



Clinical trial results:

A phase Ib, open label study to evaluate the safety, tolerability, pharmacokinetics and pharmacodynamics of multiple ascending oral doses of Rimeporide in patients with Duchenne Muscular Dystrophy

Summary

| | |
|--------------------------|------------------|
| EudraCT number | 2015-002530-50 |
| Trial protocol | ES GB FR IT |
| Global end of trial date | 20 December 2017 |

Results information

| | |
|--------------------------------|--------------|
| Result version number | v1 (current) |
| This version publication date | 07 July 2018 |
| First version publication date | 07 July 2018 |

Trial information

Trial identification

| | |
|-----------------------|------------------|
| Sponsor protocol code | EspeRare_RIM_001 |
|-----------------------|------------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT02710591 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | QED Clinical Services |
| Sponsor organisation address | The Old School Newport Road, Woughton Park, Milton Keynes, United Kingdom, |
| Public contact | Director of Clinical Operations, QED Clinical Services, +44 1908 251 480, nmaruf@qed-clinical.com |
| Scientific contact | Director of Clinical Operations, QED Clinical Services, +44 1908 251 480, nmaruf@qed-clinical.com |
| Sponsor organisation name | EspeRare Foundation |
| Sponsor organisation address | 14 chemin des Aulx, Plan les Ouates, Switzerland, CH-1228 |
| Public contact | Caroline Kant, EspeRare Foundation, kant.caroline@esperare.org |
| Scientific contact | Florence Porte-Thomé, EspeRare Foundation, porte.florence@esperare.org |

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 | 20 December 2017 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 20 December 2017 |
| Global end of trial reached? | Yes |
| Global end of trial date | 20 December 2017 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

Primary objective:

To determine the preliminary safety and tolerability profile of multiple oral administrations of rimeporide.

Secondary objective:

To evaluate the pharmacokinetic profile of rimeporide in pediatric patients with DMD.

Protection of trial subjects:

Prior to enrolment subjects received a full explanation of the nature and purpose of the study, the safety of the drug under investigation, and discussion of any potential therapeutic benefit, and that they were free to withdraw from the study at any time without prejudice. An informed consent form approved by the IEC was signed by the subject and legal representative and the Investigator before any study-related procedures were performed. The Investigator provided copies of the signed informed consent to the subject or legal representative, and the original was retained by the Investigator.

Background therapy:

Patients on a stable dose of corticosteroids at least 6 months prior to baseline

Evidence for comparator:

No comparator used

| | |
|---|---------------|
| Actual start date of recruitment | 17 March 2016 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | Spain: 3 |
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Country: Number of subjects enrolled | France: 6 |
| Country: Number of subjects enrolled | Italy: 6 |
| Worldwide total number of subjects | 20 |
| EEA total number of subjects | 20 |

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) | 20 |
| Adolescents (12-17 years) | 0 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

The recruitment period varied depending on the recruitment speed ; started in March 2016 to November 2017. it was competitive among the 4 sites: France, Spain, Italy and UK. A time interval of at least 1 week was maintained between administration of first dose in the first 3 patients of each cohort. It was extended to all patients for cohort 4.

Pre-assignment

Screening details:

Screening was carried out within 4 week prior to first administration of rimeporide (SD1) to enable confirmation of patient eligibility and following the signature of the Informed Consent Form.

Period 1

| | |
|------------------------------|--------------------------------|
| Period 1 title | Overall trial (overall period) |
| Is this the baseline period? | Yes |
| Allocation method | Not applicable |
| Blinding used | Not blinded |

Arms

| | |
|------------------------------|----------|
| Are arms mutually exclusive? | Yes |
| Arm title | Cohort 1 |

Arm description:

5 patients with a body weight less than or equal to 30kg at baseline were administered 50 mg TID. Patients with a body weight more than 30kg at baseline were administered 75 mg TID. Each patient received rimeporide during 4 weeks.

| | |
|--|---------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rimeporide |
| Investigational medicinal product code | EMD 87 580 |
| Other name | |
| Pharmaceutical forms | Capsule, hard |
| Routes of administration | Oral use |

Dosage and administration details:

Eligible subjects received rimeporide 3 times per day (TID) over 4 weeks. Rimeporide was supplied to the sites in hard gel capsules at 25mg in bottles of 50 capsules each. The drug was appropriately labeled in the local language and adapted to the national requirements.

| | |
|------------------|----------|
| Arm title | Cohort 2 |
|------------------|----------|

Arm description:

5 patients with a body weight less than or equal to 30kg at baseline were administered 100 mg TID. Patients with a body weight more than 30kg at baseline were administered 150 mg TID. Each patient received rimeporide during 4 weeks

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rimeporide |
| Investigational medicinal product code | EMD 87 580 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Eligible subjects received rimeporide 3 times per day (TID) over 4 weeks. Rimeporide was supplied to the sites in hard gel capsules at 50mg in bottles of 50 capsules each. The drug was appropriately labeled in the local language and adapted to the national requirements.

| | |
|------------------|----------|
| Arm title | Cohort 3 |
|------------------|----------|

Arm description:

5 patients with a body weight less than or equal to 30kg at baseline were administered 150 mg TID.

Patients with a body weight more than 30kg at baseline were administered 200 mg TID. Each patient received rimeporide during 4 weeks.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rimeporide |
| Investigational medicinal product code | EMD 87 580 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Eligible subjects received rimeporide 3 times per day (TID) over 4 weeks. Rimeporide was supplied to the sites in hard gel capsules at 50mg in bottles of 50 capsules each. The drug was appropriately labeled in the local language and adapted to the national requirements.

| | |
|------------------|----------|
| Arm title | Cohort 4 |
|------------------|----------|

Arm description:

5 patients with a body weight less than or equal to 30kg at baseline were administered 200 mg TID. Patients with a body weight more than 30kg at baseline were administered 300 mg TID. Each patient received rimeporide during 4 weeks

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Rimeporide |
| Investigational medicinal product code | EMD 87 580 |
| Other name | |
| Pharmaceutical forms | Capsule |
| Routes of administration | Oral use |

Dosage and administration details:

Eligible subjects received rimeporide 3 times per day (TID) over 4 weeks. Rimeporide was supplied to the sites in hard gel capsules at 50mg in bottles of 50 capsules each. The drug was appropriately labeled in the local language and adapted to the national requirements.

| Number of subjects in period 1 | Cohort 1 | Cohort 2 | Cohort 3 |
|---------------------------------------|----------|----------|----------|
| Started | 5 | 5 | 5 |
| Completed | 5 | 5 | 5 |

| Number of subjects in period 1 | Cohort 4 |
|---------------------------------------|----------|
| Started | 5 |
| Completed | 5 |

Baseline characteristics

Reporting groups

| | |
|--|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: 5 patients with a body weight less than or equal to 30kg at baseline were administered 50 mg TID. Patients with a body weight more than 30kg at baseline were administered 75 mg TID. Each patient received rimeporide during 4 weeks. | |
| Reporting group title | Cohort 2 |
| Reporting group description: 5 patients with a body weight less than or equal to 30kg at baseline were administered 100 mg TID. Patients with a body weight more than 30kg at baseline were administered 150 mg TID. Each patient received rimeporide during 4 weeks | |
| Reporting group title | Cohort 3 |
| Reporting group description: 5 patients with a body weight less than or equal to 30kg at baseline were administered 150 mg TID. Patients with a body weight more than 30kg at baseline were administered 200 mg TID. Each patient received rimeporide during 4 weeks. | |
| Reporting group title | Cohort 4 |
| Reporting group description: 5 patients with a body weight less than or equal to 30kg at baseline were administered 200 mg TID. Patients with a body weight more than 30kg at baseline were administered 300 mg TID. Each patient received rimeporide during 4 weeks | |

| Reporting group values | Cohort 1 | Cohort 2 | Cohort 3 |
|---|----------|----------|----------|
| Number of subjects | 5 | 5 | 5 |
| 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) | 5 | 5 | 5 |
| Adolescents (12-17 years) | 0 | 0 | 0 |
| Adults (18-64 years) | 0 | 0 | 0 |
| From 65-84 years | 0 | 0 | 0 |
| 85 years and over | 0 | 0 | 0 |
| Age continuous | | | |
| Age of patient at Screening Units: years | | | |
| arithmetic mean | 8.4 | 8.2 | 8.8 |
| standard deviation | ± 1.7 | ± 1.5 | ± 1.6 |
| Gender categorical Units: Subjects | | | |
| Male | 5 | 5 | 5 |
| Ethnicity/Race Units: Subjects | | | |
| White | 5 | 4 | 5 |
| Black or African American | 0 | 1 | 0 |

| Reporting group values | Cohort 4 | Total | |
|---|----------|-------|--|
| Number of subjects | 5 | 20 | |
| 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) | 5 | 20 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 0 | 0 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Age continuous | | | |
| Age of patient at Screening | | | |
| Units: years | | | |
| arithmetic mean | 9.2 | | |
| standard deviation | ± 0.4 | - | |
| Gender categorical | | | |
| Units: Subjects | | | |
| Male | 5 | 20 | |
| Ethnicity/Race | | | |
| Units: Subjects | | | |
| White | 5 | 19 | |
| Black or African American | 0 | 1 | |

End points

End points reporting groups

| | |
|--|----------|
| Reporting group title | Cohort 1 |
| Reporting group description: 5 patients with a body weight less than or equal to 30kg at baseline were administered 50 mg TID. Patients with a body weight more than 30kg at baseline were administered 75 mg TID. Each patient received rimeporide during 4 weeks. | |
| Reporting group title | Cohort 2 |
| Reporting group description: 5 patients with a body weight less than or equal to 30kg at baseline were administered 100 mg TID. Patients with a body weight more than 30kg at baseline were administered 150 mg TID. Each patient received rimeporide during 4 weeks | |
| Reporting group title | Cohort 3 |
| Reporting group description: 5 patients with a body weight less than or equal to 30kg at baseline were administered 150 mg TID. Patients with a body weight more than 30kg at baseline were administered 200 mg TID. Each patient received rimeporide during 4 weeks. | |
| Reporting group title | Cohort 4 |
| Reporting group description: 5 patients with a body weight less than or equal to 30kg at baseline were administered 200 mg TID. Patients with a body weight more than 30kg at baseline were administered 300 mg TID. Each patient received rimeporide during 4 weeks | |

Primary: Primary: overview of adverse events

| | |
|--|--|
| End point title | Primary: overview of adverse events ^[1] |
| End point description: End point description: No hypothesis testing performed. Observations are given for the safety population (all patients who received at least one dose of study drug). Categorical data are presented with the number of subjects with at least one event for the following selections: <ul style="list-style-type: none">• treatment-emergent AEs (TEAEs) • study drug-related TEAEs (ADRs)• serious TEAEs• study drug-related serious TEAEs (serious ADRs)• TEAEs leading to withdrawal• study drug-related TEAEs (ADRs) leading to withdrawal• serious TEAEs leading to withdrawal• TEAEs leading to death as outcome | |
| End point type | Primary |
| End point timeframe: The safety reporting period is defined as the interval between the time of first dosing and the end of the follow-up period. Adverse events falling into this time window are classified as treatment-emergent Adverse Events (TEAE) | |
| 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: Descriptive statistics only (open label study with analysis of the safety profile of Rimeporide as primary endpoint) | |

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|---|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 5 | 5 | 5 | 5 |
| Units: Subjects | | | | |
| Treatment emergent adverse events | 2 | 1 | 5 | 4 |
| Emergent adverse drug reactions | 0 | 0 | 0 | 2 |
| Serious treatment emergent adverse events | 0 | 0 | 1 | 0 |
| Serious emergent adverse event drug reactions | 0 | 0 | 0 | 0 |
| TEAEs leading to withdrawal | 0 | 0 | 0 | 0 |
| TEAEs leading to death | 0 | 0 | 0 | 0 |

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of Rimeporide-Cmax

| | |
|-----------------|-------------------------------|
| End point title | PK profile of Rimeporide-Cmax |
|-----------------|-------------------------------|

End point description:

PK samples were collected according to the following schedule:

- At Day 1: for half of the patients: just before first administration, and one sample in each of the following time frames after the first dose:

- o 0.5 to 1h after dosing,
- o 1 to 2h after dosing,
- o 2.5 to 3.5h after dosing,
- o 6h after dosing

- At Day 1: for the other half of the patients: just before first administration, and one sample in each of the following time frames after the second dose:

- o 0.5 to 1h after dosing,
- o 1 to 2h after dosing,
- o 2.5 to 3.5h after dosing,
- o 6h after dosing

Finally, at week 4 (Day 28) after the last dose:

- o 0.5 to 1h after dosing,
- o 6h after dosing

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

End point timeframe:

PK samples were collected on Study Day 1 (SD1) and on W4 visit (day of last rimeporide administration) according to a PK profile allocation. See Description section for the details

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|--------------------------------------|-----------------|-----------------|-----------------|-----------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 5 | 5 |
| Units: ng/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| Cmax | 1299 (± 419) | 1974 (± 955) | 2658 (± 667) | 3663 (± 825) |

Statistical analyses

No statistical analyses for this end point

Secondary: PK profile of Rimeporide-AUC

| | |
|-----------------|------------------------------|
| End point title | PK profile of Rimeporide-AUC |
|-----------------|------------------------------|

End point description:

PK samples were collected according to the following schedule:

- At Day 1: for half of the patients: just before first administration, and one sample in each of the following time frames after the first dose:

- o 0.5 to 1h after dosing,
- o 1 to 2h after dosing,
- o 2.5 to 3.5h after dosing,
- o 6h after dosing

- At Day 1: for the other half of the patients: just before first administration, and one sample in each of the following time frames after the second dose:

- o 0.5 to 1h after dosing,
- o 1 to 2h after dosing,
- o 2.5 to 3.5h after dosing,
- o 6h after dosing

Finally, at week 4 (Day 28) after the last dose:

- o 0.5 to 1h after dosing,
- o 6h after dosing

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

End point timeframe:

PK samples were collected on Study Day 1 (SD1) and on W4 visit (day of last rimeporide administration) according to a PK profile allocation. See Description section for the details

| End point values | Cohort 1 | Cohort 2 | Cohort 3 | Cohort 4 |
|--------------------------------------|--------------------|---------------------|---------------------|---------------------|
| Subject group type | Reporting group | Reporting group | Reporting group | Reporting group |
| Number of subjects analysed | 4 | 5 | 5 | 5 |
| Units: ng.h/mL | | | | |
| arithmetic mean (standard deviation) | | | | |
| AUC | 9530 (\pm 1388) | 16975 (\pm 5565) | 23565 (\pm 3237) | 32013 (\pm 6879) |

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Full study period

Adverse event reporting additional description:

Treatment Emergent AEs and SAEs (starting on SD1)

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

Dictionary used

| | |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

| | |
|--------------------|------|
| Dictionary version | 18.1 |
|--------------------|------|

Reporting groups

| | |
|-----------------------|----------|
| Reporting group title | Cohort 1 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Cohort 2 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Cohort 3 |
|-----------------------|----------|

Reporting group description: -

| | |
|-----------------------|----------|
| Reporting group title | Cohort 4 |
|-----------------------|----------|

Reporting group description: -

| Serious adverse events | Cohort 1 | Cohort 2 | Cohort 3 |
|---|---------------|---------------|----------------|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |
| Vomiting | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| occurrences causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 1 |
| deaths causally related to treatment / all | 0 / 0 | 0 / 0 | 0 / 0 |

| Serious adverse events | Cohort 4 | | |
|---|---------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from | 0 | | |

| | | | |
|---|---------------|--|--|
| adverse events | | | |
| Gastrointestinal disorders | | | |
| Diarrhoea | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Vomitting | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | | |
| occurrences causally related to treatment / all | 0 / 0 | | |
| deaths causally related to treatment / all | 0 / 0 | | |

Frequency threshold for reporting non-serious adverse events: 1 %

| Non-serious adverse events | Cohort 1 | Cohort 2 | Cohort 3 |
|---|----------------|----------------|-----------------|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 5 (40.00%) | 1 / 5 (20.00%) | 5 / 5 (100.00%) |
| Injury, poisoning and procedural complications | | | |
| Fall | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 1 | 0 | 0 |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Nervous system disorders | | | |
| Headache | | | |
| subjects affected / exposed | 1 / 5 (20.00%) | 0 / 5 (0.00%) | 2 / 5 (40.00%) |
| occurrences (all) | 1 | 0 | 2 |
| Dizziness | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 5 (0.00%) | 1 / 5 (20.00%) |
| occurrences (all) | 0 | 0 | 1 |
| Presyncope | | | |
| subjects affected / exposed | 0 / 5 (0.00%) | 0 / 5 (0.00%) | 0 / 5 (0.00%) |
| occurrences (all) | 0 | 0 | 0 |
| General disorders and administration site conditions | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Chills subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Pyrexia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Ear and labyrinth disorders Tympanic membrane perforation subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Gastrointestinal disorders Diarrhoea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 | 2 / 5 (40.00%) 3 |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 2 |
| Vomiting subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 |
| Mouth ulceration subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | 0 / 5 (0.00%) 0 |
| Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | 1 / 5 (20.00%) 1 |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Musculoskeletal and connective tissue disorders | | | |

| | | | |
|--|---------------------|---------------------|---------------------|
| Pain in extremity subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 2 | 0 / 5 (0.00%) 0 | 0 / 5 (0.00%) 0 |
| Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | 1 / 5 (20.00%) 1 | 2 / 5 (40.00%) 2 |

| | | | |
|---|--|--|--|
| Non-serious adverse events | Cohort 4 | | |
| Total subjects affected by non-serious adverse events subjects affected / exposed | 4 / 5 (80.00%) | | |
| Injury, poisoning and procedural complications Fall subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Vascular disorders Flushing subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 2 | | |
| Nervous system disorders Headache subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Presyncope subjects affected / exposed occurrences (all) | 2 / 5 (40.00%) 3 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1 | | |
| General disorders and administration site conditions Chills subjects affected / exposed occurrences (all) Pyrexia subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 1 / 5 (20.00%) 1 | | |
| Ear and labyrinth disorders | | | |

| | | | |
|---|---------------------|--|--|
| Tympanic membrane perforation subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Gastrointestinal disorders | | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Abdominal pain upper subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Mouth ulceration subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Cough subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Oropharyngeal pain subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Urticaria subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |
| Musculoskeletal and connective tissue disorders | | | |
| Pain in extremity subjects affected / exposed occurrences (all) | 0 / 5 (0.00%) 0 | | |
| Infections and infestations | | | |
| Nasopharyngitis subjects affected / exposed occurrences (all) | 1 / 5 (20.00%) 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|---|
| 15 December 2015 | <p>Main Changes:</p> <p>Inclusion criteria: Ability to swallow capsules has been added</p> <p>Exclusion criteria : "Use of antibiotics with predominant renal secretion (e.g., cephalosporins), immunosuppressive agents exception corticosteroids, continuous treatment with non-steroidal, anti- inflammatory drugs (NSAIDs), or lithium" has been added. "Patients with specific contraindication to MRI (e.g.: metallic foreign body, claustrophobia, etc.)" has been extended to all patients</p> <p>Secondary objectives and Exploratory objectives: The biomarkers endpoints in the study are reclassified as exploratory.</p> <p>Recruitment plan: For safety reasons, the SMC has advised that a time interval of at least one week should be maintained between administrations of the first dose in the first three patients in each cohort.</p> |

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported