

**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
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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
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Arm title	Cohort 1
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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
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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
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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
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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
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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
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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
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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
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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
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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
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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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	18.1
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Reporting groups

Reporting group title	Cohort 1
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Reporting group description: -

Reporting group title	Cohort 2
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Reporting group description: -

Reporting group title	Cohort 3
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Reporting group description: -

Reporting group title	Cohort 4
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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	Main Changes: Inclusion criteria: Ability to swallow capsules has been added 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 Secondary objectives and Exploratory objectives: The biomarkers endpoints in the study are reclassified as exploratory. 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.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported