



Clinical trial results:

A Phase II, dose ranging, multicentre, double-blind, placebo controlled study to evaluate safety and efficacy of (R)-roscovitine in subjects with Cystic Fibrosis, homozygous for the F508del-CFTR mutation and chronically infected with Pseudomonas aeruginosa, a study involving 34 CF patients (24 treated, 10 controls).

Summary

EudraCT number	2015-002911-13
Trial protocol	FR
Global end of trial date	26 July 2019

Results information

Result version number	v1 (current)
This version publication date	05 May 2021
First version publication date	05 May 2021
Summary attachment (see zip file)	Final report (Rapport final Rosco-CF_Avril 2019.pdf)

Trial information

Trial identification

Sponsor protocol code	RB15.098
-----------------------	----------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02649751
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHRU de Brest
Sponsor organisation address	2, avenue Foch, Brest, France, 29 609
Public contact	Florence MORVAN, CHRU de Brest, 00 +33298223319, florence.morvan@chu-brest.fr
Scientific contact	Florence MORVAN, CHRU de Brest, 00 +33298223319, florence.morvan@chu-brest.fr

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	26 July 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 July 2019
Global end of trial reached?	Yes
Global end of trial date	26 July 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to assess the safety of increasing doses of roscovitine administered orally for 4 cycles of 4 consecutive days (treatment "on") separated by a 3 days treatment free period (treatment "off") in adult CF subjects who are homozygous for F508del mutation.

Protection of trial subjects:

- unblinding procedure via the National Poisons Centre (PAC) in Lyon, available 24/24
- IDSMB
- Emergency Medical support and Subject card

Background therapy:

Information regarding all prior and concomitant treatment, including the subject's CF medication (i.e. long term inhaled antibiotics), other medications (including over-the-counter medications, supplemental oxygen, and complementary/alternative medicines) and non-drug therapies (including physical therapy and blood transfusions), administered from 28 days before the Screening (V1) through the Safety Follow-Up visit (V8) will be recorded in each subject's source documents and on the Concomitant medications/Significant non-drug therapies CRF. Information recorded will include indications for use, dosage, route and dates of administration. For subjects who are screened but are not subsequently randomized in the study, details of prior medication will only be documented in the subjects' source documents.

Evidence for comparator: -

Actual start date of recruitment	22 February 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety
Long term follow-up duration	2 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	France: 34
Worldwide total number of subjects	34
EEA total number of subjects	34

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)	34
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment in 12 French centres from February 22nd, 2016 to July 26th, 2018.

Pre-assignment

Screening details:

49 patients have been recruited and 34 patients were randomized and treated.

15 screen failures : 4 without *Pseudomonas aeruginosa* + 1 non-inclusion criteria not respected with antibiotic taking + 4 exacerbation with antibiotics taken + 1 with sporanox taken (forbidden treatment) + 2 with HB1AC > 8% + 2 with FEV around 28 % + 1 with ALAT > 1.5ULN

Pre-assignment period milestones^[1]

Number of subjects started	49 ^[2]
Intermediate milestone: Number of subjects	group 1: 12
Intermediate milestone: Number of subjects	group 2: 12
Intermediate milestone: Number of subjects	group 3: 10
Number of subjects completed	34

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Protocol deviation: 2
Reason: Number of subjects	Non randomization criteria: 13

Notes:

[1] - The number of subjects at the milestone is less than the number that completed the pre-assignment period. It is expected the number of subjects at the milestones will be greater than, or equal to the number that completed the pre-assignment period.

Justification: The protocol provided for the replacement of non-randomized subjects. 49 subjects were therefore included but it is not possible to indicate this in the trial information.

36 randomized subjects were expected but only 34 were randomized.

12/12 in the first dose group

12/12 in the second dose group

10/12 in the third group

[2] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: The protocol provided for the replacement of non-randomized subjects. 49 subjects were therefore included but it is not possible to indicate this in the trial information.

36 randomized subjects were expected but only 34 were randomized.

12/12 in the first dose group

12/12 in the second dose group

10/12 in the third group

Period 1

Period 1 title	All experimental groups (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Assessor

Blinding implementation details:

Throughout the trial, the study medication kit number(s) of a subject is given by the number on the medication label. Patients, investigators and the steering committee will remain blinded as to which study drug is administered. In the event of an emergency, the investigator will follow the emergency procedure via the National Poisons Centre (PAC) in Lyon, available 24/24.

Arms

Are arms mutually exclusive?	Yes
------------------------------	-----

Arm title	Placebo
Arm description: Placebo	
Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: Placebo was administered orally for 4 cycles of 4 consecutive days (treatment "on") separated by a 3 days treatment free period (treatment "off") every 7 days for 28 days Treatment was provided by oral administration of capsules	
Arm title	Group 1 IMPD
Arm description: 200mg of seliciclib	
Arm type	Experimental
Investigational medicinal product name	Seliciclib (CYC202, R-ROSCOVITINE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 200 mg doses of seliciclib were administered orally for 4 cycles of 4 consecutive days (treatment "on") separated by a 3 days treatment free period (treatment "off") every 7 days for 28 days Treatment was provided by oral administration of capsules	
Arm title	Group 2 IMPD
Arm description: 400 mg of seliciclib	
Arm type	Experimental
Investigational medicinal product name	Seliciclib (CYC202, R-ROSCOVITINE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 400 mg doses of seliciclib were administered orally for 4 cycles of 4 consecutive days (treatment "on") separated by a 3 days treatment free period (treatment "off") every 7 days for 28 days Treatment was provided by oral administration of capsules	
Arm title	Group 3 IMPD
Arm description: 800 mg of seliciclib	
Arm type	Experimental
Investigational medicinal product name	Seliciclib (CYC202, R-ROSCOVITINE)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use
Dosage and administration details: 800 mg doses of seliciclib were administered orally for 4 cycles of 4 consecutive days (treatment "on") separated by a 3 days treatment free period (treatment "off") every 7 days for 28 days Treatment was provided by oral administration of capsules	

Number of subjects in period 1	Placebo	Group 1 IMPD	Group 2 IMPD
Started	11	8	8
Completed	11	6	6
Not completed	0	2	2
One capsule lost	-	1	-
Adverse event, non-fatal	-	1	2

Number of subjects in period 1	Group 3 IMPD
Started	7
Completed	4
Not completed	3
One capsule lost	-
Adverse event, non-fatal	3

Baseline characteristics

Reporting groups

Reporting group title	Placebo
Reporting group description: Placebo	
Reporting group title	Group 1 IMPD
Reporting group description: 200mg of seliciclib	
Reporting group title	Group 2 IMPD
Reporting group description: 400 mg of seliciclib	
Reporting group title	Group 3 IMPD
Reporting group description: 800 mg of seliciclib	

Reporting group values	Placebo	Group 1 IMPD	Group 2 IMPD
Number of subjects	11	8	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)	11	8	8
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
arithmetic mean	33.82	34.75	31.75
full range (min-max)	21 to 50	28 to 50	22 to 41
Gender categorical Units: Subjects			
Female	5	3	4
Male	6	5	4

Reporting group values	Group 3 IMPD	Total	
Number of subjects	7	34	
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)	7	34	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous			
Units: years			
arithmetic mean	37.00		
full range (min-max)	28 to 51	-	
Gender categorical			
Units: Subjects			
Female	3	15	
Male	4	19	

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Placebo	
Reporting group title	Group 1 IMPD
Reporting group description:	
200mg of seliciclib	
Reporting group title	Group 2 IMPD
Reporting group description:	
400 mg of seliciclib	
Reporting group title	Group 3 IMPD
Reporting group description:	
800 mg of seliciclib	
Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis
Subject analysis set description:	
All randomised patients	

Primary: Safety evaluation

End point title	Safety evaluation ^[1]
End point description:	
Safety of seliciclib vs. placebo, measured by incidence and severity of higher grade treatment-emergent adverse event until Day 56.	
End point type	Primary
End point timeframe:	
Day 56	

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: safety evaluation correspond to a specific endpoint, the result are presented in an endpoint section

End point values	Placebo	Group 1 IMPD	Group 2 IMPD	Group 3 IMPD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	8	7
Units: Number of adverse events				
AE Grade 1	4	4	0	1
AE Grade 2	7	4	6	5
AE Grade 3	0	0	1	1
AE Grade 4	0	0	1	0

Statistical analyses

No statistical analyses for this end point

Secondary: Pseudomonas aeruginosa (P.A.)

End point title	Pseudomonas aeruginosa (P.A.)
-----------------	-------------------------------

End point description:

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

End point timeframe:

Change from Day 1 to Day 28 in *Pseudomonas aeruginosa* (P.A.) log-concentration

End point values	Placebo	Group 1 IMPD	Group 2 IMPD	Group 3 IMPD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	8	7
Units: log-concentration(D28)-log-concentration(D1)				
arithmetic mean (standard deviation)	-0.09 (± 1.38)	-0.38 (± 0.74)	-0.50 (± 1.31)	0.57 (± 0.98)

Statistical analyses

Statistical analysis title	ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.502
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 400mg)
Comparison groups	Placebo v Group 2 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.463
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 800mg)
Comparison groups	Placebo v Group 3 IMPD
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.359
Method	ANOVA

Secondary: C-reactive protein (CRP)

End point title	C-reactive protein (CRP)
-----------------	--------------------------

End point description:

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

End point timeframe:

Change from Day 1 to Day 28 in C-reactive protein (CRP)

End point values	Placebo	Group 1 IMPD	Group 2 IMPD	Group 3 IMPD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	8	7
Units: CRP(D28)-CRP(D1)				
arithmetic mean (standard deviation)	-2.67 (± 20.09)	-1.74 (± 4.22)	-3.88 (± 9.92)	2.31 (± 16.79)

Statistical analyses

Statistical analysis title	ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.362
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 400mg)
Comparison groups	Placebo v Group 2 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.182
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 800mg)
Comparison groups	Group 3 IMPD v Placebo

Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.81
Method	ANOVA

Secondary: Forced expiratory volume in 1 second (FEV1)

End point title	Forced expiratory volume in 1 second (FEV1)
End point description:	
End point type	Secondary
End point timeframe:	
Change from Day 1 to Day 28 in Forced expiratory volume in 1 second (FEV1)	

End point values	Placebo	Group 1 IMPD	Group 2 IMPD	Group 3 IMPD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	8	7
Units: FEV1(D28)-FEV1(D1)				
arithmetic mean (standard deviation)	-0.27 (± 2.62)	0.03 (± 2.73)	-1.25 (± 6.48)	-0.29 (± 1.11)

Statistical analyses

Statistical analysis title	ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.394
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 400mg)
Comparison groups	Group 2 IMPD v Placebo
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.681
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 800mg)
Comparison groups	Placebo v Group 3 IMPD
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.417
Method	ANOVA

Secondary: Body mass index (BMI)

End point title	Body mass index (BMI)
End point description:	
End point type	Secondary
End point timeframe:	
Change from Day 1 to Day 28 in Body mass index (BMI)	

End point values	Placebo	Group 1 IMPD	Group 2 IMPD	Group 3 IMPD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	8	7
Units: BMI(D28)-BMI(D1)				
arithmetic mean (standard deviation)	0.20 (± 0.45)	-0.24 (± 0.29)	0.19 (± 0.48)	-0.05 (± 0.24)

Statistical analyses

Statistical analysis title	ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 400mg)
Comparison groups	Placebo v Group 2 IMPD

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 800mg)
Comparison groups	Placebo v Group 3 IMPD
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.218
Method	ANOVA

Secondary: Sweat Chloride Concentration

End point title	Sweat Chloride Concentration
End point description:	
End point type	Secondary
End point timeframe:	
Change from Day 1 to Day 28 in Sweat Chloride Concentration	

End point values	Placebo	Group 1 IMPD	Group 2 IMPD	Group 3 IMPD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	8	7
Units: Concentration(D28)- Concentration(D1)				
arithmetic mean (standard deviation)	1.09 (± 6.14)	-1.93 (± 9.78)	2.14 (± 10.21)	3.71 (± 3.83)

Statistical analyses

Statistical analysis title	ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.332
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 400mg)
Comparison groups	Placebo v Group 2 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.823
Method	ANOVA

Statistical analysis title	ANOVA (Placebo vs. 800mg)
Comparison groups	Placebo v Group 3 IMPD
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.451
Method	ANOVA

Secondary: Cystic Fibrosis Questionnaire-Revised

End point title	Cystic Fibrosis Questionnaire-Revised
End point description:	
End point type	Secondary
End point timeframe:	
Change from Day 1 to Day 28 in Cystic Fibrosis Questionnaire-Revised (CFQ-R)	

End point values	Placebo	Group 1 IMPD	Group 2 IMPD	Group 3 IMPD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	8	7
Units: D28-D1				
arithmetic mean (standard deviation)				
Perception of health status	-4.13 (± 13.71)	-6.82 (± 9.41)	-1.14 (± 13.25)	-16.88 (± 25.94)
Weight	3.03 (± 23.35)	8.33 (± 15.43)	4.17 (± 27.82)	-4.76 (± 12.60)
Digestive symptoms	3.03 (± 16.36)	-2.08 (± 30.13)	4.17 (± 19.42)	-2.38 (± 15.00)
Respiratory symptoms	3.97 (± 6.63)	10.12 (± 15.57)	2.38 (± 16.30)	-5.44 (± 13.86)
Energy	-3.79 (± 17.23)	-3.13 (± 11.73)	-5.21 (± 16.63)	-11.90 (± 9.45)
Physical	3.03 (± 15.93)	-2.60 (± 8.61)	-3.65 (± 12.68)	0.00 (± 10.21)
Psychic	0.00 (± 15.49)	3.33 (± 11.27)	2.50 (± 10.65)	-7.62 (± 11.17)
Role	-1.79 (± 4.72)	-6.25 (± 12.50)	0.00 (± 0.00)	-2.08 (± 9.41)

Social	-6.82 (± 12.81)	2.08 (± 15.27)	5.21 (± 12.55)	-5.95 (± 9.27)
Food	1.52 (± 11.68)	4.17 (± 7.72)	-4.17 (± 11.79)	-2.38 (± 6.30)
Body Image	-3.03 (± 11.21)	5.56 (± 18.78)	5.56 (± 18.78)	4.76 (± 17.98)
Marginalisation	1.01 (± 18.89)	9.72 (± 9.27)	1.39 (± 16.20)	0.00 (± 6.42)
Treatments	-9.09 (± 15.57)	4.17 (± 7.72)	0.00 (± 8.91)	2.38 (± 6.30)

Statistical analyses

No statistical analyses for this end point

Secondary: Cytokines

End point title	Cytokines
End point description:	
End point type	Secondary
End point timeframe:	
Change from Day 1 to Day 28 in Cytokines (log-transformed)	

End point values	Placebo	Group 1 IMPD	Group 2 IMPD	Group 3 IMPD
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	11	8	8	7
Units: D28-D1				
log mean (standard deviation)				
IL-1beta	0.03 (± 0.07)	0.02 (± 0.09)	-0.16 (± 0.19)	0.11 (± 0.16)
IL-8	0.14 (± 0.38)	-0.40 (± 0.36)	0.01 (± 0.30)	0.16 (± 0.33)
MDC	0.04 (± 0.24)	0.03 (± 0.12)	-0.09 (± 0.16)	-0.09 (± 0.25)
MIP-1beta	0.07 (± 0.24)	-0.05 (± 0.13)	-0.12 (± 0.19)	-0.21 (± 0.23)

Statistical analyses

Statistical analysis title	IL-1Beta - ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.472
Method	ANOVA

Statistical analysis title	IL-1Beta - ANOVA (Placebo vs. 400mg)
Comparison groups	Placebo v Group 2 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.012
Method	ANOVA

Statistical analysis title	IL-1Beta - ANOVA (Placebo vs. 800mg)
Comparison groups	Group 3 IMPD v Placebo
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.762
Method	ANOVA

Statistical analysis title	IL-8 - ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.02
Method	ANOVA

Statistical analysis title	IL-8 - ANOVA (Placebo vs. 400mg)
Comparison groups	Placebo v Group 2 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.631
Method	ANOVA

Statistical analysis title	IL-8 - ANOVA (Placebo vs. 800mg)
Comparison groups	Placebo v Group 3 IMPD
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 1
Method	ANOVA

Statistical analysis title	MDC - ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.368
Method	ANOVA

Statistical analysis title	MDC - ANOVA (Placebo vs. 400mg)
Comparison groups	Placebo v Group 2 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.044
Method	ANOVA

Statistical analysis title	MDC - ANOVA (Placebo vs. 800mg)
Comparison groups	Placebo v Group 3 IMPD
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.316
Method	ANOVA

Statistical analysis title	MIP-1beta - ANOVA (Placebo vs. 200mg)
Comparison groups	Placebo v Group 1 IMPD
Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.15
Method	ANOVA

Statistical analysis title	MIP-1beta - ANOVA (Placebo vs. 400mg)
Comparison groups	Placebo v Group 2 IMPD

Number of subjects included in analysis	19
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.052
Method	ANOVA

Statistical analysis title	MIP-1beta - ANOVA (Placebo vs. 800mg)
Comparison groups	Placebo v Group 3 IMPD
Number of subjects included in analysis	18
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.05
Method	ANOVA

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

Adverse event was recorded during all study duration. In case of unexpected withdrawal from the study, adverse event was recorded at least 28 days after the last treatment administration.

Adverse event reporting additional description:

A regular investigator assessment was made by the investigator at each visit and a regular laboratory testing was done.

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

Dictionary used

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

Dictionary version	21.0
--------------------	------

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: safety evaluation correspond to a specific endpoint, the result are presented in an endpoint section

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
27 November 2015	Modification of the inclusion criteria about genotype + title modification
08 December 2015	Addition of a pain questionnaire + revalorization of the patient allowance + protocol update following with ANSM's remarks
05 January 2016	Update of the insurance company
02 February 2016	Summary corrections at the request of the coordinator + modifications of the safety paragraph following the first CSI meeting + modification of the evaluation schedule.
05 April 2016	Modifications of the centers and investigators list
04 October 2016	Modifications of the centers and investigators list
13 December 2016	Modifications of the centers and investigators list
02 May 2017	Modifications of the centers and investigators list
05 September 2017	Increase of the period of inclusion + possibility to recruit patients who had participated in previous groups
09 January 2018	Modifications of the consent letter + modifications of the exclusion criteria (hepatic criteria) and more controls of hepatic monitoring + modifications of investigators list

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

None reported

Notes: