



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 |
| Public contact | Jennine Walker, Dermal Laboratories Ltd, +44 1462458866, clinical@dermal.co.uk |
| 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, Diprobace 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. Diprobace 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, Diprobace 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 Diprobace 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 | Diprobace Cream |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Cream |
| Routes of administration | Topical use |

Dosage and administration details:

Diprobace 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 Diprobace 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 Diprobace 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 Diprobace Cream. Diprobace 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 Diprobace 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 Diprobace 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/Diprobace 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 Diprobace 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 Diprobace 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 Diprobace 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 Diprobace 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 Diprobace 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 Diprobace 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 Diprobace. | |
| 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 Diprobace 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 Diprobace 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 Diprobace 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 Diprobace 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 Diprobace 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 Diprobace Cream. The total number of applications ranged from 17 to 28 for RB Lotion and from 9 to 15 for Diprobace Cream. Mean compliance was 79.0% (range 59.4% to 89.3%) with RB Lotion and 92.7% (range 85.71% to 100%) with Diprobace 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

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|--|--|
| 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 (Diprobace Cream). | |
| This would indicate that for this subject, RB Lotion had a greater soothing and/or analgesic effect compared to Diprobace Cream. Overall, these results show that minimum pain was reported in the study and that RB Lotion and Diprobace 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 occurrences (all) Fatigue subjects affected / exposed occurrences (all) Death subjects affected / exposed occurrences (all) | 3 / 9 (33.33%) 4 2 / 9 (22.22%) 2 1 / 9 (11.11%) 1 | | |
| Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 | | |
| Gastrointestinal disorders Oesophagitis subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Constipation subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Odynophagia subjects affected / exposed occurrences (all) | 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 1 / 9 (11.11%) 1 | | |
| Respiratory, thoracic and mediastinal disorders Dyspnoea subjects affected / exposed occurrences (all) Pulmonary embolism | 4 / 9 (44.44%) 5 | | |

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

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 05 October 2016 | <ul style="list-style-type: none">- 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 | <ul style="list-style-type: none">- 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: