion and 92.7% (range 85.71% to 100%) with Diprobase Cream.

End point type	Secondary

End point timeframe:

Compliance was during the RT treatment period (Visits 2 to 6).

End point values	Active and Comparator	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	9		
Units: No units	10	9		

Attachments (see zip file)	Table 14.1-4 Compliance - Safety Population.pdf

Statistical analyses

No statistical analyses for this end point

Secondary: RISR Symptoms Assessment Questionnaire

End point title	RISR Symptoms Assessment Questionnaire

End point description:

Questionnaire to assess any skin pain, itching, irritation or skin burning experienced by the subject on either side of the treatment field. Questionnaire completed at Visits 1, 6 & 7 and if required each subsequent until RTOG 0 (see listing attached).

Eight subjects reported no skin burning sensation, irritation, itching or skin pain at the treatment site. One subject reported skin pain at the treatment site during Visit 8 and did not confirm whether this was worse on the right/left treatment side. One subject reported skin burning sensation at the treatment site during Visit 8 and confirmed that this was worse on the left side (Diprobase Cream).

This would indicate that for this subject, RB Lotion had a greater soothing and/or analgesic effect compared to Diprobase Cream. Overall, these results show that minimum pain was reported in the study and that RB Lotion and Diprobase Cream were not associated with adverse pain, irritation or itching in

subjects undergoing RT treatment

End point type	Secondary

End point timeframe:

RISR questionnaire was completed at Visits 1, 6 & 7 and Visit 8, if applicable, until RTOG 0 on both sides confirmed.

End point values	Active and Comparator	Randomised Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: No units	10	10		

Attachments (see zip file)	Listing 16.2.6-1 RISR Symptoms Assessment Questionnaire -

Statistical analyses

No statistical analyses for this end point

Secondary: Treatment Acceptability Questionnaire

End point title	Treatment Acceptability Questionnaire

End point description:

Questionnaire was to assess the subjects perception of the following medication related characteristics: pleasant to use, non-odorous, non-greasy, non-sticky, easily absorbed and did not mess clothes or bedding. Assessment was completed at the visit where RTOG 0 was confirmed (Visits 7 or 8).

Refer to table attached. Nearly all cases for the eight subjects who completed the questionnaire was 'strongly agree', with only a few cases of 'somewhat agree'. In the case where 'somewhat agree' was selected, this was selected for both RB Lotion and Diprobase Cream. These results indicate the high subject acceptability of RB Lotion and Diprobase Cream.

End point type	Secondary

End point timeframe:

Treatment acceptability questionnaire was completed at the visit where RTOG 0 was confirmed (Visits 7 or 8).

End point values	Active and Comparator	Safety Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	9		
Units: No units	10	9		

Attachments (see zip file)	Table 14.3.4-2 Treatment Acceptability Questionnaire - Safety

Statistical analyses

No statistical analyses for this end point

Secondary: Any serious adverse events, including grade 3 RTOG skin reaction

End point title	Any serious adverse events, including grade 3 RTOG skin reaction

End point description:

No SAEs were reported during this study. For the purposes of this study the following events did not require reporting as SAEs: death as a result of disease progression;and hospitalisation for disease progression, supportive and palliative therapies, not associated with any deterioration in RISR.

End point type	Secondary

End point timeframe:

Reported from Visits 2 to 13

End point values	Active and Comparator	Randomised Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	10	10		
Units: No units	10	10		

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma levels of ibuprofen at final day of RT treatment (Visit 6)

End point title	Plasma levels of ibuprofen at final day of RT treatment (Visit 6)

End point description:

Refer to table attached. Mean (SD) plasma ibuprofen concentration at Visit 6 was 24.3 (19.44) ng/ml-1, with a median of 19.8 ng/ml-1 and range of Below Limit of Quantification (BLQ [0.0]) to 55.9 ng/ml-1 (plasma ibuprofen population). Systemic absorption of ibuprofen from RB Lotion was expected to be minimal (due to the low formulated strength and the small area of treated skin) and was explored for safety by measuring plasma ibuprofen levels. These plasma level results indicate the low level of systemic absorption and illustrate there is no compound effect over time with administration of RB Lotion.

End point type	Secondary

End point timeframe:

Visit 6

End point values	Active and Comparator	Plasma Ibuprofen Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[4]	7		
Units: ng/ml				
arithmetic mean (inter-quartile range (Q1-Q3))	(to)	24.3 (10.1 to 39.8)		

Notes:

[4] - Analysis not performed on randomised population.

Attachments (see zip file)	Table 14.3.4-3 Plasma Ibuprofen Levels at Visit 6 - Plasma

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Exploratory Endpoint - Plasma levels of ibuprofen at Visit 7 (for subjects who continued to use study medication beyond Visit 6)

End point title	Exploratory Endpoint - Plasma levels of ibuprofen at Visit 7 (for subjects who continued to use study medication beyond Visit 6)

End point description:

End point type	Other pre-specified

End point timeframe:

Visit 7

End point values	Active and Comparator	Plasma Ibuprofen Population		
Subject group type	Reporting group	Subject analysis set		
Number of subjects analysed	0[5]	7		
Units: ng/ml				
arithmetic mean (inter-quartile range (Q1-Q3))	(to)	16.9 (0.0 to 35.5)		

Notes:

[5] - Analysis not performed on randomised population.

Attachments (see zip file)	Table 14.3.4-4 Exploratory Analysis of Plasma Ibuprofen Levels

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events reported from Visits 2 (Study Day 1) to 13 (Study Day 54 ±3).	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0
Reporting groups	
Reporting group title	All randomised subjects
Reporting group description:	
For the purposes of this study the following events do not require reporting as SAEs: death as a result of disease progression; and hospitalisation for disease progression, supportive and palliative therapies, not associated with any deterioration in RISR.	

Serious adverse events	All randomised subjects		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	All randomised subjects		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 9 (88.89%)		
Nervous system disorders			
Neuralgia	Additional description: Neuropathic Pain in left arm		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dizziness			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
General disorders and administration			

site conditions			
Chest pain			
subjects affected / exposed	3 / 9 (33.33%)		
occurrences (all)	4		
Fatigue			
subjects affected / exposed	2 / 9 (22.22%)		
occurrences (all)	2		
Death			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Gastrointestinal disorders			
Oesophagitis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Odynophagia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 9 (44.44%)		
occurrences (all)	5		
Pulmonary embolism			

subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Erythema	Additional description: Erythema on right side of treatment site		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Musculoskeletal pain	Additional description: Pain between shoulder blades		
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Infections and infestations			
Oral candidiasis			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Pneumonia			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		
Lower respiratory tract infection			
subjects affected / exposed	1 / 9 (11.11%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 October 2016	- Study period changed to reflect a Quarter 4 2016 commencement date instead of Quarter 3 2016. - Inclusion criterion 16: to avoid any ambiguities and safeguard against subject pregnancies occurring during the study, a comprehensive list of contraceptive methods considered acceptable for this specific study was included. - Discontinuation criterion, 'There is any relevant health deterioration including progression of cancer that could alter the benefit/risk assessment for the subject, including AEs, laboratory parameters, vital signs' was changed from optional to compulsory discontinuation to safeguards subject safety. - The mechanism for rapid unblinding was more comprehensive and the requirement to contact the Sponsor before unblinding was removed but the Investigator should inform the Sponsor as soon as possible after the unbinding had been performed.
14 December 2017	- Study period changed to reflect a Quarter 3 2017 commencement date instead of Quarter 4 2016. - Inclusion Criterion 9 and Exclusion Criterion 4 amended to allow the inclusion of subjects who were using low dose oral aspirin up to a maximum daily dose of 75 mg from 72 hours prior to randomisation until at least Visit 7 or until the skin at the treatment site was assessed to be RTOG 0 on both sides if this was not confirmed at Visit 7. A significant number of patients had been excluded because they were taking once daily (OD) aspirin 75 mg. It was considered acceptable to include such patients as a low dose of 75 mg OD is sufficient to inhibit platelet generation of thromboxane A2, resulting in an antithrombotic effect, but is much lower than doses required (650 mg-4 g) to block prostaglandin production and have analgesic, antipyretic or anti-inflammatory effects [1] that might 'mask' adverse effects of RB Lotion, which is the rationale for currently excluding all NSAIDs other than the IMP in the subject population. - Visit 0, pre-study visit changed to allow the possibility for the activities associated with this visit to be completed at a PIC when patients were being referred to attend an RT planning visit at the study site. Additionally, if necessary, it was changed to allow the pre-study visit to be conducted on the same day as the RT planning visit if, in the Investigator's opinion, the subject had been provided with sufficient time and opportunity to consider their participation in the study. These changes were made to better reflect the 'patient pathway' for subjects seen at the study site and to acknowledge that a separate pre-study visit was not always possible because of resource constraints at the study site.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date

10 August 2018	For this pilot study, the objective was to recruit 35 subjects within a clinical phase anticipated to last 6 months. Despite a protocol amendment, extension to the recruitment period and concerted efforts to support the study site, a total of 10 subjects were randomised in 12 months. As a result, the Sponsor made the decision to terminate the study on the 10 Aug 2018.	-

Notes:

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Early trial termination leading to a small number of subjects analysed. The objective was to recruit 35 subjects, however only 10 subjects were randomised.

Notes: