# 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-concentrati(D28)-log-concentrati(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: