	Clinical Study Report **« A Phase 2, dose ranging, multicenter, double-blind, placebo controlled study to evaluate safety and effects of seliciclib (R-roscovitine) in adults subjects with Cystic Fibrosis, carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation and chronically infected with *Pseudomonas aeruginosa*, a study involving 36 CF patients (24 treated, 12 controls). ROSCO-CF. »**

EudraCT: n° 2015-002911-13

Identification of Ethics Committee: CPP Ouest VI - 899

N° Clinical Trial.gov: NCT02649751

Sponsor :

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Author of clinical study report	Dr Gilles RAULT, coordinating investigator Florence Gatineau, Emmanuel NOWAK, biostatisticians Dr Dominique CARLHANT-KOWALSKI, Safety officer Florence MORVAN, project manager
Study Typology	- Roscovitine (seliciclib or CYC202) experimental drug candidate in the family of pharmacological cyclin-dependent kinase (CDK) inhibitors - Phase de développement: Phase II - Cystic fibrosis
A brief desciption of study design	- This is a phase 2, dose ranging, multicenter, randomized, double-blind, placebo-controlled study - Study duration : 30 months (28 months of patient recruitment and 2 months of patient follow-up) - Comparator: placebo treatment as lactose capsules - Number of participants : 49 participants among which 34 randomized patients
Ethics Committee approval date	September 29th, 2015

Competent Authority approval date	September 15th, 2015
Data protection authority approval date (if applicable)	CNIL – MR001 Not Applicable
Date of first enrolment	February 22nd, 2016
Date of last visit of last patient	July 26th, 2018
History of substantial amendments	**MS n°1**: Modification of the inclusion criteria about genotype + title modification **MS n°2**: Addition of a pain questionnaire + revalorization of the patient allowance + protocol's update with ANSM's remarks **MS n°3:** Update of the insurance company **MS n°4:** Summary's corrections at the request of the coordinator + modifications of the safety's paragraph following the first CSI meeting + modification of the evaluation schedule **MS n°5:** Modifications of the centers and investigators' list **MS n°6:** Modifications of the centers and investigators' list **MS n°7:** Modifications of the centers and investigators' list **MS n°8:** Modifications of the centers and investigators' list **MS n°9:** Increase of the period of inclusion + possibility to recruit patients who have previously participated in previous groups **MS n°10:** Modifications of the consent letter + modifications of the exclusion criteria (hepatic criteria) and strengthening of hepatic monitoring + modifications of investigators' list
Date of the final report	December 19th, 2018
Number of centres and investigators	13 centers and 47 investigators : **ROSCOFF (01):** Gilles Rault ; Jean Le Bihan ; Sophie Ramel ; Carole Sizun; Anne Dirou ; Krista Revert ; Thomas Ropars. **LYON (02):** Isabelle Durieu ; Raphaële Nove-Josserand ; Stéphane Durupt ; Quitterie Reynaud. **MONTPELLIER (03) :** Raphaël Chiron ; Anne-Sophie Gamez-Dubuis ; Davide-Paolo Caimmi. **FOCH (04):** Dominique Grenet ; Sandra De Miranda **LILLE (05):** Anne Prévotat ; Benoit Wallaert ; Liwine Wemeau-Stervinou ; Thierry Perez ; Aurélie Cottereau ; Nawal Waucquier ; Maria-Claire Migaud. **PARIS-COCHIN (06):** Dominique Hubert ; Pierre-Régis BURGEL ; Frédérique Aubourg ; Isabelle Fajac. **TOULOUSE (07):** Marlène Murris-Espin ; Laurent Têtu **VANNES (08):** Sandrine Hugé **NANTES (09):** Isabelle Danner-Boucher **;** Alain Haloun ; François-Xavier Blanc. **REIMS (10):** Bruno Ravoninjatovo **NICE (11):** Sylvie Leroy ; Johana Pradelli ; Claude Clary ; Sylvia Korzeniewski ; Charles-Hugo Marquette ; Andréa Mazetta ; Michèle Benhayoun ; Céline Sanfiorenzo ; Linda Bouhlel **BORDEAUX (12):** Julie Macey **ANGERS (13):** Thierry Urban ; Christine Person ; Marc-Antoine Custaud.

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LIST OF ABBREVIATIONS

ABPA	Allergic broncho-pulmonary aspergillosis
AE	Adverse event
ALAT	Alanine Aminotranferase
ANSM	French National Public Health and Drug Security Agency
ASAT	Aspartate Aminotranferase
AT	Anterior Turbinate
AUC	Area Under the Curve
AV	Auriculo-ventricular
BCC	Blood Count Cells
BMI	Body Mass Index
CDK	Cyclin-Dependent Kinases
CF	Cystic Fibrosis
CFFT	Cystic Fibrosis Foundation Therapeutics
CFQ-R	Revised Cystic Fibrosis Quality of life questionnaire
CFTR	Cystic Fibrosis Transmembrane Conductance Regulator
CHMP	Committee for Medicinal Products for Human use
C_{max}	Maximum concentration
CNIL	Official French National Data Protection and Privacy Commission
CRA	Clinical Research Assistant
CRF	Case Report Form
CRP	C-reactive Protein
CTCAE	Clinical Trial Classification of Adverse Event
DLT	Dose Limiting Toxicity
DNA	Deoxyribonucleic acid
DSUR	Data Safety Update Report
ECFS-CTN	European Cystic Fibrosis Society – Clinical Trials Network
ECG	Electrocardiogram
ECo	Ethics Committee
e-CRF	electronic Case Report Form
EMEA-CHMP	European Medicines Agency - Committee for Medicinal Products for Human Use
FEF	Forced Expiratory Flow
FEV	Forced Expiratory Volume
FVC	Forced Vital Capacity
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
ICF	Inform Consent Form
ICH	International Conference of Harmonization
IDSMB	Independent Data Safety Monitoring Board
IFN	Interferon
IL	Interleukine
ITT	Intention To Treat
MedDRA	Medical Dictionary for Regulatory Activity
MI	Myocardial Infarction
mL	milliliter
MTD	Maximum Tolerated Dose
NPD	Nasal Potential Difference
NTEAE	Non Treatment Emergent Adverse Event
NYHA	New York Heart Association
PA	Pseudomonas aeruginosa
PAL	Alkaline Phosphatase
PE	Physical Examination
PK	Pharmacokinetics
PP	Per Protocol
QaD	Quaque altera die (every other day)
QC	Quality Control
QD	Quaque die (each day)
QI	Quality Insurance

RT	Room Temperature
SAE	Serious Adverse Event
SC	Scientific Committee
SD	Standard Deviation
SEM	Standard Error of the Mean
SOP	Standard Operating Procedures
TCS	Total Chloride Secretion
TDN	Therapeutics Development Network
TEAE	Treatment Emergent Adverse event
T_{max}	Time to reach C_{max}
t1/2	Half time
UH	University Hospital
ULN	Upper Limit of Normal
V	Visit

DEFINITIONS OF TERMS

Adverse events: events that induce a change in the patient care

Adverse effect and/or adverse reaction: adverse events potentially due to the experimental treatment

Deviation: the action of departing from an established course or accepted standard (study protocol, study procedure, investigator brochure …).

INTRODUCTION

The cyclin-dependent kinase (CDK) inhibitor seliciclib (roscovitine) is a clinical drug which has been developed to treat various cancers (Meijer et al., 1997; review in Meijer & Raymond, 2003; Bruyère and Meijer, 2013; Meijer et al., 2016). Two independent discoveries suggested potential beneficial effects of seliciclib for chronically infected CF patients (Norez et al., 2014; Riazanski et al., 2016; review in Meijer et al., 2016). As 500 patients (cancer patients and healthy volunteers) had already been treated with seliciclib, some solid safety data was available and allowed us to propose a clinical trial in CF patients. It was therefore decided to investigate the safety of seliciclib in chronically infected CF patients, as the first objective. A secondary objective was to investigate whether signs of efficacy at the infection and inflammatory levels could be detected in this small trial.[1]

1 Primary and secondary objectives

Primary objective:
To assess the safety of increasing doses of seliciclib 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 carrying 2 Cystic Fibrosis causing mutations with at least F508de-CFTR mutation.

Secondary objectives

- To assess microbiological levels of infection by *Pseudomonas aeruginosa*;
- To assess the pharmacokinetics of seliciclib and its M3 metabolite and pharmacodynamics;
- To assess the levels of pro- and anti- inflammatory cytokines some of which known to be modified by seliciclib;
- To assess seliciclib target engagement by measurement of the expression level of Mcl-1 at day 1 and day 5, a survival factor expressed in neutrophils, the degradation of which is triggered by seliciclib, leading to apoptotic cell death.

2 Treatments

2.1 Name and description of investigational products

Experimental medical product:
Roscovitine (seliciclib or CYC202) is an experimental drug candidate in the family of pharmacological cyclin-dependent kinase (CDK) inhibitors that preferentially inhibit multiple

[1] Bruyère, C. and Meijer, L., 2013. Targeting cyclin-dependent kinases in anti-neoplastic therapy. "Cell Cycle, Differentiation and Disease" issue. **Curr. Opinion Cell Biol. 25**, 772-779.

Meijer, L., Borgne, A., Mulner, O., Chong, J.P.J., Blow, J.J., Inagaki, N., Inagaki, M., Delcros, J.G. and Moulinoux, J.P., 1997. Biochemical and cellular effects of roscovitine, a potent and selective inhibitor of the cyclin-dependent kinases cdc2, cdk2 and cdk5. **Eur. J. Biochem. 243,** 527-536.

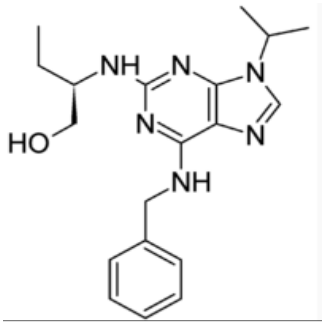
Meijer, L., Nelson, D., Riazanski, V., Gabdoulkhakova, A.G., Hery-Arnaud, G., Leberre, R., Loaëc, N., Oumata, N., Galons, H., Nowak, E., Gueganton, L., Dorothée, G., Prochazkova, M., Hall, B., Kulkarni, A.B., Gray, R.D., Rossi, A.G., Witko-Sarsat, V., Norez, C., Becq, F., Ravel, D., Mottier, D. and Rault, G., 2016. Modulating innate and adaptative immunity by (R)-roscovitine: potential therapeutic opportunity in cystic fibrosis **J. Innate Immunity 8**, 330-349.

Meijer, L. and Raymond, E., 2003. Roscovitine and other purines as kinase inhibitors. From starfish oocytes to clinical trials. **Accounts Chem. Res. 36**, 417-425.

Norez, C., Vandebrouck, C., Bertrand, J., Noel, S., Durieu, E., Oumata, N., Galons, H., Antigny, F., Chatelier, A., Bois, P., Meijer, L. and Becq, F., 2014. Roscovitine is a proteostasis regulator that corrects the trafficking defect of F508del-CFTR by a CDK-independent mechanism. **Br. J. Pharmacol. 171**, 4831-4849.

Riazanski, V., Gabdulkhakova, A.G., Boynton, L.S., Eguchi, R.R., Deriy, L.V., Hogarth, D.K., Loaëc, N., Oumata, N., Galons, H., Brown, M.E., Shevchenko, P., Gallan, A.J., Yoo, S.G., Naren, A.P., Villereal, M.L., Beacham, D.W., Bindokas, V.P., Birnbaumer, L., Meijer, L. and Nelson, D.J., 2015. TRPC6 channel translocation into phagosomal membrane augments phagosomal function. **Proc. Natl. Acad. Sci. USA 112**, E6486-6495.

enzyme targets including CDK1, CDK2, CDK5, CDK7 and CDK9. Seliciclib is a 2,6,9-substituted purine.



Molecular formula: $C_{19}H_{26}N_6O$
Relative molecular mass: 354.45
Chirality: R
Physical characteristics: white to off white crystalline powder
CAS N°: 186692-46-6

The active treatment is 200 mg of seliciclib oral capsules. Capsules of active treatment were be provided by Cyclacel Pharmaceuticals Inc.

Comparator group :
The placebo treatment is lactose capsules.

2.2 Treatment administration

The capsules were stored at controlled room temperature (20-25°C) in a closed container, protected from light, in a secure, limited-access storage area.

Seliciclib/placebo was given according to an intermittent schedule in all groups: 4 consecutive days every 7 days for 28 days.

- **Group 1:** 200 mg seliciclib (8 patients) or placebo (4 patients) once daily for 4 cycles of 7 days (4 days “on” and 3 days “off”);
- **Group 2**: 400 mg (2x200 mg) seliciclib (8 patients) or placebo (4 patients) once daily for 4 cycles of 7 days (4 days “on” and 3 days “off”);
- **Group 3**: 800 mg (4x200 mg) seliciclib (8 patients) or placebo (4 patients) once daily for 4 cycles of 7 days (4 days “on” and 3 days “off*”).*

2.3 Prior and Concomitant therapy

Prior and concomitant treatment
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) was recorded in each subject’s source documents and on the Concomitant medications/Significant non-drug therapies in the electronic Case Report Form (eCRF). Information recorded includes indications for use, dosage, route and dates of administration.
Information about bronchodilator use during the study was collected and is documented in the subject's source documents and eCRF.

Forbidden treatments

Use of the prohibited medications and certain food displayed was not allowed after the start of the study drug administration.
Ongoing or prior participation in an investigational drug study within 30 days of screening was prohibited.
Ongoing participation in a no interventional study (including observational studies) was permitted.

3 Methodology and investigational plan

3.1 Study design and plan description

ROSCO-CF was a phase 2, dose ranging, multicenter, randomized, double-blind, placebo-controlled study.

Thirty six patients were allocated to 3 groups of 12 adult subjects who were randomized in a 2:1 ratio. In each group, 8 patients have received seliciclib (200 mg, 400 mg, 800 mg in group 1, 2 and 3, respectively) and 4 have received a matching placebo. Treatment was provided by oral administration of capsules. Each patient has received the same treatment throughout the study. Subjects were outpatients during the study except for Day1 (hospitalization).

For safety reason:
- Recruitment of the first patient of group 2 was started only when the last patient of group 1 had reached at D28 and after IDSMB recommendations,
- Treatment of group 3 was started when the last patient of group 2 had reached at Day 28 and after IDSMB recommendations.

Toxicity was graded on a scale from 1 to 5, with severe and life-threatening events graded as 3, 4 and 5 based on the protocol terminology. For any subject with toxicity grade of 3 or more judged to be potentially due to seliciclib, study medication was stopped for the patient.

The patient could participated in 2 groups at different doses if no AE with toxicity grade 3 or more judged to be potentially related to seliciclib and if the last dose of treatment was taken at least 3 months prior to the inclusion in the next group.

Table 1: Investigational schedule

Visit	1	2		3	4	4 bis	5	5 bis	6	6 bis	7 or completion	8
Day	-14/-7	1	2	5	8	12**	15	19**	22	26**	28	56
Time windows (±days) from V2	-14 to -7											+/-7
Period	Screening	Treatment										Safety Follow-Up
Informed Consent	X											
Inclusion/Exclusion Criteria Review	X	X										
Randomisation		X										
CFQ-R		X		X	X		X		X		X	X
Pain QOL		X		X	X		X		X		X	X
Demographics	X											
Medical History	X											
Complete Physical Examination	X	X		X	X		X		X		X	
Vital Signs	X	X		X	X		X		X		X	
Pulse Oximetry	X	X		X	X		X		X		X	
Height and weight	X	X		X	X		X		X		X	
Standard Digital 12-lead ECG	X	X		X	X		X		X		X	
Spirometry	X	X		X	X		X		X		X	
CF Genotype *	X											
Concentration (CFU/mL) of *P. aeruginosa* in the sputum	X	X		X	X		X		X		X	
Serum Chemistry	X	X		X	X		X		X		X	
Hematology / Coagulation studies	X	X		X	X		X		X		X	
Liver Function Test	X	X		X	X	X	X	X	X	X	X	
Urinalysis	X	X		X	X		X		X		X	
FSH	X										X	
Pregnancy Test	X	X		X	X		X		X		X	
Sweat Chloride Concentration		X		X			X				X	
Mcl-1		X		X								
Interleukins sampling	X	X		X							X	
Serum bank CRB	X			X								
Nasal Potential Difference (Only for Cochin Patient)	X								X			
Dosing (Dispense trial medication)		X										
PK sampling		X	X	X								
Stool sampling		X		X	X		X		X		X	X
Prior and Concomitant Medications	X	X	X	X	X		X		X		X	X
AEs and SAEs		X	X	X	X		X		X		X	X
Other events related to outcomes		X		X	X		X		X		X	X
Conclusion of participation												X

3.2 Description of planned study population

3.2.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

- Male or female aged over 18 years of age on the date of informed consent
- Diagnosed CF patients. Confirmed diagnosis of CF is defined as (Rosenstein and Cutting, 1998):
    - A sweat chloride value ≥ 60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations
    - AND chronic sinopulmonary disease OR gastrointestinal/nutritional abnormalities
- Patients carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation, genotype to be confirmed at screening;
- Forced expiratory volume at 1 second (FEV1)≥ 40% of normal predicted values for age, sex and height based on the Knudson equation;
- FEV1 at Day 1 must be within 15% of FEV1 at Screening. If FEV1 at Day 1 is not within 15% of FEV1 at Screening, Visit 2 can be repeated within 7 days and rescheduled once;
- Chronic lung *Pseudomonas aeruginosa* infection according to the definition from the French Consensus Conference as recommended by the Committee for Medicinal Products for Human use (CMPH) of the European Medicines Agency (EMA).Clinically stable CF disease in the opinion of the investigator;
- Able to understand and comply with all protocol requirements, restrictions and instructions and likely to complete the study as planned (as judged by the investigator);
- Provide written informed consent prior to the performance of any study-related procedure;
- Be affiliated to health insurance;
- Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in the protocol.

3.2.2 Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

- Acute upper or lower respiratory infection, pulmonary exacerbation or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before V2
- Recent patient reported history of
    - non recovered viral upper respiratory tract infection
    - solid organ or hematological transplantation
- Undergone major surgery within 1 month prior to screening
- Currently treated allergic broncho-pulmonary aspergillosis (ABPA)
- Diabetic patients whose blood glucose is poorly controlled as evidenced by HbA1C>8%
- Hemoptysis more than 60 mL at any time within 4 weeks prior to first study drug administration (V2)
- History of any other comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
- Any other clinically significant conditions (not associated with the study indication) at Screening (V1) which might interfere with the assessment of this study
- Any of the following abnormal laboratory values at screening:
    - Hemoglobin <10 g/dL
    - Abnormal liver function defined as any 3 or more of the following:

        - >1.5 x upper limit of normal (ULN) aspartate aminotransferase (ASAT)
        - >1.5 x ULN alanine aminotransferase (ALAT)
        - ≥3 x ULN gamma-glutamyl transpeptidase (GGT)
        - ≥3 x ULN alkaline phosphatase (PAL)
        - Or ≥2 x ULN total biliburin
    - Serum K+ <3,5 mmol/L
    - Abnormal renal function defined as a creatinine clearance <50 mL/min/m^2/ glomerular filtration rate ≤50 mL/min/1,73 m^2 (calculated by the Modification of Diet in Renal Disease Study Equation)
- Any clinically significant laboratory abnormalities (not associated with the study indication) at screening that would interfere with the study assessment or pose an undue risk for the subject (as judged by the investigator)
- Patients who have clinically significant impairment in cardiovascular function or are at risk thereof, as evidenced by:
    - Congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, high grade AV block, history of acute MI less than one year prior to study entry
    - A 12- lead electrocardiogram at screening demonstrating QTcF>450 or showing clinically significant abnormality including prolonged QT. If the QTcF exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the screening period, and the average of the 3 QTcF values should be used to determine the subject's eligibility.
    - History of syncope or family history of idiopathic sudden death
    - Risk factors for Torsades de Pointes such as uncorrected hypokalemia, uncorrected hypomagnesemia, cardiac failure
- Concomitant disease(s) that could prolong the QT interval.
- Patients with a history of alcohol or drug abuse in the past year, including but not limited to tobacco, cannabis, cocaine, and opiates as deemed by investigator
- Patients with a history of noncompliance to medical regimens and patients or caregivers who are considered potentially unreliable
- Use of one (or several) prohibited medications and/or food within 30 days prior to Screening (V1)
- Administration of any investigational drug within 30 days prior to Screening (V1) or 5 half-lives, whichever is longer
- Use of systemic anti-pseudomonal antibiotics within 28 days prior to first study drug administration (V2). However use of inhaled anti-pseudomonal antibiotic treatment is allowed if initiated for more than 28 days.
- Use of loop diuretics within 7 days prior to first study drug administration (V2)
- Patients with galactose intolerance, the Lapp lactase deficiency or malabsorption of glucose and galactose
- Pregnant or nursing females: females of childbearing potential must have a negative pregnancy test at screening
- Sexually active subjects of reproductive potential who are not willing to follow the contraception requirement

3.3 Efficacy and safety assessments

Primary endpoint:

Safety, and tolerability of seliciclib vs. placebo, measured by incidence and severity of treatment-emergent adverse events, clinical laboratory values (serum chemistry, hematocrit,

Blood Cells Count (BCC), electrolytes, and urinalysis), 12-lead ECG outcomes, vital signs at each visit and until Day56.

Secondary endpoint:

- Change in the concentration (CFU/mL) of *Pseudomonas aeruginosa* in the sputum at each visit from V1 (Screening) up to V7 (Completion Visit);
- PK parameters: Maximum Concentration (C_{max}), Time to reach C_{max} (T_{max}), Area Under Curve (AUC_t and AUC_{Inf}), Half-life (t1/2) for seliciclib and its M3 metabolite;
- Monitoring the levels of pro- and anti-inflammatory cytokines, in particular: interleukin (IL)-17A , IL-5, IFN-γ, IL-1 receptor antagonist, IL-4, IL-6, IL-10, tumor necrosis factor-alpha, and IL-18 on V1, V2, V3 and V7 (Completion Visit);
- Measure the expression level of Mcl-1 at Day 1 and Day 5 to evaluate seliciclib target engagement;
- Change in C-reactive protein (CRP) at each visit from V1 (Screening) up to V7 (Completion);
- Change in Cystic Fibrosis Questionnaire-Revised (CFQ-R) at each visit from V2 up to V8 (Safety Follow-up);
- Evaluate of the pain and of the impact of the pain in patients with cystic fibrosis on V2 to V8;
- Change in body mass index (BMI) at each visit from V1 (Screening) up to V7 (Completion Visit);
- Change in forced expiratory volume in 1 second (FEV1) at each visit from V1 (Screening) up to V7 (Completion Visit);
- Change in Sweat Chloride Concentration at V2, V3, V5 and V7 (Completion);
- Change in Nasal Potential Difference (NPD) at V1 (Screening) and V6 (for patients included in Cochin).

3.4 Statistical methods planned in the protocol and determination of sample size

Brest University Hospital statistical and data management center were in charge of statistical analysis. SAS software was used except for pharmacokinetic analysis which used WinNonlin® Software.

3.4.1 Planned methods

All individual data for all included subjects were presented in data listings, sorted by subject within treatment group unless otherwise specified.

3.4.2 Descriptive statistics

Descriptive statistics for quantitative parameters were provided using mean, standard deviation (SD), standard error of the mean (SEM), minimum, median, maximum, and number of observations, and descriptive statistics for qualitative parameters were provided using absolute frequencies (n) and relative frequencies (%).

(i) Subject demographic characteristics, medical history and diagnoses:

Continuous variables (age, height, weight, body mass index (BMI)) and qualitative variables (gender) were summarized in descriptive statistics on the included subjects and for the activity and/or pharmacokinetic population, if relevant. Medical history was listed and summarized by system organ class and preferred term, if relevant (MedDRA). Abnormal physical findings at baseline were listed.

(ii) Baseline safety parameters:

Individual safety data (clinical laboratory, vital signs) measured before the first drug administration was checked for validity of entrance criteria, and abnormalities was documented. Individual abnormalities before dosing was flagged in data listings and presented along with post-dose measurements in the statistical appendices.

3.4.3 Safety analysis

Adverse events

Adverse events were coded according to the Medical Dictionary for Regulatory Activity (MedDRA). They were classified into pre-defined standard categories according to chronological criteria:
- Treatment emergent AEs (TEAE): AEs that occurred for the first time or if present before worsened during an exposure to drug(s).
- Non-treatment emergent AEs (NTEAE): AEs that occurred before the study drug administration.

Adverse events were individually listed per subject number, presenting: assigned treatment group (or treatment received), System Organ Class, Preferred term, emergence, description, date and time of onset, date and time of last study drug administration before adverse event, duration, time from onset since last study drug administration, frequency, severity and seriousness, relationship to study drug, the required action taken (corrective treatment, hospitalization….) and outcome if any.
The non-treatment emergent AEs were described by System Organ Class and Preferred term for the safety set.
The treatment emergent AEs were summarized by System Organ Class, Preferred Term and treatment group for the safety set. An AE occurring during the run-out was related to the last day of treatment administration received. It consisted in the evaluation of the number of adverse events and the number of subjects reporting these adverse events.

Laboratory parameters

All laboratory values recorded during the study was individually listed and flagged for values outside reference ranges. Quantitative parameters were summarized by descriptive statistics. The value to be used as baseline was the last assessed value prior the first drug administration. If any of the scheduled baseline tests was repeated for any subject, the repeated tests or checked values was considered as baseline, provided it was done before the drug administration. Values and clinical assessment was described at baseline, during the treatment phase and at the end of study (first evaluation at the end of study visit). Change between the value at baseline and the value at the end of study visit was described for each parameter.
All quantitative and qualitative urinary test results were listed and sorted by visit and treatment.

3.4.4 Pharmacokinetics analysis

The pharmacokinetics analysis was carried out as non-compartmental analysis using WinNonlin® software. The following parameters were determined from seliciclib and M3 metabolite plasma concentration:
- Maximum Concentration (C_{max})
- Time to reach C_{max} (T_{max})
- Area Under Curve (AUC_t and AUC_{Inf})
- Half-life ($t_{1/2}$)

Pharmacokinetics parameters were summarized by number of observations, means, standard deviation (SD) and standard deviation of the mean (SEM), median, minimum and

maximum for each treatment group. Seliciclib and M3 metabolite plasma concentrations were plotted against time for each treatment group.

3.4.5 Pharmacodynamics analysis and efficacy outcomes

With respect to the quantitative pharmacodynamic parameters, change from the baseline to Day 28 (as well as to each end of cycles) was calculated in each group. Modeling of the response (change from baseline) according to the dose was conducted via ANOVA. The measured parameters performed several times at different days will undergo a modeling via mixed model for repeated data.
Quantitative efficacy outcomes were analyzed in the same manner.
Qualitative outcomes were compared between groups using the Chi-square test or the Fisher test when required. Time-to-event outcomes were dealt with using the Kaplan-Meier method and the logrank test.

3.4.6 Sample size

The same sample size was proposed for previous studies in the same therapeutic area with similar objectives (ClinicalTrials.gov Identifier: NCT01944735).

This trial was conducted mainly to evaluate the safety of seliciclib and define the most adapted dose for further phase 2 studies and to determine the maximum dose that could be given safely. In general such phase 1/2 trials enroll small numbers of patients (20-40). Given the pilot nature of the study on a rare disease, the sample size was set as follows: 8 patients for each dose (treatment group) and 4 controls for each dose (control group).

3.4.7 Set analysis

Safety analysis results were given according to assigned treatment group and received treatment.

PK analysis excluded subjects with any protocol violations likely to affect the results of the analysis.

Efficacy (PD and clinical outcomes) results were given for the intention to treat (ITT) population and for the per protocol (PP) population.

3.4.8 Measures taken to avoid biases

Any possible selection biases were avoided by using a computer-generated list of randomization and a central randomization method to ensure proper allocation concealment.

Detection and performance biases were not expected in this trial. The participants, the treatment providers and the outcome assessors were blinded from group assignment. Appearance of placebo will be similar to seliciclib 200 mg.

To limit the number of incomplete outcome data (i.e. the attrition bias), no patient was lost-to follow up, and the main statistical analysis was performed on an intention-to-treat basis in order to avoid the introduction of any potential selection bias.

The study protocol was recorded in a public registry of randomized clinical trials with all outcomes (primary and secondary) to show the lack of reporting bias (also called the within-study publication bias) at the time of publication: clinicalTrial.gov database number NCT02649751.

4 Supervision and Quality assurance

4.1 Description of monitoring

Study data were entered from investigational centers in an electronic case report form (e-CRF). The study sponsor, Brest University Hospital, has selected a high monitoring level in accordance with its procedures regarding to the study risks. Monitoring involved a check of 100 % of medical files and 100 % of data in all investigation centers.

A total 13 centers volunteered to participate to the study, 12 centers included at least 1 patient. The monitoring duration was 1 to 2 consecutive days. In accordance with SOPs, there was a need for 197 monitoring package days (preparation, visit, reporting).

Table 2: Number of CRA's working day per center

Center	Set up (preparation + visit + report)	Number of monitoring visits	Number of CRA's visits working day	Total number of CRA's working days (preparation + visit + report)
01 - Roscoff	7	7	8	22
02 - Lyon	5	5	6	16
03 -Montpellier	5	5	5	15
04 - Foch	1	1	1	3
05 - Lille	6	6	7	19
06 –Paris/Cochin	7	7	9	23
07 - Toulouse	3	3	3	9
08 -Vannes	3	3	3	9
09 -Nantes	3	3	3	9
10 - Reims	3	3	3	9
11 - Nice	5	5	9	19
12 - Bordeaux	2	2	3	7
13 - Angers	3	3	3	9
TOTAL	53	53	63	169

4.2 Description of data management

During the study, 6403 queries were edited (4087 from the data manager and 2316 from monitoring activities), giving 45% of which required a correction and the data manager made 4% self-evident corrections.
In total, 3 data review meetings were organized: 2 data reviews at the end of the administration of treatment for group 1 (September 18th, 2017) and group 2 (February 21th, 2018). A last data review meeting was organized to review all the data of the database on September 12th, 2018.
The final lock of the database was occurred on October 5th, 2018.

4.3 Audit

An internal audit was performed on January 3rd, 2018 which concluded that its findings did not impact the conduct of the study and the relevance of data, the Sponsor deployed the required corrective actions in accordance with the audit findings.

4.4 Steering Committee

A steering committee comprised the following persons:

- Dr Gilles RAULT, Coordinating investigator, Centre de Perharidy, Roscoff
- Pr Dominique MOTTIER, Brest UH
- Dr Geneviève HERY-ARNAUD, Brest UH
- Dr Rozenn LE BERRE, Brest UH
- Mr Emmanuel NOWAK, Biostatistician, Brest UH

The steering committee was responsible for the smooth conduct of the study, it discussed possible changes to the protocol and it analyzed safety reports and alerts prepared by the sponsor or recommendations provided by IDSMB (Independent Data and Safety Monitoring Board).

Accordingly, 5 meetings were held between April 2017 and July 2018 according to table 3.

Table 3: Steering committee meetings

Date	Agenda	Conclusions	Approved by sponsor
April, 4th. 2017	STOP and GO Meeting after 12 inclusions – evaluation of the study safety	Pursuit of the study without modification	Yes
May, 10th. 2017	Additional visit to screen if it is possible to recruit patients who have previously participated to previous groups	The Steering Committee considers that there is no risk for patients' safety to be included in a second group of higher doses in the ROSCO-CF clinical study provided that : - a gap period of 3 months between the last drug administration and the new inclusion is respected, - the patient did not experience a grade 3 or more toxicity potentially related to the experimental drug in the previous groups.	Yes
September, 20th. 2017	Project management (date of unblinding and group 3 dose adjustment 400mg twice a day)	No modification	Yes
December, 15th. 2017	STOP and GO Meeting after 12 inclusions in the second group – evaluation of the study safety	Pursuit of the study with modifications on the exclusion criteria (ASAT/ALAT) and additional clinical laboratory liver tests will be performed after each period "on" at each (Day 5 of each cycle).	Yes
July, 21st. 2018	Evaluation of the premature stop of the inclusions	The committee votes unanimously to stop the study. The main reason is the experienced difficulty to recruit in the summer and the planned end of the study on August 22, 2018, The committee thus decides to close inclusions without delay with the follow-up of the last patient undergoing treatment.	Yes

4.5 Data and Safety Monitoring Board

An Independent Data and Safety Monitoring Board (IDSMB) was created.
The five members of the IDMSB were:

- Pr Patrick MISMETTI, St Etienne UH, Professor of Pharmacology
- Pr Christophe LEROYER, Brest UH, Professor of Pneumology
- Pr Michaël FAYON, Bordeaux UH, Professor of Pediatrics, director of CF center

- Pr Jean-Philippe METGES, Brest UH, Professor of Oncology
- Pr Jean-Baptiste NOUSBAUM, Brest UH, Professor of hepato-gastro-enterology

The role of IDSMB was to provide an independent expertise for the assessment of serious adverse events occurring during the research and the monitoring of benefit/risk ratio of the study. The IDSMB made recommendations to the Steering Committee and the sponsor about possible modifications of protocol, study pursuit, its modification or its premature stop. The IDSMB had a consultative vote. Any modification of the protocol was under the responsibility of the steering committee and the sponsor.

Its recommendations were transmitted to the Coordinating Investigator, the steering committee, the safety department, to the Ethic Committee and ANSM.

Accordingly, 3 meetings were held between January 2016 and December 2017 according to table 4.

Table 4: IDSMB meetings

Date	Agenda	Conclusions
January, 12th 2016	IDSMB guidelines and meeting schedule	Validation of IDSMB guidelines Validation of meeting schedule
April, 3rd 2017	STOP and GO Meeting after the 12 inclusions of the first group – evaluation of the study safety	**Pursuit of the study with escalation of the superior step (400mg/day) but following the recommendations listed in comments without changing the protocol**. → This assessment is based on the fact that no grade 3 AE was identified in this first group. According to the stop rules**, the dose escalation could continue**. Comments: Despite the cardiological findings reported in the report, we recommend that the IDSMB be notified immediately in the event of any new cardiac adverse events, changes to the ECG, and to arrange a telephone meeting within 72 hours, with a minimum of 3 members.
December, 14th 2017	STOP and GO Meeting after the 12 inclusions of the second group – evaluation of the study safety	**Pursuit of study with the following modifications:** - More controls for liver biology (ALAT, ASAT, PAL, gammaGT, total bilirubin) BEFORE and AFTER administration of the product, ie on D1 and D5 of each cycle. - Increased transaminases (ASAT, ALAT)> 1.5 N should block any introduction of the treatment, e. patients on inclusion should not have transaminases > 1.5N, as well as any long taking treatment. - In case of increased transaminases, treatment is stopped immediately and biological monitoring should be performed every 48 hours until normalization. The final judgment will be pronounced only after consultation and review of patients, case by case, by the IDSMB. - Before considering the pursuit of the study, it is necessary that monitoring be carried out in the various centers to verify that the strategy is implemented and compliant. The IDSMB recommends special monitoring in the center where the treatment was delivered despite the

		appearance of cytolysis. → According to the stop rules, **the dose escalation could continue** because only 1 grade 3 AE has been reported in this second group.

From July 2016 to July 2018, IDSMB have received monthly safety reports for each groups. This represents a total of 20 monthly safety reports: 7 monthly safety reports for group 1, 6 monthly safety reports for group 2 and 7 monthly safety reports for group 3.
The IDSMB was asked for specific expert advice on four occasions:
- On October, 11th 2018 about hepatic disturbances
- On February, 1st 2018 about hepatic enzyme elevations
- On January, 31th 2018 about a patients inclusion with ASAT>1.7xULN
- On April, 06 th 2018 about an increase in plasma creatinine

5 Changes in the conduct of study

5.1 Protocol amendments

Ethics Committee approval date: September, 29th. 2015
Competent Authority approval date: September, 15th. 2015

Table 5: Protocol amendements

Modification description	CPP approval date	ANSM approval /information date
MS1: Modification of the inclusion criteria about genotype + title modification	18-Dec-2015	27-Nov-2015
MS2: Addition of a pain questionnaire + revalorization of the patient allowance + protocol update following with ANSM's remarks	08-Dec-2015	Not applicable
MS3: Update of the insurance company	05-Jan-2016	Not applicable
MS4: Summary corrections at the request of the coordinator + modifications of the safety paragraph following the first CSI meeting + modification of the evaluation schedule.	02-Feb-2016	Not applicable
MS5: Modifications of the centers and investigators list	05-Apr-2016	Not applicable
MS6: Modifications of the centers and investigators list	04-Oct-2016	Not applicable
MS7: Modifications of the centers and investigators list	13-Dec-2016	Not applicable
MS8: Modifications of the centers and investigators list	02-May-2017	Not applicable
MS9: Increase of the period of inclusion + possibility to recruit patients who had participated in previous groups	05-Sep-2017	14-Sep-2017
MS10: Modifications of the consent letter + modifications of the exclusion criteria (hepatic	09-Jan-2018	Implicit authorization at 23-Jan-2018. Final authorization received on

criteria) and more controls of hepatic monitoring + modifications of investigators list		22-Aug-2018 (See section 5.3.1_Study protocol changes)

5.2 Protocol deviations

5.2.1 Main deviations by investigation centers

Table 6: Deviations by investigation centers

Center	Inclusion/exclusion criteria violation	Incomplete treatment compliance	Non-compliance with the rules imposed by the protocol	TOTAL
01 - Roscoff	0	0	0	0
02 - Lyon	0	0	0	0
03 -Montpellier	0	1 (patient 0349)	0	1(12,5%)
04 - Foch	0	0	0	0
05 - Lille	0	0	0	0
06 –Paris/Cochin	0	1 (patient 0614)	0	1(12,5%)
07 - Toulouse	0	0	0	0
08 -Vannes	2 (patient 0821)	0	0	2 (25%)
09 -Nantes	0	0	0	0
10 - Reims	0	0	0	0
11 - Nice	0	1 (patient 1120)	1 (patient 1139)	2 (25%)
12 - Bordeaux	0	0	0	0
13 - Angers	1 (patient 1330)	0	1 (patient 1330)	2 (25%)
TOTAL	**3**	**3**	**2**	**8 (100%)**

During the study, 8 deviations that may have had an impact on the conduct of the study were detected in the investigating centers.

Inclusion/exclusion criteria violation

For 3 of them, it corresponded to the presence of one or more exclusion criteria:

- One patient (0821) had two not respected exclusion criteria:
  - "Forced expiratory volume at 1 second (FEV1) ≥ 40% of normal predicted values for age, sex and height based on the Knudson equation",
  - "Use of one (or several) prohibited medications and/or food within 30 days prior to Screening";
- One patient (1330) did not respect the exclusion criteria:
  - "Use of systemic anti-pseudomonal antibiotics within 28 days prior to first study drug administration (V2). However use of inhaled anti-pseudomonal antibiotic treatment is allowed if initiated for more than 28 days."

Incomplete treatment compliance

3 patients did not present a complete compliance to study treatment:

- In group 1, one of them accidentally has lost one capsule on Day 4 Cycle 4.
- In group 2, one of them has vomited just after taking the capsule on Day 1 Cycle 3.
- In group 3, one of them has forgotten to take 4 capsules on Day 1 Cycle 4.

Non-compliance with the rules imposed by the protocol

In 2 centers, the protocol was not respected with a possible impact on patient safety:

- In group 2, the first day of cycle 2, October 30th, 2017 a patient presented increased ALAT to 9 ULN (corresponding to an AE of grade 3 toxicity according to CTCAE) and increased ASAT to 4,5 ULN (AE of grade 2 toxicity). Clinical examination was normal; the investigational team noted that the patient presented a mild asthenia and mild abdominal

pain without transit disorder. The investigator did not control ASAT and ALAT levels before dispensing the treatment. According to protocol rules, the treatment should have been immediately interrupted. Due to the period (non working day) it was only on November 02th, 2017 (last dose of cycle 2) that the investigational team analyzed patient results from October 30th. They immediately contacted the sponsor who decided to interrupt the patient's treatment. Unfortunately, the patient already had taken his fourth dose of cycle 2 and was in an off period of the cycle. The decision was taken with a delay of 3 days according to the protocol.
On November 2nd, 2017 despite the treatment taken by the patient, ALAT decreased to 6 ULN and ASAT decreased to 2.3 ULN. On November 06th, 2017 ALAT decreased to 2.8 ULN and ASAT was normal. According to these values treatment was reintroduced following a collegial decision between the coordinator investigator and the sponsor. On November 7th, after a control in protocol patient interruption rules, it was decided to stop the treatment for the patient and to consult the IDSMB. Note that after the new reintroduction of the treatment, ASAT on November 7th had decreased to 2.2 ULN and ASAT was still in the normal range.
Safety department and IDSMB concluded that the AE was not related to study treatment regarding the evolution of ASAT and ALAT level with treatment reintroduction (See annex 5 CIOMS 201700395).

- In group 3, one patient forgot to do the hepatic sampling at Day 19 and Day 26 according to the IDSMB's decision which advocated liver sampling on Day 5 to each cycle.

These deviations have no impact on study results.

5.2.2 Deviations in the conduct of the trial

Table 7: Deviations in the conduct of the trial

Project Management		***13 (30.23%)***
	Regulatory	*9*
	Database	*3*
	Guidelines	*1*
Quality control		***22 (51.22%)***
	Schedule plan of monitoring visit	*9*
	Report of monitoring visit	*13*
Medical products		***4 (9.30%)***
	Excursion of temperature during transport	*2*
	Treatment supply	*2*
Biocollection		***4 (9.30%)***
	Temperature record	*1*
	Monitoring visit	*3*
	TOTAL	***43***

Project Management

- ✓ **Regulatory :**

- 9 inclusion criteria were not respected at the patient screening time but received an exemption following a collegial decision between the coordinator investigator and the sponsor. These exemptions concerned:

→ For 8 patients the forced expiratory volume at 1 second (FEV1) ≥ 40% of normal predicted values for age, sex and height based on the Knudson equation;

→ For 1 patient, the exemption concerned the "Use of one (or several) prohibited medications and/or food within 30 days prior to Screening (V1)".

→ The sponsor discussed with the coordinator to propose an amendment to the protocol for FEV1. Given that this criterion has to be observed with other clinical information, it was

decided to keep this non-inclusion criterion. When an investigational team believed that a patient presented all inclusion criteria but an abnormal FEV1 value with a good clinical examination, they could contact the sponsor to obtain an exemption. These cases were systematically reviewed by the coordinator.

- ✓ **Database :**

- In group 3, patients were taking 800 mg of the study treatment (seliciclib/placebo) which corresponded to 4 capsules of 200 mg over 16 days. Treatment was conditioned in pillboxes of 16 capsules of 200 mg. This meant that the randomization system had to attribute 4 pillboxes numbers of a group 3 patient. Unfortunately the randomization system allocated only 3 numbers of pillboxes on January 25th, 2018 (patient 0534, 1136 and 1037), it was the first day of randomization of group 3 patient. Data manager corrected the system and new pillboxes were allocated to the three patients.
- Malfunction in the allocation of treatment units of group 3. The chart of shipments of treatments follow-up on site is a table shared only between the sponsor's coordinating pharmacist and the data manager in charge of the project. This table was completed by the pharmacist and the data manager with a defined role for each: the pharmacist informs the treatment number, the unit number, the expiry date, the center number, the name of the center, the date of shipping, the date of receipt and the arm; the data manager indicates whether the processing unit was entered under Capture System software (randomized system), if the processing unit was received under Capture System and if it has been assigned.

It seems that an error of completeness of this table had taken place, causing a bad attribution of treatments for randomized patients on January 25th, 2018 in the centers of Lille and Nice. Patients of Lille 0534 and Nice 1136 were attributed boxes of treatment which had never been received in their center or were placed in quarantine. Data manager updated treatment information in the software and re-allocated pillboxes numbers while keeping the arm randomly assigned. This dysfunction led to a delay in the care of patients and in all the logistics related to the time of the first study treatment: patients did not have all PK blood sample (10 and 12 hours after study drug initiation).

- The principal investigator of Vannes center who had left the service was unable to sign the patient case report form. There was no co-investigator in this center and no other Physician wanted to participate to the study. It was decided that the coordinator investigator, Dr Gilles Rault, would sign the case report form of Vannes center.

- ✓ **Guidelines :**

- The project guidelines were not respected for patient 1330 who showed an increased ASAT (> 4.5 ULN = AE of grade 2 toxicity according to CTCAE); ALAT (> 9 ULN = AE of grade 3 toxicity according to the CTCAE) and Gamma GT (> 3 ULN = grade 2 according to the CTCAE) on October 30th, 2017 before the beginning of the 3rd cycle of treatment (Blood test at 9:00 am and 1st treatment cycle 3 at 11:35). According to the protocol, the experimental drug must be immediately and definitively interrupted for any event of grade ≥ 3. However, after an interruption on November 1st, 2017, i.e. 3 days after the beginning of the hepatic disturbances, the reintroduction of the experimental treatment was authorized after control of liver values that had returned to normal. This decision was taken by the project manager in consultation with the study coordinator on November 6th, 2017. (See section 5.2.1 and annex 5 CIOMS 201700395).

These deviations have no impact on study results.

Quality control

- ✓ **Schedule plan of monitoring visit:**

The monitoring guidelines provided that the first patient had to be checked after the last administration of treatment (around 28 days after the beginning of the treatment), then after each 2 patients.

The rate of inclusions and the availability of centers did not always allow for this schedule in the first group. During the monitoring visit, no SAE was discovered, investigational data entry in e-CRF was done on time, in consequence the initial monitoring guideline was modified to realize a visit on site within a maximum of 45 days after the first treatment of the study and to check, by phone call, patient safety with investigational team at least at Day 30.

- ✓ **Report of monitoring visit:**

The initial monitoring guidelines stated that a visit report should be drawn up after each monitoring visit. For some visits, the monitors (clinical research associates or project manager) wrote a report including several visits. Given the rate of inclusions and the frequency of visits to sites, the monitoring guidelines were modified in order to take into account the specificity of the study and to allow a specific report for visits of less than 15 days.

These deviations have no impact on study results.

Medical products

In accordance with the regulations, each storage place and transporters had to a track the storage temperature of the experimental product.
Regarding to treatment stability study and European Pharmacopoeia, if the temperature was below 18°C or above 27°C in the pharmacy room, treatments had to be quarantined, until expertise by the sponsor pharmacist. If the temperature did not drop below 15°C for more than 2 hours, the pharmacist accepted to allow the use of the treatments. If the temperature was below 15°C during more than 2 hours or above 27°C, treatments were in the quarantine for destruction and the stock had to be replaced.

- ✓ Excursion of temperature during transport :

During the study defects in the tracking of products were observed such as:
- During a quality control visit on investigational center, it was noted that an excursion temperature during the transport of treatments occurred on June 27th, 2017. A phone call between the investigational center pharmacist and the sponsor's pharmacist was realized in order to decide on the procedure to follow: the sponsor pharmacist decided to quarantine the treatment numbers N°90, 91, 92, 93, 98, 99. As the sponsor pharmacist did not informed the study team of this decision, these treatments will not be removed from the list of treatment assignments by the data manager, which could have been attributed to a randomized patient between June 27th, 2017 and the closing date of the center. These treatments were never been allocated to any patient. After the quality control visit, it was asked to the sponsor pharmacist to transmit the conclusion of the phone call of June 27th, 2017.
- At the closing visit of the Reims center on June 21st, 2018, it was noted that a temperature excursion during the transport of the treatments under study occurred on December 13th, 2017 (2nd supply). The procedure of the study was not respected, the temperature curves not having been checked on reception of the on-site treatments by the pharmacist of the center. The sponsor's pharmacist, however, carried out a control of these temperature curves via the provided internet link, and authorized the use of these treatments by mail on December 15th, 2017 (no quarantine of these treatments was therefore done).

- ✓ Treatment supply

Time of supply of the treatments for the pharmacy of the center of Lyon was not respected. Lack of anticipation from the sponsor's pharmacist in sending off on-site treatments on the evening of a non-working day (November 11th, 2016) while the patient from Lyon was to begin treatment on November 14th, 2016. Consequently the visit of this patient was shifted by one week on November 21th, 2016 causing a deviation in the planning of the study (> 15 days between the inclusion and the randomization – 7 authorized in the protocol).

On June 06th, 2018, the study treatments were sent to the center Nantes instead of the center Nice for a randomization of patient 11-48 scheduled for June 07th, 2018.

Finally the patient screened in Nice did not present the randomization criteria, and the center did not need the treatment These deviations have no impact on study safety and results.

Biocollection

- ✓ Excursion of temperature :

Excursion of temperature in the freezer - 80°C in the center of Lille (center 05), where were stored the study samples, fell to -42°C on Friday, February 16th, 2018 to 15 pm, due to a prolonged opening of the door. This anomaly was reported via an alarm. On Saturday, February 17th at 9 am, the temperature was -52°C and it returned to normal on Saturday February 17th with a temperature of -68°C at 20:33 and Monday, February 19th, the temperature was -71°C.

- ✓ Monitoring visit :

The initial monitoring guidelines stated that the biocollection monitoring should be done at least at the end of the study before the removal of samples in the central laboratory in Brest.
For 3 centers, the monitors (clinical research associates or project leader) did not control these tubes because of the difficulties to have access to the laboratory where the samples were stored. Indeed these tubes were stored in another hospital than the hospital center and it was difficult to go during the monitoring day.
All the samples were controlled when they arrived in the central laboratory in Brest.

These deviations have no impact on study results.

5.3 Changes in the conduct of the research

5.3.1 Study protocol changes

During the conduct of the study, there were two important modifications in the study protocol:

- The first change was about the possibility of including patients who had already participated to the study in a lower dose group. This decision was validated by the steering committee. The sponsor sent an authorization request to ANSM on June 6th, 2017. Substantial modification authorization was obtained on September 14th, 2017 and Ethical approval was obtained on September 5th, 2017.

- The second change was requested following the STOP and GO's IDSMB meeting after the 12 inclusions of the second group which was recommended to modify the exclusion criteria about liver function. The IDSMB wanted to reduce the abnormal value of liver function at the inclusion (≥3xULN down to >1.5xULN) and add an additional clinical laboratory liver test after each "on" period (Day 5 of each cycle). Moreover, the IDSMB wanted that the study drug administration be withdrawn immediately, and the sponsor medical monitor or designee be notified if ALAT or ASAT > 1.5 × ULN. The sponsor sent an authorization request to ANSM on December 18th, 2018. The implicit authorization was obtained on January 23rd, 2018. French regulation specifies that in case of a lack of answer from ANSM within 35 days means that the request is authorized. Consequently, the sponsor decided to start the second group without the ANSM authorization notification of the substantial modification which was finally received on August 22nd, 2018. Ethical approval was obtained on January 9th, 2018.

These changes have no impact on study safety and results.

5.3.2 Supplementary secondary objectives

No supplementary secondary objectives were planned during the study.

5.3.3 Secondary objectives not presented in this final report

This final report contains all the objectives initially defined.

5.4 Changes in the statistical methods planned in the protocol

There was no change in the statistical methods planned in the protocol.

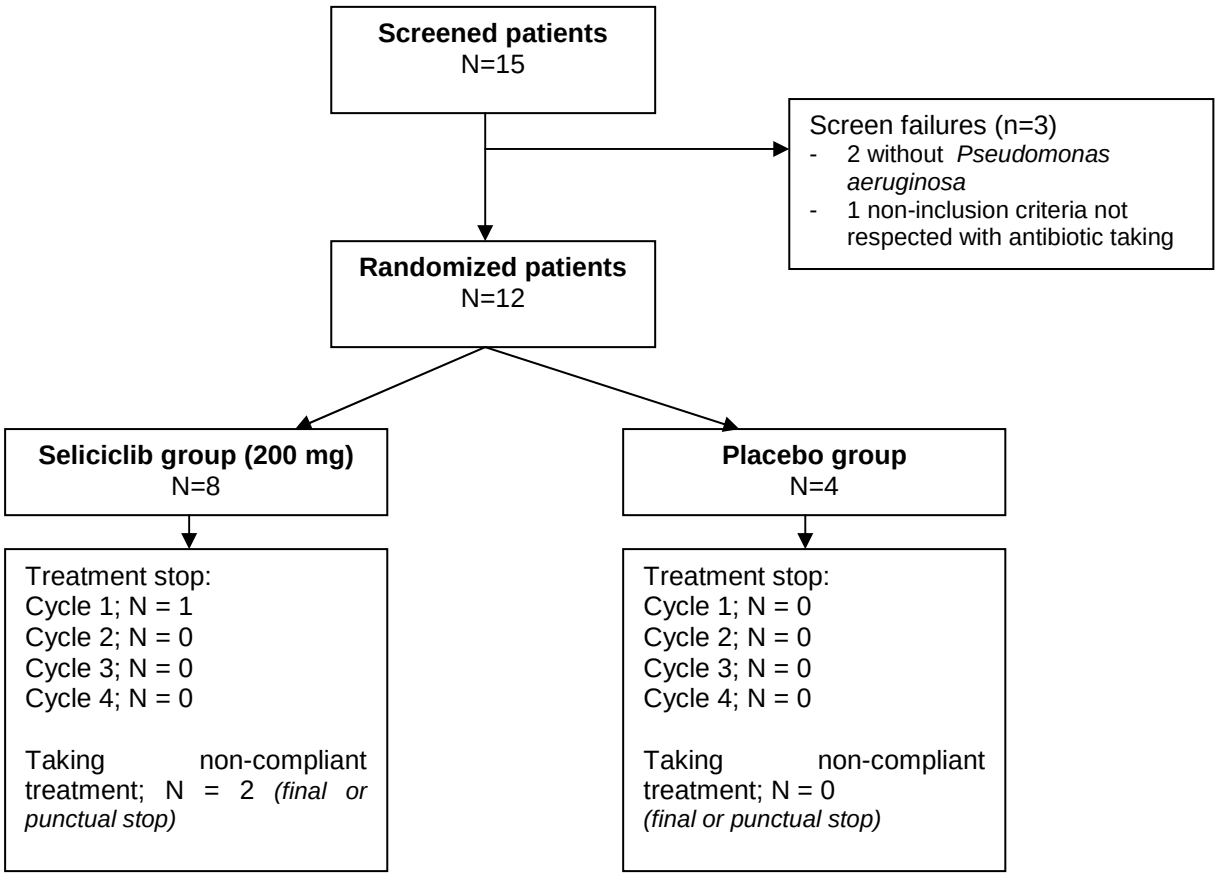
6 Results

6.1 Study population

The total number of patients to be treated in ROSCO-CF was 36 patients with a follow-up period of 2 months per participant. The first patient was included on February 22nd, 2016. At the end of the study 49 patients had been recruited and 34 patients randomized and treated. Due to difficulties inclusions in the summer period, the third group was limited to 10 randomized patients.

6.1.1 Flowchart by group

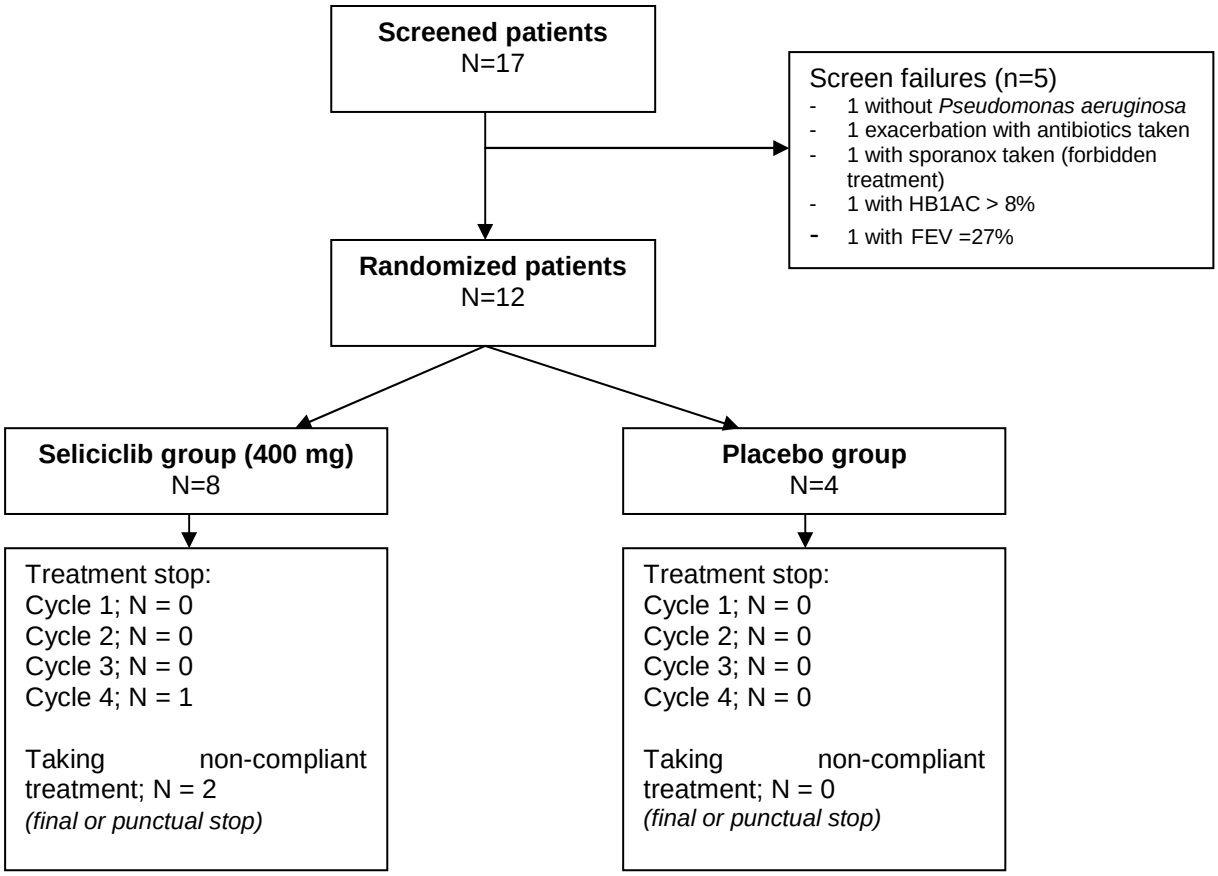
Figure 1 : Flow Chart – Group 1 (dose 200 mg)



In group 1 there were three screen failures (two patients who were not infected by *Pseudomonas aeruginosa* and one patient who took antibiotics for exacerbation which were among non inclusion criteria).

Twelve patients were randomized: the entire patients (four) placebo group realized all the visits of the study but in the seliciclib group one patient among eight who had received the experimental treatment definitively stopped the treatment after taking a single capsule of seliciclib at cycle 1 day 1 after presenting a SAE. In addition to this patient, another patient did not take the totality of the seliciclib treatment because he lost one capsule.

Figure 2 : Flow Chart – Group 2 (dose 400 mg)

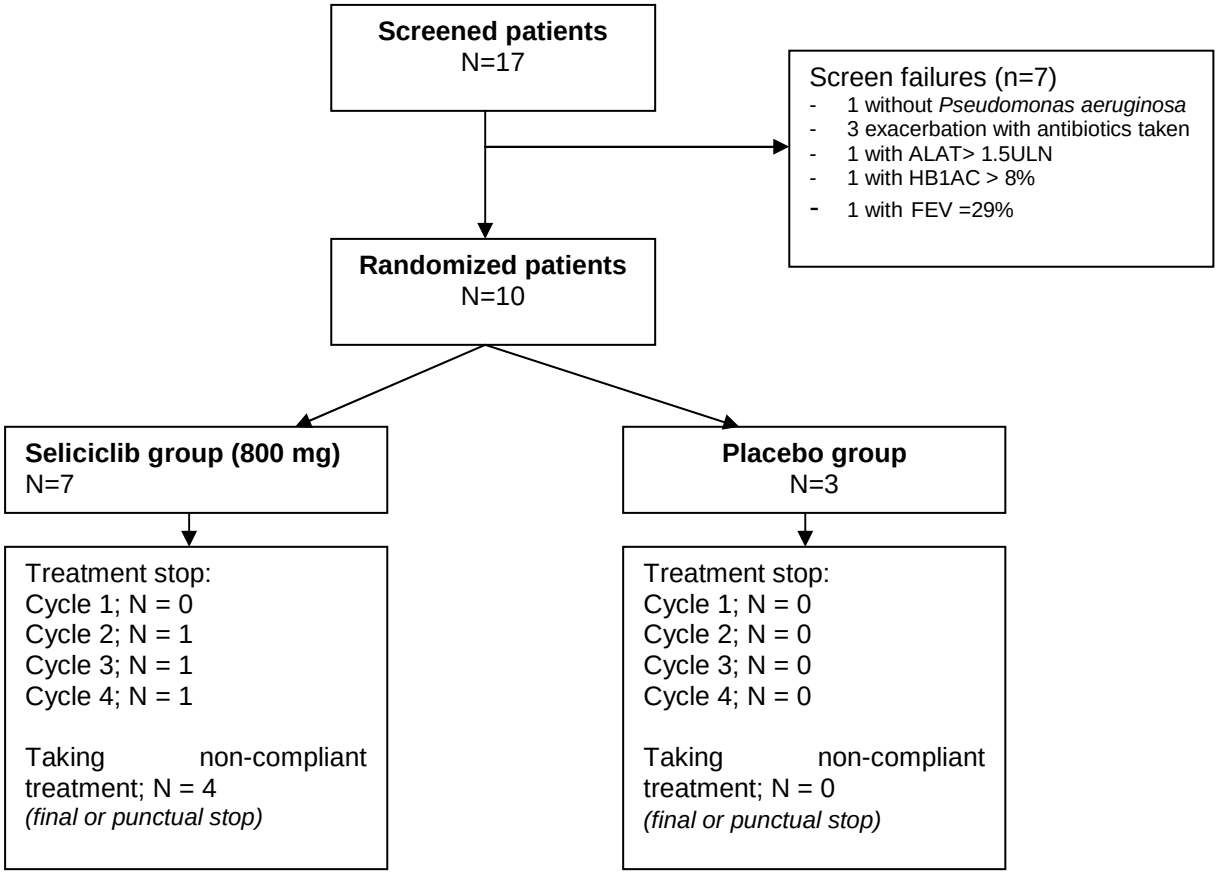


In group 2 there were five screen failures (one patient who was not infected by *Pseudomonas aeruginosa;* one patient who took antibiotics for exacerbation; one patient who took sporanox for Allergic broncho-pulmonary aspergillosis; one patient with HBA1C>8% and one patient with a FEV=27%).

Twelve patients were randomized: the entire patients (four) placebo group realized all the visits of the study but in seliciclib group, one patient among eight who had received the experimental treatment definitively stopped the treatment at cycle 4 day 2 after presenting a SAE.

In addition to this patient, another patient did not take the totality of the seliciclib treatment because he vomited a capsule.

Figure 3 : Flow Chart – Group 3 (dose 800 mg)



In group 3 there were 7 screen failures (one patient who was not infected by *Pseudomonas aeruginosa;* three patients who took antibiotics for exacerbation; one patient with ALAT>1.5 ULN; one patient with HBA1C>8% and one patient with a FEV=29%).
Ten patients were randomized: the entire patients (three) placebo group realized all the visits of the study but in the seliciclib group three patients among seven who had received the experimental treatment definitively stopped the treatment for a SAE: one patient at cycle 2 day 2, one patient at cycle day 5 and one patient at cycle 4 day 2.
In addition to these patients, another patient did not take the totality of the seliciclib treatment because he forgot to take a dose of 800 mg.

6.1.2 Demographic and other baseline characteristics

o **6.1.2.1. Group 1: seliciclib 200 mg daily**

Twelve patients were included in group 1 with a prevalence of 58% women and 42% men (note that all men were randomized in the experimental arm) and an average age of 33 years old. See table 8 below or statistical report in annex 9 for more details.

Table 8: Individual characteristics at inclusion – Group 1 (dose 200mg)

		Placebo group (N=4)	Seliciclib group (N=8)
Age	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	29.25 +/- 3.30	34.75 +/- 7.38
	Median (q1;q3)	29.0 (26.5;32.0)	34.0 (28.5;37.5)
	Min;Max	26;33	28;50
Sex	Man	0 (0.0%)	5 (62.5%)
	Woman	4 (100.0%)	3 (37.5%)
Mutation	homozygous	1 (25.0%)	3 (37.5%)
	heterozygous	3 (75.0%)	5 (62.5%)
Body Mass Index (BMI)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	19.88 +/- 1.69	22.75 +/- 3.76
	Median (q1;q3)	19.7 (18.7;21.0)	22.2 (20.3;22.9)
	Min;Max	18;22	20;32
PA log-concentration	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	5.75 +/- 1.89	6.00 +/- 0.76
	Median (q1;q3)	6.5 (4.5;7.0)	6.0 (5.5;6.5)
	Min;Max	3;7	5;7
Forced Expiratory Volume (FEV)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	62.45 +/- 17.37	55.73 +/- 14.64
	Median (q1;q3)	66.9 (50.7;74.3)	53.5 (46.0;59.0)
	Min;Max	38;78	41;88
Forced Vital Capacity (FVC)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	79.57 +/- 6.03	80.86 +/- 13.32
	Median (q1;q3)	79.1 (75.0;84.2)	83.5 (71.0;92.5)
	Min;Max	73;87	59;94
C-reactive protein (CRP)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	4.63 +/- 3.56	4.45 +/- 2.63
	Median (q1;q3)	5.0 (0.9;8.0)	5.5 (1.9;6.5)
	Min;Max	1;8	1;7

o 6.1.2.2. Group 2: seliciclib 400 mg daily

Twelve patients were included in group 2 with a prevalence of 58% men and 42% women and an average age of 33 years old.
See table 9 below or statistical report in annex 9 for more details.

Table 9: Individual characteristics at inclusion – Group 2 (dose 400mg)

		Placebo group (N=4)	Seliciclib group (N=8)
age	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	35.75 +/- 13.15	31.75 +/- 7.38
	Median (q1;q3)	36.0 (25.0;46.5)	33.0 (24.5;38.0)
	Min;Max	21;50	22;41
Sex	Man	3 (75.0%)	4 (50.0%)
	Woman	1 (25.0%)	4 (50.0%)
Mutation	homozygous	2 (50.0%)	1 (12.5%)
	heterozygous	2 (50.0%)	7 (87.5%)
BMI	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	22.14 +/- 2.37	21.06 +/- 2.45
	Median (q1;q3)	22.0 (20.4;23.9)	20.6 (19.6;23.2)
	Min;Max	19;25	17;25
PA log-concentration	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	6.75 +/- 1.26	5.88 +/- 1.73
	Median (q1;q3)	7.0 (6.0;7.5)	6.5 (5.5;7.0)
	Min;Max	5;8	2;7
FEV	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	42.50 +/- 7.33	50.50 +/- 16.37
	Median (q1;q3)	41.5 (37.0;48.0)	46.0 (39.5;59.0)
	Min;Max	35;52	32;83
FVC	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	77.00 +/- 6.68	68.75 +/- 18.73
	Median (q1;q3)	76.0 (72.5;81.5)	73.0 (56.0;77.0)
	Min;Max	70;86	38;100
CRP	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	15.83 +/- 10.25	31.05 +/- 36.46
	Median (q1;q3)	12.7 (8.3;23.4)	16.2 (5.3;48.8)
	Min;Max	8;30	4;104

o 6.1.2.3. Group 3: seliciclib 800 mg daily

Ten patients were included in group 3 with a prevalence of 70% men and 30% women and an average age of 37 years old.
See table 10 below or statistical report in annex 9 for more details.

Table 10: Individual characteristics at inclusion–Group 3 (dose 800mg)

		Placebo group (N=3)	Seliciclib group (N=7)
Age	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	37.33 +/- 5.13	37.00 +/- 7.83
	Median (q1;q3)	36.0 (33.0;43.0)	37.0 (30.0;42.0)
	Min;Max	33;43	28;51
Sex	Man	3 (100.0%)	4 (57.1%)
	Woman	0 (0.0%)	3 (42.9%)
Mutation	homozygous	2 (66.7%)	1 (14.3%)
	heterozygous	1 (33.3%)	6 (85.7%)
BMI	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	23.40 +/- 1.15	21.03 +/- 2.69
	Median (q1;q3)	23.3 (22.3;24.6)	20.7 (18.7;24.2)
	Min;Max	22;25	18;24
PA log-concentration	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	5.00 +/- 2.00	6.86 +/- 0.69
	Median (q1;q3)	5.0 (3.0;7.0)	7.0 (6.0;7.0)
	Min;Max	3;7	6;8
FEV	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	63.03 +/- 20.24	47.71 +/- 12.53
	Median (q1;q3)	71.1 (40.0;78.0)	46.0 (36.0;60.0)
	Min;Max	40;78	33;68
FVC	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	96.07 +/- 9.72	73.00 +/- 16.44
	Median (q1;q3)	100.0 (85.0;103.2)	78.0 (60.0;84.0)
	Min;Max	85;103	42;89
CRP	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	8.67 +/- 10.42	11.34 +/- 11.53
	Median (q1;q3)	2.7 (2.6;20.7)	6.0 (4.0;17.3)
	Min;Max	3;21	3;35

6.3.1.1.1. Demographic data by experimental medicinal product (placebo or seliciclib

In the placebo group the average age was 33 years old with inclusion of 5 women (45%) and 6 men (55%). In the seliciclib group the average age was 34 years old with inclusion of 10 women (43%) and 13 men (57%).
The small sample sizes did not enable to reach sufficient power when comparing groups. It is worthwhile to note that C-reactive protein (CRP) was 3-fold higher in the 400 mg dose group. Forced expiratory volume (FEV) was slightly lower in the 400 and 800 mg groups.

Table 11: Characteristics at inclusion per group

		Placebo (N=11)	Seliciclib 200 mg (N=8)	Seliciclib 400 mg (N=8)	Seliciclib 800 mg (N=7)
Âge	N (N missing)	11 (0 missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	33.82 +/- 8.60	34.75 +/- 7.38	31.75 +/- 7.38	37.00 +/- 7.83
	Median (q1;q3)	33.0 (27.0;43.0)	34.0 (28.5;37.5)	33.0 (24.5;38.0)	37.0 (30.0;42.0)
	Min;Max	21;50	28;50	22;41	28;51
Sex	HOMME	6 (54.5%)	5 (62.5%)	4 (50.0%)	4 (57.1%)
	FEMME	5 (45.5%)	3 (37.5%)	4 (50.0%)	3 (42.9%)
Mutation	Homozygote	5 (45.5%)	3 (37.5%)	1 (12.5%)	1 (14.3%)
	Hétérozygote	6 (54.5%)	5 (62.5%)	7 (87.5%)	6 (85.7%)
BMI	N (N missing)	11 (0 missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	21.66 +/- 2.25	22.75 +/- 3.76	21.06 +/- 2.45	21.03 +/- 2.69
	Median (q1;q3)	22.1 (19.5;23.3)	22.2 (20.3;22.9)	20.6 (19.6;23.2)	20.7 (18.7;24.2)
	Min;Max	18;25	20;32	17;25	18;24
PA log-concentration	N (N missing)	11 (0 missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	5.91 +/- 1.70	6.00 +/- 0.76	5.88 +/- 1.73	6.86 +/- 0.69
	Median (q1;q3)	7.0 (5.0;7.0)	6.0 (5.5;6.5)	6.5 (5.5;7.0)	7.0 (6.0;7.0)
	Min;Max	3;8	5;7	2;7	6;8
FEV	N (N missing)	11 (0 missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	55.35 +/- 17.10	55.73 +/- 14.64	50.50 +/- 16.37	47.71 +/- 12.53
	Median (q1;q3)	52.0 (39.0;71.1)	53.5 (46.0;59.0)	46.0 (39.5;59.0)	46.0 (36.0;60.0)
	Min;Max	35;78	41;88	32;83	33;68
FVC	N (N missing)	11 (0 missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	83.14 +/- 10.65	80.86 +/- 13.32	68.75 +/- 18.73	73.00 +/- 16.44
	Median (q1;q3)	81.2 (75.0;87.1)	83.5 (71.0;92.5)	73.0 (56.0;77.0)	78.0 (60.0;84.0)
	Min;Max	70;103	59;94	38;100	42;89
CRP	N (N missing)	10 (1 missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	10.32 +/- 9.33	4.45 +/- 2.63	31.05 +/- 36.46	11.34 +/- 11.53
	Median (q1;q3)	8.0 (2.7;16.7)	5.5 (1.9;6.5)	16.2 (5.3;48.8)	6.0 (4.0;17.3)
	Min;Max	1;30	1;7	4;104	3;35

6.2 Analysis of efficacy

6.2.1 Primary outcome

The primary outcome was safety evaluation which is described in details in paragraph 6.3. Briefly among 34 patients, 5 had presented a serious adverse event (SAE): 0/11 in the placebo group, 1/8 in the 200 mg group, 1/8 in the 400 mg group and 3/7 in the 800 mg group.

All patients had presented at least one adverse event. Median numbers of AE were 5 in the placebo group, 2 in the 200 mg group, 8 in the 400 mg group and 5 in the 800 mg group. The distribution of the higher grade per patient is the following:

Table 12: Adverse events per group

	Dose group (mg)				Total
Higher grade	**0**	**200**	**400**	**800**	
1	4	4	0	1	**9**
2	7	4	6	5	**22**
3	0	0	1	1	**2**
4	0	0	1	0	**1**
Total	**11**	**8**	**8**	**7**	**34**

The most frequent AE SOC name referred to gastrointestinal disorders (respectively 13, 13, 12 and 5 according to randomized doses) and infections or infestations system disorders (respectively 11, 6, 9 and 4). See the annex 1.
No particularly adverse event was more frequently observed in the seliciclib groups compared to placebo.

6.2.2 Secondary outcomes

Detailed results are given in Tables 20 to 27 of the statistical report in annex 9.
The main secondary outcomes results are summarized below.
No statistically significant differences were found between the dose groups and the placebo group, except for some cytokines (IL-1beta, IL-8, MDC, MIP-1beta). See annex 2.

Table 13: *Pseudomonas aeruginosa* (P.A.) log-concentration

	Dose group			
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**
Day 1	5.82 +/- 1.94	6.00 +/- 1.31	7.25 +/- 0.71	6.43 +/- 0.79
Day 28	5.73 +/- 2.37	5.63 +/- 1.41	6.75 +/- 1.39	7.00 +/- 0.58
Delta D28-D1	-0.09 +/- 1.38	-0.38 +/- 0.74	-0.50 +/- 1.31	0.57 +/- 0.98
p (Wilcoxon test)		0.502	0.463	0.359

P.A: *Pseudomonas aeruginosa* (log-transformed CFU/mL)

Table 14: C-reactive protein (CRP)

	Dose group			
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**
Day 1	11.63 +/- 20.19	6.46 +/- 7.27	22.05 +/- 17.56	19.23 +/- 15.98
Day 28	8.34 +/- 7.62	5.88 +/- 5.15	18.18 +/- 12.05	21.54 +/- 15.68
Delta D28-D1	-2.67 +/- 20.09	-1.74 +/- 4.22	-3.88 +/- 9.92	2.31 +/- 16.79
p (Wilcoxon test)		0.362	0.182	0.810

Table 15: Forced expiratory volume in 1 second (FEV1)

	Dose of Seliciclib			
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**
D1	54.75 +/- 16.04	54.58 +/- 17.44	51.88 +/- 18.21	45.57 +/- 12.31
D28	54.48 +/- 15.03	54.60 +/- 18.08	50.63 +/- 15.09	45.29 +/- 11.59
D28-D1	-0.27 +/- 2.62	0.03 +/- 2.73	-1.25 +/- 6.48	-0.29 +/- 1.11
p (Wilcoxon test)		0.394	0.681	0.417

Table 16: Body mass index (BMI)

	Dose group			
	0 mg (Placebo)	200 mg	400 mg	800 mg
D1	21.59 +/- 2.21	22.73 +/- 3.69	21.06 +/- 2.38	20.90 +/- 2.72
D28	21.78 +/- 2.02	22.49 +/- 3.68	21.25 +/- 2.48	20.84 +/- 2.70
Delta D28-D1	0.20 +/- 0.45	-0.24 +/- 0.29	0.19 +/- 0.48	-0.05 +/- 0.24
p (Wilcoxon test)		0.050	1.000	0.218

Table 17: Sweat Chloride Concentration

	Dose group			
Variable	0 mg (Placebo)	200 mg	400 mg	800 mg
Chlorine sweat at D1	97.00 +/- 15.10	100.25 +/- 13.64	96.81 +/- 7.39	85.29 +/- 18.60
Chlorine sweat at D28	98.09 +/- 17.31	95.93 +/- 11.78	98.29 +/- 11.82	89.00 +/- 17.04
Delta D1-D28	1.09 +/- 6.14	-1.93 +/- 9.78	2.14 +/- 10.21	3.71 +/- 3.83
p (Wilcoxon test)		0.332	0.823	0.451

Table 18: Cystic Fibrosis Questionnaire-Revised (CFQ-R)

	Dose group				
Delta D28-D1	0 mg (Placebo)	200 mg	400 mg	800 mg	P*
Perception of health status	-4.13 +/- 13.71	-6.82 +/- 9.41	-1.14 +/- 13.25	-16.88 +/- 25.94	0.342
Symptom					
Weight	3.03 +/- 23.35	8.33 +/- 15.43	4.17 +/- 27.82	-4.76 +/- 12.60	0.543
Digestive symptoms	3.03 +/- 16.36	-2.08 +/- 30.13	4.17 +/- 19.42	-2.38 +/- 15.00	0.757
Respiratory symptoms	3.97 +/- 6.63	10.12 +/- 15.57	2.38 +/- 16.30	-5.44 +/- 13.86	0.184
Quality of life - generic dimensions					
Energy	-3.79 +/- 17.23	-3.13 +/- 11.73	-5.21 +/- 16.63	-11.90 +/- 9.45	0.498
Physical	3.03 +/- 15.93	-2.60 +/- 8.61	-3.65 +/- 12.68	0.00 +/- 10.21	0.644
Psychic	0.00 +/- 15.49	3.33 +/- 11.27	2.50 +/- 10.65	-7.62 +/- 11.17	0.392
Role	-1.79 +/- 4.72	-6.25 +/- 12.50	0.00 +/- 0.00	-2.08 +/- 9.41	0.885
Social	-6.82 +/- 12.81	2.08 +/- 15.27	5.21 +/- 12.55	-5.95 +/- 9.27	0.168
Quality of life - dimensions specific to cystic fibrosis					
Food	1.52 +/- 11.68	4.17 +/- 7.72	-4.17 +/- 11.79	-2.38 +/- 6.30	0.359
Body image	-3.03 +/- 11.21	5.56 +/- 18.78	5.56 +/- 18.78	4.76 +/- 17.98	0.410
Marginalization	1.01 +/- 18.89	9.72 +/- 9.27	1.39 +/- 16.20	0.00 +/- 6.42	0.502
Treatments	-9.09 +/- 15.57	4.17 +/- 7.72	0.00 +/- 8.91	2.38 +/- 6.30	0.152

* Overall p-value

Table 19: Cytokines (log-transformed)

	Dose group			
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**
IL-1beta				
D1	0.12 +/- 0.13	0.22 +/- 0.18	0.65 +/- 0.82	0.24 +/- 0.11
D28	0.15 +/- 0.15	0.24 +/- 0.19	0.49 +/- 0.66	0.35 +/- 0.07
Delta D28-D1	0.03 +/- 0.07	0.02 +/- 0.09	-0.16 +/- 0.19	0.11 +/- 0.16
p (Wilcoxon test)		0.472	0.012	0.762
IL-8				
D1	2.89 +/- 0.24	2.97 +/- 0.57	3.20 +/- 0.38	3.17 +/- 0.30
D28	3.03 +/- 0.40	2.59 +/- 0.37	3.21 +/- 0.50	3.36 +/- 0.31
Delta D28-D1	0.14 +/- 0.38	-0.40 +/- 0.36	0.01 +/- 0.30	0.16 +/- 0.33
p (Wilcoxon test)		0.020	0.631	1.000
MDC				
D1	6.89 +/- 0.31	7.27 +/- 0.34	6.98 +/- 0.32	7.14 +/- 0.33
D28	6.95 +/- 0.36	7.31 +/- 0.40	6.89 +/- 0.27	6.95 +/- 0.43
Delta D28-D1	0.04 +/- 0.24	0.03 +/- 0.12	-0.09 +/- 0.16	-0.09 +/- 0.25
p (Wilcoxon test)		0.368	0.044	0.316
MIP-1beta				
D1	4.71 +/- 0.29	4.60 +/- 0.51	4.53 +/- 0.29	5.00 +/- 0.33
D28	4.80 +/- 0.32	4.52 +/- 0.58	4.41 +/- 0.41	4.79 +/- 0.30
Delta D28-D1	0.07 +/- 0.24	-0.05 +/- 0.13	-0.12 +/- 0.19	-0.21 +/- 0.23
p (Wilcoxon test)		0.150	0.052	0.050

6.2.3 Efficacy conclusions

No significant differences between the placebo group and the seliciclib groups were detected in terms of efficacy criteria except for some cytokines IL-1beta, IL-8, MDC, MIP-1beta but multiple testing has not be taken into account in these exploratory comparisons.
These results were not unexpected considering the small sample size and the short treatment duration. In first intention, this study was designed to assess the safety of seliciclib in CF patients and to define which dose could be used for further efficacy study.
An additional analysis of efficacy criteria according to the pharmacokinetics response has been conducted for cytokines but did not reveal any significant results.

6.3 Safety evaluation

All patients presented at least one adverse event during the ROSCO-CF study.
During the ROSCO-CF study, 60 adverse events were reported by investigators among the 11 patients receiving placebo.
For the 23 patients receiving seliciclib, 132 adverse events were reported. No signal of significant difference in the prevalence of adverse events between the 2 experimental groups was observed.

6.3.1 Extent of exposure to investigational medicinal product(s) and to active control / placebo

Withdrawal of experimental medicinal product for adverse events

A total of 11 patients received placebo and 23 patients received seliciclib. The repartition by escalading group was: 4 placebo and 8 seliciclib (200 mg daily) in group 1, 4 placebo and 8 seliciclib (400 mg daily) in group 2, and 3 placebo and 7 seliciclib (800 mg daily) in group 3.
All treated patient were followed for 56 days according to the protocol.

In group 1 (seliciclib 200 mg daily), one patient stopped the study because of an electrocardiogram T wave inversion.
In group 2 (seliciclib 400 mg daily), one patient stopped the study because of alteration of hepatic function.
In group 3 (seliciclib 800 mg daily), two patients presented adverse events leading to withdrawal from ROSCO-CF. Firstly, one patient was hospitalized for renal function degradation with associated bronchospasm. Secondly, one patient presented a hepatic function alteration.

These events are described in the annex 2.

6.3.2 Adverse events (serious and non-serious)

For this presentation, adverse events are grouped clinical reaction type using MedDRA 21.1 classification dictionary (See figures 4, 5, 6 and 7).
The three seliciclib escalating dosage groups are separated but all adverse events seen in placebo groups are aggregated.

Relative to incidence, some events are reported more frequently in patients receiving seliciclib as experimental product versus placebo corresponding to cardiac, eye, hepatobiliary and musculoskeletal disorders see in Annex 1.

For “cardiac events”, closely monitored in early phase medicinal study, there were no events reported in the placebo group but one in the seliciclib 400 mg group and two in the seliciclib 800 mg group. One of them, “sinus tachycardia”, was reported as a serious adverse event. Tachycardia and sinus tachycardia are frequent clinical reactions seen in many clinical diseases as current infectious disease.
For “eye disorders”, there was only one “non serious adverse event” reported in the seliciclib 400 mg group. A simple monitoring of this risk can be considered.

For “hepatobiliary disorders”, closely monitored in early phase medicinal study, there were six reported events in the seliciclib 400 mg daily group and three events in the seliciclib 800 mg group. A total of nine events were reported in three patients.
For “musculoskeletal disorders”, the observed reactions were non specific like myalgia, pain and arthralgia. A simple monitoring of this risk can be considered.
One “renal disorders” and one dysmenorrhoeal (in reproductive disorders) were reported only in the seliciclib 800 mg group. A simple monitoring of this risk can be considered.

Figure 4: Distribution of AE in placebo group

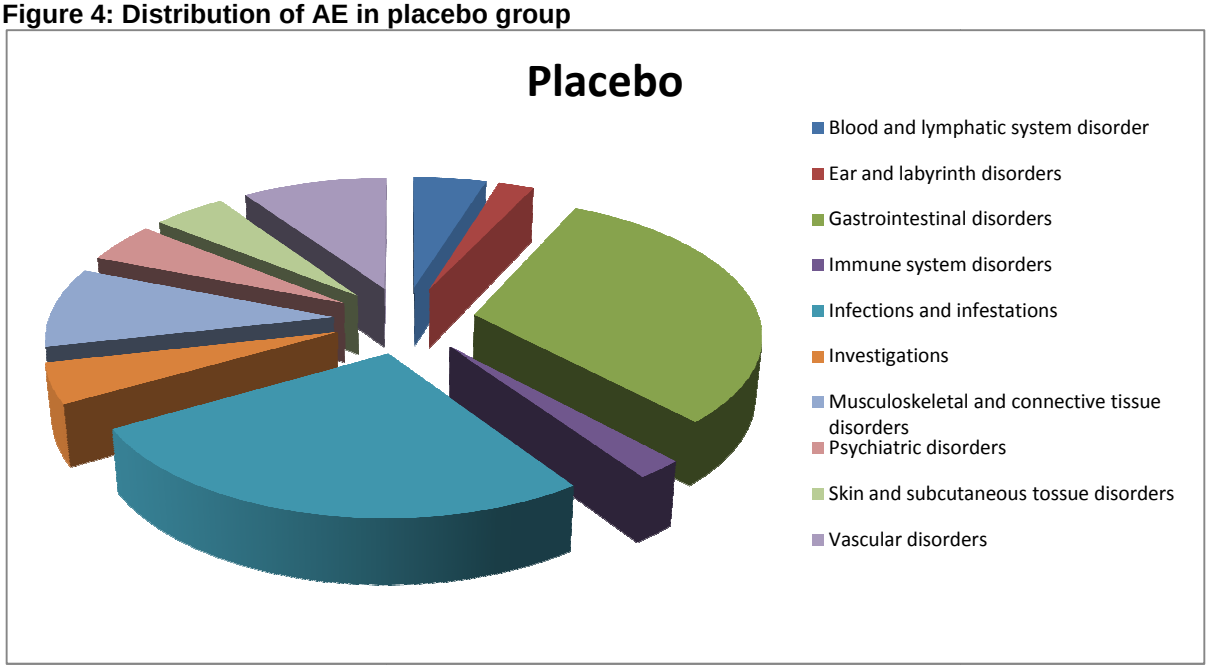


Figure 5: Distribution of AE in seliciclib 200 mg daily group

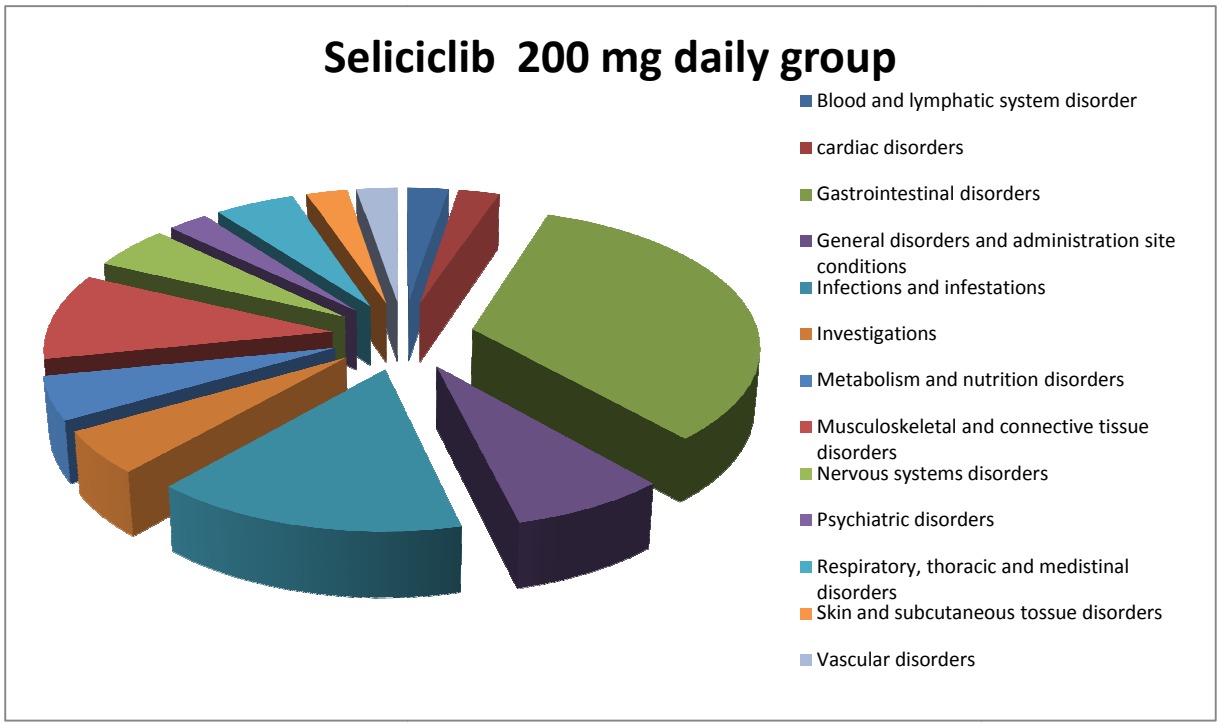


Figure 6: Distribution of AE in seliciclib 400 mg daily group

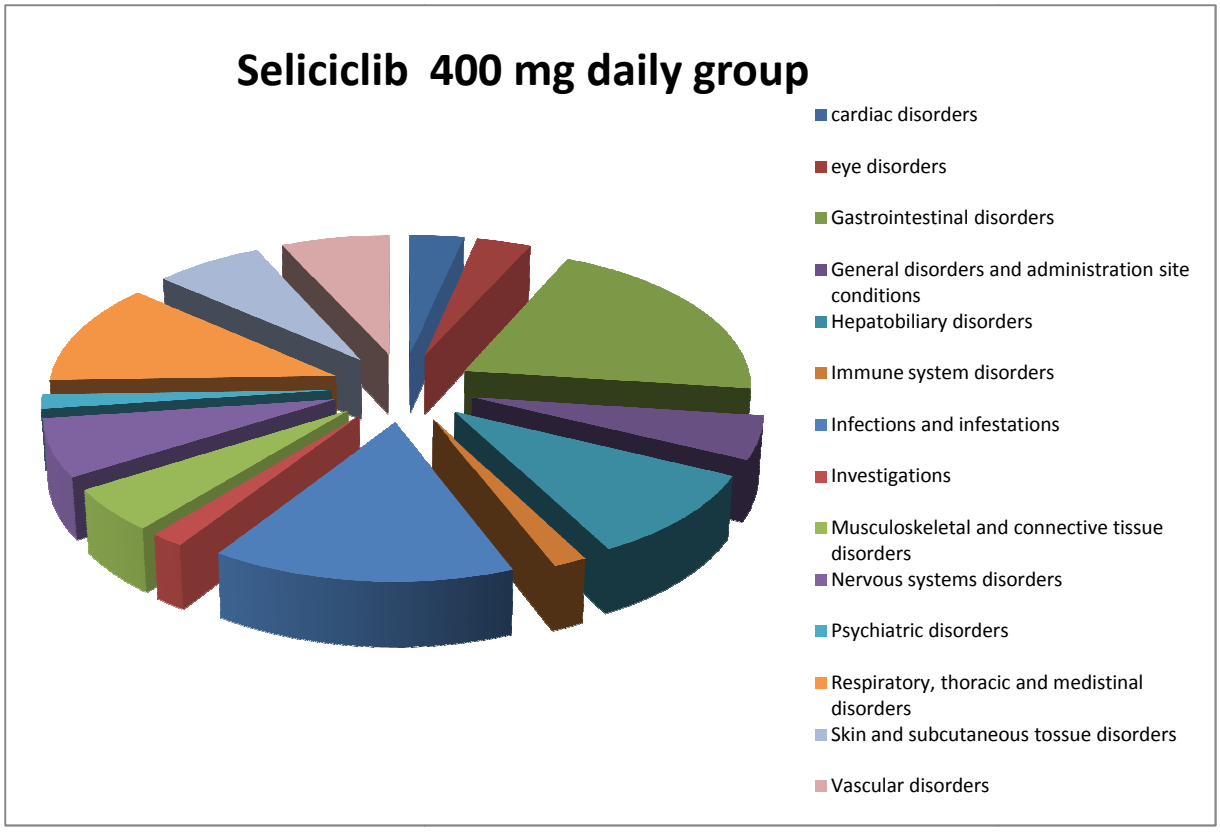
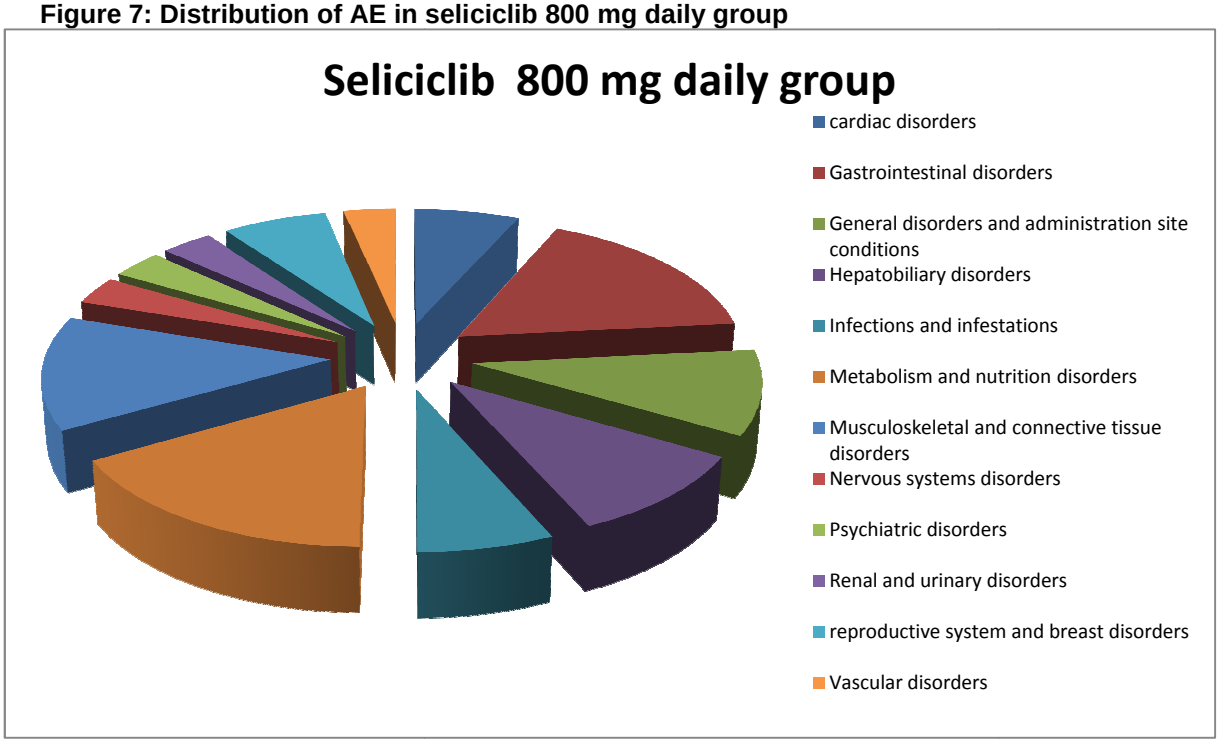


Figure 7: Distribution of AE in seliciclib 800 mg daily group



Severity of adverse events

Investigators qualified the level of severity all along the study with specific severity scales (see protocol page 47).
In the placebo group, there were reported 46 “grade 1 AE” and 14 “grade 2 AE”.
In the seliciclib groups, there were 95 “grade1 AE”, 35 “grade 2 AE” and 2 “grade 3 AE”. One AE as pulmonary cystic fibrosis exacerbation was initially mentioned as “grade 4 AE” but the investigator changed his evaluation to the graduation to a “grade 2 AE”. This change is due to an entry error in the e-CRF that was not found during the monitoring.
The distribution of AE relative to severity in the 3 groups of experimental treatment group is presented in tables 11, 12 and 13.
No signal terms of severity of adverse events has been observed in ROSCO-CF.

Table 20: Distribution of AEs severity in group 1.

SOC NAME	PT NAME	Treatment					
		Placebo (4 patients)			seliciclib (8 patients)		
		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	1	0	0	0	0	0
	LEUKOCYTOSIS	1	0	0	0	0	0
	LYMPHADENITIS	0	0	0	1	0	0
CARDIAC DISORDERS	TACHYCARDIA	0	0	0	1	0	0
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	2	1	0	2	0	0
	ABDOMINAL PAIN UPPER	0	0	0	1	0	0
	DIARRHOEA	0	3	0	3	0	0
	DYSPEPSIA	0	0	0	4	0	0
	GASTROINTESTINAL PAIN	0	0	0	1	0	0
	GASTROOESOPHAGEAL REFLUX DISEASE	1	0	0	1	0	0
	VOMITING	0	0	0	1	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	1	0	0	1	0	0
	CHEST DISCOMFORT	0	0	0	2	0	0
INFECTIONS AND INFESTATIONS	GASTROENTERITIS	0	0	0	2	0	0
	INFECTIVE PULMONARY EXACERBATION OF CF	0	1	0	1	1	0
	LUNG INFECTION	0	1	0	0	0	0
	NASOPHARYNGITIS	1	0	0	1	0	0
	ORAL HERPES	1	0	0	0	0	0
	PHARYNGITIS	1	1	0	0	0	0
	RHINITIS	0	0	0	1	0	0
	TONSILLITIS	0	1	0	0	0	0
INVESTIGATIONS	C-REACTIVE PROTEIN INCREASED	0	0	0	1	0	0
	ELECTROCARDIOGRAM T WAVE INVERSION	0	0	0	0	1	0
	FORCED EXPIRATORY VOLUME DECREASED	1	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	DEHYDRATION	0	0	0	1	0	0
	HYPERKALAEMIA	0	0	0	1	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	0	0	0	1	1	0
	BACK PAIN	1	0	0	1	0	0
	MYALGIA	0	0	0	1	0	0
	NECK PAIN	0	1	0	0	0	0
NERVOUS SYSTEM DISORDERS	HEADACHE	0	1	0	1	1	0
PSYCHIATRIC DISORDERS	INSOMNIA	1	0	0	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	BRONCHOSPASM	0	0	0	1	1	0
	COUGH	1	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	PRURITUS GENITAL	0	0	0	1	0	0
	SKIN IRRITATION	1	0	0	0	0	0
VASCULAR DISORDERS	HAEMATOMA	0	0	0	0	1	0
	HAEMOPTYSIS	3	0	0	0	0	0
	TOTAL	17	10	0	33	6	0

Table 21: Distribution of AEs severity in group 2.

SOC NAME	PT NAME	Treatment					
		Placebo (4 patients)			seliciclib (8 patients)		
		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
CARDIAC DISORDERS	TACHYCARDIA	0	0	0	2	0	0
EAR AND LABYRINTH DISORDERS	TINNITUS	0	1	0	0	0	0
EYE DISORDERS	PHOTOPHOBIA	0	0	0	1	0	0
	VISUAL IMPAIRMENT	0	0	0	1	0	0
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	4	1	0	4	0	0
	ABDOMINAL PAIN UPPER	0	0	0	1	0	0
	DIARRHOEA	0	0	0	2	0	0
	NAUSEA	1	0	0	0	0	0
	POST-TUSSIVE VOMITING	0	0	0	2	0	0
	VOMITING	0	0	0	2	1	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	0	0	0	1	0	0
	DECREASED ACTIVITY	1	0	0	1	0	0
	PYREXIA	0	0	0	1	0	0
HEPATOBILIARY DISORDERS	HEPATIC FUNCTION ABNORMAL	0	0	0	2	2	0
	HYPERTRANSAMINASAEMIA	0	0	0	1	0	1
IMMUNE SYSTEM DISORDERS	RHINITIS ALLERGIC	1	0	0	0	1	0
INFECTIONS AND INFESTATIONS	INFECTIVE PULMONARY EXACERBATION OF CF	0	0	0	1	4*	0
	LUNG INFECTION	0	0	0	1	0	0
	NASOPHARYNGITIS	1	0	0	1	1	0
	VIRAL INFECTION	0	0	0	1	0	0
INVESTIGATIONS	BLOOD CREATINE PHOSPHOKINASE INCREASED	0	0	0	1	0	0
	WEIGHT DECREASED	1	0	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	1	0	0	1	1	0
	MUSCULOSKELETAL STIFFNESS	0	0	0	1	0	0
	NECK PAIN	1	0	0	0	0	0
NERVOUS SYSTEM DISORDERS	BALANCE DISORDER	0	0	0	1	0	0
	HEADACHE	4	0	0	2	1	0
	DEPRESSED MOOD	0	0	0	0	1	0
	INSOMNIA	1	0	0	0	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ASTHMA	1	1	0	0	0	0
	BRONCHIAL OBSTRUCTION	1	0	0	0	0	0
	COUGH	3	0	0	5	2	0
	SPUTUM RETENTION	1	0	0	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ERYTHEMA	0	0	0	1	0	0
	PRURITUS	0	0	0	2	0	0
	SKIN REACTION	0	0	0	1	0	0
VASCULAR DISORDERS	EPISTAXIS	0	0	0	1	0	0
	HAEMOPTYSIS	0	0	0	3	0	0
	TOTAL	22	3	0	44	14	1

* 1 pulmonary cystic fibrosis exacerbation was initially mentioned as grade 4 AE

Table 22: Distribution of AEs severity in group 3.

SOC NAME	PT NAME	Treatment					
		Placebo (3 patients)			seliciclib (7 patients)		
		Grade 1	Grade 2	Grade 3	Grade 1	Grade 2	Grade 3
CARDIAC DISORDERS	SINUS TACHYCARDIA	0	0	0	0	1	0
	TACHYCARDIA	0	0	0	1	0	0
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	0	0	0	1	1	0
	NAUSEA	0	0	0	1	2	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	DECREASED ACTIVITY	0	0	0	0	1	0
	HYPERTHERMIA	1	0	0	0	0	0
	PYREXIA	0	0	0	2	0	0
HEPATOBILIARY DISORDERS	HEPATIC FUNCTION ABNORMAL	0	0	0	0	3	0
INFECTIONS AND INFESTATIONS	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	1	1	0	2	1	1
	RHINITIS	1	0	0	0	0	0
METABOLISM AND NUTRITION DISORDERS	DECREASED APPETITE	0	0	0	1	1	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	0	0	0	1	0	0
	MUSCULOSKELETAL PAIN	0	0	0	1	0	0
	MYALGIA	0	0	0	1	1	0
	NECK PAIN	0	0	0	0	1	0
NERVOUS SYSTEM DISORDERS	HEADACHE	1	0	0	1	2	0
	PRESYNCOPE	0	0	0	1	0	0
PSYCHIATRIC DISORDERS	INSOMNIA	0	0	0	1	0	0
RENAL AND URINARY DISORDERS	HYPERCREATININAEMIA	0	0	0	1	0	0
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	DYSMENORRHOEA	0	0	0	1	0	0
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	1	0	0	2	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	URTICARIA	1	0	0	0	0	0
VASCULAR DISORDERS	HAEMOPTYSIS	1	0	0	0	1	0
	TOTAL	7	1	0	18	15	1

6.3.3 Expectivedness of adverse events

The investigator brochure version 7 on May 22th, 2016 was used for qualification of expectivedness of adverse events.
Some unlisted AE were reported in the seliciclib groups than in the placebo group as:

- One photophobia and one visual impairment reported as a non-serious event
- The CF status can be considered as confounding factor for infectious diseases as gastroenteritis, infective pulmonary exacerbation of cystic fibrosis, nasopharyngitis, oral herpes, pharyngitis, rhinitis tonsillitis, viral infection.
-Electrocardiogram inversion T wave was sent to health authorities as a SUSAR. Cardiologic evaluation of pre-dose and post-dose ECG provided others episodes of T wave inversion in this patient.
-The case of “blood creatin phosphokinase increased” could be drawn close to aspecific musculoskeletal disorders as myalgia and arthralgia.

Table 23: Distribution of AEs expectivedness compared to Investigator Brochure (IB)

SOC NAME	PT NAME)	Placebo group (number of AE)	seliciclib group (number of AE)	Investigator brochure reference
BLOOD AND LYMPHATIC SYSTEM DISORDERS		2	1	
	ANAEMIA	1	0	yes
	LEUKOCYTOSIS	1	0	
	LYMPHADENITIS	0	1	yes
CARDIAC DISORDERS		0	5	
	SINUS TACHYCARDIA (1 *)	0	1	~
	TACHYCARDIA	0	4	~
EAR AND LABYRINTH DISORDERS		1	0	
	TINNITUS	1	0	
EYE DISORDERS		0	2	
	PHOTOPHOBIA	0	1	no
	VISUAL IMPAIRMENT	0	1	no
GASTROINTESTINAL DISORDERS		13	30	
	ABDOMINAL PAIN	8	8	yes
	ABDOMINAL PAIN UPPER	0	2	yes
	DIARRHOEA	3	5	yes
	DYSPEPSIA	0	4	~
	GASTROINTESTINAL PAIN	0	1	~
	GASTROOESOPHAGEAL REFLUX DISEASE	1	1	
	NAUSEA	1	3	yes
	POST-TUSSIVE VOMITING	0	2	~
	VOMITING	0	4	yes
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		3	9	
	ASTHENIA	1	2	yes
	CHEST DISCOMFORT	0	2	~
	DECREASED ACTIVITY	1	2	~
	HYPERTHERMIA	1	0	~
	PYREXIA	0	3	yes
HEPATOBILIARY DISORDERS		0	9	
	HEPATIC FUNCTION ABNORMAL (2*)	0	7	yes
	HYPERTRANSAMINASAEMIA (1 *)	0	2	yes
IMMUNE SYSTEM DISORDERS		1	1	
	RHINITIS ALLERGIC	1	1	
INFECTIONS AND		11	19	

INFESTATIONS	GASTROENTERITIS	0	2	no
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS (2*)	3	11	no
	LUNG INFECTION	1	1	yes
	NASOPHARYNGITIS	2	3	no
	ORAL HERPES	1	0	no
	PHARYNGITIS	2	0	no
	RHINITIS	1	1	no
	TONSILLITIS	1	0	no
	VIRAL INFECTION	0	1	no
INVESTIGATIONS		2	3	
	BLOOD CREATINE PHOSPHOKINASE INCREASED	0	1	no
	C-REACTIVE PROTEIN INCREASED	0	1	no
	ELECTROCARDIOGRAM T WAVE INVERSION (1 *)	0	1	no
	FORCED EXPIRATORY VOLUME DECREASED	1	0	
	WEIGHT DECREASED	1	0	
METABOLISM AND NUTRITION DISORDERS		0	4	
	DECREASED APPETITE	0	2	no
	DEHYDRATION	0	1	yes
	HYPERKALAEMIA	0	1	yes
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		4	12	
	ARTHRALGIA	0	3	no
	BACK PAIN	2	3	
	MUSCULOSKELETAL PAIN	0	1	no
	MUSCULOSKELETAL STIFFNESS	0	1	no
	MYALGIA	0	3	no
	NECK PAIN	2	1	
NERVOUS SYSTEM DISORDERS		6	10	
	BALANCE DISORDER	0	1	no
	HEADACHE	6	8	yes
	PRESYNCOPE	0	1	no
PSYCHIATRIC DISORDERS		2	3	
	DEPRESSED MOOD	0	1	no
	INSOMNIA	2	2	no
RENAL AND URINARY DISORDERS		0	1	
	HYPERCREATININAEMIA (1 *)	0	1	yes

REPRODUCTIVE SYSTEM AND BREAST DISORDERS		0	1	
	DYSMENORRHOEA	0	1	no
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		9	11	
	ASTHMA	2	0	no
	BRONCHIAL OBSTRUCTION	1	0	no
	BRONCHOSPASM	0	2	no
	COUGH	5	9	no
	SPUTUM RETENTION	1	0	no
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		2	5	
	ERYTHEMA	0	1	~
	PRURITUS	0	2	yes
	PRURITUS GENITAL	0	1	yes
	SKIN IRRITATION	1	0	no
	SKIN REACTION	0	1	~
	URTICARIA	1	0	~
VASCULAR DISORDERS		4	6	
	EPISTAXIS	0	1	no
	HAEMATOMA	0	1	yes
	HAEMOPTYSIS	4	4	no

(*) Number of serious event
~ Near Preferred Term listed in IB

6.3.4 Serious adverse reactions (SAE)

All patients who presented at least one SAE were treated with seliciclib.
Globally, 5 patients presented a total of 8 SAE. 3 of 5 patients have presented 2 SAEs at the same date.
The distribution of SAEs among clinical type of reaction showed that biliary events, infectious diseases are presented by more than one patient in the ROSCO-CF study (see table 15 Distribution of SAEs relative to clinical type of reaction).

The distribution among seliciclib dose escalating groups showed that patients treated with high dosage presented more SAEs. There were 5 SAEs observed in 5 patients at seliciclib 800 mg daily, 2 SAEs in one patient at seliciclib 400 mg daily and 1 SAE in one patient at seliciclib 200 mg daily (see table 16 Distribution of SAE relative to seliciclib ascending dose group).

The sponsor considered that 6 SAE (observed in 5 patients) should be qualified as possibly related and unlikely related to seliciclib (see table 17 Distribution of SAEs relative to sponsor seliciclib causality assessment):

-2 patients reported 3 hepatic possibly related SAEs

-1 patient experienced an electrocardiogram T wave inversion qualified as unlikely related to seliciclib
-1 patient experienced a sinus tachycardia associated with seliciclib, levothyrox and pulmonary infection
-1 patient was hospitalized for renal dysfunction (hypercreatinemia) qualified related to seliciclib.

Table 24: Distribution of SAEs relative to clinical type of reaction

SOC MedDRA	Number of SAE (number of patients)
Cardiac disorders *(atrial fibrillation)*	1
Infectious disorders *(pulmonary cystic fibrosis exacerbation)*	2 (2 patients)
Hepatobiliary disorders*(ASAT increased and hepatic function alteration)*	3 (2 patients)
Renal and urinary disorders *(renal function alteration)*	1
Investigations *(T wave inversion)*	1
TOTAL	8

Table 25: Distribution of SAEs relative to seliciclib ascending dose group

SOC MedDRA	Number SAE group 1	Number SAE group 2	Number SAE group 3
Cardiac disorders *(atrial fibrillation)*	0	0	1
Infectious disorders *(pulmonary cystic fibrosis exacerbation)*	0	0	2 (2 patients)
Hepatobiliary disorders*(ASAT increased and hepatic function alteration)*	0	2 (1 patient)	1
Renal and urinary disorders *(renal function alteration)*	0	0	1
Investigations *(T wave inversion)*	1	0	0
TOTAL	1	2	5

Table 26: Distribution of SAEs relative to sponsor seliciclib causality assessment

SOC MedDRA	Not related	Unlikely related	Possibly related
Cardiac disorders *(atrial fibrillation)*	0	0	1
Infectious disoders *(pulmonary cystic fibrosis exacerbation)*	2 (2 patients)	0	0
Hepatobiliary disorders *(ASAT increased and hepatic function alteration)*	0	0	3 (2 patients)
Renal and urinary disorders *(renal function alteration)*	0	0	1
Investigations *(Twave inversion)*	0	1	0
TOTAL	2	1	5

6.3.5 Deaths, other significant adverse events/reactions

No death was reported in the 34 young adults treated by the experimental treatment during the 30 months of ROSCO-CF.

In a phase 2 study all adverse events must be analyzed as suspected significant clinical reaction.

6.3.6 Safety conclusions

In the ROSCO-CF study, seliciclib has been administered to young adult cystic fibrosis patients. Serious adverse events were reported only in the seliciclib group. A dose-dependent serious toxicity of seliciclib has been observed. No signal of unexpected risk has been set up.

Safety data analysis of ROSCO-CF study pointed 4 relevant discussion points:

- ✓ Two patients treated with seliciclib 400 mg daily and 1 patient with 800 mg daily presented hepatobiliary SAEs. Hepatobiliary events were observed at the end of the second cycle of treatment. A dose dependent hepatotoxicity is possible. There was only one severe (grade 3) reaction with increased ASAT >9 N. All hepatobiliary SAEs corresponded to biological abnormalities without relevant clinical reaction. All SAEs resolved in one or several weeks.
- ✓ One patient presented an electrocardiogram T wave inversion after the first seliciclib administration. Cardiologic evaluation of pre-dose and post-dose ECG provided others episodes of T wave inversion.
- ✓ 5 tachycardia or sinus tachycardia were reported. The role of seliciclib cannot totally be eliminated in the tachycardia initiation. Two patients who reported tachycardia had a current pulmonary cystic fibrosis exacerbation.
- ✓ Renal function degradation is questioning because positive rechallenge. Immunological mediated reaction has been evoked but the institutional sponsor did not find relative elements in Cyclacel's investigator brochure about this risk.

7 Discussion and overall conclusions

In first intention, this study was designed to assess the safety of seliciclib in adult cystic fibrosis patients and to define which dose (200mg, 400mg or 800mg) could be used for further efficacy studies.

Concerning the primary endpoint, safety of use of seliciclib was analyzed by collecting all adverse events within the 56 days of the study.
A dose-dependent serious toxicity of seliciclib has been observed. Recommended dose seems to be 400 mg daily (4 cycles of 4 consecutive days) according to SAEs frequencies.
No signal of unexpected risk has been identified.

No significant differences between the placebo group and the seliciclib groups were detected in terms of efficacy criteria, except for some cytokines (IL-1beta, IL-8, MDC and MIP-1beta).

In conclusion, no signal of unexpected risk has been identified, which was the main objective of the study. As expected, the small sample size and the short treatment duration did not allow drawing conclusions regarding efficacy.

In this context, the next step will be to design a prospective randomized study evaluating the efficacy of seliciclib in a larger cohort of patients treated for a longer period of time.

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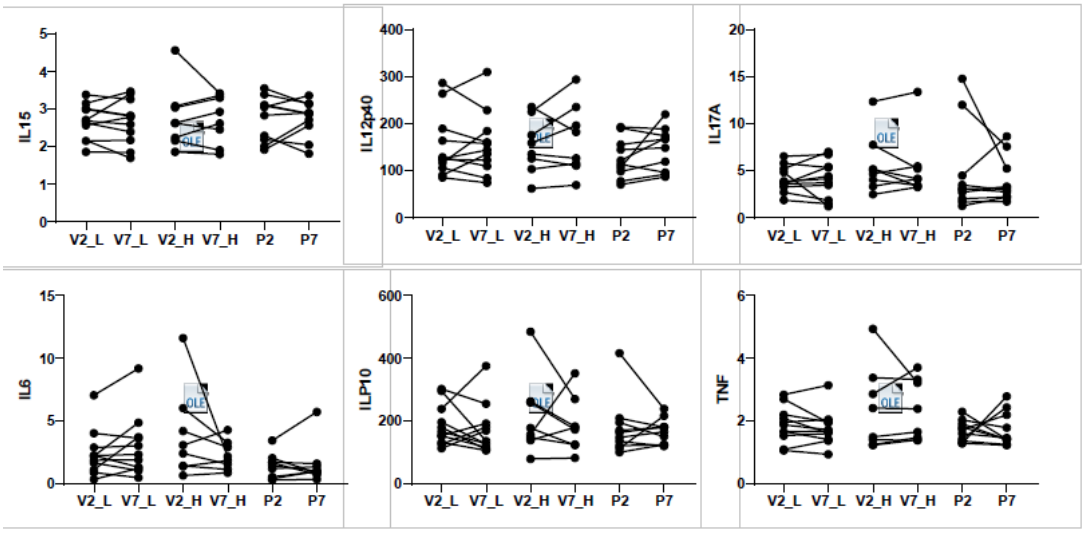
APPENDIX

ANNEX 1: Distribution of AE (number and percentage per group) among placebo and seliciclib dosage escalading groups

SOC MedDRA	Placebo group	Seliciclib 200 mg daily group	Seliciclib 400 mg daily group	Seliciclib 800 mg daily group
BLOOD AND LYMPHATIC SYSTEM DISORDERS	2 (3.3%)	1 (2.6%)	0	0
CARDIAC DISORDERS	0	1 (2.6%)	2 (3.4%)	2 (5,9%)
EAR AND LABYRINTH DISORDERS	1 (1.6%)	0	0	0
EYE DISORDERS	0	0	2 (3,4%)	0
GASTROINTESTINAL DISORDERS	13 (21.6%)	13 (33.3%)	12 (20,3%)	5 (14,7%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (5%)	3 (7.7%)	3 (5.1%)	3 (8,8%)
HEPATOBILIARY DISORDERS	0	0	6 (10.2%)	3 (8,8%)
IMMUNE SYSTEM DISORDERS	1 (1.6%)	0	1 (1,7%)	0
INFECTIONS AND INFESTATIONS	11 (18.3%)	6 (15,4%)	9 (15,25%)	4 (11,8%)
INVESTIGATIONS	2 (3.3%)	2 (5.1%)	1 (1,7%)	0
METABOLISM AND NUTRITION DISORDERS	0	2 (5.1%)	0	2 (5,9%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	4 (6.6%)	4 (10.2%)	3 (5.1%)	5 (14,7%)
NERVOUS SYSTEM DISORDERS	6 (10%)	2 (5.1%)	4 (6.8%)	4 (11,8%)
PSYCHIATRIC DISORDERS	2 (3.3%)	1 (2.6%)	1 (1,7%)	1 (2.9%)
RENAL AND URINARY DISORDERS	0	0	0	1 (2.9%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0	0	0	1 (2.9%)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9 (15%)	2 (5.1%)	7 (11.9%)	2 (5,9%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (3.3%)	1 (2.6%)	4 (6,8%)	0
VASCULAR DISORDERS	4 (6.6%)	1 (2.6%)	4 (6,8%)	1 (2.9%)
TOTAL	**60 (100%)**	**39 (100%)**	**59 (100%)**	**34 (100%)**

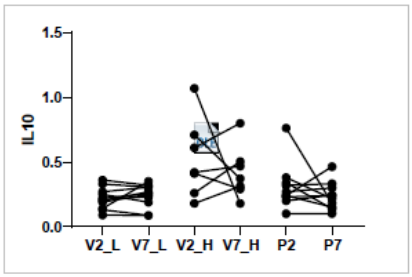
ANNEX 2: Cytokines

Pro-inflammatory cytokines

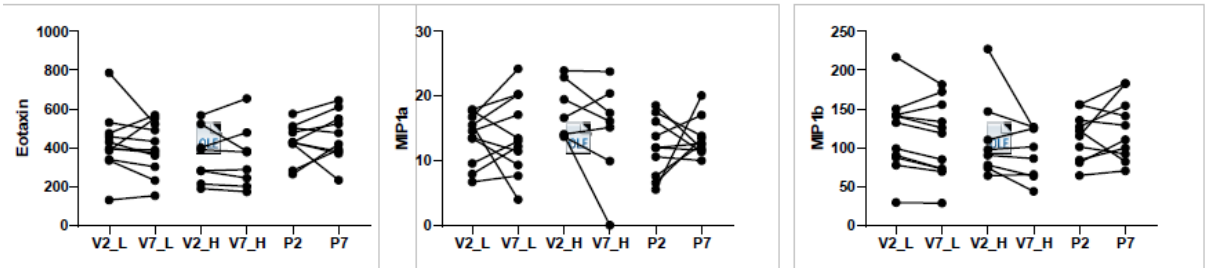


Cytokines expression according to the patient's exposition group : L :Low exposition, H: High exposition, P : Placebo , V2 and V7 primary and end point.

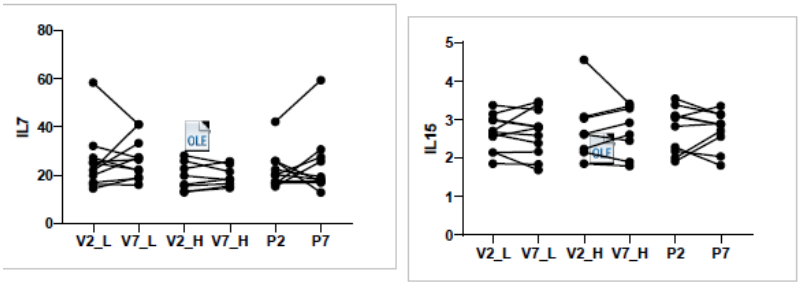
Anti-inflammatory cytokines



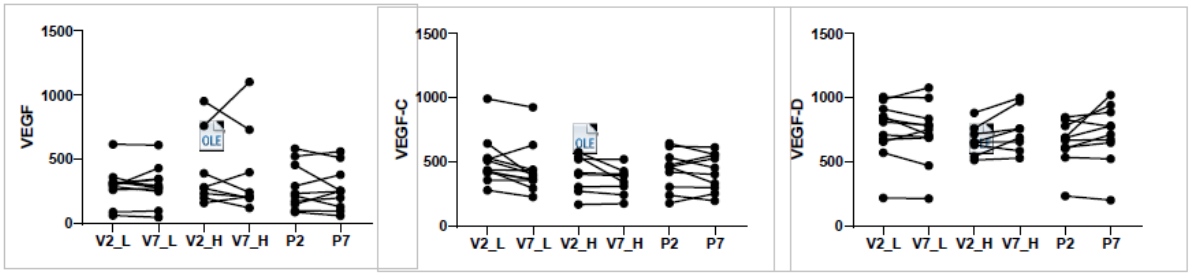
Chemokines Macrophages

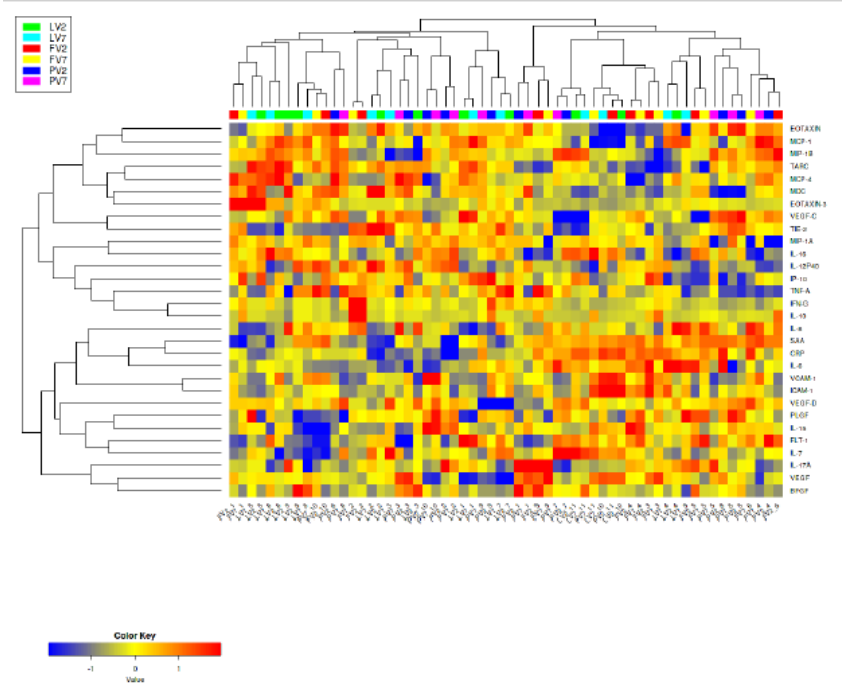


Facteurs de croissance lymphocytaires



Angiogenese





Hierarchical clustering of cytokine expression according to the patient's exposition group : L :Low exposition, H: High exposition, P : Placebo , V2 and V7 primary and end point.

ANNEX 3: Line listing of the SAE

SOC : Cardiac disorders - 10007541 (1)													
Patient & Case ID				Drug		Unexpected	Event / Reaction				Causality Assessment			
Patient	Case ID	Trial arm	Age / Sex	Dates or duration	Drug & dose		PT (verbatim)	Seriousness	Onset date	Outcome	Drug assessed	Reaction assessed	Source	Result
1139	FR-CHUBR-201800079	Roscovitine	42 Year(s) / Female	08-Feb-2018 / 02-Mar-2018 / 23 Day(s)	R-Roscovitine (seliciclib)	No	Sinus tachycardia (Tachycardie sinusale)	Other medically important condition	20-Feb-2018	recovered	R-Roscovitine	Sinus tachycardia	Sponsor Investigator	Reasonable possibility Reasonable possibility
					LEVOTHYROX (LÉVOTHYROXINE SODIQUE)	Yes	Infective pulmonary exacerbation of cystic fibrosis (Exacerbation pulmonaire)	Other medically important condition	19-Feb-2018	recovered	R-Roscovitine	Cystic fibrosis pulmonary exacerbation	Sponsor Investigator	No reasonable possibility No reasonable possibility
SOC : Hepatobiliary disorders - 10019805 (2)														
Patient & Case ID				Drug		Unexpected	Event / Reaction				Causality Assessment			
Patient	Case ID	Trial arm	Age / Sex	Dates or duration	Drug & dose		PT (verbatim)	Seriousness	Onset date	Outcome	Drug assessed	Reaction assessed	Source	Result
1130	FR-CHUBR-201700395	Roscovitine	27 Year(s) / Male	16-Oct-2017 / 07-Nov-2017 / 17 Day(s)	R-Roscovitine (seliciclib | 400 | milligram)	Yes	Hypertransaminasaemia (ALAT > 9*ULN)	Other medically important condition	30-Oct-2017	recovered	R-Roscovitine	Hypertransaminasaemia	Sponsor Investigator	Reasonable possibility Reasonable possibility
						No	Hepatic function abnormal (ASAT > 4.7*ULN)	Other medically important condition	30-Oct-2017	recovered	R-Roscovitine	Hepatic dysfunction non-icteric	Sponsor Investigator	Reasonable possibility Reasonable possibility
0247	FR-CHUBR-201800206	Roscovitine	40 Year(s) / Male	28-May-2018 / 07-Jun-2018 / 11 Day(s)	R-Roscovitine (SELICICLIB | 800 | milligram)	No	Hepatic function abnormal (Perturbation du bilan hépatique (ALAT >4*ULN))	Other medically important condition	08-Jun-2018	recovered	R-Roscovitine	Hepatic dysfunction NOS	Sponsor Investigator	Reasonable possibility Reasonable possibility
SOC : Renal and urinary disorders - 10038359 (1)														
Patient & Case ID				Drug		Unexpected	Event / Reaction				Causality Assessment			
Patient	Case ID	Trial arm	Age / Sex	Dates or duration	Drug & dose		PT (verbatim)	Seriousness	Onset date	Outcome	Drug assessed	Reaction assessed	Source	Result
0142	FR-CHUBR-201800110	Roscovitine	30 Year(s) / Male	19-Mar-2018 / 27-Mar-2018 / 9 Day(s)	R-Roscovitine (seliciclib)	No	Hypercreatininaemia (Dégradation de la fonction rénale)	Other medically important condition	23-Mar-2018	recovered	R-Roscovitine	Hypercreatininaemia	Sponsor Investigator	Reasonable possibility Reasonable possibility
						No	Infective pulmonary exacerbation of cystic fibrosis (Exacerbation de la mucoviscidose)	Other medically important condition	20-Mar-2018	recovered	R-Roscovitine	Cystic fibrosis pulmonary exacerbation	Sponsor Investigator	No reasonable possibility Reasonable possibility
SOC : Investigations - 10022891 (1)														
Patient & Case ID				Drug		Unexpected	Event / Reaction				Causality Assessment			
Patient	Case ID	Trial arm	Age / Sex	Dates or duration	Drug & dose		PT (verbatim)	Seriousness	Onset date	Outcome	Drug assessed	Reaction assessed	Source	Result
0111	FR-CHUBR-201600393	Roscovitine	32 Year(s) / Male	18-Nov-2016 / 18-Nov-2016 / 1 Day(s)	R-Roscovitine (seliciclib)	Yes	Electrocardiogram T wave inversion (Onde T négative)	Other medically important condition	18-Nov-2016	recovered	R-Roscovitine	Negative T wave	Sponsor Investigator	Reasonable possibility No reasonable possibility

ANNEX 4: CIOMS of Unexpected Serious Adverse Reaction (201600393)

Mfr. Control Number : 201600393

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. INITIALS	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6. REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
QUI-YAN	FR	Day 29	Month Sep	Year 1964	52 Years	M	Day 18	Month Nov	Year 2016	

7+13.DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [Low Level Term]

#1 Onde T négative [Negative T wave] (10058100 v21.0) - recovered

8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION

- ☐ PATIENT DIED
- ☐ LIFE THREATENING
- ☐ HOSPITALIZATION
- ☐ DISABILITY OR INCAPACITY
- ☐ CONGENITAL ANOMALY/BIRTH DEFECT
- ■ OTHER MEDICALLY IMPORTANT CONDITION

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

#1 R-Roscovitine (seliciclib); Batch/Lot number : [UNK]

22. DID REACTION ABATE AFTER STOPPING DRUG?

☐ YES ■ NO ☐ NA

15. DAILY DOSE(S) (dose per intake/unit/separate dose/form)

#1 200 mg milligram(s) /

16. ROUTE(S) OF ADMINISTRATION

#1 Buccal

17. INDICATION(S) FOR USE

#1 Cystic fibrosis

21. DID REACTION REAPPEAR AFTER REINTRODUCTION ?

☐ YES ■ NO ☐ NA

18. THERAPY DATES (from/to)

#1 18-Nov-2016 / 18-Nov-2016

19. THERAPY DURATION

#1 1 Day

III. CONCOMITANT DRUG(S) AND HISTORY

23. CONCOMITANT DRUG(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

24. OTHER RELEVANT HISTORY (e.g. diagnostics, allergies, pregnancy with last month of period, etc.)

From / To Dates Description

#1 / /Continuing : Yes / Cystic fibrosis

#2 / /Continuing : No / Lung lobectomy

#3 / /Continuing : No / Gynecomastia

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

CHU de Brest

2, avenue Foch

29609 Brest FR

26. REMARKS

Last receipt date : 01-Jun-2017

EudraCT number : 2015-002911-13 (EU)

Sponsor study number : RB15.098

Treatment number :

Study no : RB15.098

Center no : 01

Patient no : 0111

24b. MFR CONTROL NO

FR-CHU99-201600393

25a. NAME AND ADDRESS OF REPORTER

#1 [Privacy]

24c. DATE RECEIVED BY MANUFACTURER

21-Nov-2016

24d. REPORT SOURCE

■ STUDY ☐ LITERATURE ☐ AUTHORITY

■ HEALTH PROFESSIONAL ☐ OTHER

DATE OF THIS REPORT

03-Dec-2016

25a. REPORT TYPE

☐ INITIAL ■ FOLLOW-UP : 1

Mfr. Control Number : 201600380

10. RELEVANT TESTS (date / test / result / value / units / normal low range / normal high range / result unstructured data)

#1 15-Nov-2016 / Abnormal ECG / / / / /
#2 19-Nov-2016 / ECG normal / / / / /
#3 19-Nov-2016 / Cardiac troponin / / < / ng/l / /
#4 15-Nov-2016 / Plasma potassium / / / / / / 5.09 mmol/l
#5 15-Nov-2016 / Blood calcium / / 2.41 / mmol/l / /
#6 15-Dec-2016 / ECG / / / / /
#7 23-Jan-2017 / ECG / / / / /

CASE DESCRIPTION

Protocol :
RB15.098 : A Phase II, dose ranging, multicenter, double-blind, placebo controlled study to evaluate safety and effects of (R)-roscovitine in adults subjects with Cystic Fibrosis, carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation and chronically infected with Pseudomonas aeruginosa, a study involving 36 CF patients (24 treated, 12 controls). ROSCO-CF. --(2015-002901-13)

Patient : QUI-YAN - 0111
A 32 years old male patient with medical history of cystic fibrosis,had been treated with 200 mg per os Seliciclib/Placebo once a time the 15-nov-2016.

Concomitant treatment consisted of cystic fibrosis therapy as vitamines, pancreatic enzyme, urso desoxycholic acid, omeprazole, azithromycin, domperidone, beta-2 mimetic agents, ...)

PAST MEDICAL HISTORY : Cystic fibrosis; Lung lobectomy; Gynecomastia.

On 15-Nov-2016, the patient experienced negative T wave without associated clinical reaction (ECG was abnormal on 14:14 and ECG was normal on 16:24).
On 19-Nov-2016, ECG was normal and Cardiac troponin was <ng/l.

Outcome :
The patient had spontaneously recovered from negative T wave on 15-Nov-2016 (2 hours after the beginning of the negative T wave).

Assessment :
Negative T wave is unexpected
The investigator and sponsor suspected a relationship between the Negative T wave and the study medication.

ANNEX 5: CIOMS of Unexpected Serious Adverse Reaction (201700395)

CIOMS FORM Page 1 of 3 **Mfr. Control Number : 201700395**

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. INITIALS	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6. REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
B-G	FR				27 Year(s)	M	30	Oct	2017	

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [Low Level Term]

Alanine aminotransferase increase [Hypertransaminasaemia] (10068237 v20.1) - Recovered

Aspartate aminotransferase increased [Hepatic dysfunction non-icteric] (10057707 v20.1) - Recovered

- ☐ PATIENT DIED
- ☐ LIFE THREATENING
- ☐ HOSPITALIZATION
- ☐ DISABILITY OR INCAPACITY
- ☐ CONGENITAL ANOMALY/BIRTH DEFECT
- ■ OTHER MEDICALLY IMPORTANT CONDITION

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUG(S) (include generic name)

#1 R-Roscovitine (seliciclib)

20. DID REACTION ABATE AFTER STOPPING DRUG? ☐YES ☐NO ☐NA

15. DAILY DOSE(S)	16. ROUTE(S) OF ADMINISTRATION
#1 Please see next page	#1 Buccal

17. INDICATION(S) FOR USE

#1 Cystic fibrosis

21. DID REACTION REAPPEAR AFTER REINTRODUCTION ? ☐YES ☐NO ☐NA

18. THERAPY DATES (from/to)	19. THERAPY DURATION
#1 16-Oct-2017/07-Nov-2017	#1 17 Day(s)

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUGS(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

From / To Dates	Description
# 1	Cystic fibrosis

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER

CHU de Brest
2, avenue Foch
29609 Brest FR

26. REMARKS

Last receipt date : 15-Nov-2017
EudraCT no : 2015-002911-13

Study no : RB15.098

Center no : 13
Patient no : 1330

24b. MFR CONTROL NO.
201700395

25b. NAME AND ADDRESS OF REPORTER

24c. DATE RECEIVED BY MANUFACTURER
03-Nov-2017

24d. REPORT SOURCE
■ STUDY ☐ LITERATURE ☐ AUTHORITY
■ HEALTH PROFESSIONAL ☐ OTHER

DATE OF THIS REPORT
17-Nov-2017

25a. REPORT TYPE
■ INITIAL ☐ FOLLOW UP :

CIOMS FORM Page 2 of 3 **Mfr. Control Number : 201700395**

ADDITIONAL INFORMATION

7+13. DESCRIBE REACTION(S) continued

Case description : CASE DESCRIPTION: CASE FOR15-DAY ALERT.

This case is a report from a clinical trial entitled: A Phase II, dose ranging, multicenter, double-blind, placebo controlled study to evaluate safety and effects of (R)-roscovitine in adults subjects with Cystic Fibrosis, carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation and chronically infected with Pseudomonas aeruginosa, a study involving 36 CF patients (24 treated, 12 controls). ROSCO-CF.

EudraCT # 2015-002911-13
The main inclusion criteria is/are: Cystic fibrosis.
The Investigational Medicinal Products (IMP) of the study is seliciclib

The patient was included in the study on the 02-Oct-2017 .
Patient (B-G) - (13 - 1330) - 27 years-old male
This case occurred in FRANCE and was reported from an investigator by phone and fax on the 03-Nov-2017;

PAST MEDICAL HISTORY / CONCURRENT CONDITIONS-ALLERGIES
Cystic fibrosis;
□□

IMP DETAILS:
The patient was treated with seliciclib, 400 milligram (the second dose step of this escalating dose study); Buccal, for Cystic fibrosis from 16-Oct-2017 to 01-Nov-2017, action taken: Drug withdrawn temporaly. Then the patient took again the treatment on 06-Nov and on 07-Nov before to stop definitively the treatment to follow the protocol.
Follow up information received in writing/by phone/by fax on the 15-Nov-2017;

PAST MEDICAL HISTORY / CONCURRENT CONDITIONS-ALLERGIES
Cystic fibrosis;

HISTORY OF THE SERIOUS ADVERSE EVENT:
On the 30-Oct-2017, the patient had to receive the first dose of the third cycle of treatment. The experimental product was administered in spite of existence of an abnormal hepatic analysis : Alanine aminotransferase increased (9xN) , Aspartate aminotransferase increased (4.5xN), elevation of gamma glutamyl transferase level and alkaline phosphatase (mixt hepatic disorder with R=4.5).
Clinical exam of the liver was normal. Mild asthenia was observed with mild abdominal pain without transit disorder. No coagulation abnormality was noted.

The experimental product was stopped on 1 november but no exploratory exams was performed.
The hepatic parameters quickly improved in one week.
The experimental product was temporary administered on 6 to 7 november and then stopped definitively.
Viral and biliary exploration were normal (after 7 november).
The expert gastroenterologist considers that the medicinal hypothesis cannot be totally excluded.
The patient had recovered from Alanine aminotransferase increase on 13-Nov-2017 and from AST high on 09-Nov-2017

2 punctual administrations of acetaminophen (paracetamol) in the week before the event is noted in the CRF.
□□
SERIOUSNESS CRITERIA: Serious case: SAE grade 3
□□
FINDINGS:
On 30-Oct-2017 ALT high was 355 per international unit, Normal values = [7 - 40]
On 02-Nov-2017 ALT high was 245 per international unit, Normal values = [7 - 40]
On 30-Oct-2017 AST high was 191 per international unit, Normal values = [13 - 40]
On 02-Nov-2017 AST high was 93 per international unit, Normal values = [13 - 40]
On 06-Nov-2017 ALT high was 112 per international unit, Normal values = [7 - 40]
On 07-Nov-2017 ALT high was 88 per international unit, Normal values = [7 - 40]
On 06-Nov-2017 AST high was 21 per international unit, Normal values = [13 - 40]
On 07-Nov-2017 AST high was 19 per international unit, Normal values = [13 - 40]
On 23-Oct-2017 ALT high was 15 per international unit, Normal values = [7 - 40]
On 23-Oct-2017 AST high was 13 per international unit, Normal values = [13 - 40]
On 09-Nov-2017 ALT high was 52 per international unit, Normal values = [13 - 40]
On 13-Nov-2017 ALT high was 24 per international unit, Normal values = [13 - 40]
On 07-Nov-2017 AST high was 19 per international unit, Normal values = [13 - 40]
On 09-Nov-2017 AST high was 13 per international unit, Normal values = [13 - 40]
On 13-Nov-2017 AST high was 15 per international unit, Normal values = [13 - 40]
On 30-Oct-2017 GGT increased was 225 per international unit, Normal values = [9 - 73]
On 02-Nov-2017 GGT increased was 209 per international unit, Normal values = [9 - 73]
On 06-Nov-2017 GGT increased was 146 per international unit, Normal values = [9 - 73]
On 07-Nov-2017 GGT increased was 146 per international unit, Normal values = [9 - 73]
On 09-Nov-2017 GGT increased was 121 per international unit, Normal values = [9 - 73]
On 13-Nov-2017 GGT increased was 91 per international unit, Normal values = [9 - 73]
On 30-Oct-2017 Alkaline phosphatase increased was 225 per international unit, Normal values = [46 - 116]
On 02-Nov-2017 Alkaline phosphatase increased was 243 per international unit, Normal values = [46 - 116]
On 06-Nov-2017 Alkaline phosphatase increased was 181 per international unit, Normal values = [46 - 116]
On 07-Nov-2017 Alkaline phosphatase increased was 182 per international unit, Normal values = [46 - 116]
On 09-Nov-2017 Alkaline phosphatase increased was 153 per international unit, Normal values = [46 - 116]
On 13-Nov-2017 Alkaline phosphatase increased was 114 per international unit, Normal values = [46 - 116]
On 30-Oct-2017 CRP increased was 31 per international unit, Normal values = [0 - 5]
On 02-Nov-2017 CRP increased was 23 per international unit, Normal values = [0 - 5]
On 06-Nov-2017 CRP increased was 31 per international unit, Normal values = [0 - 5]
On 07-Nov-2017 CRP increased was 38 per international unit, Normal values = [0 - 5]
On 09-Nov-2017 CRP increased was 31 per international unit, Normal values = [0 - 5]
On 13-Nov-2017 CRP increased was 27 per international unit, Normal values = [0 - 5]
On 13-Nov-2017 CMV IgG antibody negative
On 13-Nov-2017 Herpes simplex test negative

□□
DIAGNOSIS: hypertransaminasemia and hepatic dysfunction anicteric.
□□
OUTCOME: The patient had recovered from Alanine aminotransferase increased on 13-Nov-2017 and from Aspartate aminotransferase increased on 09-Nov-2017.
□□□
STATUS OF THE REPORT: Closed

CIOMS FORM Page 3 of 3 **Mfr. Control Number : 201700395**

Onset since FIRST administration: 15 Day.

Case is related
Case expectedness: Expected partially in investigator leaflet.

The Sponsor assessed on the relationship of the hypertransaminase and on the relashioship of the hepatic dysfunction anicteric to the seliciclib as Reasonable possibility.

The Investigator assessed on the relationship of thehypertransaminaseto the seliciclib and the relationship of the hepatic dysfunction anicteric to the seliciclib as Reasonable possibility.

CASE DESCRIPTION: CASE FOR 15-DAY ALERT.
Section 15. Continued :
Daily dose #1 : 4 days on and 3 days off during 4 weeks [400 milligram]

13. Relevant Tests (date/test/results/units/normal low range/normal high range)

Test date	Test Name	Test results (Code / Numeric Unit / Unstructured)	Low / high
#1 : 30-Oct-2017	ALT high	355 per international unit /	7 / 40
#2 : 02-Nov-2017	ALT high	245 per international unit /	7 / 40
#3 : 30-Oct-2017	AST high	191 per international unit /	13 / 40
#4 : 02-Nov-2017	AST high	93 per international unit /	13 / 40
#5 : 06-Nov-2017	ALT high	112 per international unit /	7 / 40
#6 : 07-Nov-2017	ALT high	88 per international unit /	7 / 40
#7 : 06-Nov-2017	AST high	21 per international unit /	13 / 40
#8 : 07-Nov-2017	AST high	19 per international unit /	13 / 40
#9 : 23-Oct-2017	ALT high	15 per international unit /	7 / 40
#10 : 23-Oct-2017	AST high	13 per international unit /	13 / 40
#11 : 09-Nov-2017	ALT high	52 per international unit /	13 / 40
#12 : 13-Nov-2017	ALT high	24 per international unit /	13 / 40
#13 : 07-Nov-2017	AST high	19 per international unit /	13 / 40
#14 : 09-Nov-2017	AST high	13 per international unit /	13 / 40
#15 : 13-Nov-2017	AST high	15 per international unit /	13 / 40
#16 : 30-Oct-2017	GGT increased	225 per international unit /	9 / 73
#17 : 02-Nov-2017	GGT increased	209 per international unit /	9 / 73
#18 : 06-Nov-2017	GGT increased	146 per international unit /	9 / 73
#19 : 07-Nov-2017	GGT increased	146 per international unit /	9 / 73
#20 : 09-Nov-2017	GGT increased	121 per international unit /	9 / 73
#21 : 13-Nov-2017	GGT increased	91 per international unit /	9 / 73
#22 : 30-Oct-2017	Alkaline phosphatase increased	225 per international unit /	46 / 116
#23 : 02-Nov-2017	Alkaline phosphatase increased	243 per international unit /	46 / 116
#24 : 06-Nov-2017	Alkaline phosphatase increased	181 per international unit /	46 / 116
#25 : 07-Nov-2017	Alkaline phosphatase increased	182 per international unit /	46 / 116
#26 : 09-Nov-2017	Alkaline phosphatase increased	153 per international unit /	46 / 116
#27 : 13-Nov-2017	Alkaline phosphatase increased	114 per international unit /	46 / 116
#28 : 30-Oct-2017	CRP increased	31 per international unit /	0 / 5
#29 : 02-Nov-2017	CRP increased	23 per international unit /	0 / 5
#30 : 06-Nov-2017	CRP increased	31 per international unit /	0 / 5
#31 : 07-Nov-2017	CRP increased	38 per international unit /	0 / 5
#32 : 09-Nov-2017	CRP increased	31 per international unit /	0 / 5
#33 : 13-Nov-2017	CRP increased	27 per international unit /	0 / 5
#34 : 13-Nov-2017	CMV IgG antibody	Negative /	/
#35 : 13-Nov-2017	Herpes simplex test negative	Negative /	/

ANNEX 6: CIOMS of Unexpected Serious Adverse Reaction (201800079)

Page 1 of 2

Mfr. Control Number : 201800079

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. INITIALS	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6. REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
A-M	FR				42 Years	F	20	Feb	2018	

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [Low Level Term]

#1 Tachycardie sinusale [Sinus tachycardia] (10040752 v21.0) - recovered

#2 Exacerbation pulmonaire [Cystic fibrosis pulmonary exacerbation] (10068288 v21.0) - recovered

- ☐ PATIENT DIED
- ☐ LIFE THREATENING
- ☐ HOSPITALIZATION
- ☐ DISABILITY OR INCAPACITY
- ☐ CONGENITAL ANOMALY/BIRTH DEFECT
- ■ OTHER MEDICALLY IMPORTANT CONDITION

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUGS(S) (include generic name)
#1 R-Roscovitine (seliciclib); Batch/Lot number : [UNK]

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐YES ☐NO ☐NA

15. DAILY DOSE(S) (dose per interval/unit/separate dose/text)
Unknown

16. ROUTE(S) OF ADMINISTRATION
#1 ORAL USE

17. INDICATION(S) FOR USE
#1 Cystic fibrosis

21. DID REACTION REAPPEAR AFTER REINTRODUCTION ?
☐YES ☐NO ☐NA

18. THERAPY DATES (from/to)
#1 08-Feb-2018 / 02-Mar-2018

19. THERAPY DURATION
#1 23 Day

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUGS(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)
#1 LEVOTHYROX (LÉVOTHYROXINE SODIQUE) ; / ; ; ; ; Unknown

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)
From / To Dates Description
#1 / Continuing : Yes / Cystic fibrosis

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
CHU de Brest
2, avenue Foch
29609 Brest FR

26. REMARKS
Last receipt date : 08-Mar-2018
EudraCT number : 2015-002911-13 (EU)
Sponsor study number : RB15.098
Treatment number :

Study no : RB15.098
Center no : 11
Patient no : 1139

24b. MFR CONTROL NO.
FR-CHUBR-201800079

25b. NAME AND ADDRESS OF REPORTER
#1 Dr Sylvie LE ROY / Hôpital Pasteur / 06000 NICE / FRANCE

24c. DATE RECEIVED BY MANUFACTURER
02-Mar-2018

24d. REPORT SOURCE
■ STUDY ☐ LITERATURE ☐ AUTHORITY
■ HEALTH PROFESSIONAL ☐ OTHER

DATE OF THIS REPORT
03-Dec-2018

25a. REPORT TYPE
■ INITIAL ☐FOLLOW UP :

13. RELEVANT TESTS (date / test / result / value / units / normal low range / normal high range / result unstructured data)

#1 02-Mar-2018 / C-reactive protein increased / / 30.4 / milligram per litre / /

#2 02-Mar-2018 / Leucocyte count / / 17.8 / billion per litre / /

#3 02-Mar-2018 / Absolute neutrophil count / / 15.4 / billion per litre / /

CASE DESCRIPTION

CASE DESCRIPTION : CASE FOR ANNUAL SAFETY REPORT.

This case is a report from a clinical trial entitled : A Phase II, dose ranging, multicenter, double-blind, placebo controlled study to evaluate safety and effects of (R)-roscovitine in adults subjects with Cystic Fibrosis, carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation and chronically infected with Pseudomonas aeruginosa, a study involving 36 CF patients (24 treated, 12 controls). ROSCO-CF.

EudraCT number : 2015-002911-13 (EU).
Study site ID : 11.
The main inclusion criteria is Cystic fibrosis.
The Investigational Medicinal Products (IMP) of the study is seliciclib
The patient A-M - 11-39 was included in the study on 01-Feb-2018.
This case occurred in null and refers to a 42 year-old female subject.
It was reported on 02-Mar-2018.
Follow up information received on 02-Mar-2018.

PAST MEDICAL HISTORY / CONCURRENT CONDITIONS-ALLERGIES :
The patient's concurrent illness included : Cystic fibrosis.

CONCOMITANT THERAPY :
LEVOTHYROX (LÉVOTHYROXINE SODIQUE)

SUSPECT DRUGS :
The patient was treated with R-Roscovitine (seliciclib) for Cystic fibrosis from 08-Feb-2018 to 02-Mar-2018.

SUMMARY OF THE SERIOUS ADVERSE EVENT :
On 20-Feb-2018, the patient experienced Sinus tachycardia and on 19-Feb-2018, the patient experienced Cystic fibrosis pulmonary exacerbation.

SERIOUSNESS CRITERIA :
Serious case : Other medically important condition.

FINDINGS :
On 02-Mar-2018, C-reactive protein increased was 30.4 milligram per litre.
On 02-Mar-2018, Leucocyte count was 17.8 billion per litre.
On 02-Mar-2018, Absolute neutrophil count was 15.4 billion per litre.

DIAGNOSIS :
No diagnosis was reported.

OUTCOME :
The patient recovered from Sinus tachycardia on 03-Mar-2018 and has not yet recovered from Cystic fibrosis pulmonary exacerbation.

RELATEDNESS / EXPECTEDNESS :
The case is not related.
The case is unexpected.

CAUSALITY ASSESSMENTS :
Sponsor assessed the relationship of the Sinus tachycardia to the seliciclib as Reasonable possibility.
Investigator assessed the relationship of the Sinus tachycardia to the seliciclib as Reasonable possibility.
Sponsor assessed the relationship of the Cystic fibrosis pulmonary exacerbation to the seliciclib as No reasonable possibility.
Investigator assessed the relationship of the Cystic fibrosis pulmonary exacerbation to the seliciclib as No reasonable possibility.

STATUS OF THE REPORT :
More information is awaited.

ANNEX 7: CIOMS of Unexpected Serious Adverse Reaction (201800110)

Page 1 of 3

Mfr. Control Number : 201800110

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. INITIALS	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6. REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
G-C	FR	Day	Month	Year	30 Years	M	Day 23	Month Mar	Year 2018	

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [Low Level Term]

#1 Dégradation de la fonction rénale [Hypercreatininaemia] (10062747 v21.0) - recovered

#2 Exacerbation de la mucoviscidose [Cystic fibrosis pulmonary exacerbation] (10068288 v21.0) - recovered

- ☐ PATIENT DIED
- ☐ LIFE THREATENING
- ☐ HOSPITALIZATION
- ☐ DISABILITY OR INCAPACITY
- ☐ CONGENITAL ANOMALY/BIRTH DEFECT
- ■ OTHER MEDICALLY IMPORTANT CONDITION

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUGS(S) (include generic name)
#1 R-Roscovitine (seliciclib); Batch/Lot number : [UNK]

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐YES ☐NO ☐NA

15. DAILY DOSE(S) (dose per interval/unit/separate dose/text)
#1 800 milligram every 4 Total / The event (renal impairment [...]

16. ROUTE(S) OF ADMINISTRATION
#1 ORAL USE

17. INDICATION(S) FOR USE
#1 Cystic fibrosis

21. DID REACTION REAPPEAR AFTER REINTRODUCTION ?
■YES ☐NO ☐NA

18. THERAPY DATES (from/to)
#1 19-Mar-2018 / 27-Mar-2018

19. THERAPY DURATION
#1 9 Day

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUGS(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

From / To Dates Description
#1 / Continuing : Yes / Cystic fibrosis

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
CHU de Brest
2, avenue Foch
29609 Brest FR

26. REMARKS
Last receipt date : 04-Apr-2018
EudraCT number : 2015-002911-13 (EU)
Sponsor study number : RB15.098
Treatment number :

Study no : RB15.098
Center no : 01
Patient no : 0142

24b. MFR CONTROL NO.
FR-CHUBR-201800110

25b. NAME AND ADDRESS OF REPORTER
#1 Jean LE BIHAN / Clinique Mucoviscidose / 29684 ROSCOFF / FRANCE

24c. DATE RECEIVED BY MANUFACTURER
23-Mar-2018

24d. REPORT SOURCE
■ STUDY ☐ LITERATURE ☐ AUTHORITY
■ HEALTH PROFESSIONAL ☐ OTHER

DATE OF THIS REPORT
03-Dec-2018

25a. REPORT TYPE
■ INITIAL ☐ FOLLOW UP :

13. RELEVANT TESTS (date / test / result / value / units / normal low range / normal high range / result unstructured data)

#1 19-Mar-2018 / Plasma creatinine / / 59 / millimole / /
#2 23-Mar-2018 / Plasma creatinine / / 123 / millimole / /
#3 26-Mar-2018 / Plasma creatinine / / 86 / micromole per litre / /
#4 28-Mar-2018 / Plasma creatinine / / 160 / micromole per litre / /
#5 30-Mar-2018 / Plasma creatinine / / 105 / micromole per litre / /
#6 23-Mar-2018 / Creatinine clearance / / 68 / millilitre per minute per litre / /
#7 26-Mar-2018 / Creatinine clearance / / 104 / millilitre per minute per litre / /
#8 28-Mar-2018 / Creatinine clearance / / 49.07 / millilitre per minute / /
#9 30-Mar-2018 / Creatinine clearance / / 82 / millilitre per minute / /
#10 19-Mar-2018 / Band neutrophil count / / 10890 / number per millilitre / /
#11 30-Mar-2018 / Band neutrophil count / / 5050 / number per millilitre / /
#12 19-Mar-2018 / CRP increased / / 15.5 / milligram per litre / /
#13 30-Mar-2018 / CRP increased / / 3.3 / milligram per litre / /
#14 26-Mar-2018 / Ultrasound abdomen / Negative / / / /
#15 04-Apr-2018 / Plasma creatinine / / 84.9 / millimole / /
#16 04-Apr-2018 / Creatinine clearance / / 105.64 / millilitre per minute / /
#17 04-Apr-2018 / Band neutrophil count / / 4940 / number per millilitre / /

14-19. SUSPECTS DRUGS continued

Seq. No. : 1
Drug : R-Roscovitine (seliciclib)
Charact. of drug role : Suspect
Daily dose : 800 milligram every 4 Total / The event (renal impairment and exacerbation of cystic fibrosis with bronchospasm and expectoration) begun at C1J2 after cumulative dosage of 1600mg of experimental product. The patient took the experimental product all cycle 1 since 22/03/18 as protocol instruction. Then the patient took a complete cycle 1 of experimental product. On 2è/03/18 stopped the administration (after one day of cycle 2 treatment) because he presented back pain. The plasma creatinine dosage showed renal impairment.
Route of administration : ORAL USE
Batch / Lot number : [UNK]
Indication for use : Cystic fibrosis (10011762 v21.1)
Therapy dates (start/end) : 19-Mar-2018 / 27-Mar-2018
Therapy duration : 9 Day

CASE DESCRIPTION

CASE DESCRIPTION : CASE FOR ANNUAL SAFETY REPORT.

This case is a report from a clinical trial entitled : A Phase II, dose ranging, multicenter, double-blind, placebo controlled study to evaluate safety and effects of (R)-roscovitine in adults subjects with Cystic Fibrosis, carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation and chronically infected with Pseudomonas aeruginosa, a study involving 36 CF patients (24 treated, 12 controls). ROSCO-CF.

EudraCT number : 2015-002911-13 (EU).
Study site ID : 01.
The main inclusion criteria is/are : Cystic fibrosis.
The Investigational Medicinal Products (IMP) of the study is seliciclib
The patient was included in the study on 05-Mar-2018.
Patient : (G-C) - (0142).
This case occurred in null and refers to a 30 year-old male subject; UNK Weight (kg); UNK Height (cm).
It was reported on 23-Mar-2018.
Follow up information received on 23-Mar-2018.

PAST MEDICAL HISTORY / CONCURRENT CONDITIONS-ALLERGIES :
The patient's concurrent illness included : Cystic fibrosis.

CONCOMITANT THERAPY :
Concomitant medications were not reported.

SUSPECT DRUGS :
The patient was treated with R-Roscovitine (seliciclib), 800 milligram; posology : UNK X 4 / Total; ORAL USE for Cystic fibrosis from 19-Mar-2018 to 27-Mar-2018.

SUMMARY OF THE SERIOUS ADVERSE EVENT :
On 23-Mar-2018, the patient experienced Hypercreatininaemia and on 20-Mar-2018, the patient experienced Cystic fibrosis pulmonary exacerbation.

SERIOUSNESS CRITERIA :
Serious case : Other medically important condition.

FINDINGS :
On 19-Mar-2018, Plasma creatinine was 59 millimole, Normal values = [-].
On 23-Mar-2018, Plasma creatinine was 123 millimole, Normal values = [-].
On 26-Mar-2018, Plasma creatinine was 86 micromole per litre, Normal values = [-].
On 28-Mar-2018, Plasma creatinine was 160 micromole per litre, Normal values = [-].
On 30-Mar-2018, Plasma creatinine was 105 micromole per litre, Normal values = [-].
On 23-Mar-2018, Creatinine clearance was 68 millilitre per minute per litre, Normal values = [-].
On 26-Mar-2018, Creatinine clearance was 104 millilitre per minute per litre, Normal values = [-].
On 28-Mar-2018, Creatinine clearance was 49.07 millilitre per minute, Normal values = [-].
On 30-Mar-2018, Creatinine clearance was 82 millilitre per minute, Normal values = [-].
On 19-Mar-2018, Band neutrophil count was 10890 number per millilitre, Normal values = [-].
On 30-Mar-2018, Band neutrophil count was 5050 number per millilitre, Normal values = [-].

Mfr. Control Number : 201800110

On 19-Mar-2018, CRP increased was 15.5 milligram per litre, Normal values = [-].
On 30-Mar-2018, CRP increased was 3.3 milligram per litre, Normal values = [-].
On 26-Mar-2018, Ultrasound abdomen was , Normal values = [-].
On 04-Apr-2018, Plasma creatinine was 84.9 millimole, Normal values = [-].
On 04-Apr-2018, Creatinine clearance was 105.64 millilitre per minute, Normal values = [-].
On 04-Apr-2018, Band neutrophil count was 4940 number per millilitre, Normal values = [-].

DIAGNOSIS :
No diagnosis was reported.

OUTCOME :
The patient is recovering from Hypercreatininaemia and is recovering from Cystic fibrosis pulmonary exacerbation.

RELATEDNESS / EXPECTEDNESS :
The case is related.
The case is not unexpected.

CAUSALITY ASSESSMENTS :
Sponsor asseesed the relationship of the Hypercreatininaemia to the seliciclib as Reasonable possibility.
Investigator assessed the relationship of the Hypercreatininaemia to the seliciclib as Reasonable possibility.
Sponsor assessed the relationship of the Cystic fibrosis pulmonary exacerbation to the seliciclib as No reasonable possibility.
Investigator assessed the relationship of the Cystic fibrosis pulmonary exacerbation to the seliciclib as Reasonable possibility.

STATUS OF THE REPORT :
No closed / More information is awaited.

ANNEX 8: CIOMS of Unexpected Serious Adverse Reaction (201800206)

Page 1 of 3

Mfr. Control Number : 201800206

CIOMS FORM

SUSPECT ADVERSE REACTION REPORT

I. REACTION INFORMATION

1. INITIALS	1a. COUNTRY	2. DATE OF BIRTH			2a. AGE	3. SEX	4-6. REACTION ONSET			8-12 CHECK ALL APPROPRIATE TO ADVERSE REACTION
		Day	Month	Year			Day	Month	Year	
C-T	FR				40 Years	M	08	Jun	2018	

7+13 DESCRIBE REACTION(S) (including relevant tests/lab data) Event Verbatim [Low Level Term]

#1 Perturbation du bilan hépatique (ALAT >4*ULN) [Hepatic dysfunction NOS] (10019657 v21.0) - recovered

- ☐ PATIENT DIED
- ☐ LIFE THREATENING
- ☐ HOSPITALIZATION
- ☐ DISABILITY OR INCAPACITY
- ☐ CONGENITAL ANOMALY/BIRTH DEFECT
- ■ OTHER MEDICALLY IMPORTANT CONDITION

II. SUSPECT DRUG(S) INFORMATION

14. SUSPECT DRUGS(S) (include generic name)
#1 R-Roscovitine (SELICICLIB | 800 | milligram)

20. DID REACTION ABATE AFTER STOPPING DRUG?
☐YES ☐NO ☐ NA

15. DAILY DOSE(S) (dose per interval/unit/separate dose/text)
#1 800 milligram every 4 Total / 4 days on and 3 days off du [...]

16. ROUTE(S) OF ADMINISTRATION
#1 ORAL USE

17. INDICATION(S) FOR USE
#1 Cystic fibrosis

21. DID REACTION REAPPEAR AFTER REINTRODUCTION ?
☐YES ☐NO ☐ NA

18. THERAPY DATES (from/to)
#1 28-May-2018 / 07-Jun-2018

19. THERAPY DURATION
#1 11 Day

III. CONCOMITANT DRUG(S) AND HISTORY

22. CONCOMITANT DRUGS(S) AND DATES OF ADMINISTRATION (exclude those used to treat reaction)

23. OTHER RELEVANT HISTORY (e.g. diagnostics, allergics, pregnancy with last month of period, etc.)

From / To Dates Description
#1 / Continuing : Yes / Cystic fibrosis

IV. MANUFACTURER INFORMATION

24a. NAME AND ADDRESS OF MANUFACTURER
CHU de Brest
2, avenue Foch
29609 Brest FR

26. REMARKS
Last receipt date : 06-Jul-2018
EudraCT number : 2015-002911-13 (EU)
Sponsor study number : RB15.098
Treatment number :

Study no : RB15.098
Center no : 13
Patient no : 0247

24b. MFR CONTROL NO.
FR-CHUBR-201800206

25b. NAME AND ADDRESS OF REPORTER
#1 Dr Raphaele NOVE-JOSSERAND / Centre Hospitalier Lyon Sud-CRCM / 69495 PIERRE-BENITE / FRANCE

24c. DATE RECEIVED BY MANUFACTURER
13-Jun-2018

24d. REPORT SOURCE
■ STUDY ☐ LITERATURE ☐ AUTHORITY
■ HEALTH PROFESSIONAL ☐ OTHER

DATE OF THIS REPORT
03-Dec-2018

25a. REPORT TYPE
■ INITIAL ☐FOLLOW UP :

13. RELEVANT TESTS (date / test / result / value / units / normal low range / normal high range / result unstructured data)

#1 28-May-2018 / ALT normal / / 16 / per international unit / 0 / 55
#2 01-Jun-2018 / ALT normal / / 21 / per international unit / 0 / 55
#3 04-Jun-2018 / ALT normal / / 17 / per international unit / 0 / 55
#4 08-Jun-2018 / ALT high / / 201 / per international unit / 10 / 50
#5 11-Jun-2018 / ALT high / / 162 / per international unit / 0 / 55
#6 15-Jun-2018 / ALT high / / 102 / per international unit / 10 / 50
#7 22-Jun-2018 / ALT high / / 45 / per international unit / 10 / 50
#8 29-Jun-2018 / ALT high / / 29 / per international unit / 10 / 50
#9 28-May-2018 / Aspartate aminotransferase normal / / 28 / per international unit / 5 / 34
#10 01-Jun-2018 / Aspartate aminotransferase normal / / 32 / per international unit / 5 / 34
#11 04-Jun-2018 / Aspartate aminotransferase normal / / 25 / per international unit / 5 / 34
#12 08-Jun-2018 / AST high / / 147 / per international unit / 10 / 50
#13 11-Jun-2018 / AST high / / 81 / per international unit / 5 / 34
#14 15-Jun-2018 / Aspartate aminotransferase normal / / 50 / per international unit / 10 / 50
#15 22-Jun-2018 / Aspartate aminotransferase normal / / 40 / per international unit / 10 / 50
#16 29-Jun-2018 / Aspartate aminotransferase normal / / 31 / per international unit / 10 / 50
#17 28-May-2018 / GGT / / 16 / per international unit / 12 / 64
#18 01-Jun-2018 / GGT / / 17 / per international unit / 12 / 64
#19 04-Jun-2018 / GGT / / 14 / per international unit / 12 / 64
#20 08-Jun-2018 / GGT increased / / 122 / per international unit / 0 / 60
#21 11-Jun-2018 / GGT increased / / 100 / per international unit / 0 / 60
#22 15-Jun-2018 / GGT increased / / 95 / per international unit / 0 / 60
#23 22-Jun-2018 / GGT increased / / 66 / per international unit / 0 / 60
#24 29-Jun-2018 / GGT normal / / 46 / per international unit / 0 / 60
#25 28-May-2018 / Alkaline phosphatase normal / / 146 / per international unit / 40 / 150
#26 01-Jun-2018 / Alkaline phosphatase increased / / 155 / per international unit / 40 / 150
#27 04-Jun-2018 / Alkaline phosphatase normal / / 142 / per international unit / 40 / 150
#28 08-Jun-2018 / Alkaline phosphatase increased / / 342 / per international unit / 40 / 150
#29 11-Jun-2018 / Alkaline phosphatase increased / / 433 / per international unit / 40 / 150
#30 15-Jun-2018 / Alkaline phosphatase increased / / 367 / per international unit / 40 / 130
#31 22-Jun-2018 / Alkaline phosphatase increased / / 285 / per international unit / 40 / 130
#32 29-Jun-2018 / Alkaline phosphatase increased / / 238 / per international unit / 40 / 130
#33 28-May-2018 / Bilirubin total normal / / 8 / micromole per litre / 0 / 20
#34 01-Jun-2018 / Bilirubin total normal / / 9 / micromole per litre / 0 / 20
#35 04-Jun-2018 / Bilirubin total normal / / 6 / micromole per litre / 0 / 20
#36 08-Jun-2018 / Bilirubin total increased / / 40.6 / micromole per litre / 0 / 21
#37 11-Jun-2018 / Bilirubin total normal / / 19 / micromole per litre / 3 / 21
#38 15-Jun-2018 / Bilirubin total normal / / 8.5 / micromole per litre / 3 / 21
#39 22-Jun-2018 / Bilirubin total normal / / 9.7 / micromole per litre / 3 / 21
#40 29-Jun-2018 / Bilirubin total normal / / 6.7 / micromole per litre / 3 / 21

14-19. SUSPECTS DRUGS continued

Seq. No.	:	1
Drug	:	R-Roscovitine (SELICICLIB | 800 | milligram)
Charact. of drug role	:	Suspect
Daily dose	:	800 milligram every 4 Total / 4 days on and 3 days off during 4 weeks. THe patient stopped treatment on cycle 2 and D4
Route of administration	:	ORAL USE
Batch / Lot number	:	
Indication for use	:	Cystic fibrosis (10011762 v21.0)
Therapy dates (start/end)	:	28-May-2018 / 07-Jun-2018
Therapy duration	:	11 Day

CASE DESCRIPTION

CASE DESCRIPTION : CASE FOR ANNUAL SAFETY REPORT.

This case is a report from a clinical trial entitled : A Phase II, dose ranging, multicenter, double-blind, placebo controlled study to evaluate safety and effects of (R)-roscovitine in adults subjects with Cystic Fibrosis, carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation and chronically infected with Pseudomonas aeruginosa, a study involving 36 CF patients (24 treated, 12 controls). ROSCO-CF..

EudraCT number : 2015-002911-13 (EU).
Study site ID : 13.
The main inclusion criteria is/are : Cystic fibrosis.
The Investigational Medicinal Products (IMP) of the study is/are :
SELICICLIB | 800 | milligram
The patient was included in the study on .
Patient : (C-T) - (0247).
This case occurred in null and refers to a 40 year-old male subject; UNK Weight (kg); UNK Height (cm).

Mfr. Control Number : 201800206

It was reported on 13-Jun-2018.
Follow up information received on 13-Jun-2018.

PAST MEDICAL HISTORY / CONCURRENT CONDITIONS-ALLERGIES :
The patient's concurrent illness included : Cystic fibrosis.

CONCOMITANT THERAPY :
Concomitant medications were not reported.

SUSPECT DRUGS :
The patient was treated with R-Roscovitine (SELICICLIB | 800 | milligram), 800 milligram; posology : UNK X 4 / Total; ORAL USE for Cystic fibrosis from 28-May-2018 to 07-Jun-2018.

SUMMARY OF THE SERIOUS ADVERSE EVENT :
On 08-Jun-2018, the patient experienced Hepatic dysfunction NOS.

SERIOUSNESS CRITERIA :
Serious case : Other medically important condition.

FINDINGS :
On 28-May-2018, ALT normal was 16 per international unit, Normal values = [0 - 55].
On 01-Jun-2018, ALT normal was 21 per international unit, Normal values = [0 - 55].
On 04-Jun-2018, ALT normal was 17 per international unit, Normal values = [0 - 55].
On 08-Jun-2018, ALT high was 201 per international unit, Normal values = [10 - 50].
On 11-Jun-2018, ALT high was 162 per international unit, Normal values = [0 - 55].
On 28-May-2018, Aspartate aminotransferase normal was 28 per international unit, Normal values = [5 - 34].
On 01-Jun-2018, Aspartate aminotransferase normal was 32 per international unit, Normal values = [5 - 34].
On 04-Jun-2018, Aspartate aminotransferase normal was 25 per international unit, Normal values = [5 - 34].
On 08-Jun-2018, AST high was 147 per international unit, Normal values = [10 - 50].
On 11-Jun-2018, AST high was 81 per international unit, Normal values = [5 - 34].
On 28-May-2018, GGT was 16 per international unit, Normal values = [12 - 64].
On 01-Jun-2018, GGT was 17 per international unit, Normal values = [12 - 64].
On 04-Jun-2018, GGT was 14 per international unit, Normal values = [12 - 64].
On 08-Jun-2018, GGT increased was 122 per international unit, Normal values = [0 - 60].
On 11-Jun-2018, GGT increased was 100 per international unit, Normal values = [0 - 60].
On 28-May-2018, Alkaline phosphatase normal was 146 per international unit, Normal values = [40 - 150].
On 01-Jun-2018, Alkaline phosphatase increased was 155 per international unit, Normal values = [40 - 150].
On 04-Jun-2018, Alkaline phosphatase normal was 142 per international unit, Normal values = [40 - 150].
On 08-Jun-2018, was 342 per international unit, Normal values = [40 - 130].
On 11-Jun-2018, Alkaline phosphatase increased was 433 per international unit, Normal values = [40 - 150].
On 28-May-2018, Bilirubin total normal was 8 micromole per litre, Normal values = [0 - 20].
On 01-Jun-2018, Bilirubin total normal was 9 micromole per litre, Normal values = [0 - 20].
On 04-Jun-2018, Bilirubin total normal was 6 micromole per litre, Normal values = [0 - 20].
On 08-Jun-2018, Bilirubin total increased was 40.6 micromole per litre, Normal values = [0 - 21].
On 11-Jun-2018, Bilirubin total normal was 19 micromole per litre, Normal values = [3 - 21].

DIAGNOSIS :
No diagnosis was reported.

OUTCOME :
The patient is recovering from Hepatic dysfunction NOS.

RELATEDNESS / EXPECTEDNESS :
No information about relatedness were reported.
No information about expectedness were reported.

CAUSALITY ASSESSMENTS :
Sponsor assessed the relationship of the Hepatic dysfunction NOS to the SELICICLIB | 800 | milligram as .
Investigator assessed the relationship of the Hepatic dysfunction NOS to the SELICICLIB | 800 | milligram as Reasonable possibility.

STATUS OF THE REPORT :
No closed / More information is awaited.

ANNEX 9: Statistical analysis plan

The ROSCO-CF Study

A Phase 2, dose ranging, multicenter, double-blind, placebo controlled study to evaluate safety and effects of seliciclib (R-roscovitine) in adults subjects with Cystic Fibrosis, carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation and chronically infected with Pseudomonas aeruginosa, a study involving 36 CF patients (24 treated, 12 controls). ROSCO-CF

Statistical analyses Repport

Principal investigator:
Dr Gilles RAULT Date16/01/2019 Signature

Prepared by :
Unité de Gestion des Données (UGD)
DRCI - CHRU de Brest
29 609 Brest Cedex

Biostatistician :
Florence GATINEAU Date16/01/2019 Signature

Emmanuel NOWAK

Writing date : 14.12.2018

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1. Introduction

The cyclin-dependent kinase (CDK) inhibitor seliciclib (roscovitine) is a clinical drug which has been developed to treat various cancers (Meijer et al., 1997; review in Meijer & Raymond, 2003; Bruyère and Meijer, 2013; Meijer et al., 2016). Two independent discoveries suggested potential beneficial effects of seliciclib for chronically infected CF patients (Norez et al., 2014; Riazanski et al., 2016; review in Meijer et al., 2016). As 500 patients (cancer patients and healthy volunteers) had already been treated with seliciclib, some solid safety data was available and allowed us to propose a clinical trial in CF patients. It was therefore decided to investigate the safety of seliciclib in chronically infected CF patients, as the first objective. A secondary objective was to investigate whether signs of efficacy at the infection and inflammatory levels could be detected in this small trial.

2. Study presentation

2.1. Study design and plan description

This is a phase II, dose ranging, multicenter, randomized, double-blind, placebo-controlled study.

2.2. Objectifs de l'étude

2.2.1. Primary objective

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 carrying 2 Cystic Fibrosis causing mutations with at least F508del mutation.

2.2.2. Secondary objectives

The secondary objecrtives are :

- To assess microbiological levels of infection by Pseudomonas aeruginosa;
- To assess pharmacokinetics of roscovitine and its M3 metabolite and pharmacodynamics;
- To assess the levels of pro- and anti- inflammatory cytokines some of which are known to be modified by roscovitine;
- To assess roscovitine target engagement by measurement of the expression level of Mcl-1 at day 1 and day 5, a survival factor expressed in neutrophils, the degradation of which is triggered by roscovitine, leading to apoptotic cell death.

2.3. Inclusion criteria

Patients eligible for inclusion in this study have to fulfill all of the following criteria:

- Male or female aged over 18 years of age on the date of informed consent
- Diagnosed CF patients. Confirmed diagnosis of CF is defined as (Rosenstein and Cutting, 1998):
    - A sweat chloride value 60 mmol/L by quantitative pilocarpine iontophoresis OR 2 CF-causing mutations
    - AND chronic sinopulmonary disease OR gastrointestinal/nutritional abnormalities
- Patients carrying 2 Cystic Fibrosis causing mutations with at least one F508del-CFTR mutation, genotype to be confirmed at screening;
- Forced expiratory volume at 1 second (FEV1) 40% of normal predicted values for age, sex and height based on the Knudson equation;
- FEV1 at Day 1 must be within 15% of FEV1 at Screening. If FEV1 at Day 1 is not within 15% of FEV1 at Screening, Visit 2 can be repeated within 7 days and rescheduled once;
- Chronic lung Pseudomonas aeruginosa infection according to the definition from the French Consensus Conference [ ] as recommended by the Committee for Medicinal Products for

Human use (CMPH) of the European Medicines Agency (EMA) [ ].Clinically stable CF disease in the opinion of the investigator;

- Able to understand and comply with all protocol requirements, restrictions and instructions and likely to complete the study as planned (as judged by the investigator);
- Provide written informed consent prior to the performance of any study-related procedure;
- Be affiliated to health insurance;
- Male subjects and female subjects of childbearing potential who engage in heterosexual intercourse must agree to use protocol specified method(s) of contraception as described in 7.7.7 Contraception and pregnancy.

2.4. Exclusion criteria

Patients fulfilling any of the following criteria are not eligible for inclusion in this study:

- Acute upper or lower respiratory infection, pulmonary exacerbation or changes in therapy (including antibiotics) for pulmonary disease within 4 weeks before V2
- Recent patient reported history of
- non recovered viral upper respiratory tract infection
- solid organ or hematological transplantation
- Undergone major surgery within 1 month prior to screening
- Currently treated allergic broncho-pulmonary aspergillosis (ABPA)
- Diabetic patients whose blood glucose is poorly controlled as evidenced by HbA1C >8%
- Hemoptysis more than 60 mL at any time within 4 weeks prior to first study drug administration (V2)
- History of any other comorbidity that, in the opinion of the investigator, might confound the results of the study or pose an additional risk in administering study drug to the subject.
- Any other clinically significant conditions (not associated with the study indication) at Screening (V1) which might interfere with the assessment of this study
- Any of the following abnormal laboratory values at screening:
    - Hemoglobin <10 g/dL
    - Abnormal liver function defined as any 3 or more of the following:
        - >1.5 x upper limit of normal (ULN) aspartate aminotransferase (AST)
        - >1.5 x ULN alanine aminotransferase (ALT)
        - ≥3 x ULN gamma-glutamyl transpeptidase
        - ≥3 x ULN alkaline phosphatase
        - Or ≥2 x ULN total biliburin
    - Serum K+ <3,5 mmol/L
    - Abnormal renal function defined as a creatinine clearance <50 mL/min/m2 / glomerular filtration rate ≤50 mL/min/1,73 m2 (calculated by the Modification of Diet in Renal Disease Study Equation) (Levey et al, 1999, 2006)
- Any clinically significant laboratory abnormalities (not associated with the study indication) at screening that would interfere with the study assessment or pose an undue risk for the subject (as judged by the investigator)
- Patients who have clinically significant impairment in cardiovascular function or are at risk thereof, as evidenced by:
    - Congestive heart failure (NYHA Class III or IV), unstable angina, sustained ventricular tachycardia, clinically significant bradycardia, high grade AV block, history of acute MI less than one year prior to study entry
    - A 12- lead ECG at screening demonstrating QTcF>450 or showing clinically significant abnormality including prolonged QT. If the QTcF exceeds 450 msec for the screening ECG, the ECG should be repeated 2 more times during the screening period, and the average of the 3 QTcF values should be used to determine the subject's eligibility.
    - History of syncope or family history of idiopathic sudden death
    - Risk factors for Torsades de Pointes such as uncorrected hypokalemia, uncorrected hypomagnesemia, cardiac failure
- Concomitant disease(s) that could prolong the QT interval.
- Patients with a history of alcohol or drug abuse in the past year, including but not limited to tobacco, cannabis, cocaine, and opiates as deemed by investigator
- Patients with a history of noncompliance to medical regimens and patients or caregivers who are considered potentially unreliable
- Use of one (or several) prohibited medications and/or food (Section 6.6) within 30 days prior to Screening (V1)

- Administration of any investigational drug within 30 days prior to Screening (V1) or 5 half-lives, whichever is longer
- Use of systemic anti-pseudomonal antibiotics within 28 days prior to first study drug administration (V2). However use of inhaled anti-pseudomonal antibiotic treatment is allowed if initiated for more than 28 days.
- Use of loop diuretics within 7 days prior to first study drug administration (V2)
- Patients with galactose intolerance, the Lapp lactase deficiency or malabsorption of glucose and galactose
- Pregnant or nursing females: females of childbearing potential must have a negative pregnancy test at screening
- Sexually active subjects of reproductive potential who are not willing to follow the contraception requirement (Section 7.7.7).

2.5. Sample Size

The same sample size was proposed for previous studies in the same therapeutic area with similar objectives (ClinicalTrials.gov Identifier: NCT01944735).
This trial is conducted mainly to evaluate the safety of roscovitine and define the most adapted dose for further phase II studies. It helps determine the maximum dose that can be given safely. In general such phase I/II trials enroll small numbers of patients (20 / 40). Given the pilot nature of the study on a rare disease, the sample size was set as follows: 8 patients per each dose (treatment group) and 4 controls for each dose (control group).
Expected numbers of patients eligible in the centers are about 2 in each centers except in Paris: 8, Lyon: 6, Lille: 5, Montpellier: 3, Reims: 8, Nice: 8, Bordeaux: 8 and Angers 6

3. Study population

The analyzes will be carried out according to the treatment received (+ in intention to treat if necessary).

4. Statistical methods and data analysis

4.1. Planned analyses

The final analysis will be realised after data freezing following the data review. The data will be analysed by UGD (Unité de Gestion des Données) of CHRU de Brest. A statistical analyses report will be provided to the principal investigator. The statistical analyses will be assessed using SAS software 9.4. The tests will be realized with alpha = 5%.

4.2. Principal analyses

- Individual characteristics at inclusion

Individual characteristics at inclusion were described by group and according to treatment received (Placebo or Roscovitine): frequenct and percentage were computed for qualitatives variables; number, mean, standard deviation, median, quartiles, minimum and maximum for quantitative variables.

- Description of adverse events

For each group, adverse events were described according to: grade, SOC, Meddra. The number and percentage of each combination Grade-SOC-Meddra was computed.

4.3. Secondary analyses

- Changes in extractions parameters: hematology, biochemistry, urine

For each group, parameters evolution for extractions (hematology, biochemistry, urine) between the first (D0) and the last (D28) measurement were compared in mean according to treatment (Roscovitine vs Placeboà. Tests were also realized to compare the mean evolutions of both treatment groups (student t test or Wicoxon test).

Graphics :

- For each parameters and each group, individual evolution was represented (D0 to D28 in abscissa ; parameter values in ordinate)

- Pharmacokinetics

For each group, Roscovitine and M3 pharamcokinetics were assessed. Tests were then realized to compare the means of both treatment groups (student t test or Wicoxon test), for each parmacokinectics parameter.

- Efficacy criteria

Placebo of each group were pooled (0 mg / 200 mg / 400 mg / 800 mg). The evolution of amount of PA, of CRP, of CFQ-R domains, of VEMS, of Chlore, of BMI and cythokines levels were compared according to treatment dose received (0 mg / 200 mg / 400 mg / 800 mg). An Anova was realized to determin if there is a significant difference between the mean evolutions of each efficacy criteria according to treatment dose received.

Graphics :

- For each parameter, the difference of D28-D0 values for each groupe according to treatment dose received was represented (Roscovitine dose: 0mg, 200mg, 400mg et 800mg in abscissa; the difference of D28-D0 in ordinate)

4.4. Disposition of patients

See flow chart

4.5. Protocol violations / significant deviations

No significant deviation.

4.6. SAP deviation

No significant deviation

4.7. Changes made to the protocol

No significant change.

5. Statistical software

Statistical analyzes were performed with SAS Version 9.4 software.

6. Tables and figures

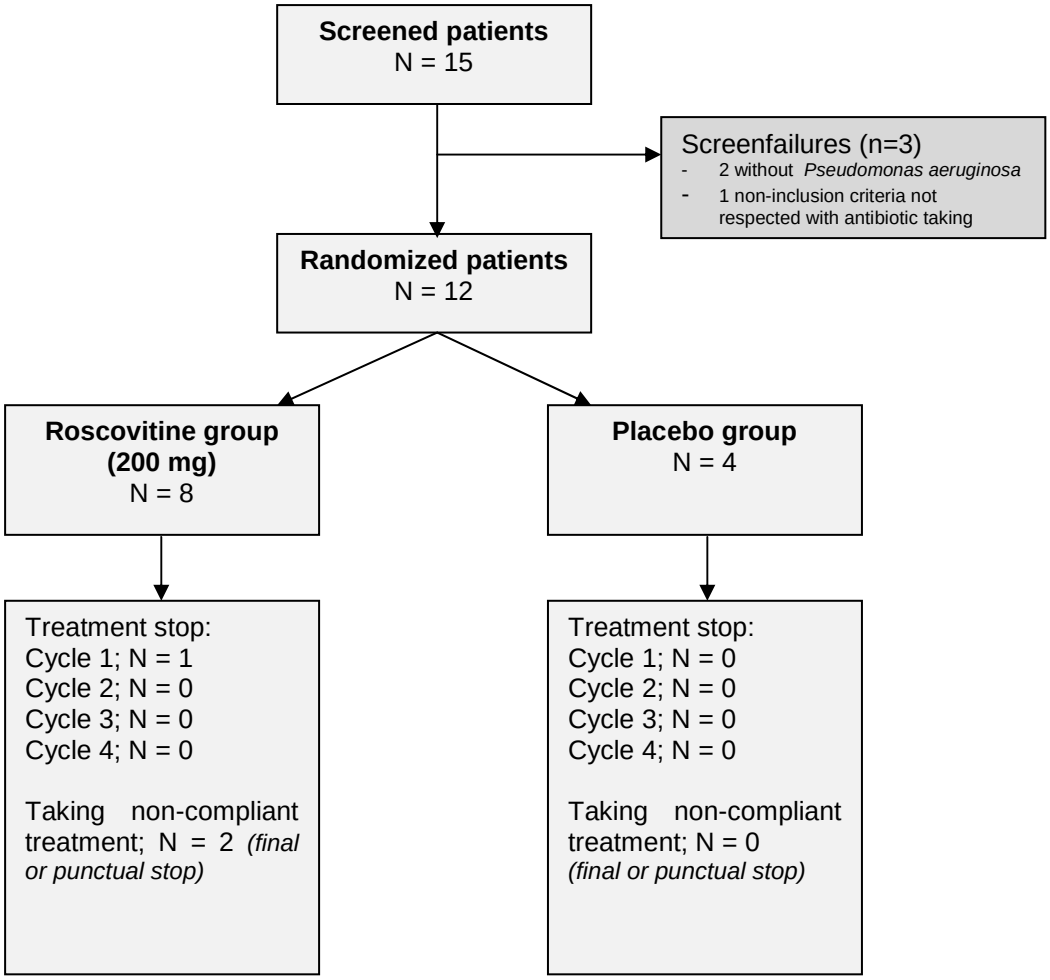


Figure 4 : Flow Chart – Groupe 1 (dose 200 mg)

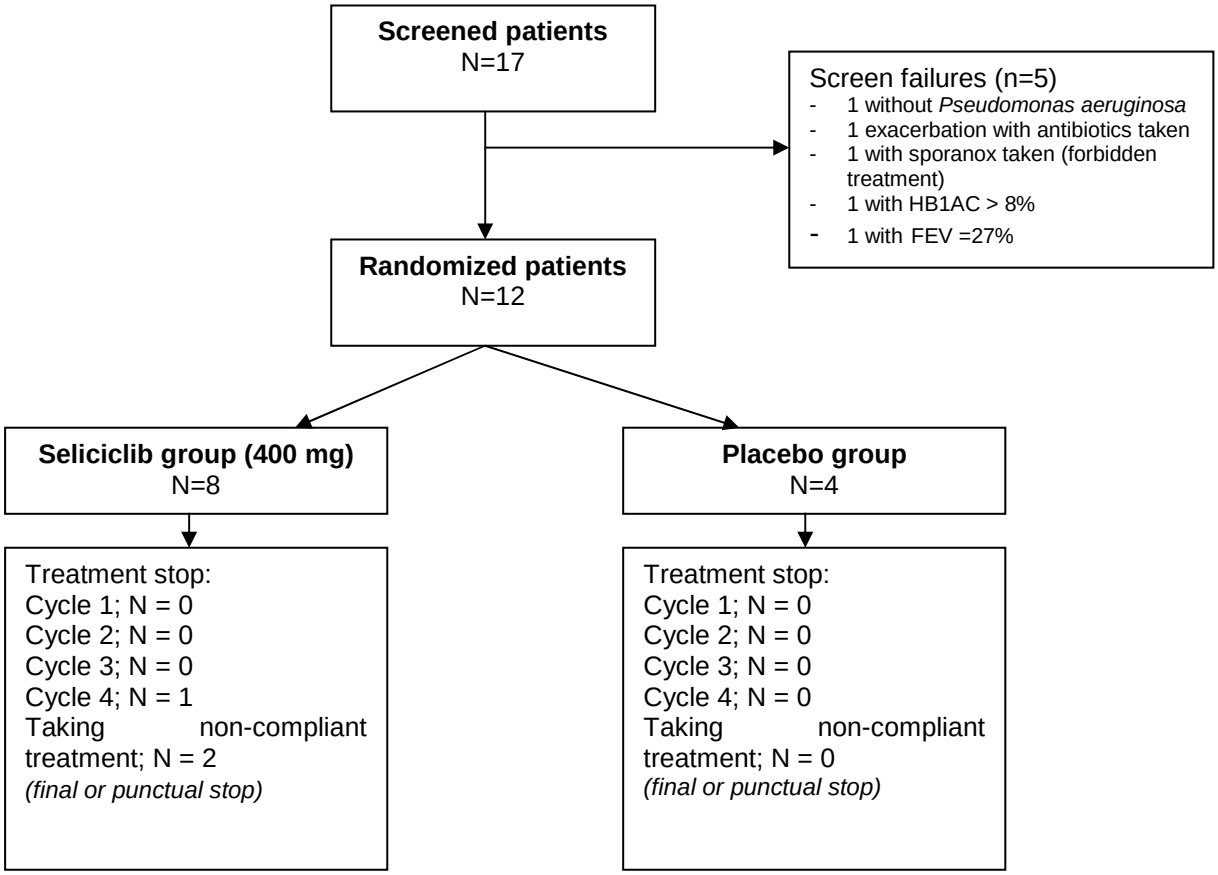


Figure 5 : Flow Chart – Groupe 2 (dose 400 mg)

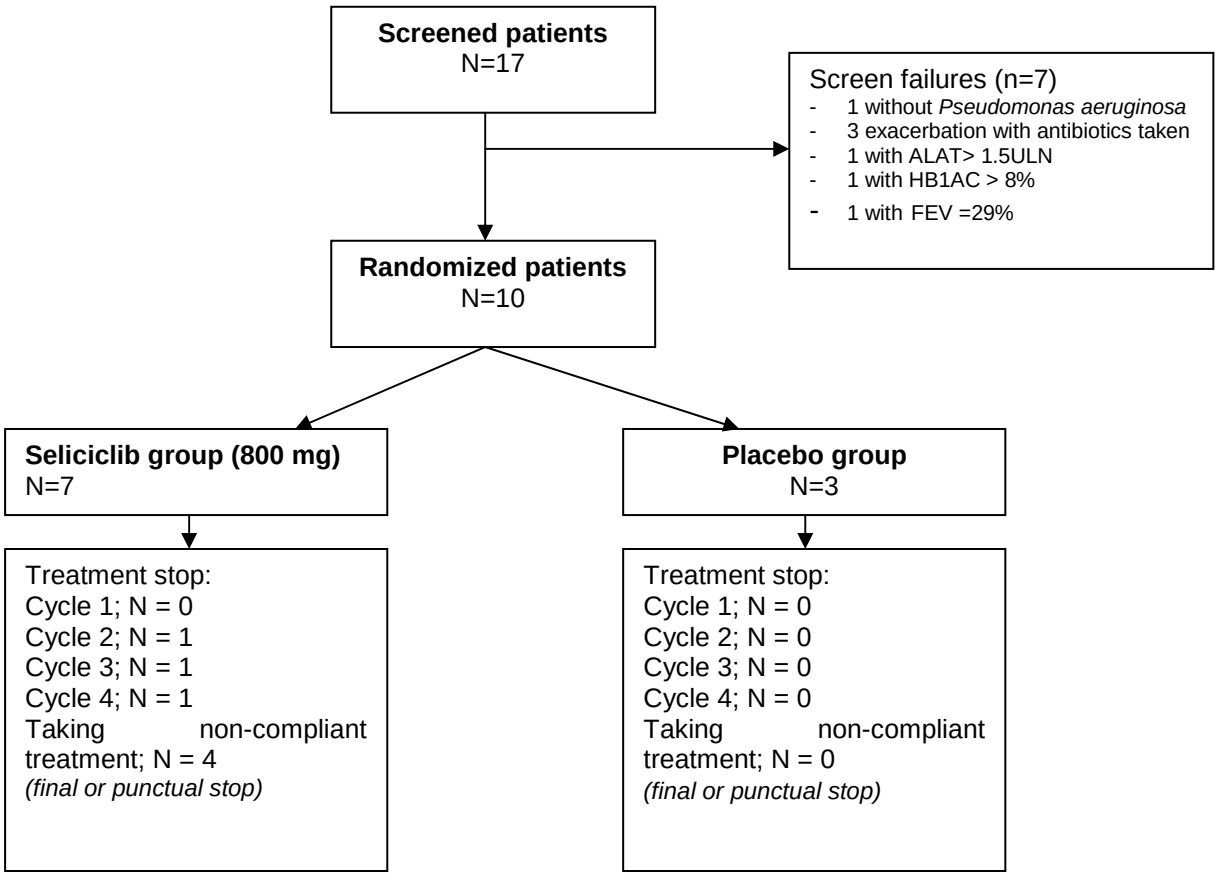


Figure 6 : Flow Chart – Groupe 3 (dose 800 mg)

1. CHARATERISTICS AT INCLUSION

Table 1 : Individual charateristics at inclusion – Group 1 (dose 200mg)

		Placebo group (N=4)	Roscovitine group (N=8)
Age	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	29.25 +/- 3.30	34.75 +/- 7.38
	Median (q1;q3)	29.0 (26.5;32.0)	34.0 (28.5;37.5)
	Min;Max	26;33	28;50
Sex	Man	0 (0.0%)	5 (62.5%)
	Woman	4 (100.0%)	3 (37.5%)
Mutation	homozygous	1 (25.0%)	3 (37.5%)
	heterozygous	3 (75.0%)	5 (62.5%)
Respiratory rate	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	15.00 +/- 4.97	16.63 +/- 2.97
	Median (q1;q3)	15.0 (11.5;18.5)	17.0 (14.5;19.0)
	Min;Max	9;21	12;20
BMI	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	19.88 +/- 1.69	22.75 +/- 3.76
	Median (q1;q3)	19.7 (18.7;21.0)	22.2 (20.3;22.9)
	Min;Max	18;22	20;32
Amount of PA	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	5.75 +/- 1.89	6.00 +/- 0.76
	Median (q1;q3)	6.5 (4.5;7.0)	6.0 (5.5;6.5)
	Min;Max	3;7	5;7
Forced Expiratory Volume (FEV)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	62.45 +/- 17.37	55.73 +/- 14.64
	Median (q1;q3)	66.9 (50.7;74.3)	53.5 (46.0;59.0)
	Min;Max	38;78	41;88
Forced Vital Capacity (FVC)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	79.57 +/- 6.03	80.86 +/- 13.32
	Median (q1;q3)	79.1 (75.0;84.2)	83.5 (71.0;92.5)
	Min;Max	73;87	59;94
DEM25-75	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	38.65 +/- 24.43	28.33 +/- 25.82
	Median (q1;q3)	30.3 (22.6;54.8)	21.5 (14.1;27.5)
	Min;Max	20;74	11;90
Hematology			
Hemoglobin result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	13.35 +/- 0.74	13.98 +/- 1.96
	Median (q1;q3)	13.3 (12.9;13.9)	14.8 (12.8;15.2)
	Min;Max	13;14	11;16
Red blood cell result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	4.60 +/- 0.42	4.96 +/- 0.42
	Median (q1;q3)	4.5 (4.3;4.9)	5.1 (5.0;5.2)
	Min;Max	4;5	4;5
Hematocrit result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	40.10 +/- 2.82	42.19 +/- 4.30
	Median (q1;q3)	40.6 (38.2;42.1)	44.0 (39.3;45.0)
	Min;Max	36;43	35;46
VGM result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	87.38 +/- 3.96	84.73 +/- 5.29
	Median (q1;q3)	86.7 (85.0;89.8)	86.1 (85.3;87.6)
	Min;Max	83;93	72;88
reticulocytes result	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	56.79 +/- 21.51	66.73 +/- 11.85
	Median (q1;q3)	56.8 (41.6;72.0)	69.0 (54.0;75.3)
	Min;Max	42;72	52;85
platelets result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	282.00 +/- 46.41	309.00 +/- 84.86
	Median (q1;q3)	287.5 (249.5;314.5)	277.0 (247.5;378.5)
	Min;Max	221;332	212;454

		Placebo group (N=4)	Roscovitine group (N=8)
leukocytes result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	7.47 +/- 2.96	9.74 +/- 4.25
	Median (q1;q3)	8.4 (5.6;9.4)	8.1 (7.0;11.8)
	Min;Max	3;10	6;18
eosinophils result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.14 +/- 0.04	0.26 +/- 0.19
	Median (q1;q3)	0.1 (0.1;0.2)	0.2 (0.1;0.3)
	Min;Max	0;0	0;1
basophils result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.05 +/- 0.04	0.06 +/- 0.03
	Median (q1;q3)	0.0 (0.0;0.1)	0.1 (0.0;0.1)
	Min;Max	0;0	0;0
neutrophils result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	4.69 +/- 2.40	6.57 +/- 4.35
	Median (q1;q3)	5.3 (2.9;6.4)	4.6 (4.0;9.2)
	Min;Max	1;7	3;14
lymphocytes result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	2.12 +/- 0.58	2.15 +/- 0.79
	Median (q1;q3)	2.1 (1.7;2.5)	1.9 (1.6;2.5)
	Min;Max	1;3	2;4
monocytes result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.51 +/- 0.17	0.70 +/- 0.21
	Median (q1;q3)	0.5 (0.4;0.6)	0.7 (0.6;0.7)
	Min;Max	0;1	0;1
TCA result	N (N missing)	2 (2 missing)	8 (0 missing)
	Mean +/- SD	32.45 +/- 1.48	32.08 +/- 2.75
	Median (q1;q3)	32.5 (31.4;33.5)	31.6 (30.4;34.0)
	Min;Max	31;34	28;37
Control TCA result	N (N missing)	2 (2 missing)	8 (0 missing)
	Mean +/- SD	31.00 +/- 4.24	31.31 +/- 2.58
	Median (q1;q3)	31.0 (28.0;34.0)	31.3 (29.0;34.0)
	Min;Max	28;34	28;34
TP result	N (N missing)	1 (3 missing)	7 (1 missing)
	Mean +/- SD	99.00 +/- .	97.00 +/- 10.46
	Median (q1;q3)	99.0 (99.0;99.0)	97.0 (88.0;106.0)
	Min;Max	99;99	82;113
INR result	N (N missing)	1 (3 missing)	5 (3 missing)
	Mean +/- SD	1.00 +/- .	0.98 +/- 0.05
	Median (q1;q3)	1.0 (1.0;1.0)	1.0 (1.0;1.0)
	Min;Max	1;1	1;1
Biochemistry			
Blood Sugar result	N (N missing)	2 (2 missing)	8 (0 missing)
	Mean +/- SD	4.23 +/- 2.09	4.81 +/- 0.63
	Median (q1;q3)	4.2 (2.8;5.7)	4.6 (4.4;5.1)
	Min;Max	3;6	4;6
Urea result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	3.88 +/- 1.08	4.89 +/- 1.41
	Median (q1;q3)	4.2 (3.1;4.7)	4.8 (3.8;6.0)
	Min;Max	2;5	3;7
creatinine result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	58.75 +/- 13.33	62.63 +/- 10.88
	Median (q1;q3)	58.0 (48.5;69.0)	62.0 (54.0;72.0)
	Min;Max	44;75	48;77
Sodium result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	140.25 +/- 2.06	138.75 +/- 1.75
	Median (q1;q3)	140.5 (138.5;142.0)	138.5 (138.0;139.5)
	Min;Max	138;142	136;142
Potassium result	N (N missing)	4 (0 missing)	8 (0 missing)

		Placebo group (N=4)	Roscovitine group (N=8)
	Mean +/- SD	3.97 +/- 0.21	4.50 +/- 0.43
	Median (q1;q3)	4.0 (3.8;4.1)	4.5 (4.2;4.7)
	Min;Max	4;4	4;5
Calcium result	N (N missing)	3 (1 missing)	7 (1 missing)
	Mean +/- SD	2.30 +/- 0.13	2.36 +/- 0.07
	Median (q1;q3)	2.3 (2.2;2.4)	2.4 (2.3;2.4)
	Min;Max	2;2	2;2
Chlorine result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	101.50 +/- 1.73	100.63 +/- 2.77
	Median (q1;q3)	102.0 (100.5;102.5)	100.0 (99.0;101.0)
	Min;Max	99;103	98;107
Magnesium result	N (N missing)	2 (2 missing)	8 (0 missing)
	Mean +/- SD	0.88 +/- 0.02	0.78 +/- 0.03
	Median (q1;q3)	0.9 (0.9;0.9)	0.8 (0.8;0.8)
	Min;Max	1;1	1;1
CO2 result	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	25.10 +/- 1.65	26.11 +/- 2.17
	Median (q1;q3)	25.0 (23.5;26.8)	26.9 (24.9;27.3)
	Min;Max	24;27	22;29
Phosphorus result	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	1.12 +/- 0.03	1.11 +/- 0.19
	Median (q1;q3)	1.1 (1.1;1.1)	1.1 (1.0;1.3)
	Min;Max	1;1	1;1
Total bilirubin result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	5.98 +/- 2.60	9.46 +/- 11.05
	Median (q1;q3)	5.1 (4.5;7.5)	5.9 (3.5;9.0)
	Min;Max	4;10	3;36
Indirect bilirubin result	N (N missing)	1 (3 missing)	0 (8 missing)
	Mean +/- SD	4.10 +/- .	. +/- .
	Median (q1;q3)	4.1 (4.1;4.1)	. (.;.)
	Min;Max	4;4	.;.
PAL result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	82.25 +/- 8.58	98.63 +/- 17.19
	Median (q1;q3)	84.5 (77.0;87.5)	102.0 (83.0;109.0)
	Min;Max	70;90	75;126
ASAT result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	17.75 +/- 3.30	23.00 +/- 7.71
	Median (q1;q3)	18.0 (15.0;20.5)	19.5 (18.0;29.5)
	Min;Max	14;21	14;36
ALAT result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	19.75 +/- 2.99	23.63 +/- 17.26
	Median (q1;q3)	19.0 (18.0;21.5)	17.0 (14.5;23.5)
	Min;Max	17;24	14;65
LDH result	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	167.00 +/- 14.14	208.57 +/- 56.29
	Median (q1;q3)	167.0 (157.0;177.0)	190.0 (160.0;258.0)
	Min;Max	157;177	148;302
GGT result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	10.75 +/- 2.75	16.25 +/- 2.96
	Median (q1;q3)	10.5 (8.5;13.0)	15.0 (14.0;19.0)
	Min;Max	8;14	13;21
Total Proteins result	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	75.93 +/- 5.66	75.53 +/- 2.42
	Median (q1;q3)	75.0 (70.8;82.0)	76.8 (73.0;77.4)
	Min;Max	71;82	72;78
Albumin result	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	42.60 +/- 4.08	42.79 +/- 2.88
	Median (q1;q3)	44.0 (38.0;45.8)	42.5 (41.3;44.7)

		Placebo group (N=4)	Roscovitine group (N=8)
	Min;Max	38;46	38;47
CK result	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	74.33 +/- 32.13	86.00 +/- 27.73
	Median (q1;q3)	71.0 (44.0;108.0)	79.0 (75.0;96.0)
	Min;Max	44;108	47;141
CRP result	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	4.63 +/- 3.56	4.45 +/- 2.63
	Median (q1;q3)	5.0 (0.9;8.0)	5.5 (1.9;6.5)
	Min;Max	1;8	1;7
Urine			
Glucose result	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	0.20 +/- 0.20	0.47 +/- 0.86
	Median (q1;q3)	0.2 (0.0;0.4)	0.2 (0.1;0.3)
	Min;Max	0;0	0;3
Urinary protein result	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	0.06 +/- 0.05	0.08 +/- 0.03
	Median (q1;q3)	0.0 (0.0;0.1)	0.1 (0.0;0.1)
	Min;Max	0;0	0;0
Microalbumin result	N (N missing)	1 (3 missing)	7 (1 missing)
	Mean +/- SD	12.00 +/- .	7.71 +/- 4.23
	Median (q1;q3)	12.0 (12.0;12.0)	7.0 (3.0;12.0)
	Min;Max	12;12	3;12
Potassium result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	19.45 +/- 12.72	61.13 +/- 42.79
	Median (q1;q3)	19.0 (9.0;29.9)	44.5 (26.5;103.0)
	Min;Max	6;34	18;123
Sodium result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	65.50 +/- 48.58	106.50 +/- 56.77
	Median (q1;q3)	67.0 (23.5;107.5)	85.5 (68.0;138.0)
	Min;Max	20;108	48;221
Urea result	N (N missing)	4 (0 missing)	5 (3 missing)
	Mean +/- SD	171.04 +/- 193.62	145.40 +/- 93.26
	Median (q1;q3)	94.5 (44.5;297.6)	152.0 (69.0;159.0)
	Min;Max	42;453	57;290
Creatinine result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	5.09 +/- 4.56	8.25 +/- 8.64
	Median (q1;q3)	4.0 (1.6;8.6)	5.4 (2.7;10.9)
	Min;Max	1;11	1;27
Uric acid result	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	1.24 +/- 1.16	100.25 +/- 260.06
	Median (q1;q3)	1.2 (0.4;2.1)	2.2 (1.3;3.2)
	Min;Max	0;2	1;690
Blood result	Missing	2 (50.0%)	1 (12.5%)
	Absent	2 (100.0%)	6 (85.7%)
	Présent	0 (0.0%)	1 (14.3%)
Density result	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	1.02 +/- 0.00	1.02 +/- 0.01
	Median (q1;q3)	1.0 (1.0;1.0)	1.0 (1.0;1.0)
	Min;Max	1;1	1;1
ketone result	Missing	2 (50.0%)	1(12.5%)
	Negative	2 (100.0%)	7 (100.0%)
bilirubin result	Missing	4 (100.0%)	5 (62.5%)
	Negative	0 (0.0%)	3 (100.0%)
leukocytes result	Missing	2 (50.0%)	1 (12.5%)
	Traces	1 (50.0%)	0 (0.0%)
	Negative	1 (50.0%)	7 (100.0%)
Nitrite result	Missing	2 (50.0%)	1 (12.5%)
	Negative	2 (100.0%)	7 (100.0%)

		Placebo group (N=4)	Roscovitine group (N=8)
History			
History of abnormal exocrine pancreatic function	NO	0 (0.0%)	1 (12.5%)
	YES	4 (100.0%)	7 (87.5%)
History of hepatic enzyme elevation (1.5 times the upper limit)	NO	4 (100.0%)	8 (100.0%)
History of cirrhosis	NO	4 (100.0%)	8 (100.0%)
History of portal hypertension	NO	4 (100.0%)	8 (100.0%)
History of digestive hemorrhage	NO	4 (100.0%)	8 (100.0%)
History of glucose intolerance	NO	3 (75.0%)	6 (75.0%)
	YES	1 (25.0%)	2 (25.0%)
History of non-insulin-treated diabetes	NO	4 (100.0%)	8 (100.0%)
History of diabetes treated with insulin	NO	3 (75.0%)	7 (87.5%)
	YES	1 (25.0%)	1 (12.5%)
History of degenerative complications of diabetes	NO	4 (100.0%)	8 (100.0%)
History of gallstones	NO	4 (100.0%)	8 (100.0%)
History of Acute Pancreatitis	NO	4 (100.0%)	8 (100.0%)
History of Distal Intestinal Obstruction Syndrome	NO	3 (75.0%)	8 (100.0%)
	YES	1 (25.0%)	0 (0.0%)
History of treated gastroesophageal reflux	NO	1 (25.0%)	5 (62.5%)
	YES	3 (75.0%)	3 (37.5%)
History of hemoptysis	NO	3 (75.0%)	7 (87.5%)
	YES	1 (25.0%)	1 (12.5%)
History of nasal polyps	NO	2 (50.0%)	7 (87.5%)
	YES	2 (50.0%)	1 (12.5%)
History of pneumothorax	NO	4 (100.0%)	8 (100.0%)
History of Thoracic Drain for Pneumothorax	NO	4 (100.0%)	8 (100.0%)
History of arthropathy	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)
History of bone pathology	NO	4 (100.0%)	6 (75.0%)
	YES	0 (0.0%)	2 (25.0%)
History of urinary incontinence	NO	3 (75.0%)	8 (100.0%)
	YES	1 (25.0%)	0 (0.0%)
History of cancer	NO	4 (100.0%)	8 (100.0%)
History of asthma	NO	4 (100.0%)	6 (75.0%)
	YES	0 (0.0%)	2 (25.0%)
History of depression	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)
History of end stage renal failure	NO	4 (100.0%)	8 (100.0%)
History of deafness / hearing loss	NO	3 (75.0%)	6 (75.0%)
	YES	1 (25.0%)	2 (25.0%)

Table 2 : Individual charateristics at inclusion – Group 2 (dose 400mg)

		Placebo group (N=4)	Roscovitine group (N=8)
age	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	35.75 +/- 13.15	31.75 +/- 7.38
	Median (q1;q3)	36.0 (25.0;46.5)	33.0 (24.5;38.0)
	Min;Max	21;50	22;41
Sex	Man	3 (75.0%)	4 (50.0%)
	Woman	1 (25.0%)	4 (50.0%)
Mutation	homozygous	2 (50.0%)	1 (12.5%)
	heterozygous	2 (50.0%)	7 (87.5%)
Respiratory rate	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	18.00 +/- 4.24	20.86 +/- 5.52
	Median (q1;q3)	19.5 (15.0;21.0)	24.0 (16.0;26.0)
	Min;Max	12;21	12;26
BMI	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	22.14 +/- 2.37	21.06 +/- 2.45
	Median (q1;q3)	22.0 (20.4;23.9)	20.6 (19.6;23.2)
	Min;Max	19;25	17;25
Amount of PA	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	6.75 +/- 1.26	5.88 +/- 1.73
	Median (q1;q3)	7.0 (6.0;7.5)	6.5 (5.5;7.0)
	Min;Max	5;8	2;7
FEV	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	42.50 +/- 7.33	50.50 +/- 16.37
	Median (q1;q3)	41.5 (37.0;48.0)	46.0 (39.5;59.0)
	Min;Max	35;52	32;83
FVC	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	77.00 +/- 6.68	68.75 +/- 18.73
	Median (q1;q3)	76.0 (72.5;81.5)	73.0 (56.0;77.0)
	Min;Max	70;86	38;100
DEM25-75	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	14.75 +/- 7.80	26.25 +/- 12.30
	Median (q1;q3)	12.0 (9.5;20.0)	22.5 (21.0;33.0)
	Min;Max	9;26	8;49
Hematology			
Hemoglobin result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	14.58 +/- 0.49	14.30 +/- 1.53
	Median (q1;q3)	14.4 (14.3;14.9)	14.1 (13.4;15.7)
	Min;Max	14;15	12;16
Red blood cell result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	4.98 +/- 0.38	5.21 +/- 0.47
	Median (q1;q3)	5.0 (4.7;5.3)	5.2 (5.0;5.4)
	Min;Max	5;5	5;6
Hematocrit result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	43.15 +/- 2.57	43.50 +/- 4.03
	Median (q1;q3)	42.0 (41.8;44.5)	43.3 (41.0;46.8)
	Min;Max	42;47	37;49
VGM result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	86.98 +/- 4.52	83.75 +/- 3.99
	Median (q1;q3)	87.4 (84.1;89.9)	82.6 (80.6;86.4)
	Min;Max	81;92	80;91
reticulocytes result	N (N missing)	3 (1 missing)	2 (6 missing)
	Mean +/- SD	54.81 +/- 9.41	68.44 +/- 24.66
	Median (q1;q3)	53.0 (46.4;65.0)	68.4 (51.0;85.9)
	Min;Max	46;65	51;86
platelets result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	285.25 +/- 37.03	302.38 +/- 79.25
	Median (q1;q3)	287.5 (258.0;312.5)	286.5 (234.0;359.5)
	Min;Max	239;327	216;443

		Placebo group (N=4)	Roscovitine group (N=8)
leukocytes result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	9.58 +/- 1.42	12.28 +/- 4.51
	Median (q1;q3)	9.6 (8.5;10.6)	14.0 (7.5;15.6)
	Min;Max	8;11	6;18
eosinophils result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.17 +/- 0.15	0.13 +/- 0.07
	Median (q1;q3)	0.1 (0.1;0.2)	0.1 (0.1;0.2)
	Min;Max	0;0	0;0
basophils result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.03 +/- 0.02	0.05 +/- 0.04
	Median (q1;q3)	0.0 (0.0;0.0)	0.0 (0.0;0.1)
	Min;Max	0;0	0;0
neutrophils result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	6.65 +/- 1.59	9.27 +/- 4.65
	Median (q1;q3)	6.8 (5.3;8.0)	10.4 (4.8;12.9)
	Min;Max	5;8	3;15
lymphocytes result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	1.79 +/- 0.77	2.19 +/- 0.73
	Median (q1;q3)	1.8 (1.1;2.5)	2.2 (1.6;2.9)
	Min;Max	1;3	1;3
monocytes result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.92 +/- 0.34	0.65 +/- 0.20
	Median (q1;q3)	0.9 (0.7;1.1)	0.6 (0.5;0.8)
	Min;Max	1;1	0;1
TCA result	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	29.20 +/- 6.19	33.90 +/- 5.31
	Median (q1;q3)	29.3 (23.9;34.6)	37.5 (27.7;38.1)
	Min;Max	24;35	27;39
Control TCA result	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	30.00 +/- 3.14	31.89 +/- 1.83
	Median (q1;q3)	29.3 (27.5;32.5)	32.0 (31.0;33.9)
	Min;Max	28;34	29;34
TP result	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	97.25 +/- 3.40	95.67 +/- 5.61
	Median (q1;q3)	98.0 (94.5;100.0)	98.0 (92.0;100.0)
	Min;Max	93;100	86;100
INR result	N (N missing)	2 (2 missing)	3 (5 missing)
	Mean +/- SD	1.00 +/- 0.00	1.08 +/- 0.09
	Median (q1;q3)	1.0 (1.0;1.0)	1.1 (1.0;1.2)
	Min;Max	1;1	1;1
Biochemistry			
Blood Sugar result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	4.46 +/- 1.02	5.29 +/- 1.43
	Median (q1;q3)	4.4 (3.8;5.1)	5.1 (4.6;5.9)
	Min;Max	3;6	3;8
Urea result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	4.30 +/- 0.54	4.60 +/- 1.09
	Median (q1;q3)	4.3 (3.9;4.8)	4.6 (3.7;5.2)
	Min;Max	4;5	3;7
creatinine result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	67.50 +/- 15.15	60.63 +/- 16.45
	Median (q1;q3)	74.0 (58.5;76.5)	60.0 (49.0;71.0)
	Min;Max	45;77	37;88
Sodium result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	140.50 +/- 1.29	139.13 +/- 1.73
	Median (q1;q3)	140.5 (139.5;141.5)	140.0 (138.0;140.0)
	Min;Max	139;142	136;141
Potassium result	N (N missing)	4 (0 missing)	8 (0 missing)

		Placebo group (N=4)	Roscovitine group (N=8)
	Mean +/- SD	4.25 +/- 0.08	4.02 +/- 0.28
	Median (q1;q3)	4.2 (4.2;4.3)	4.0 (3.8;4.3)
	Min;Max	4;4	4;4
Calcium result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	2.45 +/- 0.09	2.34 +/- 0.09
	Median (q1;q3)	2.4 (2.4;2.5)	2.4 (2.3;2.4)
	Min;Max	2;3	2;2
Chlorine result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	99.50 +/- 3.70	99.75 +/- 2.43
	Median (q1;q3)	100.0 (96.5;102.5)	99.5 (98.0;102.0)
	Min;Max	95;103	96;103
Magnesium result	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	0.82 +/- 0.03	0.80 +/- 0.03
	Median (q1;q3)	0.8 (0.8;0.9)	0.8 (0.8;0.8)
	Min;Max	1;1	1;1
CO2 result	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	27.50 +/- 4.34	27.12 +/- 2.82
	Median (q1;q3)	27.2 (24.8;30.3)	26.0 (26.0;28.7)
	Min;Max	23;33	24;32
Phosphorus result	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	1.08 +/- 0.22	1.02 +/- 0.12
	Median (q1;q3)	1.1 (0.9;1.2)	1.0 (1.0;1.1)
	Min;Max	1;1	1;1
Total bilirubin result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	7.63 +/- 2.38	6.96 +/- 4.12
	Median (q1;q3)	7.4 (6.0;9.3)	5.5 (4.5;8.5)
	Min;Max	5;11	3;16
Indirect bilirubin result	N (N missing)	1 (3 missing)	4 (4 missing)
	Mean +/- SD	3.00 +/- .	3.00 +/- 1.41
	Median (q1;q3)	3.0 (3.0;3.0)	2.5 (2.0;4.0)
	Min;Max	3;3	2;5
PAL result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	92.75 +/- 16.15	139.13 +/- 88.21
	Median (q1;q3)	87.5 (82.0;103.5)	108.0 (98.0;126.5)
	Min;Max	80;116	93;355
ASAT result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	18.25 +/- 4.57	31.25 +/- 30.10
	Median (q1;q3)	16.5 (15.5;21.0)	21.5 (15.5;31.0)
	Min;Max	15;25	11;103
ALAT result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	21.75 +/- 4.03	44.25 +/- 61.24
	Median (q1;q3)	22.0 (18.5;25.0)	15.5 (14.5;44.5)
	Min;Max	17;26	13;192
LDH result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	204.75 +/- 75.22	258.25 +/- 85.51
	Median (q1;q3)	185.0 (148.5;261.0)	246.0 (193.0;316.0)
	Min;Max	142;307	152;404
GGT result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	19.25 +/- 6.95	43.25 +/- 67.61
	Median (q1;q3)	19.0 (13.5;25.0)	20.5 (15.0;26.5)
	Min;Max	12;27	12;210
Total Proteins result	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	76.23 +/- 6.34	78.26 +/- 6.07
	Median (q1;q3)	77.1 (69.5;82.1)	79.5 (73.0;83.0)
	Min;Max	70;82	69;86
Albumin result	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	40.78 +/- 3.76	39.34 +/- 3.82
	Median (q1;q3)	40.9 (37.8;43.8)	40.0 (34.6;43.0)

		Placebo group (N=4)	Roscovitine group (N=8)
	Min;Max	36;45	34;43
CK result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	82.25 +/- 47.79	72.63 +/- 43.91
	Median (q1;q3)	72.5 (47.5;117.0)	70.5 (28.0;112.5)
	Min;Max	37;147	24;135
CRP result	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	15.83 +/- 10.25	31.05 +/- 36.46
	Median (q1;q3)	12.7 (8.3;23.4)	16.2 (5.3;48.8)
	Min;Max	8;30	4;104
Urine			
Glucose result	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	0.22 +/- 0.21	0.64 +/- 0.63
	Median (q1;q3)	0.2 (0.1;0.4)	0.5 (0.2;1.0)
	Min;Max	0;0	0;2
Urinary protein result	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	0.06 +/- 0.03	0.11 +/- 0.04
	Median (q1;q3)	0.0 (0.0;0.1)	0.1 (0.1;0.1)
	Min;Max	0;0	0;0
Microalbumin result	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	9.20 +/- 5.78	5.02 +/- 4.93
	Median (q1;q3)	9.0 (4.5;13.9)	3.0 (3.0;4.0)
	Min;Max	3;16	2;15
Potassium result	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	34.00 +/- 28.95	58.09 +/- 31.40
	Median (q1;q3)	24.5 (15.5;52.5)	52.0 (36.0;71.0)
	Min;Max	11;76	21;118
Sodium result	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	71.75 +/- 49.92	114.29 +/- 59.90
	Median (q1;q3)	79.5 (31.5;112.0)	98.0 (71.0;187.0)
	Min;Max	10;118	26;190
Urea result	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	182.73 +/- 118.76	285.55 +/- 111.46
	Median (q1;q3)	144.0 (111.0;254.5)	263.5 (227.1;408.0)
	Min;Max	87;356	131;420
Creatinine result	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	7.25 +/- 7.21	11.33 +/- 5.76
	Median (q1;q3)	4.2 (3.1;11.4)	10.0 (8.1;17.2)
	Min;Max	3;18	2;18
Uric acid result	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	2.13 +/- 2.43	3.45 +/- 1.83
	Median (q1;q3)	1.0 (0.8;3.4)	3.7 (2.0;4.1)
	Min;Max	1;6	1;6
Blood result	Absent	4 (100.0%)	7 (100.0%)
	Missing	0 (0.0%)	1 (12.5%)
Density result	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	1.02 +/- 0.01	1.01 +/- 0.00
	Median (q1;q3)	1.0 (1.0;1.0)	1.0 (1.0;1.0)
	Min;Max	1;1	1;1
ketone result	Missing	0 (0.0%)	1 (12.5%)
	Traces	0 (0.0%)	1 (14.3%)
	Negative	4 (100.0%)	6 (85.7%)
bilirubin result	Missing	3 (75.0%)	5 (62.5%)
	Negative	1 (100.0%)	3 (100.0%)
leukocytes result	Missing	0 (0.0%)	1 (12.5%)
	Positive	0 (0.0%)	1 (14.3%)
	Negative	4 (100.0%)	6 (85.7%)
Nitrite result	Missing	0 (0.0%)	1 (12.5%)
	Negative	4 (100.0%)	7 (100.0%)

		Placebo group (N=4)	Roscovitine group (N=8)
History			
History of abnormal exocrine pancreatic function	NO	0 (0.0%)	3 (37.5%)
	YES	4 (100.0%)	5 (62.5%)
History of hepatic enzyme elevation (1.5 times the upper limit)	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)
History of cirrhosis	NO	4 (100.0%)	8 (100.0%)
History of portal hypertension	NO	4 (100.0%)	8 (100.0%)
History of digestive hemorrhage	NO	4 (100.0%)	8 (100.0%)
History of glucose intolerance	NO	4 (100.0%)	5 (62.5%)
	YES	0 (0.0%)	3 (37.5%)
History of non-insulin-treated diabetes	NO	3 (75.0%)	7 (87.5%)
	YES	1 (25.0%)	1 (12.5%)
History of diabetes treated with insulin	NO	4 (100.0%)	8 (100.0%)
History of degenerative complications of diabetes	NO	4 (100.0%)	8 (100.0%)
History of gallstones	NO	3 (75.0%)	8 (100.0%)
	YES	1 (25.0%)	0 (0.0%)
History of Acute Pancreatitis	NO	4 (100.0%)	8 (100.0%)
History of Distal Intestinal Obstruction Syndrome	NO	4 (100.0%)	8 (100.0%)
History of treated gastroesophageal reflux	NO	1 (25.0%)	5 (62.5%)
	YES	3 (75.0%)	3 (37.5%)
History of hemoptysis	NO	4 (100.0%)	5 (62.5%)
	YES	0 (0.0%)	3 (37.5%)
History of nasal polyps	NO	3 (75.0%)	6 (75.0%)
	YES	1 (25.0%)	2 (25.0%)
History of pneumothorax	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)
History of Thoracic Drain for Pneumothorax	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)
History of arthropathy	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)
History of bone pathology	NO	2 (50.0%)	7 (87.5%)
	YES	2 (50.0%)	1 (12.5%)
History of urinary incontinence	NO	4 (100.0%)	8 (100.0%)
History of cancer	NO	4 (100.0%)	8 (100.0%)
History of asthma	NO	2 (50.0%)	4 (50.0%)
	YES	2 (50.0%)	4 (50.0%)
History of depression	NO	4 (100.0%)	6 (75.0%)
	YES	0 (0.0%)	2 (25.0%)
History of end stage renal failure	NO	4 (100.0%)	8 (100.0%)
History of deafness / hearing loss	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)

Table 3 : Individual charateristics at inclusion – Group 3 (dose 800mg)

		Placebo group (N=3)	Roscovitine group (N=7)
Age	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	37.33 +/- 5.13	37.00 +/- 7.83
	Median (q1;q3)	36.0 (33.0;43.0)	37.0 (30.0;42.0)
	Min;Max	33;43	28;51
Sex	Man	3 (100.0%)	4 (57.1%)
	Woman	0 (0.0%)	3 (42.9%)
Mutation	homozygous	2 (66.7%)	1 (14.3%)
	heterozygous	1 (33.3%)	6 (85.7%)
Respiratory rate	N (N missing)	3 (0 missing)	6 (1 missing)
	Mean +/- SD	17.00 +/- 2.65	17.00 +/- 2.45
	Median (q1;q3)	16.0 (15.0;20.0)	16.0 (16.0;20.0)
	Min;Max	15;20	14;20
BMI	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	23.40 +/- 1.15	21.03 +/- 2.69
	Median (q1;q3)	23.3 (22.3;24.6)	20.7 (18.7;24.2)
	Min;Max	22;25	18;24
Amount of PA	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	5.00 +/- 2.00	6.86 +/- 0.69
	Median (q1;q3)	5.0 (3.0;7.0)	7.0 (6.0;7.0)
	Min;Max	3;7	6;8
FEV	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	63.03 +/- 20.24	47.71 +/- 12.53
	Median (q1;q3)	71.1 (40.0;78.0)	46.0 (36.0;60.0)
	Min;Max	40;78	33;68
FVC	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	96.07 +/- 9.72	73.00 +/- 16.44
	Median (q1;q3)	100.0 (85.0;103.2)	78.0 (60.0;84.0)
	Min;Max	85;103	42;89
DEM25-75	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	25.18 +/- 15.47	22.14 +/- 11.28
	Median (q1;q3)	29.6 (8.0;38.0)	17.0 (14.0;32.0)
	Min;Max	8;38	11;42
Hematology			
Hemoglobin result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	14.63 +/- 0.59	14.11 +/- 1.43
	Median (q1;q3)	14.4 (14.2;15.3)	14.0 (12.9;15.3)
	Min;Max	14;15	12;16
Red blood cell result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	4.85 +/- 0.21	4.88 +/- 0.44
	Median (q1;q3)	4.9 (4.6;5.0)	5.0 (4.6;5.1)
	Min;Max	5;5	4;5
Hematocrit result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	42.47 +/- 2.63	42.61 +/- 4.12
	Median (q1;q3)	42.0 (40.1;45.3)	42.0 (38.0;47.3)
	Min;Max	40;45	38;48
VGM result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	87.63 +/- 2.12	87.39 +/- 5.70
	Median (q1;q3)	87.0 (85.9;90.0)	87.1 (81.0;91.7)
	Min;Max	86;90	79;95
reticulocytes result	N (N missing)	2 (1 missing)	3 (4 missing)
	Mean +/- SD	62.50 +/- 4.95	75.00 +/- 6.08
	Median (q1;q3)	62.5 (59.0;66.0)	72.0 (71.0;82.0)
	Min;Max	59;66	71;82
platelets result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	265.00 +/- 71.51	332.86 +/- 34.76
	Median (q1;q3)	266.0 (193.0;336.0)	333.0 (303.0;342.0)
	Min;Max	193;336	299;401

		Placebo group (N=3)	Roscovitine group (N=7)
leukocytes result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	8.26 +/- 4.05	10.66 +/- 2.40
	Median (q1;q3)	7.6 (4.6;12.6)	11.2 (8.7;12.7)
	Min;Max	5;13	7;13
eosinophils result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	0.12 +/- 0.13	0.26 +/- 0.18
	Median (q1;q3)	0.1 (0.0;0.3)	0.2 (0.1;0.4)
	Min;Max	0;0	0;1
basophils result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	0.03 +/- 0.04	0.05 +/- 0.04
	Median (q1;q3)	0.0 (0.0;0.1)	0.1 (0.0;0.1)
	Min;Max	0;0	0;0
neutrophils result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	5.20 +/- 3.55	7.66 +/- 2.51
	Median (q1;q3)	4.6 (2.0;9.0)	8.1 (5.2;10.6)
	Min;Max	2;9	5;11
lymphocytes result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	2.09 +/- 0.08	1.80 +/- 0.64
	Median (q1;q3)	2.1 (2.0;2.2)	1.8 (1.2;2.4)
	Min;Max	2;2	1;3
monocytes result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	0.79 +/- 0.48	0.89 +/- 0.37
	Median (q1;q3)	0.5 (0.5;1.3)	1.0 (0.5;1.3)
	Min;Max	1;1	0;1
TCA result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	28.97 +/- 3.61	30.40 +/- 4.91
	Median (q1;q3)	28.2 (25.8;32.9)	31.1 (25.0;32.3)
	Min;Max	26;33	25;39
Control TCA result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	29.67 +/- 2.78	30.31 +/- 1.50
	Median (q1;q3)	28.7 (27.5;32.8)	31.0 (28.9;31.3)
	Min;Max	28;33	28;31
TP result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	92.00 +/- 7.00	96.43 +/- 5.77
	Median (q1;q3)	89.0 (87.0;100.0)	100.0 (88.0;100.0)
	Min;Max	87;100	88;100
INR result	N (N missing)	2 (1 missing)	6 (1 missing)
	Mean +/- SD	1.07 +/- 0.10	0.98 +/- 0.04
	Median (q1;q3)	1.1 (1.0;1.1)	1.0 (0.9;1.0)
	Min;Max	1;1	1;1
Biochemistry			
Blood Sugar result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	4.25 +/- 0.65	5.13 +/- 0.62
	Median (q1;q3)	4.6 (3.5;4.7)	5.3 (4.6;5.5)
	Min;Max	4;5	4;6
Urea result	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	4.75 +/- 0.64	4.72 +/- 1.35
	Median (q1;q3)	4.8 (4.3;5.2)	4.5 (3.6;6.0)
	Min;Max	4;5	3;6
creatinine result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	72.33 +/- 7.37	67.14 +/- 20.33
	Median (q1;q3)	75.0 (64.0;78.0)	64.0 (46.0;88.0)
	Min;Max	64;78	44;99
Sodium result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	141.00 +/- 1.00	138.57 +/- 2.30
	Median (q1;q3)	141.0 (140.0;142.0)	138.0 (138.0;141.0)
	Min;Max	140;142	135;142
Potassium result	N (N missing)	3 (0 missing)	7 (0 missing)

		Placebo group (N=3)	Roscovitine group (N=7)
	Mean +/- SD	3.92 +/- 0.19	4.29 +/- 0.16
	Median (q1;q3)	4.0 (3.7;4.1)	4.4 (4.1;4.4)
	Min;Max	4;4	4;5
Calcium result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	2.27 +/- 0.03	2.32 +/- 0.11
	Median (q1;q3)	2.3 (2.2;2.3)	2.4 (2.2;2.4)
	Min;Max	2;2	2;2
Chlorine result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	101.33 +/- 1.15	100.86 +/- 4.14
	Median (q1;q3)	102.0 (100.0;102.0)	102.0 (98.0;104.0)
	Min;Max	100;102	93;105
Magnesium result	N (N missing)	2 (1 missing)	5 (2 missing)
	Mean +/- SD	0.81 +/- 0.08	0.81 +/- 0.05
	Median (q1;q3)	0.8 (0.8;0.9)	0.8 (0.8;0.8)
	Min;Max	1;1	1;1
CO2 result	N (N missing)	3 (0 missing)	5 (2 missing)
	Mean +/- SD	27.00 +/- 3.00	26.24 +/- 2.45
	Median (q1;q3)	27.0 (24.0;30.0)	26.0 (25.0;28.0)
	Min;Max	24;30	23;29
Phosphorus result	N (N missing)	3 (0 missing)	5 (2 missing)
	Mean +/- SD	0.78 +/- 0.27	0.86 +/- 0.12
	Median (q1;q3)	0.9 (0.5;1.0)	0.8 (0.8;0.9)
	Min;Max	0;1	1;1
Total bilirubin result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	6.97 +/- 1.70	5.74 +/- 3.24
	Median (q1;q3)	7.9 (5.0;8.0)	5.0 (4.0;5.2)
	Min;Max	5;8	4;13
Indirect bilirubin result	N (N missing)	1 (2 missing)	3 (4 missing)
	Mean +/- SD	3.00 +/- .	4.00 +/- 3.46
	Median (q1;q3)	3.0 (3.0;3.0)	2.0 (2.0;8.0)
	Min;Max	3;3	2;8
PAL result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	98.67 +/- 26.50	119.86 +/- 22.46
	Median (q1;q3)	99.0 (72.0;125.0)	120.0 (101.0;144.0)
	Min;Max	72;125	93;153
ASAT result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	19.67 +/- 6.66	26.71 +/- 8.90
	Median (q1;q3)	18.0 (14.0;27.0)	28.0 (16.0;36.0)
	Min;Max	14;27	15;38
ALAT result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	19.33 +/- 6.03	27.71 +/- 11.84
	Median (q1;q3)	20.0 (13.0;25.0)	28.0 (18.0;33.0)
	Min;Max	13;25	14;49
LDH result	N (N missing)	2 (1 missing)	6 (1 missing)
	Mean +/- SD	178.50 +/- 3.54	260.17 +/- 82.81
	Median (q1;q3)	178.5 (176.0;181.0)	284.5 (188.0;307.0)
	Min;Max	176;181	138;359
GGT result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	16.33 +/- 4.04	21.29 +/- 12.93
	Median (q1;q3)	17.0 (12.0;20.0)	16.0 (12.0;36.0)
	Min;Max	12;20	10;43
Total Proteins result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	73.43 +/- 1.69	75.24 +/- 6.16
	Median (q1;q3)	73.0 (72.0;75.3)	77.0 (67.7;80.0)
	Min;Max	72;75	66;82
Albumin result	N (N missing)	3 (0 missing)	6 (1 missing)
	Mean +/- SD	42.93 +/- 5.10	38.20 +/- 5.61
	Median (q1;q3)	43.0 (37.8;48.0)	38.0 (35.2;42.0)

		Placebo group (N=3)	Roscovitine group (N=7)
	Min;Max	38;48	30;46
CK result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	84.33 +/- 25.48	79.14 +/- 51.70
	Median (q1;q3)	97.0 (55.0;101.0)	71.0 (34.0;132.0)
	Min;Max	55;101	21;156
CRP result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	8.67 +/- 10.42	11.34 +/- 11.53
	Median (q1;q3)	2.7 (2.6;20.7)	6.0 (4.0;17.3)
	Min;Max	3;21	3;35
Urine			
Glucose result	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	32.21 +/- 44.99	0.63 +/- 0.62
	Median (q1;q3)	32.2 (0.4;64.0)	0.5 (0.2;0.6)
	Min;Max	0;64	0;2
Urinary protein result	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	0.07 +/- 0.03	0.16 +/- 0.21
	Median (q1;q3)	0.1 (0.1;0.1)	0.1 (0.1;0.1)
	Min;Max	0;0	0;1
Microalbumin result	N (N missing)	2 (1 missing)	5 (2 missing)
	Mean +/- SD	3.95 +/- 1.34	13.48 +/- 18.88
	Median (q1;q3)	4.0 (3.0;4.9)	5.0 (4.3;8.0)
	Min;Max	3;5	3;47
Potassium result	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	59.00 +/- 41.01	50.04 +/- 25.44
	Median (q1;q3)	59.0 (30.0;88.0)	48.0 (34.9;71.0)
	Min;Max	30;88	11;89
Sodium result	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	131.00 +/- 107.48	139.29 +/- 38.92
	Median (q1;q3)	131.0 (55.0;207.0)	126.0 (123.0;182.0)
	Min;Max	55;207	83;198
Urea result	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	313.00 +/- 176.78	243.26 +/- 153.14
	Median (q1;q3)	313.0 (188.0;438.0)	268.2 (128.5;328.4)
	Min;Max	188;438	4;483
Creatinine result	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	11.60 +/- 6.36	10.11 +/- 5.94
	Median (q1;q3)	11.6 (7.1;16.1)	7.8 (5.1;14.8)
	Min;Max	7;16	5;21
Uric acid result	N (N missing)	1 (2 missing)	5 (2 missing)
	Mean +/- SD	438.00 +/- .	2.61 +/- 1.81
	Median (q1;q3)	438.0 (438.0;438.0)	2.2 (1.8;2.7)
	Min;Max	438;438	1;6
Blood result	Absent	3 (100.0%)	6 (85.7%)
	Present	0 (0.0%)	1 (14.3%)
Density result	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	1.02 +/- 0.00	1.02 +/- 0.01
	Median (q1;q3)	1.0 (1.0;1.0)	1.0 (1.0;1.0)
	Min;Max	1;1	1;1
ketone result	Negative	3 (100.0%)	7 (100.0%)
bilirubin result	Missing	1 (33.3%)	2 (28.6%)
	Negative	2 (100.0%)	5 (100.0%)
leukocytes result	Negative	3 (100.0%)	5 (71.4%)
	Traces	0 (0.0%)	1 (14.3%)
	Positive	0 (0.0%)	1 (14.3%)
Nitrite result	Negative	3 (100.0%)	7 (100.0%)
History			
History of abnormal exocrine pancreatic function	YES	3 (100.0%)	7 (100.0%)

		Placebo group (N=3)	Roscovitine group (N=7)
History of hepatic enzyme elevation (1.5 times the upper limit)	NO	3 (100.0%)	7 (100.0%)
History of cirrhosis	NO	3 (100.0%)	7 (100.0%)
History of portal hypertension	NO	3 (100.0%)	7 (100.0%)
History of digestive hemorrhage	NO	3 (100.0%)	7 (100.0%)
History of glucose intolerance	NO	2 (66.7%)	5 (71.4%)
	YES	1 (33.3%)	2 (28.6%)
History of non-insulin-treated diabetes	NO	2 (66.7%)	7 (100.0%)
	YES	1 (33.3%)	0 (0.0%)
History of diabetes treated with insulin	NO	3 (100.0%)	7 (100.0%)
History of degenerative complications of diabetes	NO	3 (100.0%)	7 (100.0%)
History of gallstones	NO	3 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)
History of Acute Pancreatitis	NO	3 (100.0%)	7 (100.0%)
History of Distal Intestinal Obstruction Syndrome	NO	3 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)
History of treated gastroesophageal reflux	NO	1 (33.3%)	2 (28.6%)
	YES	2 (66.7%)	5 (71.4%)
History of hemoptysis	NO	2 (66.7%)	5 (71.4%)
	YES	1 (33.3%)	2 (28.6%)
History of nasal polyps	NO	3 (100.0%)	5 (71.4%)
	YES	0 (0.0%)	2 (28.6%)
History of pneumothorax	NO	3 (100.0%)	7 (100.0%)
History of Thoracic Drain for Pneumothorax	NO	3 (100.0%)	7 (100.0%)
History of arthropathy	NO	3 (100.0%)	7 (100.0%)
History of bone pathology	NO	2 (66.7%)	6 (85.7%)
	YES	1 (33.3%)	1 (14.3%)
History of urinary incontinence	NO	3 (100.0%)	7 (100.0%)
History of cancer	NO	3 (100.0%)	7 (100.0%)
History of asthma	NO	2 (66.7%)	5 (71.4%)
	YES	1 (33.3%)	2 (28.6%)
History of depression	NO	3 (100.0%)	7 (100.0%)
History of end stage renal failure	NO	3 (100.0%)	7 (100.0%)
History of deafness / hearing loss	NO	3 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)

2. PAIN

Table 4 : Pain – Group 1 (dose 200mg)

		Placebo group (N=4)	Roscovitine group (N=8)
Age of diagnosis	< 2 yo	3 (75.0%)	6 (75.0%)
	2 yo - 12 yo	0 (0.0%)	2 (25.0%)
	13 yo - 18 yo	1 (25.0%)	0 (0.0%)
Pancreatic insufficiency	NO	0 (0.0%)	1 (12.5%)
	YES	4 (100.0%)	7 (87.5%)
History of pneumothorax	NO	4 (100.0%)	8 (100.0%)
pyocyanic	YES	4 (100.0%)	8 (100.0%)
Insulin-dependent diabetes	NO	3 (75.0%)	7 (87.5%)
	YES	1 (25.0%)	1 (12.5%)
gastrostomy	NO	4 (100.0%)	8 (100.0%)
Nasogastric tube	NO	4 (100.0%)	8 (100.0%)
Port A Cath	NO	2 (50.0%)	2 (25.0%)
	YES	2 (50.0%)	6 (75.0%)
Non Invasive Ventilation	NO	4 (100.0%)	8 (100.0%)
Pain on the day of the interrogation	NO	4 (100.0%)	5 (62.5%)
	YES	0 (0.0%)	3 (37.5%)
Pain in the previous month	NO	0 (0.0%)	3 (37.5%)
	YES	4 (100.0%)	5 (62.5%)
Treatment of pain in the previous month	NO	1 (25.0%)	5 (62.5%)
	YES	3 (75.0%)	3 (37.5%)
Consequences of pain on the daily life of the patient - D1			
Asthenia	NO	1 (25.0%)	6 (75.0%)
	YES	3 (75.0%)	2 (25.0%)
Limitation of physical activity	NO	1 (25.0%)	2 (25.0%)
	YES	3 (75.0%)	6 (75.0%)
Impact on family life	NO	3 (75.0%)	6 (75.0%)
	YES	1 (25.0%)	2 (25.0%)
Insomnia	NO	2 (50.0%)	6 (75.0%)
	YES	2 (50.0%)	2 (25.0%)
School absenteeism	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)
Cystic Fibrosis Pain - D1			
Pain related to cystic fibrosis	NO	0 (0.0%)	5 (62.5%)
	YES	4 (100.0%)	3 (37.5%)
Paraclinical exploration	NO	3 (75.0%)	8 (100.0%)
	YES	1 (25.0%)	0 (0.0%)
Pain on the day of the exam	NO	0 (0.0%)	1 (12.5%)
	YES	4 (100.0%)	7 (87.5%)
Chest pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	7 (100.0%)
	YES	1 (25.0%)	0 (0.0%)
Back pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	5 (71.4%)
	YES	0 (0.0%)	2 (28.6%)
Lumbar pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	6 (85.7%)
	YES	1 (25.0%)	1 (14.3%)
Cervical pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)
Joint pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	3 (42.9%)
	YES	1 (25.0%)	4 (57.1%)
Muscular pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	5 (71.4%)
	YES	0 (0.0%)	2 (28.6%)

		Placebo group (N=4)	Roscovitine group (N=8)
Gastric pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	7 (100.0%)
	YES	1 (25.0%)	0 (0.0%)
Abdominal pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	2 (50.0%)	6 (85.7%)
	YES	2 (50.0%)	1 (14.3%)
Headache pain present	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	4 (57.1%)
	YES	1 (25.0%)	3 (42.9%)
Pain following a medical gesture	NO	3 (75.0%)	5 (62.5%)
	YES	1 (25.0%)	3 (37.5%)
Presence of pain following physiotherapy	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Presence of pain following noninvasive ventilation	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Presence of pain following a venous puncture	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	2 (66.7%)
	YES	0 (0.0%)	1 (33.3%)
Presence of pain following a Port Puncture at Cath	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Presence of pain following Arterial Blood Gas	Missing	3 (75.0%)	5 (62.5%)
	NO	0 (0.0%)	2 (66.7%)
	YES	1 (100.0%)	1 (33.3%)
Presence of pain following capillary blood gas	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Presence of pain following implantable chamber placement	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	2 (66.7%)
	YES	0 (0.0%)	1 (33.3%)
Presence of pain following the insertion of nasogastric tube	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Presence of pain following gastrostomy	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Presence of pain following the use of gastrostomy	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Presence of soot pain at gastric fibroscopy	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Presence of pain following bronchial fibroscopy	Missing	3 (75.0%)	5 (62.5%)
	NO	1 (100.0%)	3 (100.0%)
Consequences of pain on the daily life of the patient – D28			
Asthenia	NO	2 (50.0%)	6 (75.0%)
	YES	2 (50.0%)	2 (25.0%)
Limitation of physical activity	NO	2 (50.0%)	7 (87.5%)
	YES	2 (50.0%)	1 (12.5%)
Impact on family life	NO	4 (100.0%)	8 (100.0%)
Insomnia	NO	3 (75.0%)	8 (100.0%)
	YES	1 (25.0%)	0 (0.0%)
School absenteeism	NO	4 (100.0%)	8 (100.0%)
Cystic Fibrosis Pain – D28			
Pain related to mucovisidosis	NO	3 (75.0%)	5 (62.5%)
	YES	1 (25.0%)	3 (37.5%)
Paraclinical exploration	NO	4 (100.0%)	8 (100.0%)
Pain on the day of the exam	NO	4 (100.0%)	6 (75.0%)
	YES	0 (0.0%)	2 (25.0%)
Chest pain present	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Back pain present	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)

		Placebo group (N=4)	Roscovitine group (N=8)
	YES	0 (0.0%)	1 (50.0%)
Lumbar pain present	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Cervical pain present	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Joint pain present	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Muscular pain present	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Gastric pain present	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Abdominal pain present	Missing	4 (100.0%)	6 (75.0%)
	YES	0 (0.0%)	2 (100.0%)
Headache pain present	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Pain following a medical gesture	Missing	4 (100.0%)	8 (100.0%)
Presence of pain following physiotherapy	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Presence of pain following noninvasive ventilation	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Presence of pain following a venous puncture	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Presence of pain following a Port Puncture at Cath	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Presence of pain following Arterial Blood Gas	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Presence of pain following capillary blood gas	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Presence of pain following implantable chamber placement	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Presence of pain following the insertion of nasogastric tube	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Presence of pain following gastrostomy	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Presence of pain following the use of gastrostomy	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Presence of soot pain at gastric fibroscopy	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)
Presence of pain following bronchial fibroscopy	Missing	4 (100.0%)	6 (75.0%)
	NO	0 (0.0%)	2 (100.0%)

Table 5 : Pain – Group 2 (dose 400mg)

		Placebo group (N=4)	Roscovitine group (N=8)
Age of diagnosis	Missing	0 (0.0%)	1 (12.5%)
	< 2 yo	2 (50.0%)	1 (14.3%)
	2 yo - 12 yo	0 (0.0%)	3 (42.9%)
	13 yo - 18 yo	0 (0.0%)	1 (14.3%)
	> 18 yo	2 (50.0%)	2 (28.6%)
Pancreatic insufficiency	Missing	0 (0.0%)	1 (12.5%)
	NO	0 (0.0%)	4 (57.1%)
	YES	4 (100.0%)	3 (42.9%)
History of pneumothorax	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)
pyocyanic	Missing	0 (0.0%)	1 (12.5%)
	YES	4 (100.0%)	7 (100.0%)
Insulin-dependent diabetes	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	7 (100.0%)
gastrostomy	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	7 (100.0%)
Nasogastric tube	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)
Port A Cath	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	4 (57.1%)
	YES	1 (25.0%)	3 (42.9%)
Non Invasive Ventilation	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	7 (100.0%)
	YES	1 (25.0%)	0 (0.0%)
Pain on the day of the interrogation	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	5 (71.4%)
	YES	1 (25.0%)	2 (28.6%)
Pain in the previous month	Missing	0 (0.0%)	1 (12.5%)
	NO	2 (50.0%)	4 (57.1%)
	YES	2 (50.0%)	3 (42.9%)
Treatment of pain in the previous month	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	3 (42.9%)
	YES	1 (25.0%)	4 (57.1%)
Consequences of pain on the daily life of the patient - D1			
Asthenia	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	4 (57.1%)
	YES	1 (25.0%)	3 (42.9%)
Limitation of physical activity	Missing	0 (0.0%)	1 (12.5%)
	NO	2 (50.0%)	4 (57.1%)
	YES	2 (50.0%)	3 (42.9%)
Impact on family life	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	5 (71.4%)
	YES	0 (0.0%)	2 (28.6%)
Insomnia	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	5 (71.4%)
	YES	1 (25.0%)	2 (28.6%)
School absenteeism	Missing	0 (0.0%)	1 (12.5%)
	NO	4 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)
Cystic Fibrosis Pain - D1			
Pain related to cystic fibrosis	Missing	0 (0.0%)	2 (25.0%)
	NO	4 (100.0%)	6 (100.0%)
Paraclinical exploration	Missing	0 (0.0%)	1 (12.5%)
	NO	3 (75.0%)	7 (100.0%)

		Placebo group (N=4)	Roscovitine group (N=8)
	YES	1 (25.0%)	0 (0.0%)
Pain on the day of the exam	Missing	0 (0.0%)	1 (12.5%)
	NO	2 (50.0%)	3 (42.9%)
	YES	2 (50.0%)	4 (57.1%)
Chest pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	1 (50.0%)	3 (75.0%)
	YES	1 (50.0%)	1 (25.0%)
Back pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	1 (50.0%)	2 (50.0%)
	YES	1 (50.0%)	2 (50.0%)
Lumbar pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	2 (100.0%)	2 (50.0%)
	YES	0 (0.0%)	2 (50.0%)
Cervical pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	0 (0.0%)	1 (25.0%)
	YES	2 (100.0%)	3 (75.0%)
Joint pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	1 (50.0%)	1 (25.0%)
	YES	1 (50.0%)	3 (75.0%)
Muscular pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	2 (100.0%)	3 (75.0%)
	YES	0 (0.0%)	1 (25.0%)
Gastric pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	1 (50.0%)	3 (75.0%)
	YES	1 (50.0%)	1 (25.0%)
Abdominal pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	1 (50.0%)	3 (75.0%)
	YES	1 (50.0%)	1 (25.0%)
Headache pain present	Missing	2 (50.0%)	4 (50.0%)
	NO	1 (50.0%)	2 (50.0%)
	YES	1 (50.0%)	2 (50.0%)
Pain following a medical gesture	NO	3 (75.0%)	3 (42.9%)
	YES	1 (25.0%)	4 (57.1%)
Presence of pain following physiotherapy	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	2 (50.0%)
	YES	0 (0.0%)	2 (50.0%)
Presence of pain following noninvasive ventilation	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	4 (100.0%)
Presence of pain following a venous puncture	Missing	3 (75.0%)	4 (50.0%)
	YES	1 (100.0%)	4 (100.0%)
Presence of pain following a Port Puncture at Cath	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	3 (75.0%)
	YES	0 (0.0%)	1 (25.0%)
Presence of pain following Arterial Blood Gas	Missing	3 (75.0%)	4 (50.0%)
	NO	0 (0.0%)	1 (25.0%)
	YES	1 (100.0%)	3 (75.0%)
Presence of pain following capillary blood gas	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	3 (75.0%)
	YES	0 (0.0%)	1 (25.0%)
Presence of pain following implantable chamber placement	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	3 (75.0%)
	YES	0 (0.0%)	1 (25.0%)
Presence of pain following the insertion of nasogastric tube	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	3 (75.0%)
	YES	0 (0.0%)	1 (25.0%)
Presence of pain following gastrostomy	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	4 (100.0%)

		Placebo group (N=4)	Roscovitine group (N=8)
Presence of pain following the use of gastrostomy	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	4 (100.0%)
Presence of soot pain at gastric fibroscopy	Missing	3 (75.0%)	4 (50.0%)
	NO	0 (0.0%)	3 (75.0%)
	YES	1 (100.0%)	1 (25.0%)
Presence of pain following bronchial fibroscopy	Missing	3 (75.0%)	4 (50.0%)
	NO	1 (100.0%)	3 (75.0%)
	YES	0 (0.0%)	1 (25.0%)
Consequences of pain on the daily life of the patient – D28			
Asthenia	NO	4 (100.0%)	6 (75.0%)
	YES	0 (0.0%)	2 (25.0%)
Limitation of physical activity	NO	3 (75.0%)	7 (87.5%)
	YES	1 (25.0%)	1 (12.5%)
Impact on family life	NO	4 (100.0%)	7 (87.5%)
	YES	0 (0.0%)	1 (12.5%)
Insomnia	NO	3 (75.0%)	7 (87.5%)
	YES	1 (25.0%)	1 (12.5%)
School absenteeism	NO	4 (100.0%)	8 (100.0%)
Cystic Fibrosis Pain – D28			
Pain related to mucovisidosis	NO	3 (75.0%)	6 (75.0%)
	YES	1 (25.0%)	2 (25.0%)
Paraclinical exploration	NO	4 (100.0%)	8 (100.0%)
Pain on the day of the exam	NO	1 (25.0%)	6 (75.0%)
	YES	3 (75.0%)	2 (25.0%)
Chest pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	3 (100.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Back pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	3 (100.0%)	0 (0.0%)
	YES	0 (0.0%)	2 (100.0%)
Lumbar pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	3 (100.0%)	0 (0.0%)
	YES	0 (0.0%)	2 (100.0%)
Cervical pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	1 (33.3%)	1 (50.0%)
	YES	2 (66.7%)	1 (50.0%)
Joint pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	3 (100.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Muscular pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	3 (100.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Gastric pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	2 (66.7%)	1 (50.0%)
	YES	1 (33.3%)	1 (50.0%)
Abdominal pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	3 (100.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Headache pain present	Missing	1 (25.0%)	6 (75.0%)
	NO	2 (66.7%)	1 (50.0%)
	YES	1 (33.3%)	1 (50.0%)
Pain following a medical gesture	Missing	4 (100.0%)	8 (100.0%)
Presence of pain following physiotherapy	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	2 (66.7%)
	YES	0 (0.0%)	1 (33.3%)
Presence of pain following noninvasive ventilation	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	3 (100.0%)

		Placebo group (N=4)	Roscovitine group (N=8)
Presence of pain following a venous puncture	Missing	4 (100.0%)	5 (62.5%)
	YES	0 (0.0%)	3 (100.0%)
Presence of pain following a Port Puncture at Cath	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	2 (66.7%)
	YES	0 (0.0%)	1 (33.3%)
Presence of pain following Arterial Blood Gas	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	2 (66.7%)
	YES	0 (0.0%)	1 (33.3%)
Presence of pain following capillary blood gas	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	3 (100.0%)
Presence of pain following implantable chamber placement	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	2 (66.7%)
	YES	0 (0.0%)	1 (33.3%)
Presence of pain following the insertion of nasogastric tube	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	2 (66.7%)
	YES	0 (0.0%)	1 (33.3%)
Presence of pain following gastrostomy	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	3 (100.0%)
Presence of pain following the use of gastrostomy	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	3 (100.0%)
Presence of soot pain at gastric fibroscopy	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	2 (66.7%)
	YES	0 (0.0%)	1 (33.3%)
Presence of pain following bronchial fibroscopy	Missing	4 (100.0%)	5 (62.5%)
	NO	0 (0.0%)	3 (100.0%)

Table 6 : Pain – Group 3 (dose 800mg)

		Placebo group (N=3)	Roscovitine group (N=7)
Age du diagnostic	< 2 yo	1 (33.3%)	3 (42.9%)
	2 yo - 12 yo	1 (33.3%)	2 (28.6%)
	13 yo - 18 yo	0 (0.0%)	1 (14.3%)
	> 18 yo	1 (33.3%)	1 (14.3%)
Pancreatic insufficiency	YES	3 (100.0%)	7 (100.0%)
History of pneumothorax	NO	3 (100.0%)	7 (100.0%)
pyocyanic	YES	3 (100.0%)	7 (100.0%)
Insulin-dependent diabetes	NO	3 (100.0%)	7 (100.0%)
gastrostomy	NO	3 (100.0%)	7 (100.0%)
Nasogastric tube	NO	3 (100.0%)	7 (100.0%)
Port A Cath	NO	2 (66.7%)	4 (57.1%)
	YES	1 (33.3%)	3 (42.9%)
Non Invasive Ventilation	NO	3 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)
Pain on the day of the interrogation	NO	2 (66.7%)	7 (100.0%)
	YES	1 (33.3%)	0 (0.0%)
Pain in the previous month	NO	1 (33.3%)	4 (57.1%)
	YES	2 (66.7%)	3 (42.9%)
Treatment of pain in the previous month	NO	1 (33.3%)	4 (57.1%)
	YES	2 (66.7%)	3 (42.9%)
Consequences of pain on the daily life of the patient - D1			
Asthenia	NO	2 (66.7%)	4 (57.1%)
	YES	1 (33.3%)	3 (42.9%)
Limitation of physical activity	NO	2 (66.7%)	5 (71.4%)
	YES	1 (33.3%)	2 (28.6%)
Impact on family life	NO	2 (66.7%)	4 (57.1%)
	YES	1 (33.3%)	3 (42.9%)
Insomnia	NO	1 (33.3%)	3 (42.9%)
	YES	2 (66.7%)	4 (57.1%)
School absenteeism	NO	3 (100.0%)	6 (85.7%)
	YES	0 (0.0%)	1 (14.3%)
Cystic Fibrosis Pain - D1			
Pain related to cystic fibrosis	NO	3 (100.0%)	5 (71.4%)
	YES	0 (0.0%)	2 (28.6%)
Paraclinical exploration	NO	2 (66.7%)	7 (100.0%)
	YES	1 (33.3%)	0 (0.0%)
Pain on the day of the exam	NO	1 (33.3%)	3 (42.9%)
	YES	2 (66.7%)	4 (57.1%)
Chest pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	1 (50.0%)	3 (75.0%)
	YES	1 (50.0%)	1 (25.0%)
Back pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	0 (0.0%)	2 (50.0%)
	YES	2 (100.0%)	2 (50.0%)
Lumbar pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	2 (100.0%)	2 (50.0%)
	YES	0 (0.0%)	2 (50.0%)
Cervical pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	1 (50.0%)	2 (50.0%)
	YES	1 (50.0%)	2 (50.0%)
Joint pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	1 (50.0%)	4 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Muscular pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	0 (0.0%)	4 (100.0%)
	YES	2 (100.0%)	0 (0.0%)

		Placebo group (N=3)	Roscovitine group (N=7)
Gastric pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	1 (50.0%)	4 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Abdominal pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	1 (50.0%)	3 (75.0%)
	YES	1 (50.0%)	1 (25.0%)
Headache pain present	Missing	1 (33.3%)	3 (42.9%)
	NO	0 (0.0%)	4 (100.0%)
	YES	2 (100.0%)	0 (0.0%)
Pain following a medical gesture	NO	1 (33.3%)	5 (71.4%)
	YES	2 (66.7%)	2 (28.6%)
Presence of pain following physiotherapy	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	2 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Presence of pain following noninvasive ventilation	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following a venous puncture	Missing	1 (33.3%)	5 (71.4%)
	YES	2 (100.0%)	2 (100.0%)
Presence of pain following a Port Puncture at Cath	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	2 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Presence of pain following Arterial Blood Gas	Missing	1 (33.3%)	5 (71.4%)
	NO	0 (0.0%)	2 (100.0%)
	YES	2 (100.0%)	0 (0.0%)
Presence of pain following capillary blood gas	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	2 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Presence of pain following implantable chamber placement	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	2 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Presence of pain following the insertion of nasogastric tube	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following gastrostomy	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following the use of gastrostomy	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of soot pain at gastric fibroscopy	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following bronchial fibroscopy	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	2 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Consequences of pain on the daily life of the patient – D28			
Asthenia	NO	2 (66.7%)	5 (71.4%)
	YES	1 (33.3%)	2 (28.6%)
Limitation of physical activity	NO	2 (66.7%)	5 (71.4%)
	YES	1 (33.3%)	2 (28.6%)
Impact on family life	NO	2 (66.7%)	6 (85.7%)
	YES	1 (33.3%)	1 (14.3%)
Insomnia	NO	1 (33.3%)	6 (85.7%)
	YES	2 (66.7%)	1 (14.3%)
School absenteeism	NO	3 (100.0%)	7 (100.0%)
Cystic Fibrosis Pain – D28			
Pain related to mucovisidosis	NO	3 (100.0%)	5 (71.4%)
	YES	0 (0.0%)	2 (28.6%)
Paraclinical exploration	NO	3 (100.0%)	7 (100.0%)
Pain on the day of the exam	NO	2 (66.7%)	5 (71.4%)
	YES	1 (33.3%)	2 (28.6%)

		Placebo group (N=3)	Roscovitine group (N=7)
Chest pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	1 (100.0%)	2 (100.0%)
Back pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	1 (100.0%)	2 (100.0%)
Lumbar pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	1 (100.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Cervical pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	1 (100.0%)	1 (50.0%)
	YES	0 (0.0%)	1 (50.0%)
Joint pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	1 (100.0%)	2 (100.0%)
Muscular pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	1 (100.0%)	2 (100.0%)
Gastric pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	1 (100.0%)	2 (100.0%)
Abdominal pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	0 (0.0%)	2 (100.0%)
	YES	1 (100.0%)	0 (0.0%)
Headache pain present	Missing	2 (66.7%)	5 (71.4%)
	NO	1 (100.0%)	2 (100.0%)
Pain following a medical gesture	Missing	3 (100.0%)	7 (100.0%)
Presence of pain following physiotherapy	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following noninvasive ventilation	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following a venous puncture	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	0 (0.0%)
	YES	1 (50.0%)	2 (100.0%)
Presence of pain following a Port Puncture at Cath	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following Arterial Blood Gas	Missing	1 (33.3%)	5 (71.4%)
	NO	0 (0.0%)	2 (100.0%)
	YES	2 (100.0%)	0 (0.0%)
Presence of pain following capillary blood gas	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	2 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Presence of pain following implantable chamber placement	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following the insertion of nasogastric tube	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following gastrostomy	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of pain following the use of gastrostomy	Missing	1 (33.3%)	5 (71.4%)
	NO	2 (100.0%)	2 (100.0%)
Presence of soot pain at gastric fibroscopy	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	2 (100.0%)
	YES	1 (50.0%)	0 (0.0%)
Presence of pain following bronchial fibroscopy	Missing	1 (33.3%)	5 (71.4%)
	NO	1 (50.0%)	2 (100.0%)
	YES	1 (50.0%)	0 (0.0%)

3. ADVERSE EVENTS

Table 7 : Adverse Events description – Group 1 (dose 200 mg)

Grade	SOC	Meddra	Roscovitine group (n;%)	Placebo group (n;%)
1-2	BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	0 (0.0%)	1 (3.7%)
		LEUKOCYTOSIS	0 (0.0%)	1 (3.7%)
		LYMPHADENITIS	1 (2.6%)	0 (0.0%)
	CARDIAC DISORDERS	TACHYCARDIA	1 (2.6%)	0 (0.0%)
	GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	2 (5.1%)	3 (11.1%)
		ABDOMINAL PAIN UPPER	1 (2.6%)	0 (0.0%)
		DIARRHOEA	3 (7.7%)	3 (11.1%)
		DYSPEPSIA	4 (10.3%)	0 (0.0%)
		GASTROINTESTINAL PAIN	1 (2.6%)	0 (0.0%)
		GASTROOESOPHAGEAL REFLUX DISEASE	1 (2.6%)	1 (3.7%)
		VOMITING	1 (2.6%)	
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	1 (2.6%)	1 (3.7%)
		CHEST DISCOMFORT	2 (5.1%)	0 (0.0%)
	INFECTIONS AND INFESTATIONS	GASTROENTERITIS	2 (5.1%)	0 (0.0%)
		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	2 (5.1%)	1 (3.7%)
		LUNG INFECTION	0 (0.0%)	1 (3.7%)
		NASOPHARYNGITIS	1 (2.6%)	1 (3.7%)
		ORAL HERPES	0 (0.0%)	1 (3.7%)
		PHARYNGITIS	0 (0.0%)	2 (7.4%)
		RHINITIS	1 (2.6%)	0 (0.0%)
		TONSILLITIS	0 (0.0%)	1 (3.7%)
	INVESTIGATIONS	C-REACTIVE PROTEIN INCREASED	1 (2.6%)	0 (0.0%)
		ELECTROCARDIOGRAM T WAVE INVERSION	1 (2.6%)	0 (0.0%)
		FORCED EXPIRATORY VOLUME DECREASED	0 (0.0%)	1 (3.7%)
	METABOLISM AND NUTRITION DISORDERS	DEHYDRATION	1 (2.6%)	0 (0.0%)
		HYPERKALAEMIA	1 (2.6%)	0 (0.0%)
	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	2 (5.1%)	0 (0.0%)
		BACK PAIN	1 (2.6%)	1 (3.7%)
		MYALGIA	1 (2.6%)	
		NECK PAIN		1 (3.7%)
	NERVOUS SYSTEM DISORDERS	HEADACHE	2 (5.1%)	1 (3.7%)
	PSYCHIATRIC DISORDERS	INSOMNIA	1 (2.6%)	1 (3.7%)
	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	BRONCHOSPASM	2 (5.1%)	0 (0.0%)
		COUGH	0 (0.0%)	1 (3.7%)
	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	PRURITUS GENITAL	1 (2.6%)	0 (0.0%)
		SKIN IRRITATION	0 (0.0%)	1 (3.7%)
	VASCULAR DISORDERS	HAEMATOMA	1 (2.6%)	0 (0.0%)
		HAEMOPTYSIS	0 (0.0%)	3 (11.1%)

Note : the percentage into the box represente the percentage of every AE for the group.
(ex : for ANEMIA, 3.7% AE of Placebo group was an ANEMIA)

Table 8 : Adverse Events description – Group 2 (dose 400 mg)

Grade	SOC	Meddra	Roscovitine group (n;%)	Placebo group (n;%)
1-2	CARDIAC DISORDERS	TACHYCARDIA	2 (3.4%)	0 (0.0%)
	EAR AND LABYRINTH DISORDERS	TINNITUS	0 (0.0%)	1 (4.0%)
	EYE DISORDERS	PHOTOPHOBIA	1 (1.7%)	0 (0.0%)
		VISUAL IMPAIRMENT	1 (1.7%)	0 (0.0%)
	GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	4 (6.8%)	5 (20.0%)
		ABDOMINAL PAIN UPPER	1 (1.7%)	0 (0.0%)
		DIARRHOEA	2 (3.4%)	0 (0.0%)
		NAUSEA	0 (0.0%)	1 (4.0%)
		POST-TUSSIVE VOMITING	2 (3.4%)	0 (0.0%)
		VOMITING	3 (5.1%)	0 (0.0%)
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	1 (1.7%)	0 (0.0%)
		DECREASED ACTIVITY	1 (1.7%)	1 (4.0%)
		PYREXIA	1 (1.7%)	0 (0.0%)
	HEPATOBILIARY DISORDERS	HEPATIC FUNCTION ABNORMAL	4 (6.8%)	0 (0.0%)
		HYPERTRANSAMINASAEMIA	1 (1.7%)	0 (0.0%)
	IMMUNE SYSTEM DISORDERS	RHINITIS ALLERGIC	1 (1.7%)	1 (4.0%)
	INFECTIONS AND INFESTATIONS	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	4 (6.8%)	0 (0.0%)
		LUNG INFECTION	1 (1.7%)	0 (0.0%)
		NASOPHARYNGITIS	2 (3.4%)	1 (4.0%)
		VIRAL INFECTION	1 (1.7%)	0 (0.0%)
	INVESTIGATIONS	BLOOD CREATINE PHOSPHOKINASE INCREASED	1 (1.7%)	0 (0.0%)
		WEIGHT DECREASED	0 (0.0%)	1 (4.0%)
	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	BACK PAIN	2 (3.4%)	1 (4.0%)
		MUSCULOSKELETAL STIFFNESS	1 (1.7%)	0 (0.0%)
		NECK PAIN	0 (0.0%)	1 (4.0%)
	NERVOUS SYSTEM DISORDERS	BALANCE DISORDER	1 (1.7%)	0 (0.0%)
		HEADACHE	3 (5.1%)	4 (16.0%)
	PSYCHIATRIC DISORDERS	DEPRESSED MOOD	1 (1.7%)	0 (0.0%)
		INSOMNIA	0 (0.0%)	1 (4.0%)
	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ASTHMA	0 (0.0%)	2 (8.0%)
		BRONCHIAL OBSTRUCTION	0 (0.0%)	1 (4.0%)
		COUGH	7 (11.9%)	3 (12.0%)
		SPUTUM RETENTION		1 (4.0%)
	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ERYTHEMA	1 (1.7%)	0 (0.0%)
		PRURITUS	2 (3.4%)	0 (0.0%)
		SKIN REACTION	1 (1.7%)	0 (0.0%)
	VASCULAR DISORDERS	EPISTAXIS	1 (1.7%)	0 (0.0%)
		HAEMOPTYSIS	3 (5.1%)	0 (0.0%)
3-4	HEPATOBILIARY DISORDERS	HYPERTRANSAMINASAEMIA	1 (1.7%)	0 (0.0%)
	INFECTIONS AND INFESTATIONS	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	1 (1.7%)	0 (0.0%)

Note : the percentage into the box represente the percentage of every AE for the group.
(ex : for TACHYCARDIA, *3.4% AE of Roscovitine group was* TACHYCARDIA*)*

Table 9 : Adverse Events description – Group 3 (dose 800 mg)

Grade	SOC	Meddra	Roscovitine group (n;%)	Placebo group (n;%)
1-2	CARDIAC DISORDERS	SINUS TACHYCARDIA	1 (2.9%)	0 (0.0%)
		TACHYCARDIA	1 (2.9%)	0 (0.0%)
	GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	2 (5.9%)	0 (0.0%)
		NAUSEA	3 (8.8%)	0 (0.0%)
	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	DECREASED ACTIVITY	1 (2.9%)	0 (0.0%)
		HYPERTHERMIA	0 (0.0%)	1 (12.5%)
		PYREXIA	2 (5.9%)	0 (0.0%)
	HEPATOBILIARY DISORDERS	HEPATIC FUNCTION ABNORMAL	3 (8.8%)	0 (0.0%)
	INFECTIONS AND INFESTATIONS	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	3 (8.8%)	2 (25.0%)
		RHINITIS	0 (0.0%)	1 (12.5%)
	METABOLISM AND NUTRITION DISORDERS	DECREASED APPETITE	2 (5.9%)	0 (0.0%)
	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	1 (2.9%)	0 (0.0%)
		MUSCULOSKELETAL PAIN	1 (2.9%)	0 (0.0%)
		MYALGIA	2 (5.9%)	0 (0.0%)
		NECK PAIN	1 (2.9%)	0 (0.0%)
	NERVOUS SYSTEM DISORDERS	HEADACHE	3 (8.8%)	1 (12.5%)
		PRESYNCOPE	1 (2.9%)	0 (0.0%)
	PSYCHIATRIC DISORDERS	INSOMNIA	1 (2.9%)	0 (0.0%)
	RENAL AND URINARY DISORDERS	HYPERCREATININAEMIA	1 (2.9%)	0 (0.0%)
	REPRODUCTIVE SYSTEM AND BREAST DISORDERS	DYSMENORRHOEA	1 (2.9%)	0 (0.0%)
	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	COUGH	2 (5.9%)	1 (12.5%)
	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	URTICARIA	0 (0.0%)	1 (12.5%)
	VASCULAR DISORDERS	HAEMOPTYSIS	1 (2.9%)	1 (12.5%)
3-4	INFECTIONS AND INFESTATIONS	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	1 (2.9%)	0 (0.0%)

Note : the percentage into the box represente the percentage of every AE for the group.
(ex : for SINUS TACHYCARDIA, *2.9% AE of Roscovitine group was* SINUS TACHYCARDIA*)*

4. HEMATOLOGY : FOLLOW-UP

Table 10 : Hematology follow-up D28-D0 – Group 1 (dose 200 mg)

		Placebo group (N=4)	Roscovitine group (N=8)
Delta Hemoglobin (g / dl)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.55 +/- 0.38	-0.01 +/- 0.72
	Median (q1;q3)	-0.4 (-0.8;-0.3)	0.1 (-0.6;0.4)
	Min;Max	-1;-0	-1;1
Delta Red blood cells (10^12/ l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.13 +/- 0.16	-0.04 +/- 0.25
	Median (q1;q3)	-0.1 (-0.2;-0.0)	-0.1 (-0.2;0.1)
	Min;Max	-0;0	-0;0
Delta Hematocrit (%)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-1.03 +/- 1.83	-0.27 +/- 2.46
	Median (q1;q3)	-1.1 (-2.6;0.5)	0.3 (-2.0;0.7)
	Min;Max	-3;1	-4;4
Delta VGM (fL)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	1.15 +/- 2.32	0.49 +/- 1.48
	Median (q1;q3)	1.4 (-0.6;2.9)	0.5 (-0.7;1.7)
	Min;Max	-2;4	-2;3
Delta Reticulocytes (10 ^ 9 / l)	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	3.37 +/- 7.59	-17.70 +/- 41.43
	Median (q1;q3)	3.4 (-2.0;8.7)	-12.4 (-22.0;-2.0)
	Min;Max	-2;9	-102;35
Delta Platelet (10^9/l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	13.00 +/- 41.50	-22.38 +/- 45.36
	Median (q1;q3)	20.5 (-14.0;40.0)	-6.5 (-57.5;13.0)
	Min;Max	-44;55	-102;25
Delta Leukocytes (10 ^ 9 / l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.41 +/- 1.82	0.79 +/- 2.48
	Median (q1;q3)	-0.2 (-1.8;0.9)	0.9 (-0.4;2.1)
	Min;Max	-3;2	-4;5
Delta Eosinophils (10 ^ 9 / l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.01 +/- 0.07	-0.01 +/- 0.10
	Median (q1;q3)	0.0 (-0.0;0.1)	0.0 (-0.1;0.1)
	Min;Max	-0;0	-0;0
Delta Basophiles (10 ^ 9 / l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.05 +/- 0.06	0.00 +/- 0.02
	Median (q1;q3)	-0.1 (-0.1;0.0)	0.0 (-0.0;0.0)
	Min;Max	-0;0	-0;0
Delta Neutrophiles (10 ^ 9 / l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.27 +/- 1.61	1.04 +/- 2.61
	Median (q1;q3)	-0.2 (-1.5;1.0)	1.3 (-0.4;2.7)
	Min;Max	-2;1	-4;5
Delta Lymphocytes (10^9/l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.16 +/- 0.25	-0.20 +/- 0.38
	Median (q1;q3)	-0.1 (-0.4;0.0)	-0.2 (-0.5;0.2)
	Min;Max	-1;0	-1;0
Delta Monocytes (10^9/l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.04 +/- 0.06	-0.05 +/- 0.08
	Median (q1;q3)	0.0 (0.0;0.1)	-0.0 (-0.1;0.0)
	Min;Max	0;0	-0;0
Delta patient TCA (secondes)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.00 +/- 0.71	-0.03 +/- 1.06
	Median (q1;q3)	-0.3 (-0.5;0.5)	-0.2 (-0.6;0.9)
	Min;Max	-1;1	-2;1
Delta control TCA (secondes)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.00 +/- 0.00	0.01 +/- 0.04
	Median (q1;q3)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
	Min;Max	0;0	0;0
Delta TP (%)	N (N missing)	3 (1 missing)	5 (3 missing)

		Placebo group (N=4)	Roscovitine group (N=8)
	Mean +/- SD	-1.00 +/- 1.73	-5.60 +/- 4.45
	Median (q1;q3)	0.0 (-3.0;0.0)	-5.0 (-9.0;-3.0)
	Min;Max	-3;0	-11;0
Delta INR	N (N missing)	3 (1 missing)	6 (2 missing)
	Mean +/- SD	0.02 +/- 0.03	0.00 +/- 0.06
	Median (q1;q3)	0.0 (0.0;0.1)	0.0 (0.0;0.0)
	Min;Max	0;0	-0;0

Table 11 : Hematology follow-up D28-D0 – Group 2 (dose 400 mg)

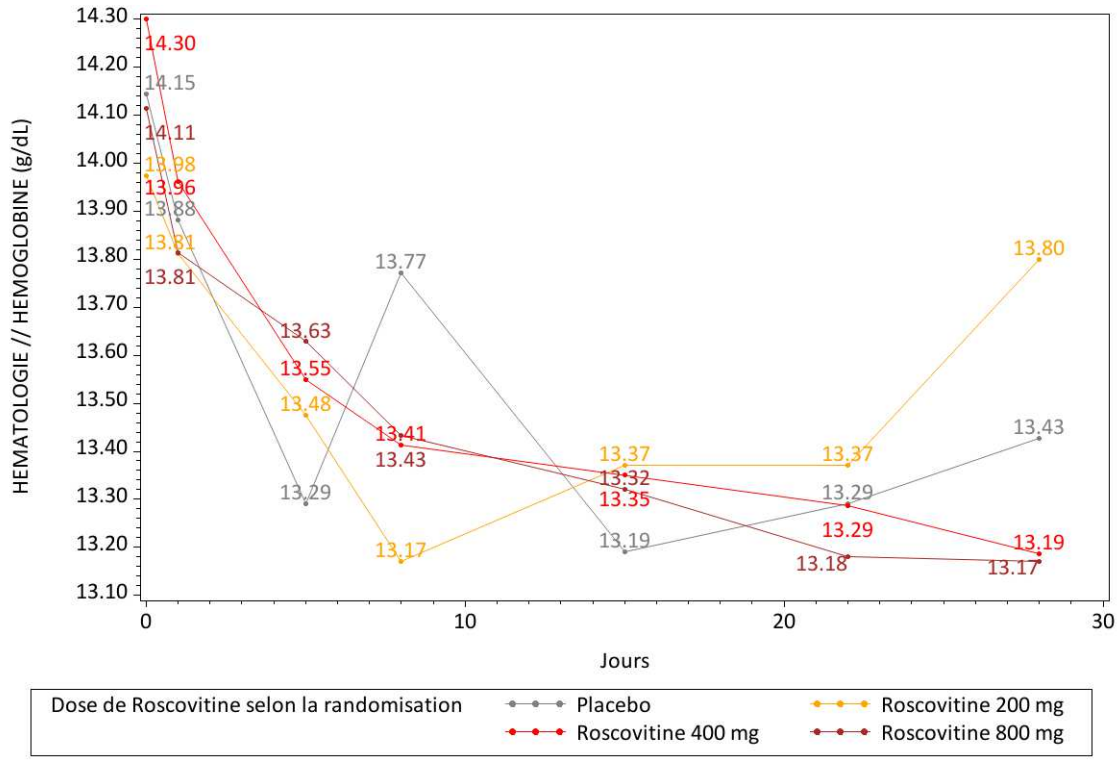
		Placebo group (N=4)	Roscovitine group (N=8)
Delta Hemoglobin (g / dl)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.05 +/- 0.33	-0.78 +/- 1.08
	Median (q1;q3)	-0.2 (-0.3;0.2)	-0.7 (-1.2;-0.1)
	Min;Max	-0;0	-3;1
Delta Red blood cells (10^12/ l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.04 +/- 0.07	-0.30 +/- 0.39
	Median (q1;q3)	-0.1 (-0.1;0.0)	-0.2 (-0.5;-0.1)
	Min;Max	-0;0	-1;0
Delta Hematocrit (%)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.78 +/- 0.52	-2.14 +/- 2.78
	Median (q1;q3)	-1.0 (-1.1;-0.5)	-1.5 (-3.5;-0.4)
	Min;Max	-1;0	-8;1
Delta VGM (fL)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.68 +/- 0.79	0.24 +/- 0.93
	Median (q1;q3)	0.8 (0.1;1.3)	0.0 (-0.4;0.5)
	Min;Max	-0;2	-1;2
Delta Reticulocytes (10 ^ 9 / l)	N (N missing)	3 (1 missing)	4 (4 missing)
	Mean +/- SD	7.10 +/- 4.26	-4.12 +/- 19.63
	Median (q1;q3)	5.0 (4.3;12.0)	-2.4 (-20.9;12.7)
	Min;Max	4;12	-25;13
Delta Platelet (10^9/l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-9.75 +/- 41.88	-10.75 +/- 30.80
	Median (q1;q3)	2.5 (-41.0;21.5)	-14.0 (-31.5;10.0)
	Min;Max	-67;23	-56;41
Delta Leukocytes (10 ^ 9 / l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-2.16 +/- 3.68	0.19 +/- 1.70
	Median (q1;q3)	-2.0 (-5.2;0.9)	0.8 (-1.0;1.5)
	Min;Max	-6;2	-3;2
Delta Eosinophils (10 ^ 9 / l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.04 +/- 0.05	-0.01 +/- 0.07
	Median (q1;q3)	0.0 (-0.0;0.1)	0.0 (-0.1;0.0)
	Min;Max	-0;0	-0;0
Delta Basophiles (10 ^ 9 / l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.01 +/- 0.01	-0.00 +/- 0.02
	Median (q1;q3)	-0.0 (-0.0;0.0)	0.0 (-0.0;0.0)
	Min;Max	-0;0	-0;0
Delta Neutrophiles (10 ^ 9 / l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-2.01 +/- 3.51	0.52 +/- 1.91
	Median (q1;q3)	-1.5 (-4.7;0.7)	1.1 (-0.9;1.9)
	Min;Max	-7;2	-3;3
Delta Lymphocytes (10^9/l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.00 +/- 0.56	-0.25 +/- 0.43
	Median (q1;q3)	0.1 (-0.3;0.3)	-0.1 (-0.5;0.0)
	Min;Max	-1;1	-1;0
Delta Monocytes (10^9/l)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.18 +/- 0.24	-0.14 +/- 0.12
	Median (q1;q3)	-0.2 (-0.4;0.0)	-0.2 (-0.2;-0.0)
	Min;Max	-0;0	-0;0
Delta patient TCA (secondes)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.65 +/- 1.36	0.82 +/- 2.25
	Median (q1;q3)	0.3 (-0.3;1.6)	0.8 (-0.3;1.3)
	Min;Max	-1;3	-3;5
Delta control TCA (secondes)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-2.50 +/- 5.00	-0.67 +/- 1.59
	Median (q1;q3)	0.0 (-5.0;0.0)	0.0 (-0.5;0.0)
	Min;Max	-10;0	-5;0
Delta TP (%)	N (N missing)	3 (1 missing)	6 (2 missing)

		Placebo group (N=4)	Roscovitine group (N=8)
	Mean +/- SD	3.33 +/- 5.77	-2.00 +/- 3.10
	Median (q1;q3)	0.0 (0.0;10.0)	-1.0 (-2.0;0.0)
	Min;Max	0;10	-8;0
Delta INR	N (N missing)	3 (1 missing)	4 (4 missing)
	Mean +/- SD	0.01 +/- 0.01	-0.01 +/- 0.01
	Median (q1;q3)	0.0 (0.0;0.0)	-0.0 (-0.0;0.0)
	Min;Max	0;0	-0;0

Table 12 : Hematology follow-up D28-D0 – Group 3 (dose 800 mg)

		Placebo group (N=3)	Roscovitine group (N=7)
Delta Hemoglobin (g / dl)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-0.87 +/- 0.99	-0.64 +/- 0.46
	Median (q1;q3)	-0.4 (-2.0;-0.2)	-0.6 (-0.7;-0.3)
	Min;Max	-2;-0	-2;-0
Delta Red blood cells (10^12/ l)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-0.36 +/- 0.35	-0.24 +/- 0.18
	Median (q1;q3)	-0.2 (-0.8;-0.1)	-0.2 (-0.3;-0.1)
	Min;Max	-1;-0	-1;-0
Delta Hematocrit (%)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-2.43 +/- 3.86	-2.33 +/- 1.80
	Median (q1;q3)	-1.0 (-6.8;0.5)	-2.0 (-3.0;-1.0)
	Min;Max	-7;1	-6;-1
Delta VGM (fL)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	1.97 +/- 2.00	-0.23 +/- 1.23
	Median (q1;q3)	1.9 (0.0;4.0)	-0.1 (-1.4;1.0)
	Min;Max	0;4	-2;1
Delta Reticulocytes (10 ^ 9 / l)	N (N missing)	2 (1 missing)	3 (4 missing)
	Mean +/- SD	6.00 +/- 26.87	-9.33 +/- 26.35
	Median (q1;q3)	6.0 (-13.0;25.0)	-17.0 (-31.0;20.0)
	Min;Max	-13;25	-31;20
Delta Platelet (10^9/l)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-50.67 +/- 45.76	0.29 +/- 30.65
	Median (q1;q3)	-45.0 (-99.0;-8.0)	3.0 (-6.0;16.0)
	Min;Max	-99;-8	-62;36
Delta Leukocytes (10 ^ 9 / l)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-1.25 +/- 3.00	-0.47 +/- 5.43
	Median (q1;q3)	0.2 (-4.7;0.8)	-0.5 (-6.6;4.0)
	Min;Max	-5;1	-7;8
Delta Eosinophils (10 ^ 9 / l)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	0.06 +/- 0.06	0.07 +/- 0.19
	Median (q1;q3)	0.1 (0.0;0.1)	0.0 (-0.1;0.2)
	Min;Max	0;0	-0;0
Delta Basophiles (10 ^ 9 / l)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	0.06 +/- 0.10	0.01 +/- 0.02
	Median (q1;q3)	0.0 (0.0;0.2)	0.0 (0.0;0.0)
	Min;Max	0;0	-0;0
Delta Neutrophiles (10 ^ 9 / l)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-1.53 +/- 2.90	-0.05 +/- 5.47
	Median (q1;q3)	-0.3 (-4.8;0.6)	0.0 (-5.8;3.8)
	Min;Max	-5;1	-7;9
Delta Lymphocytes (10^9/l)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	0.28 +/- 0.19	-0.22 +/- 0.47
	Median (q1;q3)	0.3 (0.1;0.5)	0.0 (-0.7;0.1)
	Min;Max	0;0	-1;0
Delta Monocytes (10^9/l)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-0.15 +/- 0.25	-0.26 +/- 0.25
	Median (q1;q3)	-0.0 (-0.4;0.0)	-0.2 (-0.4;-0.0)
	Min;Max	-0;0	-1;0
Delta patient TCA (secondes)	N (N missing)	3 (0 missing)	6 (1 missing)
	Mean +/- SD	-0.70 +/- 1.83	0.78 +/- 2.07
	Median (q1;q3)	-0.3 (-2.7;0.9)	0.8 (-0.3;2.9)
	Min;Max	-3;1	-3;3
Delta control TCA (secondes)	N (N missing)	3 (0 missing)	6 (1 missing)
	Mean +/- SD	0.10 +/- 0.36	0.00 +/- 0.00
	Median (q1;q3)	0.0 (-0.2;0.5)	0.0 (0.0;0.0)
	Min;Max	-0;1	0;0
Delta TP (%)	N (N missing)	3 (0 missing)	6 (1 missing)

		Placebo group (N=3)	Roscovitine group (N=7)
	Mean +/- SD	2.33 +/- 3.79	-1.83 +/- 9.58
	Median (q1;q3)	4.0 (-2.0;5.0)	-0.5 (-2.0;5.0)
	Min;Max	-2;5	-20;7
Delta INR	N (N missing)	1 (2 missing)	5 (2 missing)
	Mean +/- SD	0.00 +/- .	0.02 +/- 0.03
	Median (q1;q3)	0.0 (0.0;0.0)	0.0 (0.0;0.0)
	Min;Max	0;0	-0;0



Graph 1 : Evolution of hemoglobin according to the dose of randomized roscovitine

5. BIOCHEMISTRY : FOLLOW-UP

Table 13 : Biochemistry follow-up D28-D0 – Group 1 (dose 200 mg)

		Placebo group (N=4)	Roscovitine group (N=8)
Delta Glucose (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.20 +/- 1.55	-0.08 +/- 1.26
	Median (q1;q3)	-0.5 (-0.7;1.1)	0.0 (-0.8;0.5)
	Min;Max	-1;3	-2;2
Delta Urea (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.08 +/- 0.92	-0.56 +/- 0.95
	Median (q1;q3)	0.3 (-0.7;0.6)	-0.5 (-1.1;0.2)
	Min;Max	-1;1	-2;1
Delta Creatinine (µmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.75 +/- 4.35	-2.25 +/- 5.34
	Median (q1;q3)	0.5 (-3.5;2.0)	-2.5 (-4.0;2.0)
	Min;Max	-7;3	-13;4
Delta Sodium (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.50 +/- 1.29	0.38 +/- 2.67
	Median (q1;q3)	-0.5 (-1.5;0.5)	0.5 (-1.0;1.5)
	Min;Max	-2;1	-4;5
Delta Potassium (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.08 +/- 0.22	0.12 +/- 0.34
	Median (q1;q3)	0.1 (-0.1;0.2)	0.1 (-0.1;0.3)
	Min;Max	-0;0	-0;1
Delta Calcium (mmol/L)	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	-0.04 +/- 0.03	-0.01 +/- 0.06
	Median (q1;q3)	-0.0 (-0.1;-0.0)	-0.0 (-0.1;0.0)
	Min;Max	-0;0	-0;0
Delta Chlorine (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.25 +/- 2.36	-0.63 +/- 1.41
	Median (q1;q3)	-1.0 (-2.0;1.5)	-0.5 (-2.0;0.0)
	Min;Max	-2;3	-2;2
Delta Magnesium (mmol/L)	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	-0.02 +/- 0.01	-0.00 +/- 0.07
	Median (q1;q3)	-0.0 (-0.0;-0.0)	0.0 (-0.1;0.1)
	Min;Max	-0;-0	-0;0
Delta Bicarbonates = total CO2 (mEq/L)	N (N missing)	3 (1 missing)	7 (1 missing)
	Mean +/- SD	-1.07 +/- 2.77	0.30 +/- 2.36
	Median (q1;q3)	-0.7 (-4.0;1.5)	0.3 (-1.9;1.0)
	Min;Max	-4;2	-2;5
Delta Phosphorus (mmol/L)	N (N missing)	3 (1 missing)	6 (2 missing)
	Mean +/- SD	-0.02 +/- 0.10	0.05 +/- 0.11
	Median (q1;q3)	-0.1 (-0.1;0.1)	0.0 (-0.0;0.1)
	Min;Max	-0;0	-0;0
Delta total Bilirubine (µmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.40 +/- 2.70	1.10 +/- 2.14
	Median (q1;q3)	-0.7 (-2.3;1.6)	1.0 (-0.3;2.2)
	Min;Max	-3;3	-2;5
Delta indirect Bilirubine (µmol/L)	N (N missing)	0 (4 missing)	1 (7 missing)
	Mean +/- SD	. +/- .	-0.70 +/- .
	Median (q1;q3)	. (.;.)	-0.7 (-0.7;-0.7)
	Min;Max	.;.	-1;-1
Delta Alkaline Phosphatases (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.75 +/- 16.46	6.00 +/- 14.60
	Median (q1;q3)	5.5 (-9.0;10.5)	3.5 (-3.0;19.5)
	Min;Max	-23;15	-17;25
Delta ASAT (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.75 +/- 2.22	2.75 +/- 4.40
	Median (q1;q3)	1.0 (-1.0;2.5)	2.5 (-1.0;5.0)
	Min;Max	-2;3	-2;11
Delta ALAT (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.50 +/- 4.51	0.25 +/- 5.39

		Placebo group (N=4)	Roscovitine group (N=8)
	Median (q1;q3)	1.0 (-3.5;2.5)	0.0 (-2.5;4.0)
	Min;Max	-7;3	-9;8
Delta LDH (U/L)	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	-4.50 +/- 2.65	-4.17 +/- 46.89
	Median (q1;q3)	-4.0 (-6.5;-2.5)	-13.0 (-38.0;5.0)
	Min;Max	-8;-2	-49;83
Delta Gamma GT (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-1.75 +/- 1.50	2.13 +/- 7.02
	Median (q1;q3)	-2.0 (-3.0;-0.5)	0.5 (-1.5;1.5)
	Min;Max	-3;0	-3;19
Delta Protein Total / Protide (g/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-1.60 +/- 2.30	1.03 +/- 4.75
	Median (q1;q3)	-0.7 (-3.0;-0.2)	1.0 (-1.6;4.2)
	Min;Max	-5;0	-7;8
Delta Albumin (g/L)	N (N missing)	4 (0 missing)	5 (3 missing)
	Mean +/- SD	-1.55 +/- 2.42	-1.28 +/- 4.98
	Median (q1;q3)	-1.6 (-3.6;0.5)	1.0 (-3.0;1.0)
	Min;Max	-4;1	-9;4
Delta Creatine kiase = CK (U/L)	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	-3.00 +/- 7.07	4.43 +/- 43.07
	Median (q1;q3)	-3.0 (-8.0;2.0)	-5.0 (-15.0;5.0)
	Min;Max	-8;2	-43;95
Delta Creatinine clearance (mL/min)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.61 +/- 8.74	2.87 +/- 9.22
	Median (q1;q3)	2.0 (-6.2;7.4)	1.9 (-5.0;8.8)
	Min;Max	-11;9	-8;19
Delta CRP (mg/L)	N (N missing)	3 (1 missing)	7 (1 missing)
	Mean +/- SD	0.03 +/- 0.06	-1.74 +/- 4.22
	Median (q1;q3)	0.0 (0.0;0.1)	0.0 (-4.0;0.3)
	Min;Max	0;0	-10;2

Table 14 : Biochemistry follow-up D28-D0 – Group 2 (dose 400 mg)

		Groupe Placebo (N=4)	Groupe Roscovitine (N=8)
Delta Glucose (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.30 +/- 0.76	0.86 +/- 0.99
	Median (q1;q3)	-0.3 (-1.0;0.4)	0.5 (0.2;1.5)
	Min;Max	-1;0	-0;3
Delta Urea (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.13 +/- 1.50	-0.45 +/- 1.29
	Median (q1;q3)	-0.8 (-1.0;0.8)	-0.5 (-1.0;0.2)
	Min;Max	-1;2	-3;2
Delta Creatinine (µmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	8.00 +/- 5.03	1.50 +/- 5.42
	Median (q1;q3)	9.0 (5.0;11.0)	1.0 (0.0;5.0)
	Min;Max	1;13	-9;9
Delta Sodium (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.25 +/- 3.40	0.88 +/- 1.64
	Median (q1;q3)	-0.5 (-2.0;2.5)	0.5 (-0.5;2.5)
	Min;Max	-3;5	-1;3
Delta Potassium (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.01 +/- 0.19	-0.23 +/- 0.50
	Median (q1;q3)	-0.0 (-0.2;0.1)	-0.2 (-0.5;0.1)
	Min;Max	-0;0	-1;1
Delta Calcium (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.05 +/- 0.05	-0.05 +/- 0.06
	Median (q1;q3)	-0.1 (-0.1;-0.0)	-0.0 (-0.1;0.0)
	Min;Max	-0;0	-0;0
Delta Chlorine (mmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.25 +/- 2.06	1.38 +/- 1.69
	Median (q1;q3)	0.0 (-1.0;1.5)	1.5 (0.0;2.5)
	Min;Max	-2;3	-1;4
Delta Magnesium (mmol/L)	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	-0.01 +/- 0.03	-0.04 +/- 0.06
	Median (q1;q3)	-0.0 (-0.0;0.0)	-0.0 (-0.1;0.0)
	Min;Max	-0;0	-0;0
Delta Bicarbonates = total CO2 (mEq/L)	N (N missing)	4 (0 missing)	5 (3 missing)
	Mean +/- SD	-0.15 +/- 1.04	-2.80 +/- 1.92
	Median (q1;q3)	-0.5 (-0.9;0.6)	-2.0 (-3.0;-2.0)
	Min;Max	-1;1	-6;-1
Delta Phosphorus (mmol/L)	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	0.01 +/- 0.07	-0.11 +/- 0.18
	Median (q1;q3)	0.0 (-0.0;0.1)	-0.2 (-0.2;0.1)
	Min;Max	-0;0	-0;0
Delta total Bilirubine (µmol/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.93 +/- 1.64	-0.66 +/- 3.16
	Median (q1;q3)	-1.4 (-2.2;0.3)	0.0 (-2.0;2.0)
	Min;Max	-2;1	-7;2
Delta indirect Bilirubine (µmol/L)	N (N missing)	1 (3 missing)	4 (4 missing)
	Mean +/- SD	-1.00 +/- .	1.00 +/- 1.41
	Median (q1;q3)	-1.0 (-1.0;-1.0)	0.5 (0.0;2.0)
	Min;Max	-1;-1	0;3
Delta Alkaline Phosphatases (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	3.75 +/- 9.95	-8.38 +/- 17.61
	Median (q1;q3)	0.5 (-3.0;10.5)	-10.0 (-22.5;4.5)
	Min;Max	-4;18	-31;20
Delta ASAT (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-2.25 +/- 2.06	-2.63 +/- 10.42
	Median (q1;q3)	-2.5 (-4.0;-0.5)	0.0 (-10.5;1.0)
	Min;Max	-4;0	-18;16
Delta ALAT (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-2.75 +/- 6.70	-2.38 +/- 11.41

		Groupe Placebo (N=4)	Groupe Roscovitine (N=8)
	Median (q1;q3)	-5.0 (-7.0;1.5)	-0.5 (-8.5;4.0)
	Min;Max	-8;7	-23;14
Delta LDH (U/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	11.00 +/- 16.46	-49.00 +/- 87.31
	Median (q1;q3)	20.0 (-8.0;21.0)	-9.5 (-86.0;8.0)
	Min;Max	-8;21	-227;10
Delta Gamma GT (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-1.00 +/- 2.45	3.25 +/- 24.67
	Median (q1;q3)	-1.0 (-2.5;0.5)	-4.0 (-7.5;0.5)
	Min;Max	-4;2	-15;63
Delta Protein Total / Protide (g/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.95 +/- 1.93	-1.05 +/- 5.19
	Median (q1;q3)	-0.2 (-2.1;0.2)	-2.0 (-3.5;2.0)
	Min;Max	-4;0	-9;8
Delta Albumin (g/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-1.20 +/- 1.57	-0.46 +/- 1.77
	Median (q1;q3)	-1.1 (-2.5;0.1)	0.0 (-1.9;0.6)
	Min;Max	-3;0	-3;2
Delta Creatine kiase = CK (U/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	20.50 +/- 70.78	1.88 +/- 26.17
	Median (q1;q3)	-10.5 (-20.0;61.0)	12.5 (-16.5;18.5)
	Min;Max	-23;126	-44;30
Delta Creatinine clearance (mL/min)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-22.90 +/- 27.75	-5.06 +/- 16.91
	Median (q1;q3)	-12.2 (-38.8;-7.0)	-1.8 (-10.3;1.5)
	Min;Max	-64;-3	-39;20
Delta CRP (mg/L)	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	2.62 +/- 7.35	-3.88 +/- 9.92
	Median (q1;q3)	2.5 (-2.4;7.6)	-1.2 (-3.5;0.0)
	Min;Max	-6;12	-27;6

Table 15 : Biochemistry follow-up D28-D0 – Group 3 (dose 800 mg)

		Groupe Placebo (N=3)	Groupe Roscovitine (N=7)
Delta Glucose (mmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	0.86 +/- 1.93	0.26 +/- 1.75
	Median (q1;q3)	-0.1 (-0.4;3.1)	-0.1 (-0.9;0.6)
	Min;Max	-0;3	-2;4
Delta Urea (mmol/L)	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	0.25 +/- 0.49	-0.85 +/- 1.32
	Median (q1;q3)	0.3 (-0.1;0.6)	-0.5 (-1.8;0.1)
	Min;Max	-0;1	-3;1
Delta Creatinine (µmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	1.67 +/- 3.79	9.14 +/- 17.00
	Median (q1;q3)	0.0 (-1.0;6.0)	4.0 (0.0;9.0)
	Min;Max	-1;6	-5;46
Delta Sodium (mmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	1.00 +/- 2.00	0.86 +/- 2.91
	Median (q1;q3)	1.0 (-1.0;3.0)	1.0 (-2.0;4.0)
	Min;Max	-1;3	-3;5
Delta Potassium (mmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-0.13 +/- 0.15	0.01 +/- 0.21
	Median (q1;q3)	-0.1 (-0.3;0.0)	0.0 (-0.1;0.2)
	Min;Max	-0;0	-0;0
Delta Calcium (mmol/L)	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	-0.07 +/- 0.07	-0.01 +/- 0.06
	Median (q1;q3)	-0.1 (-0.1;-0.0)	0.0 (-0.0;0.0)
	Min;Max	-0;-0	-0;0
Delta Chlorine (mmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	3.33 +/- 1.53	0.57 +/- 1.62
	Median (q1;q3)	3.0 (2.0;5.0)	0.0 (0.0;2.0)
	Min;Max	2;5	-2;3
Delta Magnesium (mmol/L)	N (N missing)	3 (0 missing)	5 (2 missing)
	Mean +/- SD	0.00 +/- 0.04	-0.03 +/- 0.07
	Median (q1;q3)	0.0 (-0.1;0.0)	-0.0 (-0.0;0.0)
	Min;Max	-0;0	-0;0
Delta Bicarbonates = total CO2 (mEq/L)	N (N missing)	3 (0 missing)	5 (2 missing)
	Mean +/- SD	0.67 +/- 1.15	1.00 +/- 1.87
	Median (q1;q3)	0.0 (0.0;2.0)	1.0 (1.0;2.0)
	Min;Max	0;2	-2;3
Delta Phosphorus (mmol/L)	N (N missing)	3 (0 missing)	5 (2 missing)
	Mean +/- SD	0.01 +/- 0.21	0.04 +/- 0.18
	Median (q1;q3)	0.0 (-0.2;0.2)	-0.1 (-0.1;0.1)
	Min;Max	-0;0	-0;0
Delta total Bilirubine (µmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-3.10 +/- 5.37	1.00 +/- 4.90
	Median (q1;q3)	0.0 (-9.3;0.0)	0.0 (-1.0;2.0)
	Min;Max	-9;0	-5;11
Delta indirect Bilirubine (µmol/L)	N (N missing)	1 (2 missing)	3 (4 missing)
	Mean +/- SD	1.00 +/- .	-0.33 +/- 1.15
	Median (q1;q3)	1.0 (1.0;1.0)	-1.0 (-1.0;1.0)
	Min;Max	1;1	-1;1
Delta Alkaline Phosphatases (U/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-11.33 +/- 19.30	37.71 +/- 110.71
	Median (q1;q3)	-5.0 (-33.0;4.0)	1.0 (-16.0;16.0)
	Min;Max	-33;4	-23;287
Delta ASAT (U/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-2.33 +/- 1.53	5.86 +/- 21.71
	Median (q1;q3)	-2.0 (-4.0;-1.0)	2.0 (-4.0;3.0)
	Min;Max	-4;-1	-15;53
Delta ALAT (U/L)	N (N missing)	3 (0 missing)	7 (0 missing)

		Groupe Placebo (N=3)	Groupe Roscovitine (N=7)
	Mean +/- SD	5.00 +/- 1.73	18.00 +/- 56.76
	Median (q1;q3)	6.0 (3.0;6.0)	-3.0 (-5.0;4.0)
	Min;Max	3;6	-14;146
Delta LDH (U/L)	N (N missing)	3 (0 missing)	6 (1 missing)
	Mean +/- SD	-39.00 +/- 29.82	-8.83 +/- 20.88
	Median (q1;q3)	-47.0 (-64.0;-6.0)	-2.0 (-4.0;2.0)
	Min;Max	-64;-6	-51;4
Delta Gamma GT (U/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-0.67 +/- 1.15	14.14 +/- 31.81
	Median (q1;q3)	0.0 (-2.0;0.0)	3.0 (-2.0;18.0)
	Min;Max	-2;0	-8;84
Delta Protein Total / Protide (g/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-4.67 +/- 3.21	-0.16 +/- 3.56
	Median (q1;q3)	-6.0 (-7.0;-1.0)	-1.0 (-2.0;2.0)
	Min;Max	-7;-1	-5;6
Delta Albumin (g/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-1.57 +/- 1.25	0.53 +/- 2.80
	Median (q1;q3)	-1.0 (-3.0;-0.7)	0.0 (-2.0;3.7)
	Min;Max	-3;-1	-3;4
Delta Creatine kiase = CK (U/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	17.67 +/- 31.53	-11.00 +/- 31.26
	Median (q1;q3)	11.0 (-10.0;52.0)	-3.0 (-17.0;6.0)
	Min;Max	-10;52	-76;21
Delta Creatinine clearance (mL/min)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-1.52 +/- 5.33	-13.88 +/- 20.89
	Median (q1;q3)	1.5 (-7.7;1.6)	-8.0 (-17.2;0.0)
	Min;Max	-8;2	-58;3
Delta CRP (mg/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-12.43 +/- 39.06	2.31 +/- 16.79
	Median (q1;q3)	0.0 (-56.2;18.9)	4.0 (-16.0;9.2)
	Min;Max	-56;19	-18;32

6. URINE : FOLLOW-UP

Table 16 : Urine follow-up D28-D0 – Group 1 (dose 200 mg)

		Placebo group (N=4)	Roscovitine group (N=8)
Delta Glucose (mmol/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	0.10 +/- 0.10	-0.29 +/- 0.89
	Median (q1;q3)	0.1 (0.0;0.2)	0.0 (-0.6;0.3)
	Min;Max	0;0	-2;1
Delta Urinary Protein / Urinary Protein (g/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	-0.03 +/- 0.03	0.01 +/- 0.03
	Median (q1;q3)	-0.0 (-0.1;0.0)	0.0 (-0.0;0.0)
	Min;Max	-0;0	-0;0
Delta Microalbumin (mg/L)	N (N missing)	1 (3 missing)	7 (1 missing)
	Mean +/- SD	-17.00 +/- .	-0.56 +/- 3.92
	Median (q1;q3)	-17.0 (-17.0;-17.0)	0.0 (0.0;2.1)
	Min;Max	-17;-17	-9;3
Delta Potassium (mmol/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	-14.60 +/- 14.93	8.13 +/- 17.24
	Median (q1;q3)	-7.0 (-31.8;-5.0)	14.5 (-6.5;23.0)
	Min;Max	-32;-5	-21;24
Delta Sodium (mmol/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	-3.00 +/- 76.62	15.50 +/- 47.76
	Median (q1;q3)	-8.0 (-77.0;76.0)	3.0 (-14.5;48.5)
	Min;Max	-77;76	-49;99
Delta Urea (mmol/L)	N (N missing)	2 (2 missing)	5 (3 missing)
	Mean +/- SD	-40.17 +/- 45.02	-136.20 +/- 170.18
	Median (q1;q3)	-40.2 (-72.0;-8.3)	-62.0 (-304.0;-56.0)
	Min;Max	-72;-8	-324;65
Delta Creatinine (mmol/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	-2.52 +/- 0.52	-0.12 +/- 7.28
	Median (q1;q3)	-2.4 (-3.1;-2.1)	-1.4 (-3.1;0.6)
	Min;Max	-3;-2	-9;16
Delta Osmolarity	N (N missing)	0 (4 missing)	0 (8 missing)
	Mean +/- SD	. +/- .	. +/- .
	Median (q1;q3)	. (.;.)	. (.;.)
	Min;Max	.;.	.;.
Delta uric acid (mmol/L)	N (N missing)	2 (2 missing)	7 (1 missing)
	Mean +/- SD	-1.05 +/- 0.90	-19.40 +/- 50.35
	Median (q1;q3)	-1.0 (-1.7;-0.4)	-0.1 (-3.4;1.1)
	Min;Max	-2;-0	-134;2
Delta Ph	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	-0.75 +/- 0.65	0.13 +/- 0.52
	Median (q1;q3)	-0.8 (-1.3;-0.3)	0.0 (-0.3;0.5)
	Min;Max	-2;0	-1;1
Delta Density	N (N missing)	4 (0 missing)	6 (2 missing)
	Mean +/- SD	-0.01 +/- 0.01	-0.00 +/- 0.01
	Median (q1;q3)	-0.0 (-0.0;-0.0)	-0.0 (-0.0;0.0)
	Min;Max	-0;0	-0;0

Table 17 : Urine follow-up D28-D0 – Group 2 (dose 400 mg)

		Placebo group (N=4)	Roscovitine group (N=8)
Delta Glucose (mmol/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	-9.29 +/- 16.11	0.09 +/- 0.13
	Median (q1;q3)	-0.2 (-27.9;0.2)	0.1 (0.0;0.1)
	Min;Max	-28;0	-0;0
Delta Urinary Protein / Urinary Protein (g/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	-0.02 +/- 0.07	-0.02 +/- 0.04
	Median (q1;q3)	0.0 (-0.1;0.0)	-0.0 (-0.0;0.0)
	Min;Max	-0;0	-0;0
Delta Microalbumin (mg/L)	N (N missing)	3 (1 missing)	5 (3 missing)
	Mean +/- SD	-1.83 +/- 8.40	1.16 +/- 2.43
	Median (q1;q3)	0.0 (-11.0;5.5)	0.0 (0.0;2.0)
	Min;Max	-11;6	-1;5
Delta Potassium (mmol/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	-26.33 +/- 18.04	13.85 +/- 28.87
	Median (q1;q3)	-25.0 (-45.0;-9.0)	12.8 (-5.8;31.5)
	Min;Max	-45;-9	-29;63
Delta Sodium (mmol/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	-9.33 +/- 90.74	-1.88 +/- 35.19
	Median (q1;q3)	-17.0 (-96.0;85.0)	-5.5 (-29.5;15.5)
	Min;Max	-96;85	-42;66
Delta Urea (mmol/L)	N (N missing)	3 (1 missing)	7 (1 missing)
	Mean +/- SD	-26.83 +/- 186.91	30.13 +/- 113.13
	Median (q1;q3)	-18.0 (-218.0;155.5)	11.6 (-61.8;176.0)
	Min;Max	-218;156	-111;186
Delta Creatinine (mmol/L)	N (N missing)	3 (1 missing)	8 (0 missing)
	Mean +/- SD	2.00 +/- 5.99	1.45 +/- 3.50
	Median (q1;q3)	0.8 (-3.3;8.5)	1.4 (-1.9;4.4)
	Min;Max	-3;8	-3;7
Delta Osmolarity	N (N missing)	0 (4 missing)	0 (8 missing)
	Mean +/- SD	. +/- .	. +/- .
	Median (q1;q3)	. (.;.)	. (.;.)
	Min;Max	.;.	.;.
Delta uric acid (mmol/L)	N (N missing)	1 (3 missing)	2 (6 missing)
	Mean +/- SD	0.49 +/- .	0.56 +/- 1.47
	Median (q1;q3)	0.5 (0.5;0.5)	0.6 (-0.5;1.6)
	Min;Max	0;0	-0;2
Delta Ph	N (N missing)	4 (0 missing)	7 (1 missing)
	Mean +/- SD	-0.25 +/- 0.50	-0.21 +/- 0.39
	Median (q1;q3)	-0.5 (-0.5;0.0)	0.0 (-0.5;0.0)
	Min;Max	-1;1	-1;0
Delta Density	N (N missing)	4 (0 missing)	8 (0 missing)
	Mean +/- SD	0.01 +/- 0.01	-0.02 +/- 0.04
	Median (q1;q3)	0.0 (0.0;0.0)	-0.0 (-0.0;0.0)
	Min;Max	0;0	-0;0

Table 18 : Urine follow-up D28-D0 – Group 3 (dose 800 mg)

		Placebo group (N=3)	Roscovitine group (N=7)
Delta Glucose (mmol/L)	N (N missing)	2 (1 missing)	7 (0 missing)
	Mean +/- SD	-26.61 +/- 40.03	-0.04 +/- 0.13
	Median (q1;q3)	-26.6 (-54.9;1.7)	-0.0 (-0.1;0.0)
	Min;Max	-55;2	-0;0
Delta Urinary Protein / Urinary Protein (g/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	0.03 +/- 0.03	-0.04 +/- 0.09
	Median (q1;q3)	0.0 (0.0;0.1)	-0.0 (-0.0;0.0)
	Min;Max	0;0	-0;0
Delta Microalbumin (mg/L)	N (N missing)	2 (1 missing)	5 (2 missing)
	Mean +/- SD	0.60 +/- 0.85	5.92 +/- 15.91
	Median (q1;q3)	0.6 (0.0;1.2)	11.2 (-3.3;15.5)
	Min;Max	0;1	-17;23
Delta Potassium (mmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	-8.93 +/- 47.54	-25.17 +/- 24.77
	Median (q1;q3)	17.0 (-63.8;20.0)	-26.0 (-38.0;1.9)
	Min;Max	-64;20	-69;3
Delta Sodium (mmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	27.00 +/- 88.00	-28.57 +/- 59.78
	Median (q1;q3)	27.0 (-61.0;115.0)	-10.0 (-55.0;1.0)
	Min;Max	-61;115	-151;32
Delta Urea (mmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	156.00 +/- 93.15	-115.60 +/- 57.65
	Median (q1;q3)	150.0 (66.0;252.0)	-129.0 (-172.0;-76.7)
	Min;Max	66;252	-173;-8
Delta Creatinine (mmol/L)	N (N missing)	3 (0 missing)	7 (0 missing)
	Mean +/- SD	10.50 +/- 6.92	-2.74 +/- 3.63
	Median (q1;q3)	8.5 (4.8;18.2)	-3.4 (-6.2;0.1)
	Min;Max	5;18	-6;4
Delta Osmolarity	N (N missing)	0 (3 missing)	0 (7 missing)
	Mean +/- SD	. +/- .	. +/- .
	Median (q1;q3)	. (.;.)	. (.;.)
	Min;Max	.;.	.;.
Delta uric acid (mmol/L)	N (N missing)	2 (1 missing)	3 (4 missing)
	Mean +/- SD	2.80 +/- 0.93	-1.99 +/- 2.27
	Median (q1;q3)	2.8 (2.1;3.5)	-2.2 (-4.2;0.4)
	Min;Max	2;3	-4;0
Delta Ph	N (N missing)	3 (0 missing)	6 (1 missing)
	Mean +/- SD	-0.17 +/- 0.29	0.33 +/- 0.75
	Median (q1;q3)	0.0 (-0.5;0.0)	0.0 (0.0;1.0)
	Min;Max	-1;0	-1;2
Delta Density	N (N missing)	3 (0 missing)	6 (1 missing)
	Mean +/- SD	0.00 +/- 0.01	0.00 +/- 0.01
	Median (q1;q3)	0.0 (-0.0;0.0)	-0.0 (-0.0;0.0)
	Min;Max	-0;0	-0;0

7. PHARMACOKINETICS

Table 19 : Pharmacokinetics of Roscovitine and Metabolite M3 by Randomized Roscovitine Dose

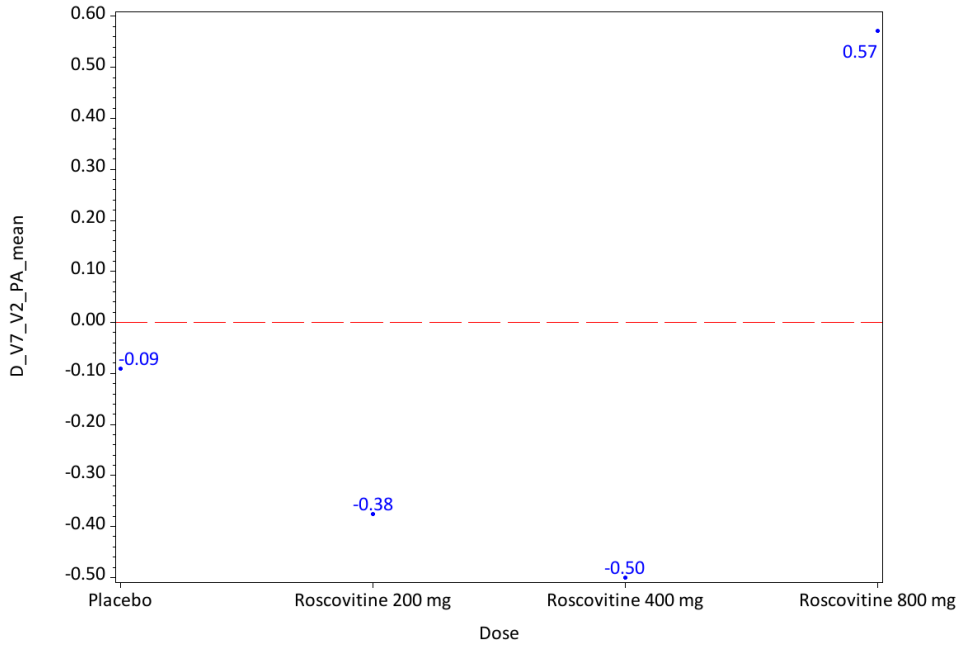
		Roscovitine 200mg (N=8)	Roscovitine 400mg (N=8)	Roscovitine 800mg (N=7)
Roscovitine				
Cmax	N (N missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	133.55 +/- 102.81	621.78 +/- 565.27	1244.86 +/- 1155.76
	Median (q1;q3)	97.4 (83.5;176.0)	417.5 (158.0;1118.0)	847.0 (759.0;1276.0)
	Min;Max	11;344	54;1533	307;3783
Tmax	N (N missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	2.13 +/- 1.25	2.25 +/- 1.16	4.29 +/- 1.80
	Median (q1;q3)	2.0 (1.0;3.0)	2.0 (1.5;3.0)	4.0 (2.0;6.0)
	Min;Max	1;4	1;4	2;6
AUCt	N (N missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	716.19 +/- 1104.61	5286.75 +/- 6770.25	25655.86 +/- 25277.61
	Median (q1;q3)	336.0 (187.5;627.0)	2425.0 (1057.0;7388.0)	23709.0 (3539.0;59508.0)
	Min;Max	44;3385	344;20210	1767;60437
AUCinf	N (N missing)	4 (4 missing)	7 (1 missing)	3 (4 missing)
	Mean +/- SD	1325.25 +/- 1561.92	5768.43 +/- 7452.57	31384.33 +/- 28487.87
	Median (q1;q3)	683.5 (364.0;2286.5)	1485.0 (811.0;9969.0)	25947.0 (6007.0;62199.0)
	Min;Max	303;3631	407;20769	6007;62199
1/2 life	N (N missing)	4 (4 missing)	7 (1 missing)	3 (4 missing)
	Mean +/- SD	9.10 +/- 14.54	13.67 +/- 14.95	31.10 +/- 9.29
	Median (q1;q3)	2.0 (1.7;16.6)	3.7 (1.4;26.8)	26.4 (25.1;41.8)
	Min;Max	2;31	1;36	25;42
Métabolite M3				
Cmax	N (N missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	651.95 +/- 443.54	1274.03 +/- 896.65	1578.14 +/- 1250.59
	Median (q1;q3)	615.0 (419.0;730.0)	1265.5 (573.0;1821.0)	906.0 (758.0;1928.0)
	Min;Max	88;1600	62;2811	754;4190
Tmax	N (N missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	1.50 +/- 0.53	2.00 +/- 1.41	2.86 +/- 1.46
	Median (q1;q3)	1.5 (1.0;2.0)	2.0 (1.0;3.0)	4.0 (1.0;4.0)
	Min;Max	1;2	0;4	1;4
AUCt	N (N missing)	8 (0 missing)	8 (0 missing)	7 (0 missing)
	Mean +/- SD	2409.88 +/- 2521.65	11297.13 +/- 13291.16	40366.29 +/- 36202.06
	Median (q1;q3)	1799.5 (1012.0;2546.0)	4714.0 (2759.0;20027.5)	29342.0 (17641.0;47944.0)
	Min;Max	270;8294	262;35114	5881;116512
AUCinf	N (N missing)	8 (0 missing)	8 (0 missing)	6 (1 missing)
	Mean +/- SD	2702.50 +/- 2830.44	12521.63 +/- 13894.35	30211.50 +/- 15576.54
	Median (q1;q3)	1985.5 (1039.5;2975.0)	6662.5 (2899.0;22631.5)	30938.0 (17965.0;40664.0)
	Min;Max	342;9278	288;35499	8577;52187
1/2 life	N (N missing)	8 (0 missing)	8 (0 missing)	6 (1 missing)
	Mean +/- SD	20.10 +/- 27.24	34.59 +/- 41.30	43.10 +/- 24.78
	Median (q1;q3)	5.0 (1.8;34.1)	29.7 (2.3;42.9)	36.2 (32.3;38.1)
	Min;Max	1;78	1;126	23;93

8. EFFICACY CRITERIA

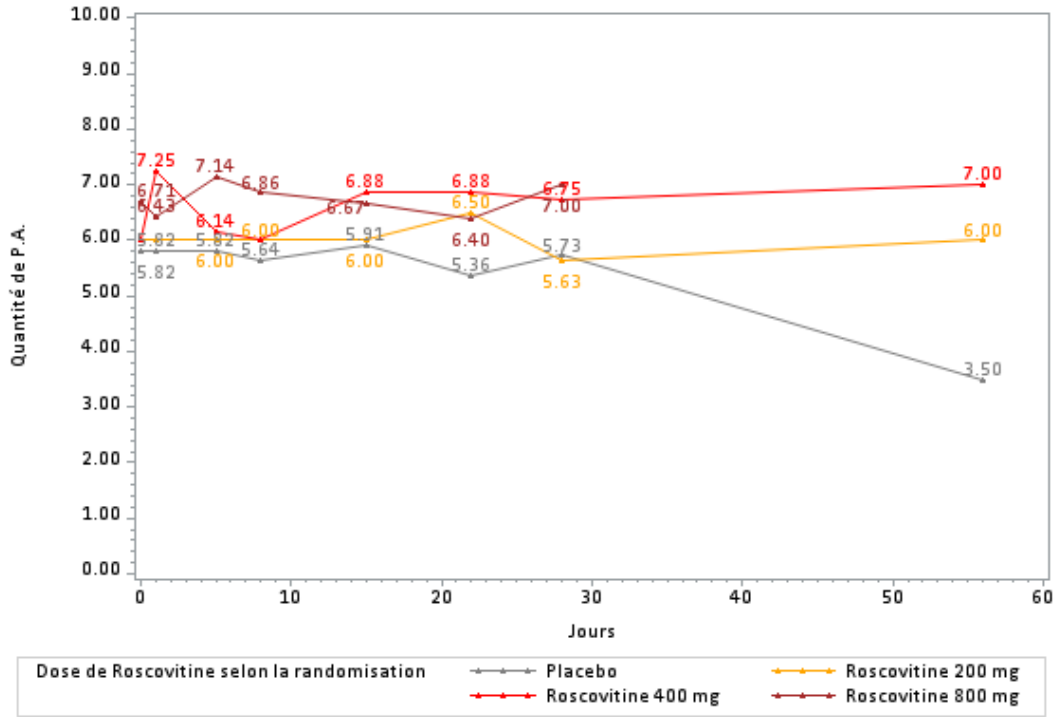
Table 20 : Concentration of PA

	Roscovitine dose				
	0 mg (Placebo)	200 mg	400 mg	800 mg	p*
D1	5.82 +/- 1.94	6.00 +/- 1.31	7.25 +/- 0.71	6.43 +/- 0.79	
D28	5.73 +/- 2.37	5.63 +/- 1.41	6.75 +/- 1.39	7.00 +/- 0.58	
Delta D28-D1	-0.09 +/- 1.38	-0.38 +/- 0.74	-0.50 +/- 1.31	0.57 +/- 0.98	0.344
p (Wilcoxon test)		0.502	0.463	0.359	

** Anova analysis, adjusted to D1 value (PROC MIXED)*
PA. for Pseudomonas Aerginosa (log transformed)



Graph 2 : representation of Delta D28-d1 for amount of P.A. according to randomized roscovitine dose

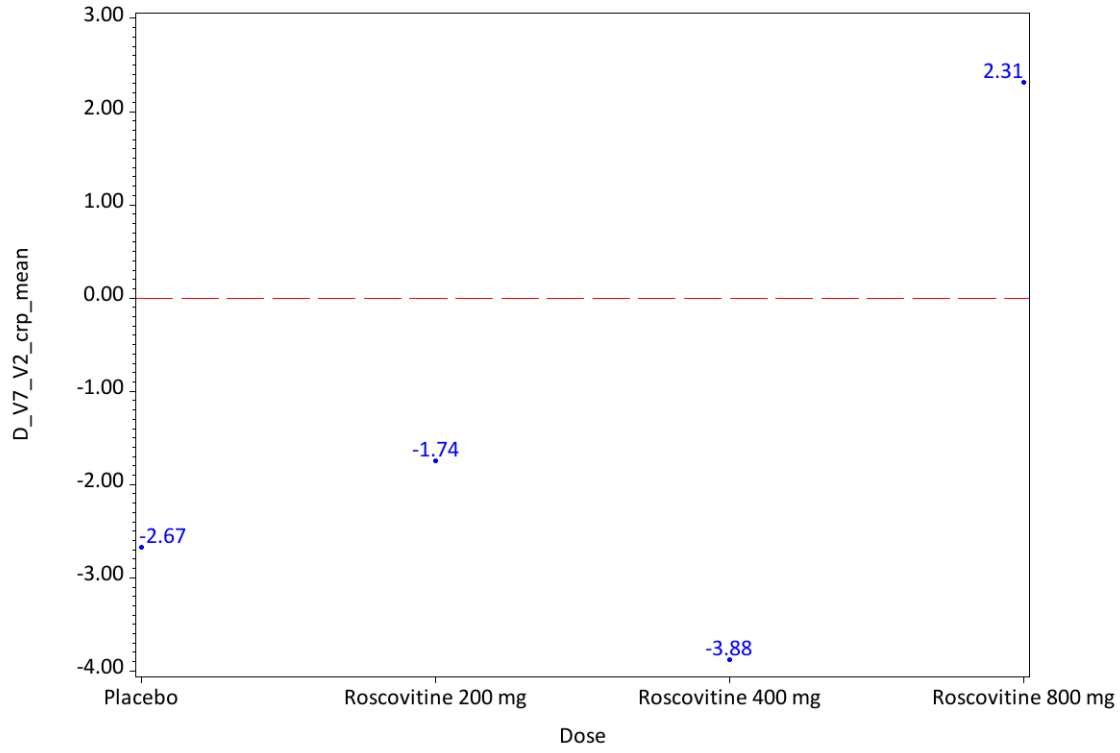


Graph 3 : Evolution of the amount of P.A. according to the dose of randomized roscovitine

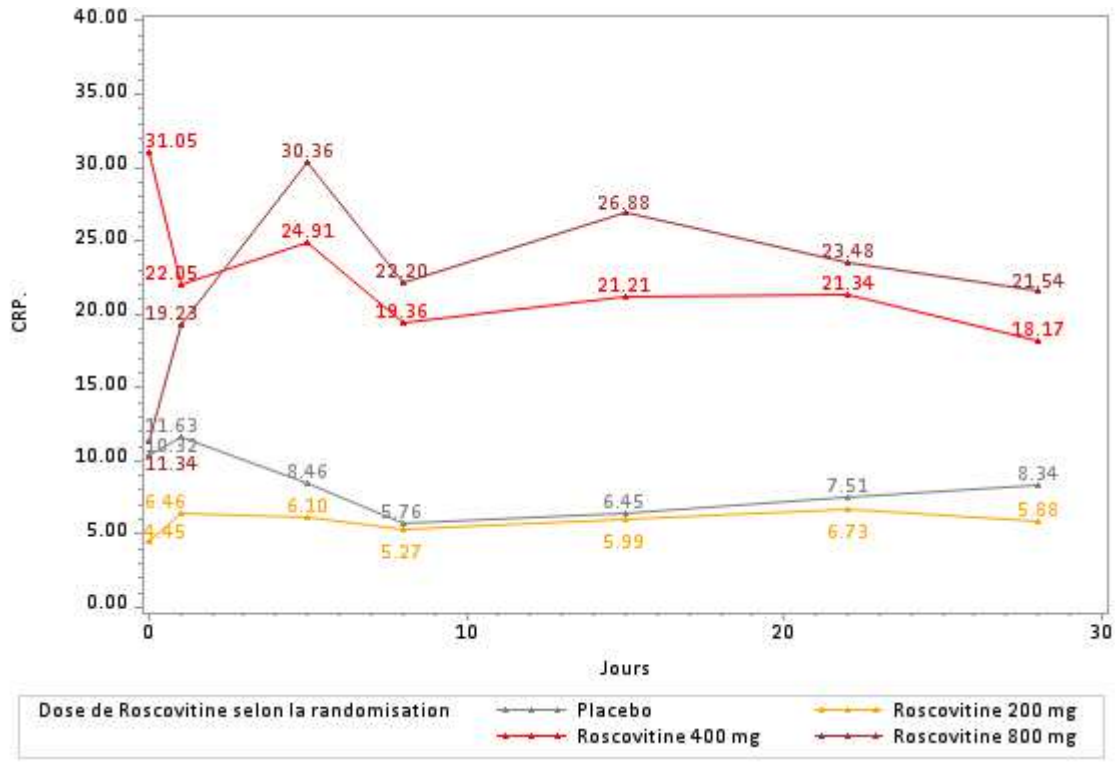
Table 21 : CRP (biochemistry)

	Roscovitine dose				
	0 mg (Placebo)	200 mg	400 mg	800 mg	p*
D1	11.63 +/- 20.19	6.46 +/- 7.27	22.05 +/- 17.56	19.23 +/- 15.98	
D28	8.34 +/- 7.62	5.88 +/- 5.15	18.18 +/- 12.05	21.54 +/- 15.68	
Delta D28-D1	-2.67 +/- 20.09	-1.74 +/- 4.22	-3.88 +/- 9.92	2.31 +/- 16.79	0.079
p (Wilcoxon test)		0.362	0.182	0.810	

** Anova analysis, adjusted to D1 value (PROC MIXED)*



Graph 4 : Representation of Delta CRP D28-D1 according to randomized roscovitine

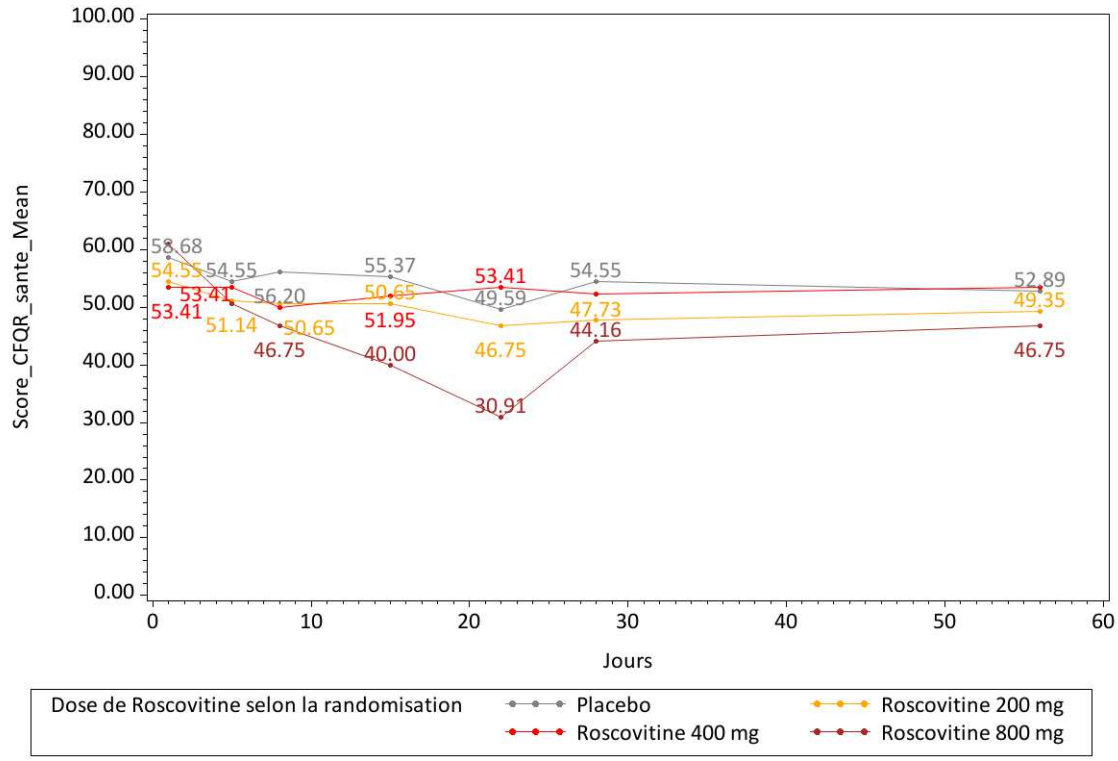


Graph 5 : Evolution of CRP according to the dose of randomized roscovitine

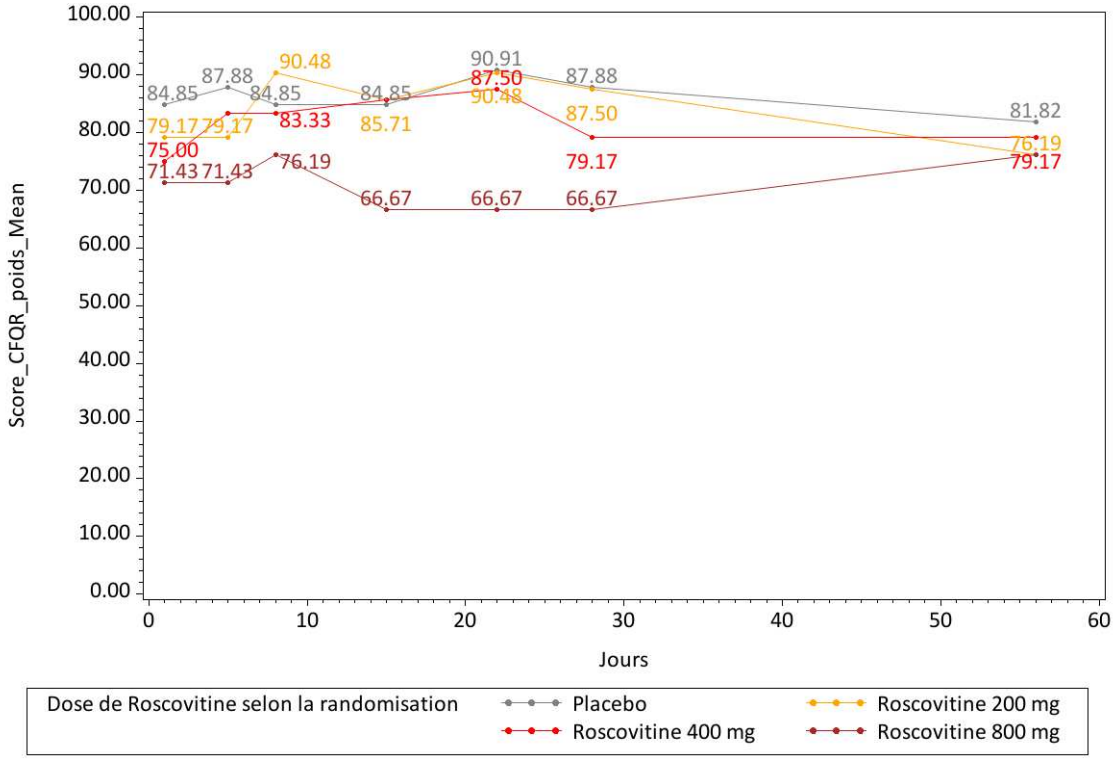
Table 22 : Fields of the CFQ-R

	Roscovitine dose				
Delta D28-D1	**0 mg (Placebo)**	**200 mg**	**400 mg**	**800 mg**	**p***
Perception of health status	-4.13 +/- 13.71	-6.82 +/- 9.41	-1.14 +/- 13.25	-16.88 +/- 25.94	0.342
Symptom					
Weight	3.03 +/- 23.35	8.33 +/- 15.43	4.17 +/- 27.82	-4.76 +/- 12.60	0.543
Digestive symptoms	3.03 +/- 16.36	-2.08 +/- 30.13	4.17 +/- 19.42	-2.38 +/- 15.00	0.757
Respiratory symptoms	3.97 +/- 6.63	10.12 +/- 15.57	2.38 +/- 16.30	-5.44 +/- 13.86	0.184
Quality of life - generic dimensions					
Energy	-3.79 +/- 17.23	-3.13 +/- 11.73	-5.21 +/- 16.63	-11.90 +/- 9.45	0.498
Physical	3.03 +/- 15.93	-2.60 +/- 8.61	-3.65 +/- 12.68	0.00 +/- 10.21	0.644
Psychic	0.00 +/- 15.49	3.33 +/- 11.27	2.50 +/- 10.65	-7.62 +/- 11.17	0.392
Role	-1.79 +/- 4.72	-6.25 +/- 12.50	0.00 +/- 0.00	-2.08 +/- 9.41	0.885
Social	-6.82 +/- 12.81	2.08 +/- 15.27	5.21 +/- 12.55	-5.95 +/- 9.27	0.168
Quality of life - dimensions specific to cystic fibrosis					
Food	1.52 +/- 11.68	4.17 +/- 7.72	-4.17 +/- 11.79	-2.38 +/- 6.30	0.359
Body image	-3.03 +/- 11.21	5.56 +/- 18.78	5.56 +/- 18.78	4.76 +/- 17.98	0.410
Marginalization	1.01 +/- 18.89	9.72 +/- 9.27	1.39 +/- 16.20	0.00 +/- 6.42	0.502
Treatments	-9.09 +/- 15.57	4.17 +/- 7.72	0.00 +/- 8.91	2.38 +/- 6.30	0.152

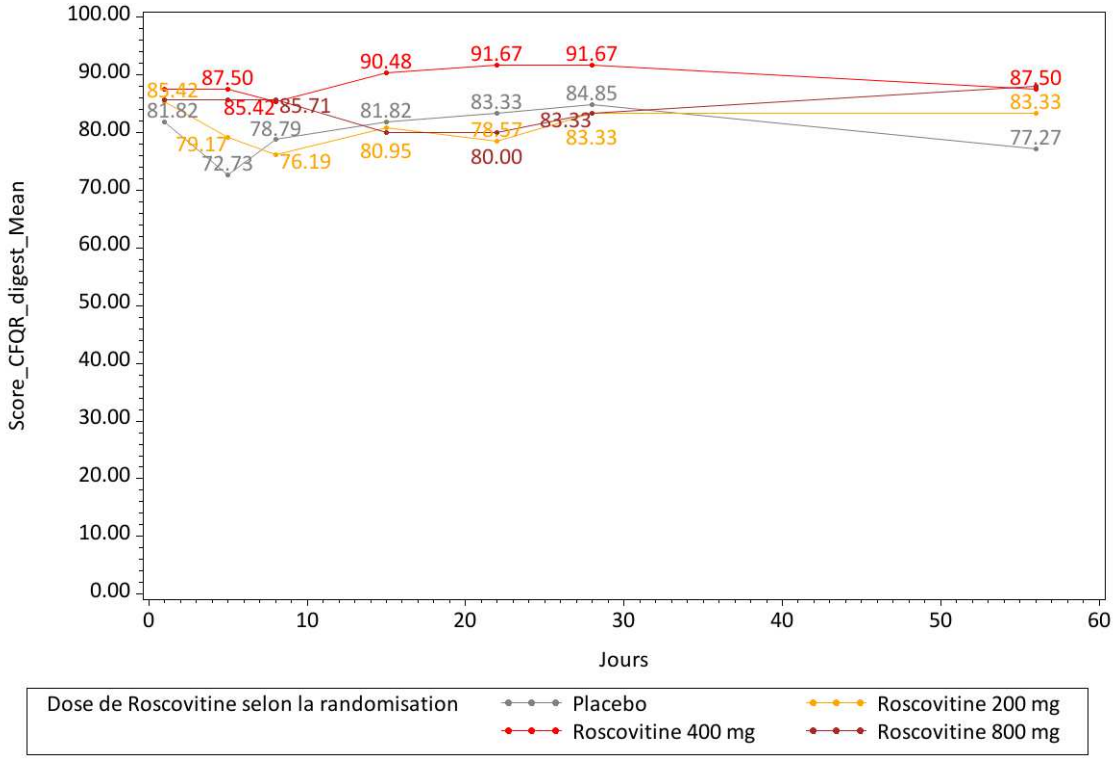
** Anova analysis, adjusted to D1 value (PROC MIXED)*



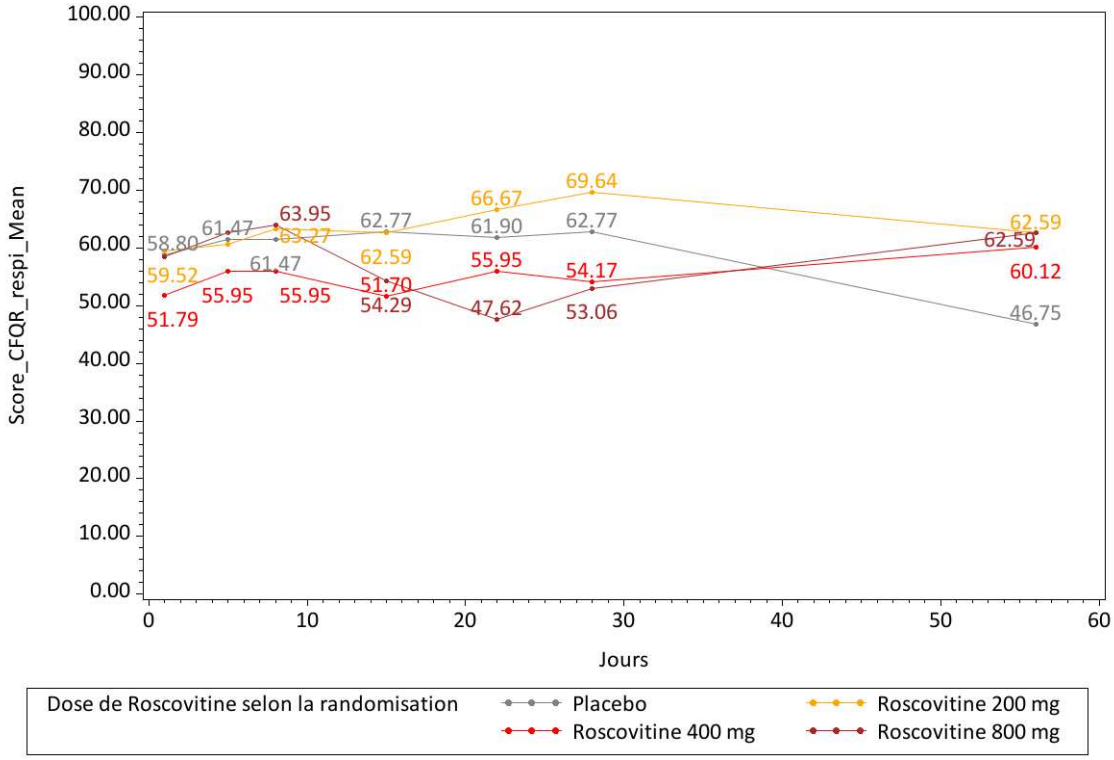
Graph 6 : Evolution of the field « Perception of health status» during the visits, for each dose of randomized Roscovitine



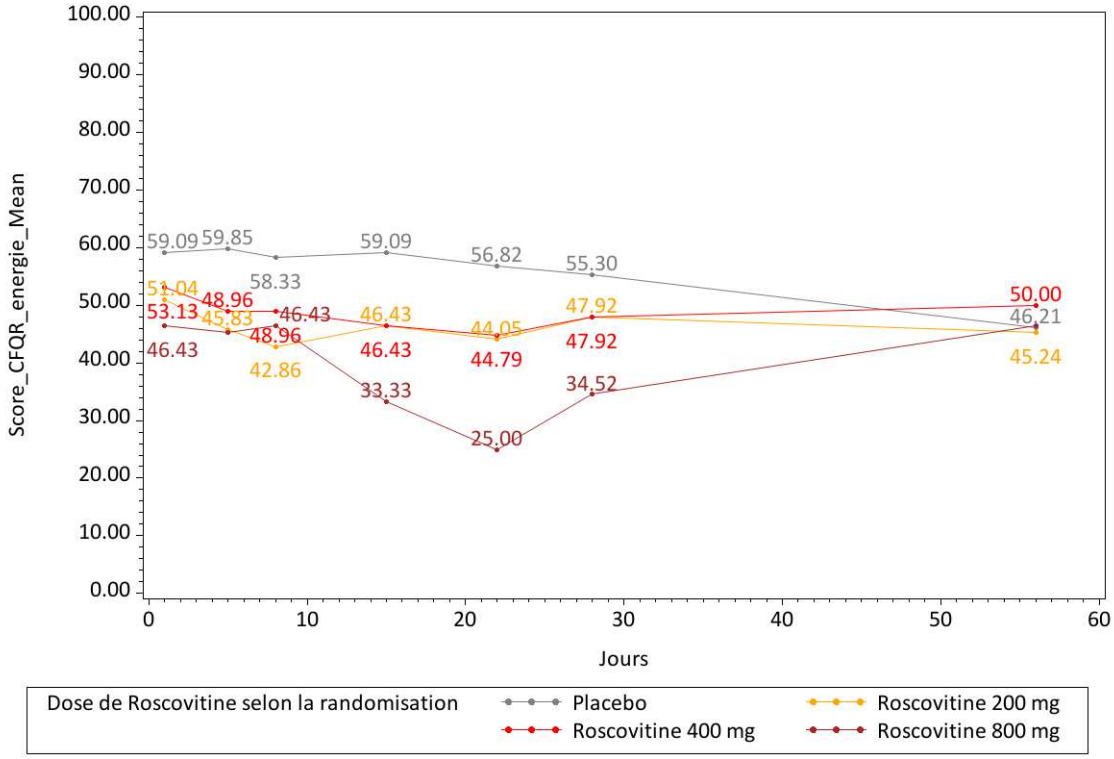
Graph 7: Evolution of the field « Weight » during the visits, for each dose of randomized Roscovitine



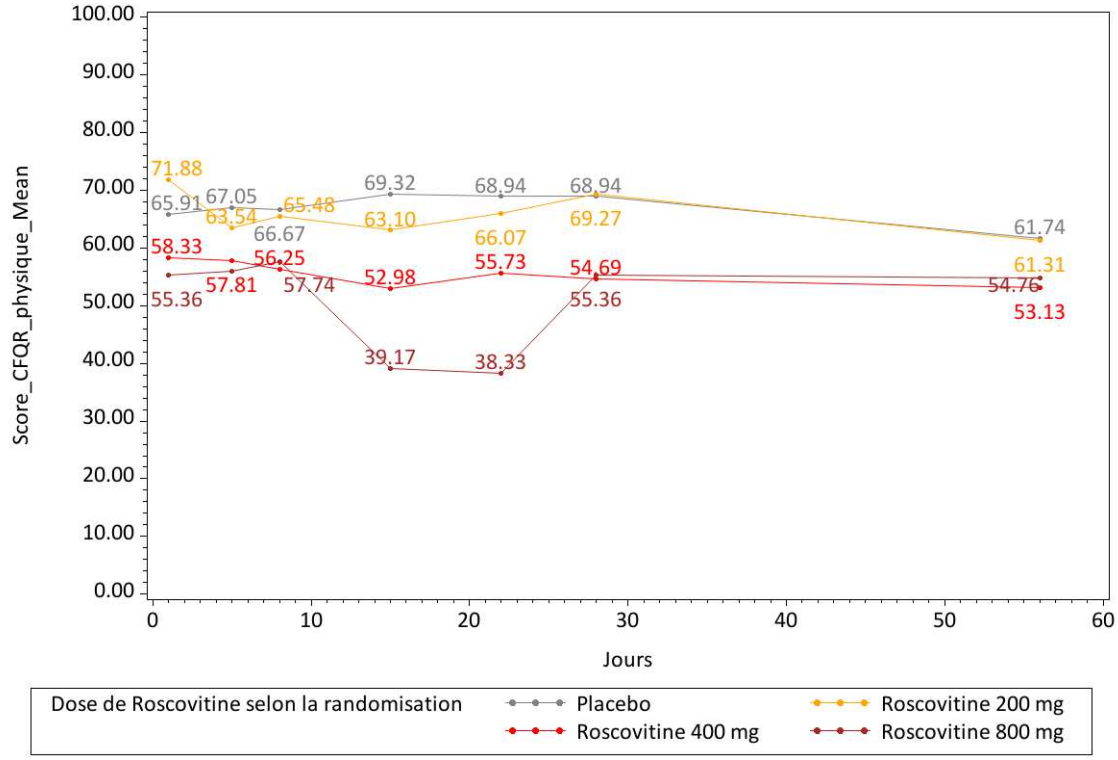
Graph 8 : Evolution of the field « Digestive symptoms » during the visits, for each dose of randomized Roscovitine



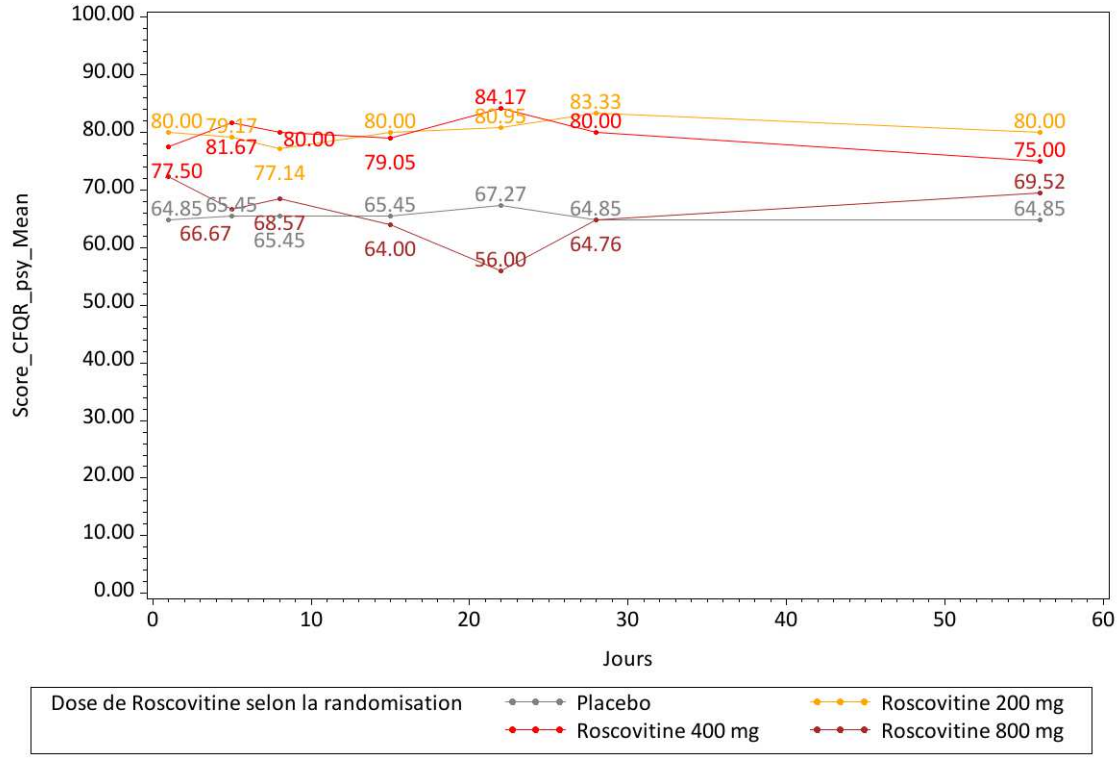
Graph 9 : Evolution of the field « Respiratory symptoms» during the visits, for each dose of randomized Roscovitine



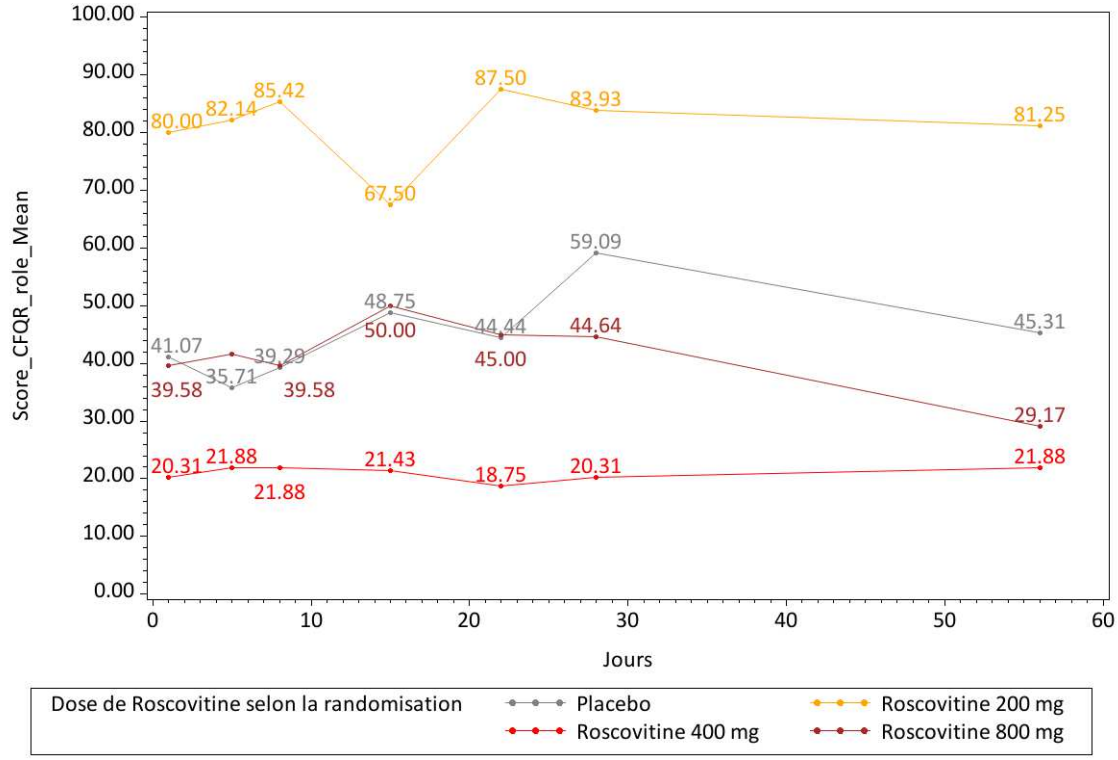
Graph 10 : Evolution of the field « Energy » during the visits, for each dose of randomized Roscovitine



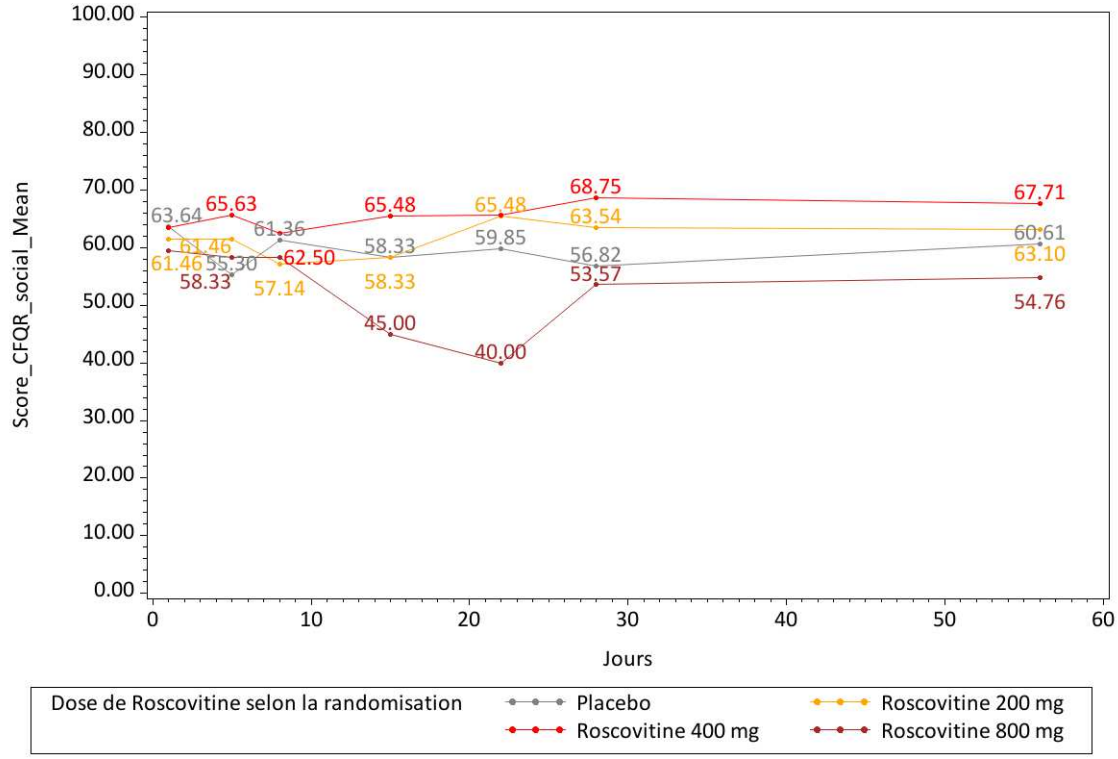
Graph 11 : Evolution of the field « physical » during the visits, for each dose of randomized Roscovitine



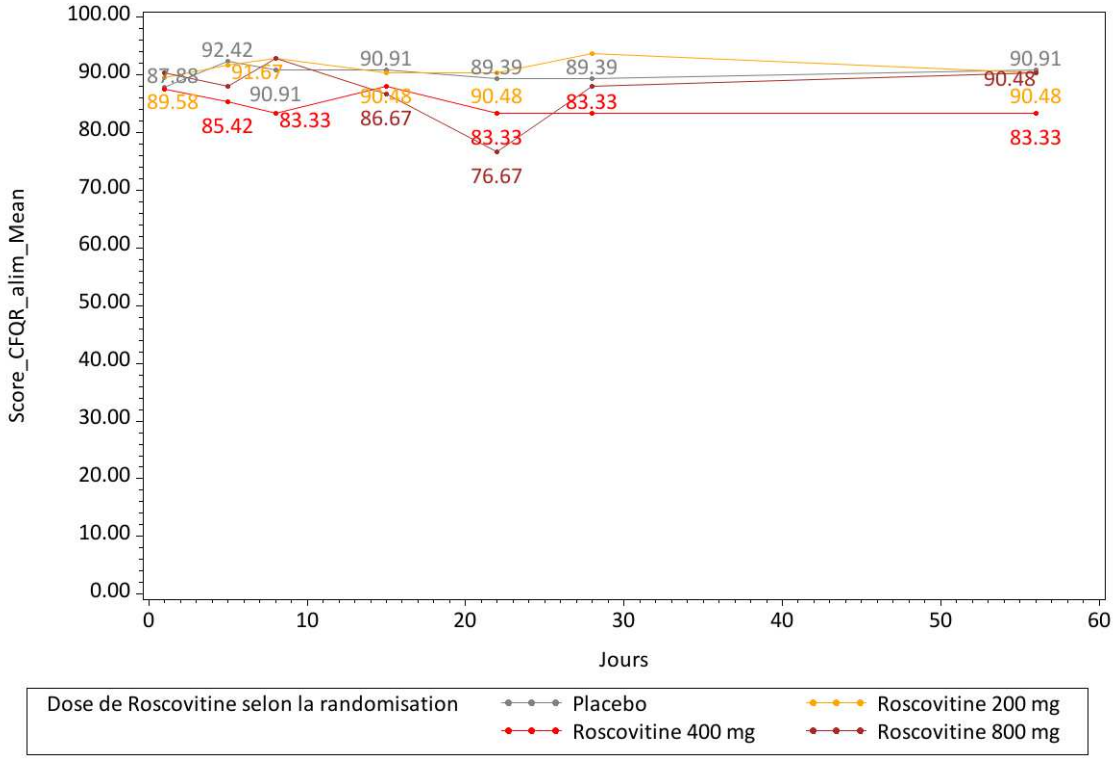
Graph 12 : Evolution of the field « psychic » during the visits, for each dose of randomized Roscovitine



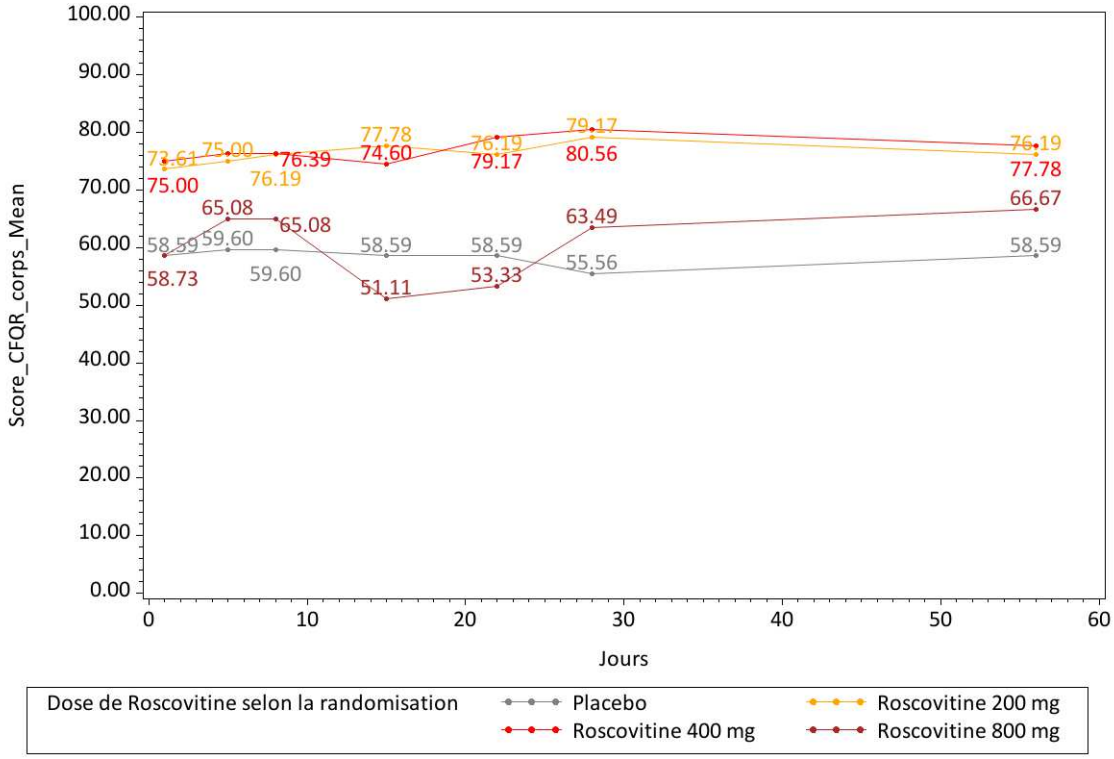
Graph 13 : Evolution of the field « Role » during the visits, for each dose of randomized Roscovitine



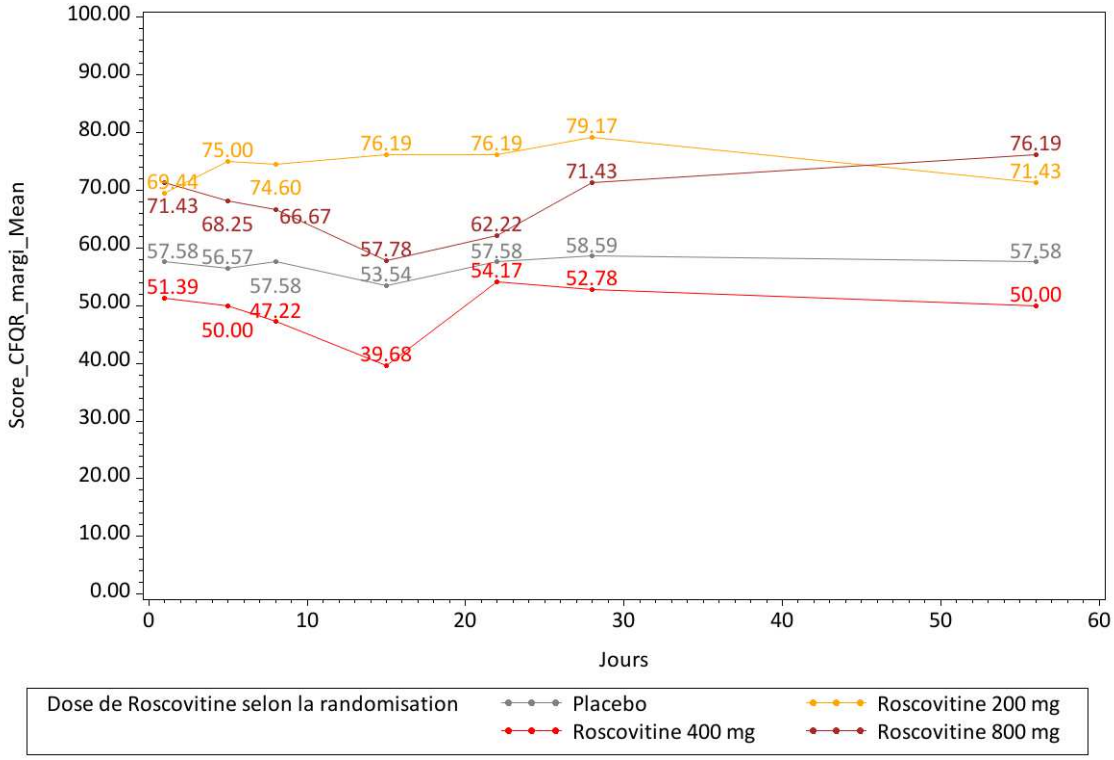
Graph 14 : Evolution of the field « Social » during the visits, for each dose of randomized Roscovitine



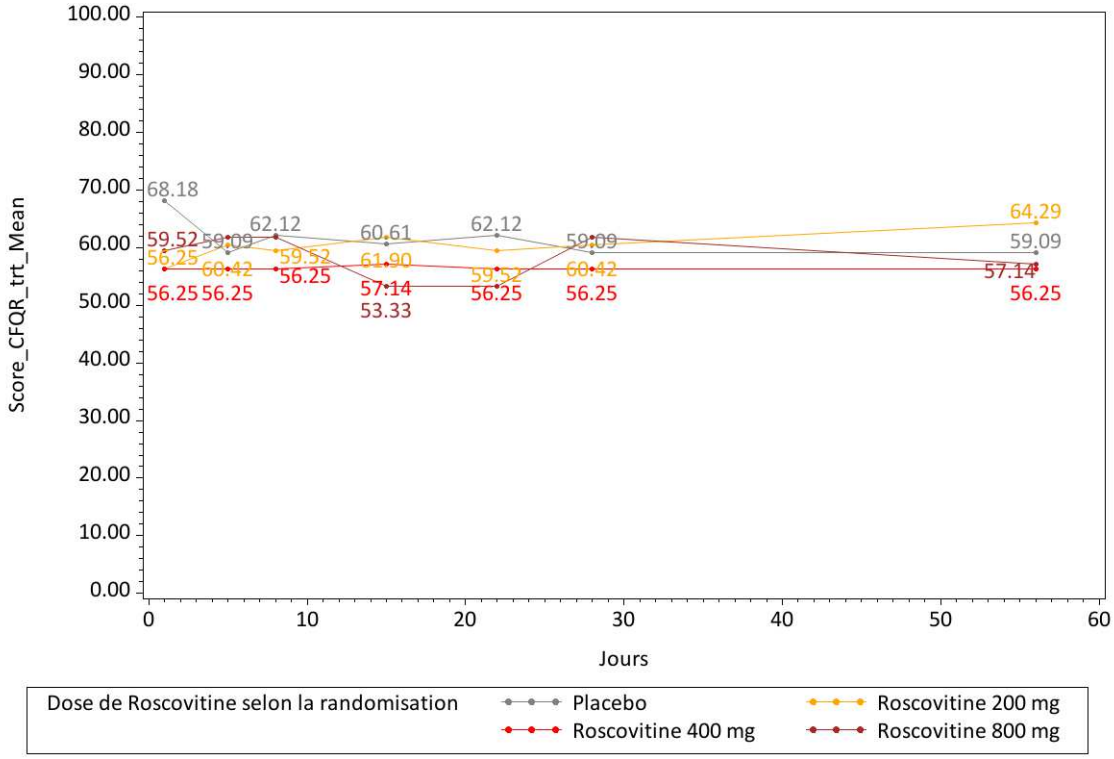
Graph 15: Evolution of the field « Food » during the visits, for each dose of randomized Roscovitine



Graph 16 : Evolution of the field « Body image » during the visits, for each dose of randomized Roscovitine



Graph 17 : Evolution of the field « Maginalization » during the visits, for each dose of randomized Roscovitine

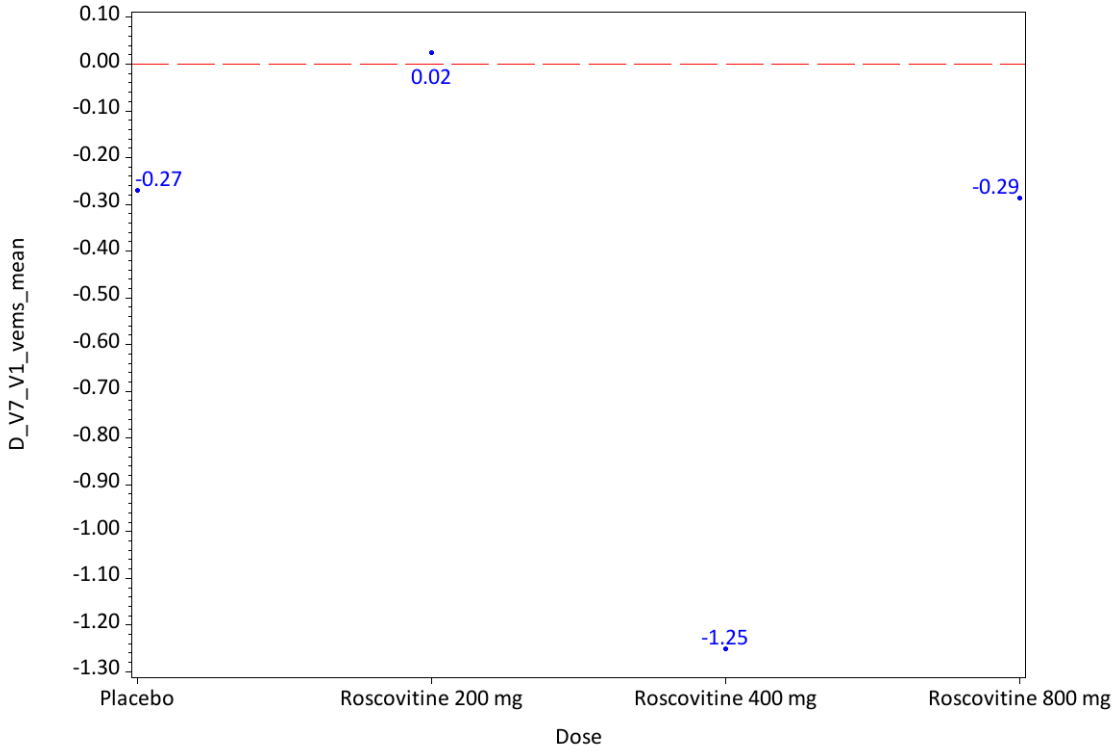


Graph 18 : Evolution of the field « Treatments » during the visits, for each dose of randomized Roscovitine

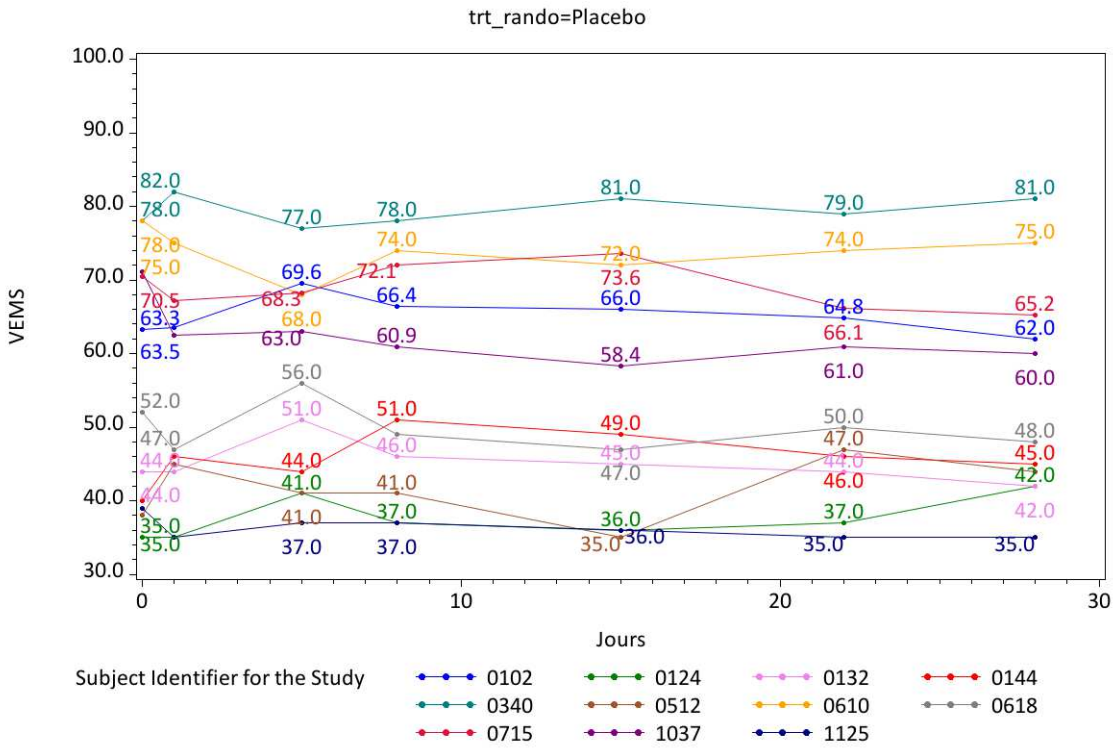
Table 23 : FME

	Roscovitine dose				
	0 mg (Placebo)	200 mg	400 mg	800 mg	p*
D1	54.75 +/- 16.04	54.58 +/- 17.44	51.88 +/- 18.21	45.57 +/- 12.31	
D28	54.48 +/- 15.03	54.60 +/- 18.08	50.63 +/- 15.09	45.29 +/- 11.59	
Delta D28-D1	-0.27 +/- 2.62	0.03 +/- 2.73	-1.25 +/- 6.48	-0.29 +/- 1.11	0.808
p (Wilcoxon test)		0.394	0.681	0.417	

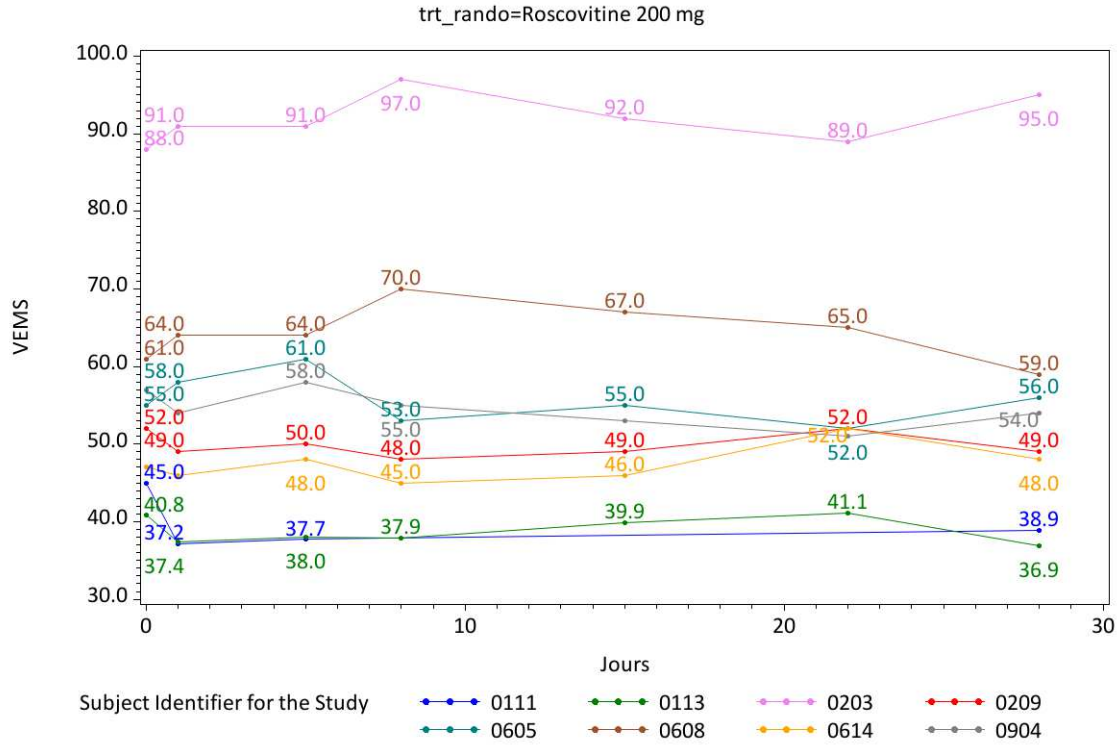
** Anova anlysis, adjusted to D1 value (PROC MIXED)*



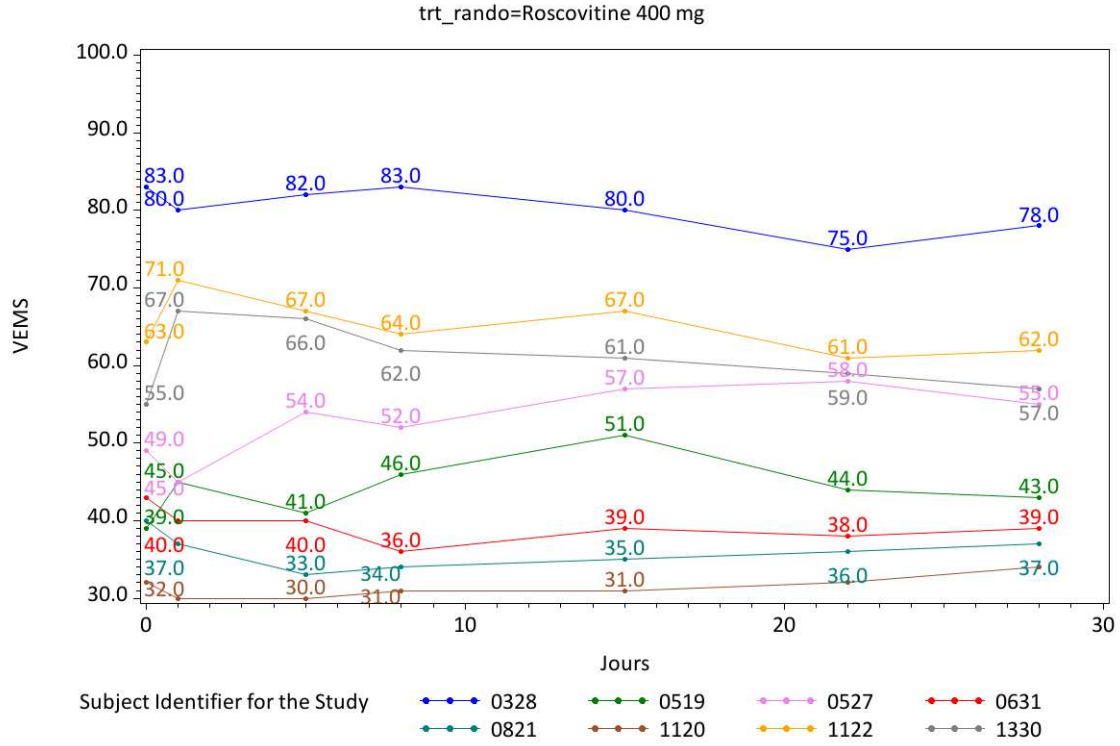
Graph 19 : Representation of Delta VEMS D0-D28 en according to randomized roscovitine dose



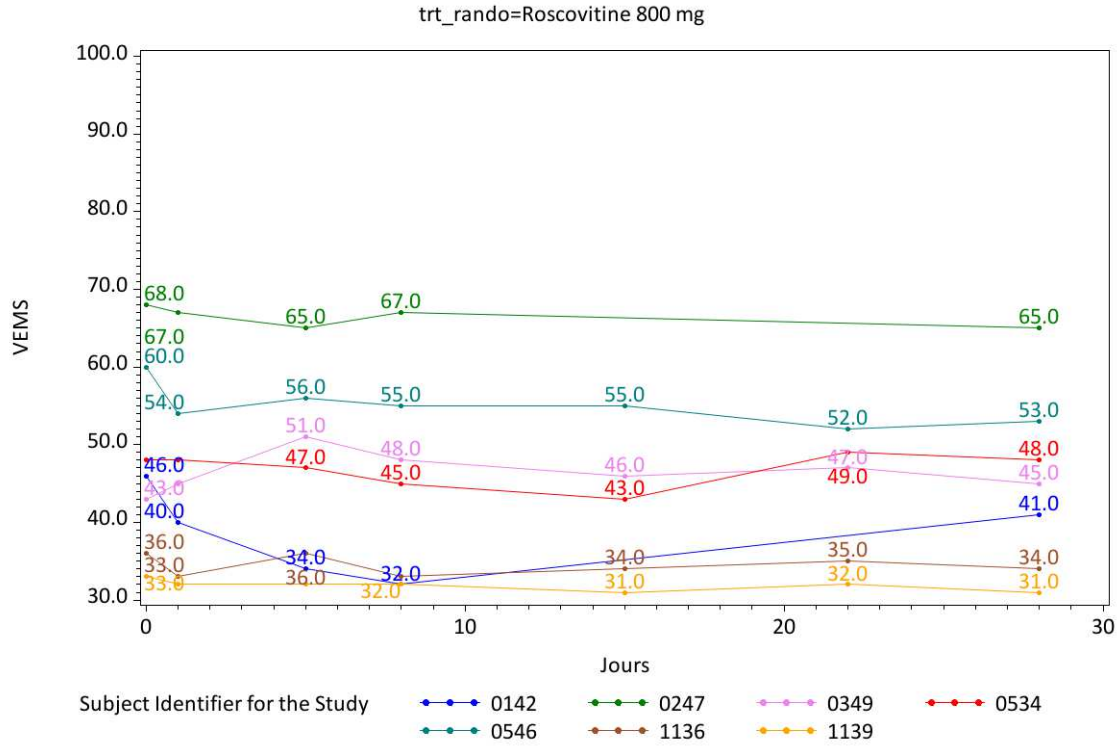
Graph 20 : VEMS evolution for patient who received placebo



Graph 21: VEMS evolution for patient who received Roscovitine 200mg



Graph 22 : VEMS evolution for patient who received Roscovitine 400mg

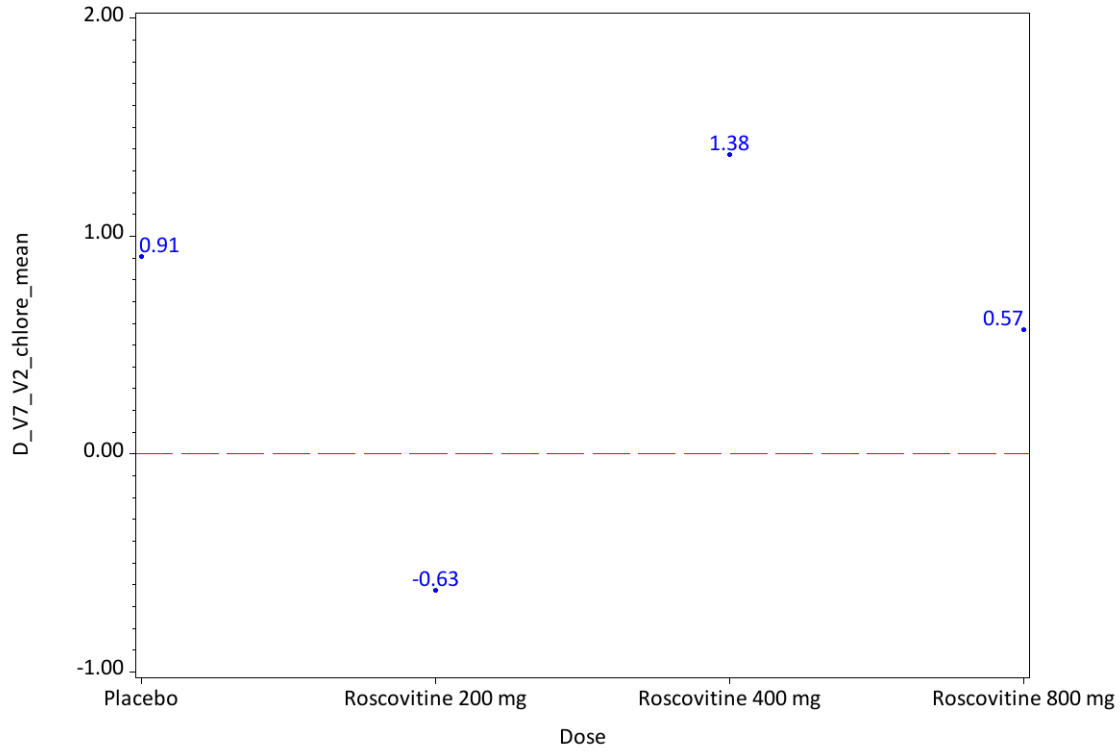


Graph 23 : VEMS evolution for patient who received Roscovitine 800mg

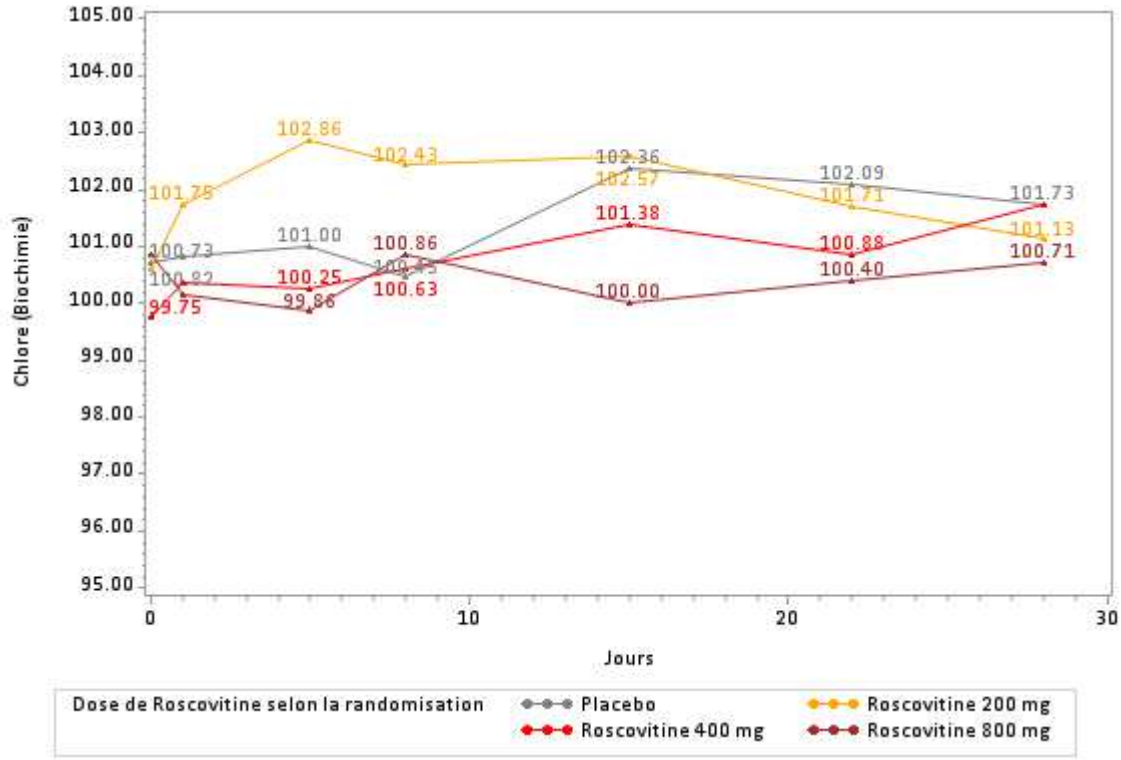
Table 24 : Chlorine

	Roscovitine dose				
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**	**p***
D1	100.82 +/- 2.44	101.75 +/- 2.66	100.38 +/- 3.25	100.14 +/- 3.18	
D28	101.73 +/- 1.10	101.13 +/- 3.14	101.75 +/- 1.75	100.71 +/- 3.99	
Delta D28-D1	0.91 +/- 2.43	-0.63 +/- 1.41	1.38 +/- 1.69	0.57 +/- 1.62	0.291
p (Wilcoxon test)		0.188	0.680	0.854	

** Anova anlysis, adjusted to D1 value (PROC MIXED)*



Graph 24 : Representation of Delta Chlorine D28-D1 en according to randomized roscovitine dose

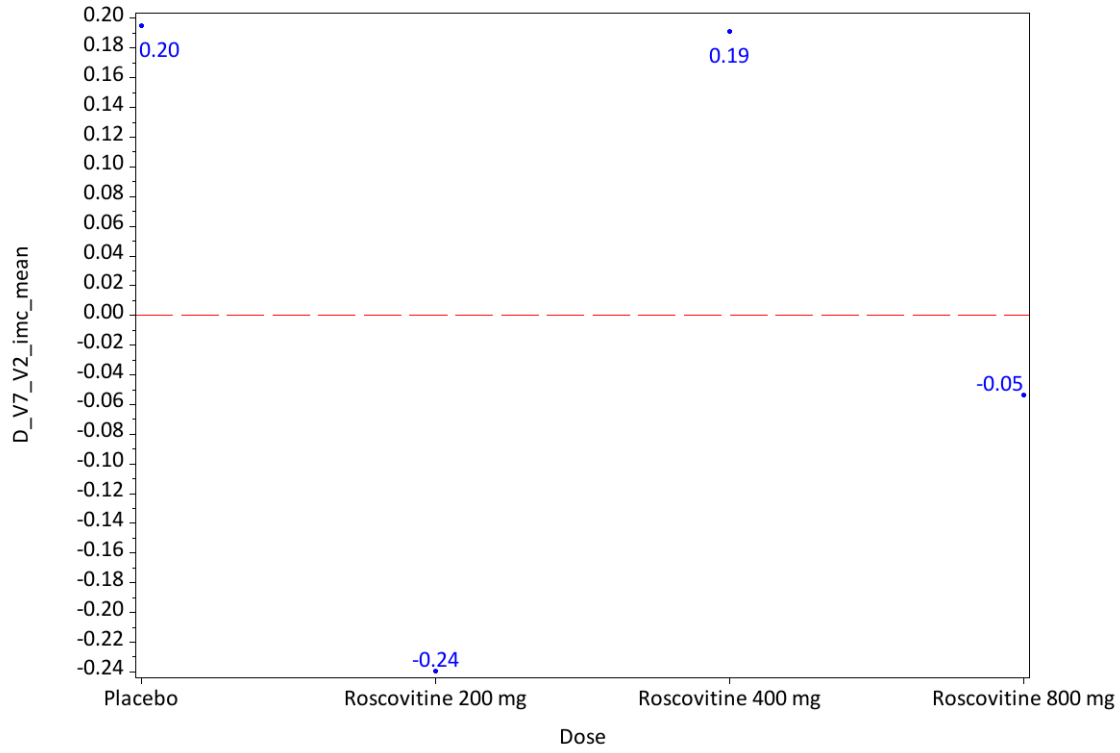


Graph 25 : Evolution of Chlorine during the visits, for each dose of randomized Roscovitine

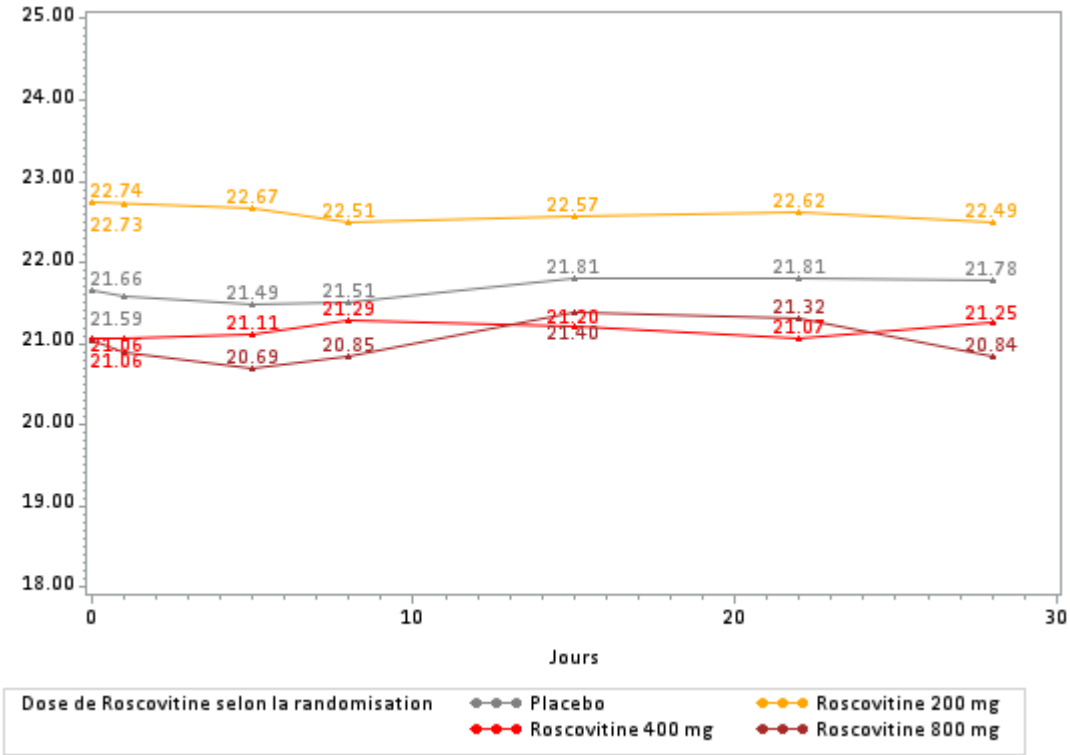
Table 25 : BMI

	Roscovitine dose				
	0 mg (Placebo)	200 mg	400 mg	800 mg	p*
D1	21.59 +/- 2.21	22.73 +/- 3.69	21.06 +/- 2.38	20.90 +/- 2.72	
D28	21.78 +/- 2.02	22.49 +/- 3.68	21.25 +/- 2.48	20.84 +/- 2.70	
Delta D28-D1	0.20 +/- 0.45	-0.24 +/- 0.29	0.19 +/- 0.48	-0.05 +/- 0.24	0.115
p (Wilcoxon test)		0.050	1.000	0.218	

** Anova anlysis, adjusted to D1 value (PROC MIXED)*



Graph 26 : Representation of Delta BMI D28-D1 en according to randomized roscovitine dose



Graph 27 : Evolution of BMI during the visits, for each dose of randomized Roscovitine

Table 26 : Levels of Cytokines (log transformed)

	Roscovitine dose				
	0 mg (Placebo)	200 mg	400 mg	800 mg	p*
CRP					
D1	15.62 +/- 1.51	15.58 +/- 1.38	17.14 +/- 1.19	17.18 +/- 1.25	
D28	15.49 +/- 1.61	15.28 +/- 1.39	16.97 +/- 1.26	17.66 +/- 0.84	
Delta D28-D1	0.09 +/- 1.06	-0.10 +/- 0.46	-0.17 +/- 0.53	0.07 +/- 1.11	0.706
p (Wilcoxon test)		0.737	0.571	0.764	
Eotaxin					
D1	6.04 +/- 0.25	6.07 +/- 0.36	5.65 +/- 0.41	5.97 +/- 0.44	
D28	6.13 +/- 0.30	6.00 +/- 0.34	5.60 +/- 0.42	5.96 +/- 0.47	
Delta D28-D1	0.05 +/- 0.30	-0.07 +/- 0.23	-0.05 +/- 0.18	0.03 +/- 0.21	0.435
p (Wilcoxon test)		0.278	0.364	0.952	
Eotaxin3					
D1	2.52 +/- 0.37	4.07 +/- 2.38	2.75 +/- 0.52	2.69 +/- 0.59	
D28	2.77 +/- 0.42	4.18 +/- 2.42	2.95 +/- 0.53	2.78 +/- 0.88	
Delta D28-D1	0.27 +/- 0.36	-0.13 +/- 0.14	0.20 +/- 0.19	0.01 +/- 0.51	0.211
p (Wilcoxon test)		0.029	0.760	0.316	
Flt-1					
D1	4.69 +/- 0.30	4.82 +/- 0.31	4.81 +/- 0.16	4.99 +/- 0.38	
D28	4.66 +/- 0.23	4.86 +/- 0.35	4.78 +/- 0.20	4.88 +/- 0.18	
Delta D28-D1	-0.02 +/- 0.21	0.05 +/- 0.09	-0.03 +/- 0.19	-0.03 +/- 0.16	0.615
p (Wilcoxon test)		0.419	0.965	0.952	
GM-CSF					
D1	0.08 +/- 0.07	0.10 +/- 0.08	0.13 +/- 0.18	0.09 +/- 0.10	
D28	0.08 +/- 0.09	0.07 +/- 0.03	0.14 +/- 0.20	0.09 +/- 0.07	
Delta D28-D1	0.00 +/- 0.05	-0.01 +/- 0.06	0.02 +/- 0.06	0.05 +/- 0.04	0.477
p (Wilcoxon test)		0.810	0.929	0.130	
ICAM-1					
D1	13.22 +/- 0.23	13.15 +/- 0.24	13.50 +/- 0.63	13.78 +/- 0.47	
D28	13.07 +/- 0.23	13.19 +/- 0.32	13.42 +/- 0.46	13.61 +/- 0.37	
Delta D28-D1	-0.17 +/- 0.38	0.03 +/- 0.37	-0.08 +/- 0.53	-0.07 +/- 0.29	0.195
p (Wilcoxon test)		0.419	0.631	0.590	
IFN-gamma					
D1	1.13 +/- 0.87	1.16 +/- 0.28	1.73 +/- 1.64	1.22 +/- 0.53	
D28	1.12 +/- 0.41	1.39 +/- 0.52	1.59 +/- 1.56	1.11 +/- 0.79	
Delta D28-D1	-0.01 +/- 0.78	0.27 +/- 0.36	-0.14 +/- 0.21	0.02 +/- 0.52	0.671
p (Wilcoxon test)		0.278	0.514	1.000	
IL-10					
D1	0.26 +/- 0.12	0.21 +/- 0.07	0.41 +/- 0.44	0.37 +/- 0.19	
D28	0.22 +/- 0.09	0.23 +/- 0.10	0.48 +/- 0.54	0.33 +/- 0.16	
Delta D28-D1	-0.05 +/- 0.15	0.04 +/- 0.07	0.07 +/- 0.14	-0.07 +/- 0.34	0.425
p (Wilcoxon test)		0.176	0.282	0.764	
IL-12/IL-23p40					
D1	4.81 +/- 0.34	4.98 +/- 0.34	4.96 +/- 0.50	4.98 +/- 0.42	
D28	4.97 +/- 0.32	5.10 +/- 0.39	4.91 +/- 0.46	4.75 +/- 0.69	
Delta D28-D1	0.14 +/- 0.25	0.14 +/- 0.26	-0.05 +/- 0.18	-0.10 +/- 0.35	0.207
p (Wilcoxon test)		0.962	0.101	0.316	
IL-12p70					
D1	0.05 +/- 0.04	0.15 +/- 0.24	0.11 +/- 0.17	0.17 +/- 0.37	
D28	0.14 +/- 0.18	0.30 +/- 0.27	0.14 +/- 0.18	0.21 +/- 0.34	
Delta D28-D1	0.10 +/- 0.21	0.13 +/- 0.23	0.03 +/- 0.09	-0.01 +/- 0.11	0.499
p (Wilcoxon test)		1.000	0.513	0.857	
IL-13					
D1	0.52 +/- 0.65	0.37 +/- 0.35	0.64 +/- 0.66	0.58 +/- 0.76	
D28	0.37 +/- 0.67	0.54 +/- 0.69	0.50 +/- 0.75	0.65 +/- 0.75	
Delta D28-D1	-0.11 +/- 0.70	0.22 +/- 0.50	-0.14 +/- 1.01	0.03 +/- 0.43	0.878
p (Wilcoxon test)		0.167	0.965	0.587	
IL-15					
D1	1.31 +/- 0.16	1.29 +/- 0.09	1.30 +/- 0.22	1.37 +/- 0.14	

	Roscovitine dose				
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**	**p***
D28	1.30 +/- 0.13	1.30 +/- 0.11	1.26 +/- 0.22	1.39 +/- 0.20	
Delta D28-D1	0.00 +/- 0.12	0.02 +/- 0.07	-0.03 +/- 0.12	0.03 +/- 0.09	0.592
p (Wilcoxon test)		0.535	0.827	0.512	
IL-16					
D1	5.35 +/- 0.22	5.39 +/- 0.31	5.39 +/- 0.37	5.62 +/- 0.35	
D28	5.22 +/- 0.28	5.36 +/- 0.22	5.30 +/- 0.34	5.55 +/- 0.67	
Delta D28-D1	-0.12 +/- 0.26	-0.05 +/- 0.24	-0.10 +/- 0.17	0.02 +/- 0.42	0.717
p (Wilcoxon test)		0.737	0.760	0.764	
IL-17A					
D1	1.56 +/- 0.64	1.60 +/- 0.25	1.73 +/- 0.34	1.86 +/- 0.49	
D28	1.55 +/- 0.41	1.65 +/- 0.34	1.51 +/- 0.45	1.71 +/- 0.57	
Delta D28-D1	-0.04 +/- 0.41	0.09 +/- 0.20	-0.22 +/- 0.35	0.00 +/- 0.15	0.375
p (Wilcoxon test)		0.535	0.215	1.000	
IL-1alpha					
D1	0.00 +/- 0.00	0.15 +/- 0.27	0.00 +/- 0.00	0.00 +/- 0.00	
D28	0.00 +/- 0.00	0.09 +/- 0.17	0.00 +/- 0.00	0.00 +/- 0.00	
Delta D28-D1	0.00 +/- 0.00	-0.08 +/- 0.24	0.00 +/- 0.00	0.00 +/- 0.00	0.722
p (Wilcoxon test)		0.747	0.445	0.581	
IL-1beta					
D1	0.12 +/- 0.13	0.22 +/- 0.18	0.65 +/- 0.82	0.24 +/- 0.11	
D28	0.15 +/- 0.15	0.24 +/- 0.19	0.49 +/- 0.66	0.35 +/- 0.07	
Delta D28-D1	0.03 +/- 0.07	0.02 +/- 0.09	-0.16 +/- 0.19	0.11 +/- 0.16	0.029
p (Wilcoxon test)		0.472	0.012	0.762	
IL-2					
D1	0.02 +/- 0.03	0.02 +/- 0.04	0.04 +/- 0.06	0.02 +/- 0.05	
D28	0.01 +/- 0.04	0.01 +/- 0.02	0.07 +/- 0.08	0.00 +/- 0.00	
Delta D28-D1	0.00 +/- 0.05	0.00 +/- 0.02	0.03 +/- 0.09	0.00 +/- 0.00	0.103
p (Wilcoxon test)		1.000	0.222	0.731	
IL-4					
D1	0.02 +/- 0.02	0.04 +/- 0.03	0.21 +/- 0.42	0.05 +/- 0.09	
D28	0.01 +/- 0.02	0.02 +/- 0.03	0.23 +/- 0.54	0.03 +/- 0.03	
Delta D28-D1	0.00 +/- 0.03	-0.01 +/- 0.02	0.02 +/- 0.15	-0.04 +/- 0.07	0.688
p (Wilcoxon test)		0.923	0.460	0.372	
IL-5					
D1	0.17 +/- 0.11	0.43 +/- 0.43	0.23 +/- 0.27	0.48 +/- 0.38	
D28	0.17 +/- 0.18	0.45 +/- 0.50	0.06 +/- 0.08	0.21 +/- 0.19	
Delta D28-D1	0.00 +/- 0.16	0.00 +/- 0.55	-0.17 +/- 0.25	-0.25 +/- 0.41	0.168
p (Wilcoxon test)		0.320	0.182	0.262	
IL-6					
D1	0.92 +/- 0.51	0.97 +/- 0.52	1.43 +/- 0.62	1.27 +/- 0.35	
D28	0.75 +/- 0.43	1.15 +/- 0.64	1.21 +/- 0.36	1.21 +/- 0.38	
Delta D28-D1	-0.16 +/- 0.57	0.18 +/- 0.39	-0.22 +/- 0.58	-0.11 +/- 0.22	0.343
p (Wilcoxon test)		0.368	0.760	0.764	
IL-7					
D1	3.10 +/- 0.29	3.11 +/- 0.37	3.05 +/- 0.28	3.48 +/- 0.42	
D28	3.12 +/- 0.41	3.22 +/- 0.33	3.06 +/- 0.24	3.37 +/- 0.37	
Delta D28-D1	0.05 +/- 0.40	0.21 +/- 0.24	0.01 +/- 0.17	-0.03 +/- 0.28	0.658
p (Wilcoxon test)		0.419	0.827	0.675	
IL-8					
D1	2.89 +/- 0.24	2.97 +/- 0.57	3.20 +/- 0.38	3.17 +/- 0.30	
D28	3.03 +/- 0.40	2.59 +/- 0.37	3.21 +/- 0.50	3.36 +/- 0.31	
Delta D28-D1	0.14 +/- 0.38	-0.40 +/- 0.36	0.01 +/- 0.30	0.16 +/- 0.33	0.010
p (Wilcoxon test)		0.020	0.631	1.000	
IL-8 (HA)					
D1	0.00 +/- 0.00	1.54 +/- 2.87	0.88 +/- 2.48	0.79 +/- 2.09	
D28	1.14 +/- 2.55	1.68 +/- 2.88	1.58 +/- 2.96	0.00 +/- 0.00	
Delta D28-D1	1.26 +/- 2.65	0.86 +/- 4.01	0.71 +/- 1.92	-1.10 +/- 2.47	0.633
p (Wilcoxon test)		0.858	1.000	0.159	

	Roscovitine dose				
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**	**p***
P-10					
D1	5.10 +/- 0.40	5.17 +/- 0.31	5.17 +/- 0.53	5.37 +/- 0.38	
D28	5.15 +/- 0.27	5.23 +/- 0.49	4.95 +/- 0.37	5.02 +/- 0.44	
Delta D28-D1	0.01 +/- 0.32	0.07 +/- 0.56	-0.22 +/- 0.30	-0.22 +/- 0.29	0.312
p (Wilcoxon test)		0.666	0.119	0.219	
MCP-1					
D1	5.68 +/- 0.21	5.76 +/- 0.30	5.70 +/- 0.32	5.77 +/- 0.34	
D28	5.70 +/- 0.20	5.76 +/- 0.38	5.56 +/- 0.41	5.65 +/- 0.49	
Delta D28-D1	0.04 +/- 0.20	0.00 +/- 0.33	-0.14 +/- 0.31	-0.08 +/- 0.21	0.540
p (Wilcoxon test)		0.885	0.215	0.264	
MCP-4					
D1	4.63 +/- 0.35	4.94 +/- 0.37	4.38 +/- 0.46	4.71 +/- 0.19	
D28	4.65 +/- 0.37	4.86 +/- 0.34	4.29 +/- 0.40	4.61 +/- 0.13	
Delta D28-D1	0.01 +/- 0.21	-0.15 +/- 0.11	-0.09 +/- 0.25	-0.05 +/- 0.25	0.494
p (Wilcoxon test)		0.127	0.321	0.857	
MDC					
D1	6.89 +/- 0.31	7.27 +/- 0.34	6.98 +/- 0.32	7.14 +/- 0.33	
D28	6.95 +/- 0.36	7.31 +/- 0.40	6.89 +/- 0.27	6.95 +/- 0.43	
Delta D28-D1	0.04 +/- 0.24	0.03 +/- 0.12	-0.09 +/- 0.16	-0.09 +/- 0.25	0.402
p (Wilcoxon test)		0.368	0.044	0.316	
MIP-1alpha					
D1	2.25 +/- 0.88	2.80 +/- 0.45	2.76 +/- 0.30	2.46 +/- 1.10	
D28	2.43 +/- 0.86	2.56 +/- 0.51	2.74 +/- 0.34	2.35 +/- 1.34	
Delta D28-D1	0.16 +/- 0.54	-0.13 +/- 0.52	-0.02 +/- 0.28	0.13 +/- 0.21	0.709
p (Wilcoxon test)		0.321	0.364	1.000	
MIP-1beta					
D1	4.71 +/- 0.29	4.60 +/- 0.51	4.53 +/- 0.29	5.00 +/- 0.33	
D28	4.80 +/- 0.32	4.52 +/- 0.58	4.41 +/- 0.41	4.79 +/- 0.30	
Delta D28-D1	0.07 +/- 0.24	-0.05 +/- 0.13	-0.12 +/- 0.19	-0.21 +/- 0.23	0.088
p (Wilcoxon test)		0.150	0.052	0.050	
PIGF					
D1	1.59 +/- 0.13	1.56 +/- 0.15	1.62 +/- 0.11	1.66 +/- 0.20	
D28	1.64 +/- 0.08	1.61 +/- 0.24	1.65 +/- 0.14	1.60 +/- 0.11	
Delta D28-D1	0.05 +/- 0.08	0.10 +/- 0.26	0.03 +/- 0.15	0.00 +/- 0.07	0.937
p (Wilcoxon test)		0.962	0.410	0.374	
SAA					
D1	17.58 +/- 1.44	16.82 +/- 1.52	18.34 +/- 1.25	18.90 +/- 0.69	
D28	17.40 +/- 1.94	16.05 +/- 1.77	18.20 +/- 1.70	19.17 +/- 0.13	
Delta D28-D1	0.14 +/- 0.72	-0.47 +/- 0.88	-0.14 +/- 0.73	0.01 +/- 0.07	0.530
p (Wilcoxon test)		0.278	0.410	1.000	
TARC					
D1	5.39 +/- 0.32	5.70 +/- 0.59	5.03 +/- 0.65	5.51 +/- 0.75	
D28	5.43 +/- 0.35	5.69 +/- 0.72	4.96 +/- 0.76	5.30 +/- 0.64	
Delta D28-D1	0.08 +/- 0.29	-0.08 +/- 0.34	-0.06 +/- 0.38	-0.02 +/- 0.40	0.772
p (Wilcoxon test)		0.278	0.571	0.675	
TNF-alpha					
D1	0.98 +/- 0.13	0.99 +/- 0.13	1.09 +/- 0.28	1.24 +/- 0.33	
D28	0.99 +/- 0.18	0.95 +/- 0.14	1.08 +/- 0.26	1.22 +/- 0.27	
Delta D28-D1	0.01 +/- 0.25	-0.02 +/- 0.08	-0.01 +/- 0.11	0.01 +/- 0.22	0.682
p (Wilcoxon test)		0.737	0.631	0.857	
TNF-beta					
D1	0.29 +/- 0.31	0.26 +/- 0.10	0.18 +/- 0.13	0.20 +/- 0.19	
D28	0.24 +/- 0.24	0.30 +/- 0.11	0.23 +/- 0.12	0.15 +/- 0.14	
Delta D28-D1	-0.06 +/- 0.13	0.05 +/- 0.08	0.05 +/- 0.07	0.01 +/- 0.09	0.088
p (Wilcoxon test)		0.176	0.128	0.674	
Tie-2					
D1	7.81 +/- 0.23	7.99 +/- 0.29	7.85 +/- 0.22	7.95 +/- 0.22	
D28	7.88 +/- 0.18	7.99 +/- 0.32	7.90 +/- 0.20	7.90 +/- 0.14	

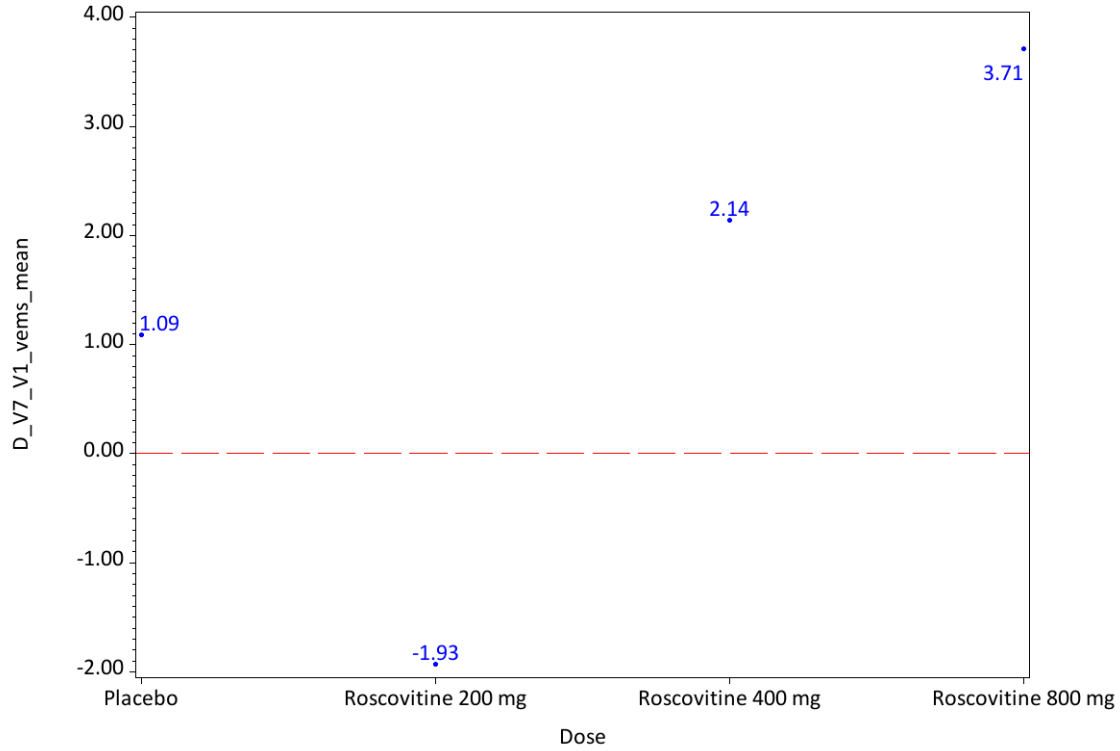
	Roscovitine dose				
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**	**p***
Delta D28-D1	0.04 +/- 0.10	0.03 +/- 0.08	0.05 +/- 0.09	0.06 +/- 0.16	0.942
p (Wilcoxon test)		1.000	0.694	0.952	
VCAM-1					
D1	13.38 +/- 0.31	13.24 +/- 0.31	13.49 +/- 0.60	13.83 +/- 0.42	
D28	13.27 +/- 0.41	13.31 +/- 0.21	13.50 +/- 0.43	13.67 +/- 0.32	
Delta D28-D1	-0.13 +/- 0.38	0.05 +/- 0.34	0.02 +/- 0.45	-0.04 +/- 0.31	0.426
p (Wilcoxon test)		0.535	0.364	0.857	
VEGF					
D1	5.45 +/- 0.66	5.61 +/- 0.47	5.59 +/- 0.83	5.96 +/- 0.51	
D28	5.50 +/- 0.76	5.48 +/- 0.41	5.53 +/- 0.90	6.11 +/- 0.71	
Delta D28-D1	-0.05 +/- 0.35	-0.11 +/- 0.22	-0.05 +/- 0.30	0.07 +/- 0.31	0.797
p (Wilcoxon test)		0.737	0.965	0.512	
VEGF-C					
D1	6.01 +/- 0.42	6.19 +/- 0.37	5.96 +/- 0.40	6.10 +/- 0.32	
D28	6.01 +/- 0.37	6.07 +/- 0.36	5.81 +/- 0.38	5.95 +/- 0.31	
Delta D28-D1	-0.03 +/- 0.20	-0.13 +/- 0.18	-0.15 +/- 0.22	-0.07 +/- 0.19	0.563
p (Wilcoxon test)		0.737	0.321	0.857	
VEGF-D					
D1	6.43 +/- 0.37	6.69 +/- 0.19	6.36 +/- 0.42	6.67 +/- 0.24	
D28	6.52 +/- 0.44	6.59 +/- 0.23	6.38 +/- 0.43	6.75 +/- 0.24	
Delta D28-D1	0.07 +/- 0.15	-0.06 +/- 0.09	0.02 +/- 0.09	0.15 +/- 0.08	0.014
p (Wilcoxon test)		0.052	0.410	0.219	
bFGF					
D1	2.11 +/- 1.11	1.69 +/- 0.68	2.16 +/- 1.16	1.76 +/- 0.93	
D28	1.68 +/- 0.59	1.46 +/- 0.64	1.51 +/- 0.75	2.26 +/- 0.73	
Delta D28-D1	-0.40 +/- 0.86	-0.30 +/- 1.09	-0.65 +/- 0.72	0.25 +/- 0.88	0.125
p (Wilcoxon test)		0.885	0.460	0.219	

** Anova anlysis, adjusted to D1 value (PROC MIXED)*

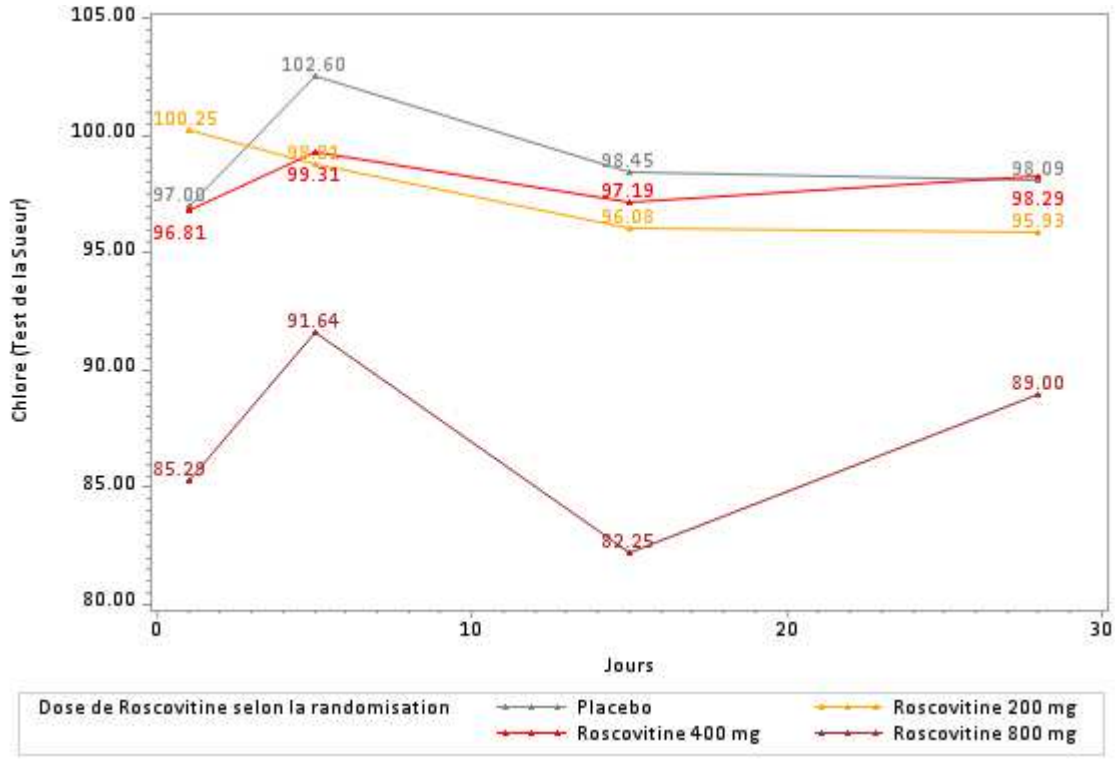
Table 27 : Sweat test (Chlorine)

	Roscovitine dose				
	0 mg (Placebo)	**200 mg**	**400 mg**	**800 mg**	**p***
D1	97.00 +/- 15.10	100.25 +/- 13.64	96.81 +/- 7.39	85.29 +/- 18.60	
D28	98.09 +/- 17.31	95.93 +/- 11.78	98.29 +/- 11.82	89.00 +/- 17.04	
Delta D28-D1	1.09 +/- 6.14	-1.93 +/- 9.78	2.14 +/- 10.21	3.71 +/- 3.83	0.716
p (Wilcoxon test)		0.332	0.823	0.451	

** Anova anlysis, adjusted to D1 value (PROC MIXED)*



Graph 28 : Representation of Delta sweat chlorine according to randomized roscovitine dose



Graph 28 : Evolution of sweat chlorine during the visits, for each dose of randomized Roscovitine

9. ANNEXES

List 1 : Summary of AEs, by subject and by group (randomized patients)

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0608	Group 1	37	Woman	Roscovitine 200 mg	BLOOD AND LYMPHATIC SYSTEM DISORDERS	LYMPHADENITIS	Grade 1	20/12/2016		Possibly related to treatment	Stable - No change
0610	Group 1	33	Woman	Placebo		ANAEMIA	Grade 1	28/11/2016	06/12/2016	Possibly related to treatment	Healing
0715	Group 1	26	Woman	Placebo		LEUKOCYTOSIS	Grade 1	10/03/2017	14/03/2017	Not related to treatment	Healing
0142	Group 3	30	Man	Roscovitine 800 mg	CARDIAC DISORDERS	TACHYCARDIA	Grade 1	19/03/2018	19/03/2018	Not related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		TACHYCARDIA	Grade 1	03/11/2016	03/11/2016	Possibly related to treatment	Healing
0631	Group 2	37	Woman	Roscovitine 400 mg		TACHYCARDIA	Grade 1	30/10/2017	30/10/2017	Not related to treatment	Healing
0821	Group 2	22	Man	Roscovitine 400 mg		TACHYCARDIA	Grade 1	29/05/2017	29/05/2017	Possibly related to treatment	Healing
1139	Group 3	42	Woman	Roscovitine 800 mg		SINUS TACHYCARDIA	Grade 2	20/02/2018	03/03/2018	Possibly related to treatment	Healing
0132	Group 2	43	Man	Placebo	EAR AND LABYRINTH DISORDERS	TINNITUS	Grade 2	20/11/2017		Not related to treatment	Stable - No change
0527	Group 2	33	Man	Roscovitine 400 mg	EYE DISORDERS	VISUAL IMPAIRMENT	Grade 1	08/09/2017	08/09/2017	Not related to treatment	Healing
1330	Group 2	27	Man	Roscovitine 400 mg		PHOTOPHOBIA	Grade 1	17/10/2017	08/11/2017	Possibly related to treatment	Healing
0102	Group 1	31	Woman	Placebo	GASTROINTESTINAL DISORDERS	GASTROOESOPHAGEAL REFLUX DISEASE	Grade 1	09/05/2016		Not related to treatment	Improvement
0102	Group 1	31	Woman	Placebo		ABDOMINAL PAIN	Grade 2	18/04/2016		Not related to treatment	Improvement
0113	Group 1	29	Woman	Roscovitine 200 mg		DIARRHOEA	Grade 1	06/12/2016		Not related to treatment	Improvement
0113	Group 1	29	Woman	Roscovitine 200 mg		VOMITING	Grade 1	06/12/2016	06/12/2016	Not related to treatment	Healing
0113	Group 1	29	Woman	Roscovitine 200 mg		GASTROOESOPHAGEAL REFLUX DISEASE	Grade 1	09/12/2016	12/12/2016	Not related to treatment	Healing
0113	Group 1	29	Woman	Roscovitine 200 mg		GASTROINTESTINAL PAIN	Grade 1	09/12/2016	12/12/2016	Not related to treatment	Healing
0113	Group 1	29	Woman	Roscovitine 200 mg		ABDOMINAL PAIN	Grade 1	26/12/2016		Not related to treatment	Improvement
0132	Group 2	43	Man	Placebo		ABDOMINAL PAIN	Grade 1	NK/11/2017	10/11/2017	Not related to treatment	Healing

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0328	Group 2	33	Man	Roscovitine 400 mg		ABDOMINAL PAIN	Grade 1	NK/10/2017	NK/10/2017	Not related to treatment	Healing
0328	Group 2	33	Man	Roscovitine 400 mg		ABDOMINAL PAIN UPPER	Grade 1	NK/09/2017	NK/09/2017	Not related to treatment	Healing
0349	Group 3	37	Woman	Roscovitine 800 mg		NAUSEA	Grade 2	14/06/2018	09/07/2018	Possibly related to treatment	Healing
0349	Group 3	37	Woman	Roscovitine 800 mg		ABDOMINAL PAIN	Grade 2	14/06/2018		Possibly related to treatment	Stable - No change
0512	Group 1	27	Woman	Placebo		ABDOMINAL PAIN	Grade 1	22/11/2016	22/11/2016	Not related to treatment	Healing
0512	Group 1	27	Woman	Placebo		ABDOMINAL PAIN	Grade 1	NK/11/2016	17/11/2016	Not related to treatment	Improvement
0519	Group 2	39	Woman	Roscovitine 400 mg		VOMITING	Grade 1	11/05/2017	11/05/2017	Possibly related to treatment	Healing
0527	Group 2	33	Man	Roscovitine 400 mg		ABDOMINAL PAIN	Grade 1	10/09/2017	10/09/2017	Not related to treatment	Healing
0527	Group 2	33	Man	Roscovitine 400 mg		DIARRHOEA	Grade 1	28/09/2017	01/10/2017	Not related to treatment	Healing
0534	Group 3	28	Woman	Roscovitine 800 mg		NAUSEA	Grade 2	26/01/2018	17/02/2018	Possibly related to treatment	Healing
0546	Group 3	33	Man	Roscovitine 800 mg		NAUSEA	Grade 1	10/05/2018	10/05/2018	Possibly related to treatment	Healing
0546	Group 3	33	Man	Roscovitine 800 mg		ABDOMINAL PAIN	Grade 1	03/05/2018	04/05/2018	Not related to treatment	Healing
0605	Group 1	28	Woman	Roscovitine 200 mg		ABDOMINAL PAIN	Grade 1	14/09/2016	14/09/2016	Not related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		DIARRHOEA	Grade 1	11/11/2016	13/11/2016	Possibly related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		DYSPEPSIA	Grade 1	25/11/2016	27/11/2016	Possibly related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		DIARRHOEA	Grade 1	18/11/2016	22/11/2016	Possibly related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		ABDOMINAL PAIN UPPER	Grade 1	18/11/2016	22/11/2016	Possibly related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		DYSPEPSIA	Grade 1	18/11/2016	22/11/2016	Possibly related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		DYSPEPSIA	Grade 1	10/11/2016	14/11/2016	Possibly related to treatment	Healing

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0608	Group 1	37	Woman	Roscovitine 200 mg		DYSPEPSIA	Grade 1	04/11/2016	08/11/2016	Possibly related to treatment	Healing
0618	Group 2	21	Woman	Placebo		ABDOMINAL PAIN	Grade 1	17/05/2017	17/05/2017	Possibly related to treatment	Healing
0618	Group 2	21	Woman	Placebo		ABDOMINAL PAIN	Grade 1	01/05/2017	02/05/2017	Possibly related to treatment	Healing
0618	Group 2	21	Woman	Placebo		ABDOMINAL PAIN	Grade 2	22/04/2017	23/04/2017	Possibly related to treatment	Healing
0631	Group 2	37	Woman	Roscovitine 400 mg		ABDOMINAL PAIN	Grade 1	25/11/2017	19/12/2017	Not related to treatment	Healing
0715	Group 1	26	Woman	Placebo		DIARRHOEA	Grade 2	20/03/2017	23/03/2017	Possibly related to treatment	Healing
0715	Group 1	26	Woman	Placebo		DIARRHOEA	Grade 2	13/03/2017	17/03/2017	Possibly related to treatment	Healing
0715	Group 1	26	Woman	Placebo		DIARRHOEA	Grade 2	07/03/2017	10/03/2017	Possibly related to treatment	Healing
0821	Group 2	22	Man	Roscovitine 400 mg		VOMITING	Grade 2	15/05/2017	15/05/2017	Possibly related to treatment	Healing
1120	Group 2	41	Woman	Roscovitine 400 mg		POST-TUSSIVE VOMITING	Grade 1	18/05/2017	18/05/2017	Not related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		ABDOMINAL PAIN	Grade 1	07/07/2017	08/07/2017	Not related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		VOMITING	Grade 1	16/06/2017	16/06/2017	Not related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		DIARRHOEA	Grade 1	17/07/2017	04/08/2017	Not related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		POST-TUSSIVE VOMITING	Grade 1	24/06/2017	09/07/2017	Not related to treatment	Healing
1125	Group 2	50	Man	Placebo		ABDOMINAL PAIN	Grade 1	20/07/2017	20/07/2017	Possibly related to treatment	Healing
1125	Group 2	50	Man	Placebo		NAUSEA	Grade 1	26/07/2017	28/07/2017	Not related to treatment	Healing
0102	Group 1	31	Woman	Placebo	GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	Grade 1	22/04/2016		Not related to treatment	Improvement
0113	Group 1	29	Woman	Roscovitine 200 mg		ASTHENIA	Grade 1	28/11/2016		Not related to treatment	Improvement
0144	Group 3	43	Man	Placebo		HYPERTHERMIA	Grade 1	14/04/2018	15/04/2018	Not related to treatment	Healing

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0203	Group 1	28	Man	Roscovitine 200 mg		CHEST DISCOMFORT	Grade 1	25/05/2016	26/05/2016	Possibly related to treatment	Healing
0203	Group 1	28	Man	Roscovitine 200 mg		CHEST DISCOMFORT	Grade 1	02/06/2016	03/06/2016	Possibly related to treatment	Healing
0247	Group 3	38	Man	Roscovitine 800 mg		PYREXIA	Grade 1	10/06/2018	10/06/2018	Not related to treatment	Healing
0247	Group 3	38	Man	Roscovitine 800 mg		PYREXIA	Grade 1	06/06/2018	06/06/2018	Not related to treatment	Healing
1120	Group 2	41	Woman	Roscovitine 400 mg		ASTHENIA	Grade 1	08/05/2017	28/05/2017	Possibly related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		DECREASED ACTIVITY	Grade 1	21/06/2017	25/06/2017	Not related to treatment	Healing
1125	Group 2	50	Man	Placebo		DECREASED ACTIVITY	Grade 1	13/08/2017		Possibly related to treatment	Stable - No change
1139	Group 3	42	Woman	Roscovitine 800 mg		DECREASED ACTIVITY	Grade 2	10/02/2018	12/02/2018	Possibly related to treatment	Healing
1330	Group 2	27	Man	Roscovitine 400 mg		PYREXIA	Grade 1	31/10/2017	31/10/2017	Not related to treatment	Healing
0247	Group 3	38	Man	Roscovitine 800 mg	HEPATOBILIARY DISORDERS	HEPATIC FUNCTION ABNORMAL	Grade 2	08/06/2018	29/06/2018	Possibly related to treatment	Healing
0247	Group 3	38	Man	Roscovitine 800 mg		HEPATIC FUNCTION ABNORMAL	Grade 2	08/06/2018	22/06/2018	Possibly related to treatment	Healing
0247	Group 3	38	Man	Roscovitine 800 mg		HEPATIC FUNCTION ABNORMAL	Grade 2	08/06/2018	29/06/2018	Possibly related to treatment	Healing
0527	Group 2	33	Man	Roscovitine 400 mg		HEPATIC FUNCTION ABNORMAL	Grade 1	05/10/2017	03/11/2017	Possibly related to treatment	Healing
0527	Group 2	33	Man	Roscovitine 400 mg		HYPERTRANSAMINASAEMIA	Grade 1	05/10/2017	03/11/2017	Possibly related to treatment	Healing
1330	Group 2	27	Man	Roscovitine 400 mg		HEPATIC FUNCTION ABNORMAL	Grade 1	30/10/2017	13/11/2017	Possibly related to treatment	Healing
1330	Group 2	27	Man	Roscovitine 400 mg		HEPATIC FUNCTION ABNORMAL	Grade 2	30/10/2017		Possibly related to treatment	Improvement
1330	Group 2	27	Man	Roscovitine 400 mg		HEPATIC FUNCTION ABNORMAL	Grade 2	30/10/2017	06/11/2017	Possibly related to treatment	Healing
1330	Group 2	27	Man	Roscovitine 400 mg		HYPERTRANSAMINASAEMIA	Grade 3	30/10/2017	13/11/2017	Possibly related to treatment	Healing
0618	Group 2	21	Woman	Placebo	IMMUNE SYSTEM DISORDERS	RHINITIS ALLERGIC	Grade 1	15/05/2017	27/05/2017	Not related to treatment	Healing

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
1122	Group 2	22	Woman	Roscovitine 400 mg		RHINITIS ALLERGIC	Grade 2	18/06/2017		Not related to treatment	Stable - No change
0102	Group 1	31	Woman	Placebo	INFECTIONS AND INFESTATIONS	LUNG INFECTION	Grade 2	23/05/2016	05/06/2016	Not related to treatment	Healing
0124	Group 2	29	Man	Placebo		NASOPHARYNGITIS	Grade 1	17/08/2017		Not related to treatment	Improvement
0142	Group 3	30	Man	Roscovitine 800 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 1	23/04/2018		Not related to treatment	Improvement
0142	Group 3	30	Man	Roscovitine 800 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 2	20/03/2018	30/03/2018	Possibly related to treatment	Healing
0144	Group 3	43	Man	Placebo		RHINITIS	Grade 1	13/04/2018	28/04/2018	Not related to treatment	Healing
0209	Group 1	36	Man	Roscovitine 200 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 1	23/12/2016	07/01/2017	Not related to treatment	Healing
0209	Group 1	36	Man	Roscovitine 200 mg		GASTROENTERITIS	Grade 1	14/01/2017	15/01/2017	Not related to treatment	Healing
0209	Group 1	36	Man	Roscovitine 200 mg		RHINITIS	Grade 1	30/11/2016	03/12/2016	Not related to treatment	Healing
0328	Group 2	33	Man	Roscovitine 400 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 2	20/10/2017	10/11/2017	Not related to treatment	Healing
0340	Group 3	33	Man	Placebo		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 2	13/04/2018		Not related to treatment	Stable - No change
0340	Group 3	33	Man	Placebo		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 1	23/02/2018	16/03/2018	Not related to treatment	Stable - No change
0512	Group 1	27	Woman	Placebo		TONSILLITIS	Grade 2	23/12/2016	02/01/2017	Not related to treatment	Healing
0512	Group 1	27	Woman	Placebo		PHARYNGITIS	Grade 2	23/12/2016	02/01/2017	Not related to treatment	Healing
0519	Group 2	39	Woman	Roscovitine 400 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 2	03/07/2017		Not related to treatment	Improvement
0527	Group 2	33	Man	Roscovitine 400 mg		NASOPHARYNGITIS	Grade 2	24/09/2017	12/10/2017	Not related to treatment	Healing

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0534	Group 3	28	Woman	Roscovitine 800 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 1	22/03/2018		Not related to treatment	Stable - No change
0608	Group 1	37	Woman	Roscovitine 200 mg		GASTROENTERITIS	Grade 1	10/12/2016	13/12/2016	Not related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 2	15/12/2016		Not related to treatment	Aggravation
0610	Group 1	33	Woman	Placebo		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 2	22/12/2016	10/01/2017	Not related to treatment	Healing
0610	Group 1	33	Woman	Placebo		ORAL HERPES	Grade 1	03/12/2016	07/12/2016	Not related to treatment	Healing
0610	Group 1	33	Woman	Placebo		PHARYNGITIS	Grade 1	22/11/2016	24/11/2016	Not related to treatment	Healing
0610	Group 1	33	Woman	Placebo		NASOPHARYNGITIS	Grade 1	11/12/2016	NK/12/2016	Not related to treatment	Healing
0631	Group 2	37	Woman	Roscovitine 400 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 4	18/12/2017		Not related to treatment	Stable - No change
0631	Group 2	37	Woman	Roscovitine 400 mg		VIRAL INFECTION	Grade 1	04/12/2017	05/12/2017	Not related to treatment	Healing
0821	Group 2	22	Man	Roscovitine 400 mg		NASOPHARYNGITIS	Grade 1	NK/05/2017	02/06/2017	Not related to treatment	Healing
0904	Group 1	50	Man	Roscovitine 200 mg		NASOPHARYNGITIS	Grade 1	29/05/2016	02/06/2016	Not related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 2	01/07/2017	26/07/2017	Not related to treatment	Healing
1139	Group 3	42	Woman	Roscovitine 800 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 3	19/02/2018	01/04/2018	Possibly related to treatment	Healing
1330	Group 2	27	Man	Roscovitine 400 mg		LUNG INFECTION	Grade 1	06/12/2017		Not related to treatment	Stable - No change
1330	Group 2	27	Man	Roscovitine 400 mg		INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Grade 1	09/11/2017	15/11/2017	Not related to treatment	Healing
0111	Group 1	32	Man	Roscovitine 200 mg	INVESTIGATIONS	ELECTROCARDIOGRAM T WAVE INVERSION	Grade 2	18/11/2016	23/01/2017	Not related to treatment	Healing

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0512	Group 1	27	Woman	Placebo		FORCED EXPIRATORY VOLUME DECREASED	Grade 1	01/12/2016	16/12/2016	Not related to treatment	Healing
0527	Group 2	33	Man	Roscovitine 400 mg		BLOOD CREATINE PHOSPHOKINASE INCREASED	Grade 1	14/09/2017	28/09/2017	Not related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		C-REACTIVE PROTEIN INCREASED	Grade 1	24/11/2016	30/11/2016	Not related to treatment	Healing
1125	Group 2	50	Man	Placebo		WEIGHT DECREASED	Grade 1	14/09/2017		Not related to treatment	Stable - No change
0209	Group 1	36	Man	Roscovitine 200 mg	METABOLISM AND NUTRITION DISORDERS	DEHYDRATION	Grade 1	12/12/2016	14/12/2016	Possibly related to treatment	Healing
0349	Group 3	37	Woman	Roscovitine 800 mg		DECREASED APPETITE	Grade 2	14/06/2018	09/07/2018	Possibly related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		HYPERKALAEMIA	Grade 1	30/11/2016	21/12/2016	Possibly related to treatment	Healing
1136	Group 3	51	Man	Roscovitine 800 mg		DECREASED APPETITE	Grade 1	04/02/2018	05/02/2018	Possibly related to treatment	Healing
0111	Group 1	32	Man	Roscovitine 200 mg	MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	Grade 1	18/11/2016		Not related to treatment	Improvement
0113	Group 1	29	Woman	Roscovitine 200 mg		BACK PAIN	Grade 1	NK/12/2016	09/12/2016	Not related to treatment	Healing
0113	Group 1	29	Woman	Roscovitine 200 mg		MYALGIA	Grade 1	NK/12/2016	09/12/2016	Not related to treatment	Healing
0132	Group 2	43	Man	Placebo		NECK PAIN	Grade 1	NK/11/2017		Not related to treatment	Stable - No change
0142	Group 3	30	Man	Roscovitine 800 mg		MYALGIA	Grade 2	20/03/2018	30/03/2018	Possibly related to treatment	Healing
0247	Group 3	38	Man	Roscovitine 800 mg		MYALGIA	Grade 1	NK/05/2018	NK/05/2018	Not related to treatment	Healing
0328	Group 2	33	Man	Roscovitine 400 mg		BACK PAIN	Grade 1	NK/NK/2017	NK/NK/2017	Not related to treatment	Healing
0512	Group 1	27	Woman	Placebo		NECK PAIN	Grade 2	19/11/2016	20/11/2016	Not related to treatment	Healing
0512	Group 1	27	Woman	Placebo		BACK PAIN	Grade 1	NK/11/2016	17/11/2016	Not related to treatment	Healing
0546	Group 3	33	Man	Roscovitine 800 mg		ARTHRALGIA	Grade 1	07/05/2018	23/05/2018	Not related to treatment	Healing
0631	Group 2	37	Woman	Roscovitine 400 mg		BACK PAIN	Grade 2	16/11/2017	19/12/2017	Not related to treatment	Stable - No change

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0821	Group 2	22	Man	Roscovitine 400 mg		MUSCULOSKELETAL STIFFNESS	Grade 1	14/05/2017	15/05/2017	Not related to treatment	Healing
0904	Group 1	50	Man	Roscovitine 200 mg		ARTHRALGIA	Grade 2	25/05/2016	26/05/2016	Not related to treatment	Healing
1125	Group 2	50	Man	Placebo		BACK PAIN	Grade 1	12/09/2017	13/09/2017	Not related to treatment	Healing
1136	Group 3	51	Man	Roscovitine 800 mg		NECK PAIN	Grade 2	22/02/2018	24/02/2018	Not related to treatment	Healing
1136	Group 3	51	Man	Roscovitine 800 mg		MUSCULOSKELETAL PAIN	Grade 1	03/02/2018	03/02/2018	Not related to treatment	Healing
0113	Group 1	29	Woman	Roscovitine 200 mg	NERVOUS SYSTEM DISORDERS	HEADACHE	Grade 1	NK/12/2016	NK/12/2016	Not related to treatment	Healing
0132	Group 2	43	Man	Placebo		HEADACHE	Grade 1	NK/11/2017		Not related to treatment	Stable - No change
0247	Group 3	38	Man	Roscovitine 800 mg		PRESYNCOPE	Grade 1	28/05/2018	28/05/2018	Not related to treatment	Healing
0512	Group 1	27	Woman	Placebo		HEADACHE	Grade 2	19/11/2016	20/11/2016	Not related to treatment	Healing
0546	Group 3	33	Man	Roscovitine 800 mg		HEADACHE	Grade 1	31/05/2018	31/05/2018	Not related to treatment	Healing
0546	Group 3	33	Man	Roscovitine 800 mg		HEADACHE	Grade 1	22/05/2018	23/05/2018	Not related to treatment	Healing
0614	Group 1	38	Man	Roscovitine 200 mg		HEADACHE	Grade 2	08/03/2017	08/03/2017	Not related to treatment	Healing
0618	Group 2	21	Woman	Placebo		HEADACHE	Grade 1	04/05/2017	04/05/2017	Possibly related to treatment	Healing
0618	Group 2	21	Woman	Placebo		HEADACHE	Grade 1	22/04/2017	22/04/2017	Possibly related to treatment	Healing
0631	Group 2	37	Woman	Roscovitine 400 mg		HEADACHE	Grade 2	30/10/2017	30/10/2017	Not related to treatment	Healing
0821	Group 2	22	Man	Roscovitine 400 mg		HEADACHE	Grade 1	NK/05/2017	NK/05/2017	Not related to treatment	Healing
1037	Group 3	36	Man	Placebo		HEADACHE	Grade 1	26/01/2018	26/01/2018	Not related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		BALANCE DISORDER	Grade 1	17/06/2017	12/07/2017	Not related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		HEADACHE	Grade 1	21/06/2017		Not related to treatment	Stable - No change

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
1125	Group 2	50	Man	Placebo		HEADACHE	Grade 1	20/07/2017	20/07/2017	Possibly related to treatment	Healing
1139	Group 3	42	Woman	Roscovitine 800 mg		HEADACHE	Grade 1	15/02/2018	22/02/2018	Not related to treatment	Healing
0102	Group 1	31	Woman	Placebo	PSYCHIATRIC DISORDERS	INSOMNIA	Grade 1	22/04/2016		Not related to treatment	Improvement
0113	Group 1	29	Woman	Roscovitine 200 mg		INSOMNIA	Grade 1	28/11/2016	26/12/2016	Not related to treatment	Healing
0132	Group 2	43	Man	Placebo		INSOMNIA	Grade 1	03/12/2017	04/12/2017	Not related to treatment	Healing
1120	Group 2	41	Woman	Roscovitine 400 mg		DEPRESSED MOOD	Grade 2	22/05/2017	22/05/2017	Not related to treatment	Healing
1136	Group 3	51	Man	Roscovitine 800 mg		INSOMNIA	Grade 1	02/02/2018	17/02/2018	Not related to treatment	Healing
0142	Group 3	30	Man	Roscovitine 800 mg	RENAL AND URINARY DISORDERS	HYPERCREATININAEMIA	Grade 1	20/03/2018	26/03/2018	Possibly related to treatment	Healing
0534	Group 3	28	Woman	Roscovitine 800 mg	REPRODUCTIVE SYSTEM AND BREAST DISORDERS	DYSMENORRHOEA	Grade 1	30/01/2018	31/01/2018	Not related to treatment	Healing
0124	Group 2	29	Man	Placebo	RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	BRONCHIAL OBSTRUCTION	Grade 1	17/08/2017		Not related to treatment	Improvement
0534	Group 3	28	Woman	Roscovitine 800 mg		COUGH	Grade 1	27/01/2018		Possibly related to treatment	Stable - No change
0546	Group 3	33	Man	Roscovitine 800 mg		COUGH	Grade 1	22/05/2018		Possibly related to treatment	Stable - No change
0608	Group 1	37	Woman	Roscovitine 200 mg		BRONCHOSPASM	Grade 1	28/11/2016	03/12/2016	Possibly related to treatment	Healing
0608	Group 1	37	Woman	Roscovitine 200 mg		BRONCHOSPASM	Grade 2	06/11/2016	24/11/2016	Possibly related to treatment	Healing
0618	Group 2	21	Woman	Placebo		ASTHMA	Grade 2	01/06/2017		Not related to treatment	Aggravation
0618	Group 2	21	Woman	Placebo		ASTHMA	Grade 1	26/04/2017	05/05/2017	Possibly related to treatment	Healing
0631	Group 2	37	Woman	Roscovitine 400 mg		COUGH	Grade 2	16/11/2017		Possibly related to treatment	Stable - No change
0715	Group 1	26	Woman	Placebo		COUGH	Grade 1	28/03/2017		Not related to treatment	Improvement

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0821	Group 2	22	Man	Roscovitine 400 mg		COUGH	Grade 1	NK/06/2017		Not related to treatment	Stable - No change
1037	Group 3	36	Man	Placebo		COUGH	Grade 1	NK/02/2018	11/03/2018	Not related to treatment	Healing
1120	Group 2	41	Woman	Roscovitine 400 mg		COUGH	Grade 1	23/05/2017	25/05/2017	Possibly related to treatment	Healing
1120	Group 2	41	Woman	Roscovitine 400 mg		COUGH	Grade 1	15/05/2017	19/05/2017	Possibly related to treatment	Healing
1120	Group 2	41	Woman	Roscovitine 400 mg		COUGH	Grade 1	05/05/2017	10/05/2017	Possibly related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		COUGH	Grade 1	19/06/2017	25/06/2017	Possibly related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		COUGH	Grade 2	09/06/2017	16/06/2017	Not related to treatment	Healing
1125	Group 2	50	Man	Placebo		SPUTUM RETENTION	Grade 1	13/08/2017		Possibly related to treatment	Stable - No change
1125	Group 2	50	Man	Placebo		COUGH	Grade 1	13/08/2017		Possibly related to treatment	Stable - No change
1125	Group 2	50	Man	Placebo		COUGH	Grade 1	25/07/2017	28/07/2017	Not related to treatment	Healing
1125	Group 2	50	Man	Placebo		COUGH	Grade 1	14/07/2017	22/07/2017	Not related to treatment	Healing
0113	Group 1	29	Woman	Roscovitine 200 mg	SKIN AND SUBCUTANEOUS TISSUE DISORDERS	PRURITUS GENITAL	Grade 1	19/12/2016	02/01/2017	Not related to treatment	Healing
0527	Group 2	33	Man	Roscovitine 400 mg		PRURITUS	Grade 1	08/09/2017	08/09/2017	Not related to treatment	Healing
0610	Group 1	33	Woman	Placebo		SKIN IRRITATION	Grade 1	15/11/2016	15/11/2016	Not related to treatment	Healing
0631	Group 2	37	Woman	Roscovitine 400 mg		SKIN REACTION	Grade 1	27/11/2017	27/11/2017	Not related to treatment	Healing
1037	Group 3	36	Man	Placebo		URTICARIA	Grade 1	22/02/2018	22/02/2018	Not related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		ERYTHEMA	Grade 1	07/06/2017		Not related to treatment	Stable - No change
1122	Group 2	22	Woman	Roscovitine 400 mg		PRURITUS	Grade 1	07/06/2017		Not related to treatment	Stable - No change
0144	Group 3	43	Man	Placebo	VASCULAR DISORDERS	HAEMOPTYSIS	Grade 1	29/03/2018	14/04/2018	Not related to treatment	Healing

Patient number	Group	Age	Sex	Treatment	SOC	Meddra	Grade	Start date	End date	Causality	Evolution
0610	Group 1	33	Woman	Placebo		HAEMOPTYSIS	Grade 1	19/12/2016	31/12/2016	Not related to treatment	Healing
0610	Group 1	33	Woman	Placebo		HAEMOPTYSIS	Grade 1	29/11/2016	29/11/2016	Not related to treatment	Healing
0610	Group 1	33	Woman	Placebo		HAEMOPTYSIS	Grade 1	08/11/2016	12/11/2016	Not related to treatment	Healing
0614	Group 1	38	Man	Roscovitine 200 mg		HAEMATOMA	Grade 2	05/04/2017	15/04/2017	Not related to treatment	Healing
0631	Group 2	37	Woman	Roscovitine 400 mg		HAEMOPTYSIS	Grade 1	16/11/2017	16/11/2017	Not related to treatment	Healing
1120	Group 2	41	Woman	Roscovitine 400 mg		HAEMOPTYSIS	Grade 1	30/05/2017	31/05/2017	Possibly related to treatment	Healing
1120	Group 2	41	Woman	Roscovitine 400 mg		HAEMOPTYSIS	Grade 1	27/05/2017	01/06/2017	Possibly related to treatment	Healing
1122	Group 2	22	Woman	Roscovitine 400 mg		EPISTAXIS	Grade 1	20/06/2017	20/06/2017	Not related to treatment	Healing
1139	Group 3	42	Woman	Roscovitine 800 mg		HAEMOPTYSIS	Grade 2	04/04/2018	04/04/2018	Not related to treatment	Healing

List 2 : Summary of AEs, by SOC and Meddra

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
BLOOD AND LYMPHATIC SYSTEM DISORDERS	ANAEMIA	Group 1	0610	33	Woman	Placebo	Grade 1	28/11/2016	06/12/2016	Possibly related to treatment	Healing
	LEUKOCYTOSIS	Group 1	0715	26	Woman	Placebo	Grade 1	10/03/2017	14/03/2017	Not related to treatment	Healing
	LYMPHADENITIS	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	20/12/2016		Possibly related to treatment	Stable - No change
CARDIAC DISORDERS	SINUS TACHYCARDIA	Group 3	1139	42	Woman	Roscovitine 800 mg	Grade 2	20/02/2018	03/03/2018	Possibly related to treatment	Healing
	TACHYCARDIA	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	03/11/2016	03/11/2016	Possibly related to treatment	Healing
	TACHYCARDIA	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 1	30/10/2017	30/10/2017	Not related to treatment	Healing
	TACHYCARDIA	Group 2	0821	22	Man	Roscovitine 400 mg	Grade 1	29/05/2017	29/05/2017	Possibly related to treatment	Healing
	TACHYCARDIA	Group 3	0142	30	Man	Roscovitine 800 mg	Grade 1	19/03/2018	19/03/2018	Not related to treatment	Healing
EAR AND LABYRINTH DISORDERS	TINNITUS	Group 2	0132	43	Man	Placebo	Grade 2	20/11/2017		Not related to treatment	Stable - No change
EYE DISORDERS	PHOTOPHOBIA	Group 2	1330	27	Man	Roscovitine 400 mg	Grade 1	17/10/2017	08/11/2017	Possibly related to treatment	Healing
	VISUAL IMPAIRMENT	Group 2	0527	33	Man	Roscovitine 400 mg	Grade 1	08/09/2017	08/09/2017	Not related to treatment	Healing
GASTROINTESTINAL DISORDERS	ABDOMINAL PAIN	Group 1	0102	31	Woman	Placebo	Grade 2	18/04/2016		Not related to treatment	Improvement
	ABDOMINAL PAIN	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	26/12/2016		Not related to treatment	Improvement
	ABDOMINAL PAIN	Group 1	0512	27	Woman	Placebo	Grade 1	22/11/2016	22/11/2016	Not related to treatment	Healing
	ABDOMINAL PAIN	Group 1	0512	27	Woman	Placebo	Grade 1	NK/11/2016	17/11/2016	Not related to treatment	Improvement
	ABDOMINAL PAIN	Group 1	0605	28	Woman	Roscovitine 200 mg	Grade 1	14/09/2016	14/09/2016	Not related to treatment	Healing
	ABDOMINAL PAIN	Group 2	0132	43	Man	Placebo	Grade 1	NK/11/2017	10/11/2017	Not related to treatment	Healing
	ABDOMINAL PAIN	Group 2	0328	33	Man	Roscovitine 400 mg	Grade 1	NK/10/2017	NK/10/2017	Not related to treatment	Healing
	ABDOMINAL PAIN	Group 2	0527	33	Man	Roscovitine 400 mg	Grade 1	10/09/2017	10/09/2017	Not related to treatment	Healing
	ABDOMINAL PAIN	Group 2	0618	21	Woman	Placebo	Grade 1	17/05/2017	17/05/2017	Possibly related to treatment	Healing

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	ABDOMINAL PAIN	Group 2	0618	21	Woman	Placebo	Grade 1	01/05/2017	02/05/2017	Possibly related to treatment	Healing
	ABDOMINAL PAIN	Group 2	0618	21	Woman	Placebo	Grade 2	22/04/2017	23/04/2017	Possibly related to treatment	Healing
	ABDOMINAL PAIN	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 1	25/11/2017	19/12/2017	Not related to treatment	Healing
	ABDOMINAL PAIN	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	07/07/2017	08/07/2017	Not related to treatment	Healing
	ABDOMINAL PAIN	Group 2	1125	50	Man	Placebo	Grade 1	20/07/2017	20/07/2017	Possibly related to treatment	Healing
	ABDOMINAL PAIN	Group 3	0349	37	Woman	Roscovitine 800 mg	Grade 2	14/06/2018		Possibly related to treatment	Stable - No change
	ABDOMINAL PAIN	Group 3	0546	33	Man	Roscovitine 800 mg	Grade 1	03/05/2018	04/05/2018	Not related to treatment	Healing
	ABDOMINAL PAIN UPPER	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	18/11/2016	22/11/2016	Possibly related to treatment	Healing
	ABDOMINAL PAIN UPPER	Group 2	0328	33	Man	Roscovitine 400 mg	Grade 1	NK/09/2017	NK/09/2017	Not related to treatment	Healing
	DIARRHOEA	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	06/12/2016		Not related to treatment	Improvement
	DIARRHOEA	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	11/11/2016	13/11/2016	Possibly related to treatment	Healing
	DIARRHOEA	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	18/11/2016	22/11/2016	Possibly related to treatment	Healing
	DIARRHOEA	Group 1	0715	26	Woman	Placebo	Grade 2	20/03/2017	23/03/2017	Possibly related to treatment	Healing
	DIARRHOEA	Group 1	0715	26	Woman	Placebo	Grade 2	13/03/2017	17/03/2017	Possibly related to treatment	Healing
	DIARRHOEA	Group 1	0715	26	Woman	Placebo	Grade 2	07/03/2017	10/03/2017	Possibly related to treatment	Healing
	DIARRHOEA	Group 2	0527	33	Man	Roscovitine 400 mg	Grade 1	28/09/2017	01/10/2017	Not related to treatment	Healing
	DIARRHOEA	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	17/07/2017	04/08/2017	Not related to treatment	Healing
	DYSPEPSIA	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	25/11/2016	27/11/2016	Possibly related to treatment	Healing
	DYSPEPSIA	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	18/11/2016	22/11/2016	Possibly related to treatment	Healing
	DYSPEPSIA	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	10/11/2016	14/11/2016	Possibly related to treatment	Healing

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	DYSPEPSIA	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	04/11/2016	08/11/2016	Possibly related to treatment	Healing
	GASTROINTESTINAL PAIN	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	09/12/2016	12/12/2016	Not related to treatment	Healing
	GASTROOESOPHAGEAL REFLUX DISEASE	Group 1	0102	31	Woman	Placebo	Grade 1	09/05/2016		Not related to treatment	Improvement
	GASTROOESOPHAGEAL REFLUX DISEASE	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	09/12/2016	12/12/2016	Not related to treatment	Healing
	NAUSEA	Group 2	1125	50	Man	Placebo	Grade 1	26/07/2017	28/07/2017	Not related to treatment	Healing
	NAUSEA	Group 3	0349	37	Woman	Roscovitine 800 mg	Grade 2	14/06/2018	09/07/2018	Possibly related to treatment	Healing
	NAUSEA	Group 3	0534	28	Woman	Roscovitine 800 mg	Grade 2	26/01/2018	17/02/2018	Possibly related to treatment	Healing
	NAUSEA	Group 3	0546	33	Man	Roscovitine 800 mg	Grade 1	10/05/2018	10/05/2018	Possibly related to treatment	Healing
	POST-TUSSIVE VOMITING	Group 2	1120	41	Woman	Roscovitine 400 mg	Grade 1	18/05/2017	18/05/2017	Not related to treatment	Healing
	POST-TUSSIVE VOMITING	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	24/06/2017	09/07/2017	Not related to treatment	Healing
	VOMITING	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	06/12/2016	06/12/2016	Not related to treatment	Healing
	VOMITING	Group 2	0519	39	Woman	Roscovitine 400 mg	Grade 1	11/05/2017	11/05/2017	Possibly related to treatment	Healing
	VOMITING	Group 2	0821	22	Man	Roscovitine 400 mg	Grade 2	15/05/2017	15/05/2017	Possibly related to treatment	Healing
	VOMITING	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	16/06/2017	16/06/2017	Not related to treatment	Healing
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	ASTHENIA	Group 1	0102	31	Woman	Placebo	Grade 1	22/04/2016		Not related to treatment	Improvement
	ASTHENIA	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	28/11/2016		Not related to treatment	Improvement
	ASTHENIA	Group 2	1120	41	Woman	Roscovitine 400 mg	Grade 1	08/05/2017	28/05/2017	Possibly related to treatment	Healing
	CHEST DISCOMFORT	Group 1	0203	28	Man	Roscovitine 200 mg	Grade 1	25/05/2016	26/05/2016	Possibly related to treatment	Healing
	CHEST DISCOMFORT	Group 1	0203	28	Man	Roscovitine 200 mg	Grade 1	02/06/2016	03/06/2016	Possibly related to treatment	Healing

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	DECREASED ACTIVITY	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	21/06/2017	25/06/2017	Non lié au traitement	Healing
	DECREASED ACTIVITY	Group 2	1125	50	Man	Placebo	Grade 1	13/08/2017		Possibly related to treatment	Stable - No change
	DECREASED ACTIVITY	Group 3	1139	42	Woman	Roscovitine 800 mg	Grade 2	10/02/2018	12/02/2018	Possibly related to treatment	Healing
	HYPERTHERMIA	Group 3	0144	43	Man	Placebo	Grade 1	14/04/2018	15/04/2018	Not related to treatment	Healing
	PYREXIA	Group 2	1330	27	Man	Roscovitine 400 mg	Grade 1	31/10/2017	31/10/2017	Not related to treatment	Healing
	PYREXIA	Group 3	0247	38	Man	Roscovitine 800 mg	Grade 1	10/06/2018	10/06/2018	Not related to treatment	Healing
	PYREXIA	Group 3	0247	38	Man	Roscovitine 800 mg	Grade 1	06/06/2018	06/06/2018	Not related to treatment	Healing
HEPATOBILIARY DISORDERS											
	HEPATIC FUNCTION ABNORMAL	Group 2	0527	33	Man	Roscovitine 400 mg	Grade 1	05/10/2017	03/11/2017	Possibly related to treatment	Healing
	HEPATIC FUNCTION ABNORMAL	Group 2	1330	27	Man	Roscovitine 400 mg	Grade 1	30/10/2017	13/11/2017	Possibly related to treatment	Healing
	HEPATIC FUNCTION ABNORMAL	Group 2	1330	27	Man	Roscovitine 400 mg	Grade 2	30/10/2017		Possibly related to treatment	Improvement
	HEPATIC FUNCTION ABNORMAL	Group 2	1330	27	Man	Roscovitine 400 mg	Grade 2	30/10/2017	06/11/2017	Possibly related to treatment	Healing
	HEPATIC FUNCTION ABNORMAL	Group 3	0247	38	Man	Roscovitine 800 mg	Grade 2	08/06/2018	29/06/2018	Possibly related to treatment	Healing
	HEPATIC FUNCTION ABNORMAL	Group 3	0247	38	Man	Roscovitine 800 mg	Grade 2	08/06/2018	22/06/2018	Possibly related to treatment	Healing
	HEPATIC FUNCTION ABNORMAL	Group 3	0247	38	Man	Roscovitine 800 mg	Grade 2	08/06/2018	29/06/2018	Possibly related to treatment	Healing
	HYPERTRANSAMINASAEMIA	Group 2	0527	33	Man	Roscovitine 400 mg	Grade 1	05/10/2017	03/11/2017	Possibly related to treatment	Healing
	HYPERTRANSAMINASAEMIA	Group 2	1330	27	Man	Roscovitine 400 mg	Grade 3	30/10/2017	13/11/2017	Possibly related to treatment	Healing
IMMUNE SYSTEM DISORDERS	RHINITIS ALLERGIC	Group 2	0618	21	Woman	Placebo	Grade 1	15/05/2017	27/05/2017	Not related to treatment	Healing
	RHINITIS ALLERGIC	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 2	18/06/2017		Not related to treatment	Stable - No change
INFECTIONS AND INFESTATIONS	GASTROENTERITIS	Group 1	0209	36	Man	Roscovitine 200 mg	Grade 1	14/01/2017	15/01/2017	Not related to treatment	Healing

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	GASTROENTERITIS	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	10/12/2016	13/12/2016	Not related to treatment	Healing
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 1	0209	36	Man	Roscovitine 200 mg	Grade 1	23/12/2016	07/01/2017	Not related to treatment	Healing
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 2	15/12/2016		Not related to treatment	Aggravation
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 1	0610	33	Woman	Placebo	Grade 2	22/12/2016	10/01/2017	Not related to treatment	Healing
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 2	0328	33	Man	Roscovitine 400 mg	Grade 2	20/10/2017	10/11/2017	Not related to treatment	Healing
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 2	0519	39	Woman	Roscovitine 400 mg	Grade 2	03/07/2017		Not related to treatment	Improvement
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 4	18/12/2017		Not related to treatment	Stable - No change
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 2	01/07/2017	26/07/2017	Not related to treatment	Healing
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 2	1330	27	Man	Roscovitine 400 mg	Grade 1	09/11/2017	15/11/2017	Not related to treatment	Healing
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 3	0142	30	Man	Roscovitine 800 mg	Grade 1	23/04/2018		Not related to treatment	Improvement
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 3	0142	30	Man	Roscovitine 800 mg	Grade 2	20/03/2018	30/03/2018	Possibly related to treatment	Healing
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 3	0340	33	Man	Placebo	Grade 2	13/04/2018		Not related to treatment	Stable - No change
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 3	0340	33	Man	Placebo	Grade 1	23/02/2018	16/03/2018	Not related to treatment	Stable - No change
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 3	0534	28	Woman	Roscovitine 800 mg	Grade 1	22/03/2018		Not related to treatment	Stable - No change

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	Group 3	1139	42	Woman	Roscovitine 800 mg	Grade 3	19/02/2018	01/04/2018	Possibly related to treatment	Healing
	LUNG INFECTION	Group 1	0102	31	Woman	Placebo	Grade 2	23/05/2016	05/06/2016	Not related to treatment	Healing
	LUNG INFECTION	Group 2	1330	27	Man	Roscovitine 400 mg	Grade 1	06/12/2017		Not related to treatment	Stable - No change
	NASOPHARYNGITIS	Group 1	0610	33	Woman	Placebo	Grade 1	11/12/2016	NK/12/2016	Not related to treatment	Healing
	NASOPHARYNGITIS	Group 1	0904	50	Man	Roscovitine 200 mg	Grade 1	29/05/2016	02/06/2016	Not related to treatment	Healing
	NASOPHARYNGITIS	Group 2	0124	29	Man	Placebo	Grade 1	17/08/2017		Not related to treatment	Improvement
	NASOPHARYNGITIS	Group 2	0527	33	Man	Roscovitine 400 mg	Grade 2	24/09/2017	12/10/2017	Not related to treatment	Healing
	NASOPHARYNGITIS	Group 2	0821	22	Man	Roscovitine 400 mg	Grade 1	NK/05/2017	02/06/2017	Not related to treatment	Healing
	ORAL HERPES	Group 1	0610	33	Woman	Placebo	Grade 1	03/12/2016	07/12/2016	Not related to treatment	Healing
	PHARYNGITIS	Group 1	0512	27	Woman	Placebo	Grade 2	23/12/2016	02/01/2017	Not related to treatment	Healing
	PHARYNGITIS	Group 1	0610	33	Woman	Placebo	Grade 1	22/11/2016	24/11/2016	Not related to treatment	Healing
	RHINITIS	Group 1	0209	36	Man	Roscovitine 200 mg	Grade 1	30/11/2016	03/12/2016	Not related to treatment	Healing
	RHINITIS	Group 3	0144	43	Man	Placebo	Grade 1	13/04/2018	28/04/2018	Not related to treatment	Healing
	TONSILLITIS	Group 1	0512	27	Woman	Placebo	Grade 2	23/12/2016	02/01/2017	Not related to treatment	Healing
	VIRAL INFECTION	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 1	04/12/2017	05/12/2017	Not related to treatment	Healing
INVESTIGATIONS	BLOOD CREATINE PHOSPHOKINASE INCREASED	Group 2	0527	33	Man	Roscovitine 400 mg	Grade 1	14/09/2017	28/09/2017	Not related to treatment	Healing
	C-REACTIVE PROTEIN INCREASED	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	24/11/2016	30/11/2016	Not related to treatment	Healing
	ELECTROCARDIOGRAM T WAVE INVERSION	Group 1	0111	32	Man	Roscovitine 200 mg	Grade 2	18/11/2016	23/01/2017	Not related to treatment	Healing
	FORCED EXPIRATORY VOLUME DECREASED	Group 1	0512	27	Woman	Placebo	Grade 1	01/12/2016	16/12/2016	Not related to treatment	Healing

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	WEIGHT DECREASED	Group 2	1125	50	Man	Placebo	Grade 1	14/09/2017		Not related to treatment	Stable - No change
METABOLISM AND NUTRITION DISORDERS	DECREASED APPETITE	Group 3	0349	37	Woman	Roscovitine 800 mg	Grade 2	14/06/2018	09/07/2018	Possibly related to treatment	Healing
	DECREASED APPETITE	Group 3	1136	51	Man	Roscovitine 800 mg	Grade 1	04/02/2018	05/02/2018	Possibly related to treatment	Healing
	DEHYDRATION	Group 1	0209	36	Man	Roscovitine 200 mg	Grade 1	12/12/2016	14/12/2016	Possibly related to treatment	Healing
	HYPERKALAEMIA	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	30/11/2016	21/12/2016	Possibly related to treatment	Healing
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	ARTHRALGIA	Group 1	0111	32	Man	Roscovitine 200 mg	Grade 1	18/11/2016		Not related to treatment	Improvement
	ARTHRALGIA	Group 1	0904	50	Man	Roscovitine 200 mg	Grade 2	25/05/2016	26/05/2016	Not related to treatment	Healing
	ARTHRALGIA	Group 3	0546	33	Man	Roscovitine 800 mg	Grade 1	07/05/2018	23/05/2018	Not related to treatment	Healing
	BACK PAIN	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	NK/12/2016	09/12/2016	Not related to treatment	Healing
	BACK PAIN	Group 1	0512	27	Woman	Placebo	Grade 1	NK/11/2016	17/11/2016	Not related to treatment	Healing
	BACK PAIN	Group 2	0328	33	Man	Roscovitine 400 mg	Grade 1	NK/NK/2017	NK/NK/2017	Not related to treatment	Healing
	BACK PAIN	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 2	16/11/2017	19/12/2017	Not related to treatment	Stable - No change
	BACK PAIN	Group 2	1125	50	Man	Placebo	Grade 1	12/09/2017	13/09/2017	Not related to treatment	Healing
	MUSCULOSKELETAL PAIN	Group 3	1136	51	Man	Roscovitine 800 mg	Grade 1	03/02/2018	03/02/2018	Not related to treatment	Healing
	MUSCULOSKELETAL STIFFNESS	Group 2	0821	22	Man	Roscovitine 400 mg	Grade 1	14/05/2017	15/05/2017	Not related to treatment	Healing
	MYALGIA	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	NK/12/2016	09/12/2016	Not related to treatment	Healing
	MYALGIA	Group 3	0142	30	Man	Roscovitine 800 mg	Grade 2	20/03/2018	30/03/2018	Possibly related to treatment	Healing
	MYALGIA	Group 3	0247	38	Man	Roscovitine 800 mg	Grade 1	NK/05/2018	NK/05/2018	Not related to treatment	Healing
	NECK PAIN	Group 1	0512	27	Woman	Placebo	Grade 2	19/11/2016	20/11/2016	Not related to treatment	Healing

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	NECK PAIN	Group 2	0132	43	Man	Placebo	Grade 1	NK/11/2017		Not related to treatment	Stable - No change
	NECK PAIN	Group 3	1136	51	Man	Roscovitine 800 mg	Grade 2	22/02/2018	24/02/2018	Not related to treatment	Healing
NERVOUS SYSTEM DISORDERS	BALANCE DISORDER	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	17/06/2017	12/07/2017	Not related to treatment	Healing
	HEADACHE	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	NK/12/2016	NK/12/2016	Not related to treatment	Healing
	HEADACHE	Group 1	0512	27	Woman	Placebo	Grade 2	19/11/2016	20/11/2016	Not related to treatment	Healing
	HEADACHE	Group 1	0614	38	Man	Roscovitine 200 mg	Grade 2	08/03/2017	08/03/2017	Not related to treatment	Healing
	HEADACHE	Group 2	0132	43	Man	Placebo	Grade 1	NK/11/2017		Not related to treatment	Stable - No change
	HEADACHE	Group 2	0618	21	Woman	Placebo	Grade 1	04/05/2017	04/05/2017	Possibly related to treatment	Healing
	HEADACHE	Group 2	0618	21	Woman	Placebo	Grade 1	22/04/2017	22/04/2017	Possibly related to treatment	Healing
	HEADACHE	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 2	30/10/2017	30/10/2017	Not related to treatment	Healing
	HEADACHE	Group 2	0821	22	Man	Roscovitine 400 mg	Grade 1	NK/05/2017	NK/05/2017	Not related to treatment	Healing
	HEADACHE	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	21/06/2017		Not related to treatment	Stable - No change
	HEADACHE	Group 2	1125	50	Man	Placebo	Grade 1	20/07/2017	20/07/2017	Possibly related to treatment	Healing
	HEADACHE	Group 3	0546	33	Man	Roscovitine 800 mg	Grade 1	31/05/2018	31/05/2018	Not related to treatment	Healing
	HEADACHE	Group 3	0546	33	Man	Roscovitine 800 mg	Grade 1	22/05/2018	23/05/2018	Not related to treatment	Healing
	HEADACHE	Group 3	1037	36	Man	Placebo	Grade 1	26/01/2018	26/01/2018	Not related to treatment	Healing
	HEADACHE	Group 3	1139	42	Woman	Roscovitine 800 mg	Grade 1	15/02/2018	22/02/2018	Not related to treatment	Healing
	PRESYNCOPE	Group 3	0247	38	Man	Roscovitine 800 mg	Grade 1	28/05/2018	28/05/2018	Not related to treatment	Healing
PSYCHIATRIC DISORDERS	DEPRESSED MOOD	Group 2	1120	41	Woman	Roscovitine 400 mg	Grade 2	22/05/2017	22/05/2017	Not related to treatment	Healing
	INSOMNIA	Group 1	0102	31	Woman	Placebo	Grade 1	22/04/2016		Not related to treatment	Improvement

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	INSOMNIA	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	28/11/2016	26/12/2016	Not related to treatment	Healing
	INSOMNIA	Group 2	0132	43	Man	Placebo	Grade 1	03/12/2017	04/12/2017	Not related to treatment	Healing
	INSOMNIA	Group 3	1136	51	Man	Roscovitine 800 mg	Grade 1	02/02/2018	17/02/2018	Not related to treatment	Healing
RENAL AND URINARY DISORDERS	HYPERCREATININAEMIA	Group 3	0142	30	Man	Roscovitine 800 mg	Grade 1	20/03/2018	26/03/2018	Possibly related to treatment	Healing
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	DYSMENORRHOEA	Group 3	0534	28	Woman	Roscovitine 800 mg	Grade 1	30/01/2018	31/01/2018	Not related to treatment	Healing
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	ASTHMA	Group 2	0618	21	Woman	Placebo	Grade 2	01/06/2017		Not related to treatment	Aggravation
	ASTHMA	Group 2	0618	21	Woman	Placebo	Grade 1	26/04/2017	05/05/2017	Possibly related to treatment	Healing
	BRONCHIAL OBSTRUCTION	Group 2	0124	29	Man	Placebo	Grade 1	17/08/2017		Not related to treatment	Improvement
	BRONCHOSPASM	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 1	28/11/2016	03/12/2016	Possibly related to treatment	Healing
	BRONCHOSPASM	Group 1	0608	37	Woman	Roscovitine 200 mg	Grade 2	06/11/2016	24/11/2016	Possibly related to treatment	Healing
	COUGH	Group 1	0715	26	Woman	Placebo	Grade 1	28/03/2017		Not related to treatment	Improvement
	COUGH	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 2	16/11/2017		Possibly related to treatment	Stable - No change
	COUGH	Group 2	0821	22	Man	Roscovitine 400 mg	Grade 1	NK/06/2017		Not related to treatment	Stable - No change
	COUGH	Group 2	1120	41	Woman	Roscovitine 400 mg	Grade 1	23/05/2017	25/05/2017	Possibly related to treatment	Healing
	COUGH	Group 2	1120	41	Woman	Roscovitine 400 mg	Grade 1	15/05/2017	19/05/2017	Possibly related to treatment	Healing
	COUGH	Group 2	1120	41	Woman	Roscovitine 400 mg	Grade 1	05/05/2017	10/05/2017	Possibly related to treatment	Healing
	COUGH	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	19/06/2017	25/06/2017	Possibly related to treatment	Healing
	COUGH	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 2	09/06/2017	16/06/2017	Not related to treatment	Healing

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	COUGH	Group 2	1125	50	Man	Placebo	Grade 1	13/08/2017		Possibly related to treatment	Stable - No change
	COUGH	Group 2	1125	50	Man	Placebo	Grade 1	25/07/2017	28/07/2017	Not related to treatment	Healing
	COUGH	Group 2	1125	50	Man	Placebo	Grade 1	14/07/2017	22/07/2017	Not related to treatment	Healing
	COUGH	Group 3	0534	28	Woman	Roscovitine 800 mg	Grade 1	27/01/2018		Possibly related to treatment	Stable - No change
	COUGH	Group 3	0546	33	Man	Roscovitine 800 mg	Grade 1	22/05/2018		Possibly related to treatment	Stable - No change
	COUGH	Group 3	1037	36	Man	Placebo	Grade 1	NK/02/2018	11/03/2018	Not related to treatment	Healing
	SPUTUM RETENTION	Group 2	1125	50	Man	Placebo	Grade 1	13/08/2017		Possibly related to treatment	Stable - No change
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	ERYTHEMA	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	07/06/2017		Not related to treatment	Stable - No change
	PRURITUS	Group 2	0527	33	Man	Roscovitine 400 mg	Grade 1	08/09/2017	08/09/2017	Not related to treatment	Healing
	PRURITUS	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	07/06/2017		Not related to treatment	Stable - No change
	PRURITUS GENITAL	Group 1	0113	29	Woman	Roscovitine 200 mg	Grade 1	19/12/2016	02/01/2017	Not related to treatment	Healing
	SKIN IRRITATION	Group 1	0610	33	Woman	Placebo	Grade 1	15/11/2016	15/11/2016	Not related to treatment	Healing
	SKIN REACTION	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 1	27/11/2017	27/11/2017	Not related to treatment	Healing
	URTICARIA	Group 3	1037	36	Man	Placebo	Grade 1	22/02/2018	22/02/2018	Not related to treatment	Healing
VASCULAR DISORDERS	EPISTAXIS	Group 2	1122	22	Woman	Roscovitine 400 mg	Grade 1	20/06/2017	20/06/2017	Not related to treatment	Healing
	HAEMATOMA	Group 1	0614	38	Man	Roscovitine 200 mg	Grade 2	05/04/2017	15/04/2017	Not related to treatment	Healing
	HAEMOPTYSIS	Group 1	0610	33	Woman	Placebo	Grade 1	19/12/2016	31/12/2016	Not related to treatment	Healing
	HAEMOPTYSIS	Group 1	0610	33	Woman	Placebo	Grade 1	29/11/2016	29/11/2016	Not related to treatment	Healing
	HAEMOPTYSIS	Group 1	0610	33	Woman	Placebo	Grade 1	08/11/2016	12/11/2016	Not related to treatment	Healing

SOC	Meddra	Group	Patient number	Age	Sex	Treatment	Grade	Start date	End date	Causality	Evolution
	HAEMOPTYSIS	Group 2	0631	37	Woman	Roscovitine 400 mg	Grade 1	16/11/2017	16/11/2017	Not related to treatment	Healing
	HAEMOPTYSIS	Group 2	1120	41	Woman	Roscovitine 400 mg	Grade 1	30/05/2017	31/05/2017	Possibly related to treatment	Healing
	HAEMOPTYSIS	Group 2	1120	41	Woman	Roscovitine 400 mg	Grade 1	27/05/2017	01/06/2017	Possibly related to treatment	Healing
	HAEMOPTYSIS	Group 3	0144	43	Man	Placebo	Grade 1	29/03/2018	14/04/2018	Not related to treatment	Healing
	HAEMOPTYSIS	Group 3	1139	42	Woman	Roscovitine 800 mg	Grade 2	04/04/2018	04/04/2018	Not related to treatment	Healing

Table 28 : Distribution of AEs, by SOC, MedDra and by group

		Group 1		Group 2		Group 3	
SOC	**MEDDRA**	**Placebo**	**Roscovitine 200mg**	**Placebo**	**Roscovitine 400mg**	**Placebo**	**Roscovitine 800mg**
BLOOD AND LYMPHATIC SYSTEM DISORDERS		2	1	0	0	0	0
	ANAEMIA	1	0	0	0	0	0
	LEUKOCYTOSIS	1	0	0	0	0	0
	LYMPHADENITIS	0	1	0	0	0	0
CARDIAC DISORDERS		0	1	0	2	0	2
	SINUS TACHYCARDIA	0	0	0	0	0	1
	TACHYCARDIA	0	1	0	2	0	1
EAR AND LABYRINTH DISORDERS		0	0	1	0	0	0
	TINNITUS	0	0	1	0	0	0
EYE DISORDERS		0	0	0	2	0	0
	PHOTOPHOBIA	0	0	0	1	0	0
	VISUAL IMPAIRMENT	0	0	0	1	0	0
GASTROINTESTINAL DISORDERS		7	13	6	12	0	5
	ABDOMINAL PAIN	3	2	5	4	0	2
	ABDOMINAL PAIN UPPER	0	1	0	1	0	0
	DIARRHOEA	3	3	0	2	0	0
	DYSPEPSIA	0	4	0	0	0	0
	GASTROINTESTINAL PAIN	0	1	0	0	0	0
	GASTROOESOPHAGEAL REFLUX DISEASE	1	1	0	0	0	0
	NAUSEA	0	0	1	0	0	3
	POST-TUSSIVE VOMITING	0	0	0	2	0	0
	VOMITING	0	1	0	3	0	0
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		1	3	1	3	1	3
	ASTHENIA	1	1	0	1	0	0
	CHEST DISCOMFORT	0	2	0	0	0	0
	DECREASED ACTIVITY	0	0	1	1	0	1
	HYPERTHERMIA	0	0	0	0	1	0
	PYREXIA	0	0	0	1	0	2

SOC	MEDDRA	Group 1 Placebo	Group 1 Roscovitine 200mg	Group 2 Placebo	Group 2 Roscovitine 400mg	Group 3 Placebo	Group 3 Roscovitine 800mg
HEPATOBILIARY DISORDERS		0	0	0	6	0	3
	HEPATIC FUNCTION ABNORMAL	0	0	0	4	0	3
	HYPERTRANSAMINASAEMIA	0	0	0	2	0	0
IMMUNE SYSTEM DISORDERS		0	0	1	1	0	0
	RHINITIS ALLERGIC	0	0	1	1	0	0
INFECTIONS AND INFESTATIONS		7	6	1	9	3	4
	GASTROENTERITIS	0	2	0	0	0	0
	INFECTIVE PULMONARY EXACERBATION OF CYSTIC FIBROSIS	1	2	0	5	2	4
	LUNG INFECTION	1	0	0	1	0	0
	NASOPHARYNGITIS	1	1	1	2	0	0
	ORAL HERPES	1	0	0	0	0	0
	PHARYNGITIS	2	0	0	0	0	0
	RHINITIS	0	1	0	0	1	0
	TONSILLITIS	1	0	0	0	0	0
	VIRAL INFECTION	0	0	0	1	0	0
INVESTIGATIONS		1	2	1	1	0	0
	BLOOD CREATINE PHOSPHOKINASE INCREASED	0	0	0	1	0	0
	C-REACTIVE PROTEIN INCREASED	0	1	0	0	0	0
	ELECTROCARDIOGRAM T WAVE INVERSION	0	1	0	0	0	0
	FORCED EXPIRATORY VOLUME DECREASED	1	0	0	0	0	0
	WEIGHT DECREASED	0	0	1	0	0	0
METABOLISM AND NUTRITION DISORDERS		0	2	0	0	0	2
	DECREASED APPETITE	0	0	0	0	0	2
	DEHYDRATION	0	1	0	0	0	0
	HYPERKALAEMIA	0	1	0	0	0	0
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		2	4	2	3	0	5
	ARTHRALGIA	0	2	0	0	0	1

SOC	MEDDRA	Group 1 Placebo	Group 1 Roscovitine 200mg	Group 2 Placebo	Group 2 Roscovitine 400mg	Group 3 Placebo	Group 3 Roscovitine 800mg
	BACK PAIN	1	1	1	2	0	0
	MUSCULOSKELETAL PAIN	0	0	0	0	0	1
	MUSCULOSKELETAL STIFFNESS	0	0	0	1	0	0
	MYALGIA	0	1	0	0	0	2
	NECK PAIN	1	0	1	0	0	1
NERVOUS SYSTEM DISORDERS		1	2	4	4	1	4
	BALANCE DISORDER	0	0	0	1	0	0
	HEADACHE	1	2	4	3	1	3
	PRESYNCOPE	0	0	0	0	0	1
PSYCHIATRIC DISORDERS		1	1	1	1	0	1
	DEPRESSED MOOD	0	0	0	1	0	0
	INSOMNIA	1	1	1	0	0	1
RENAL AND URINARY DISORDERS		0	0	0	0	0	1
	HYPERCREATININAEMIA	0	0	0	0	0	1
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		0	0	0	0	0	1
	DYSMENORRHOEA	0	0	0	0	0	1
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS		1	2	7	7	1	2
	ASTHMA	0	0	2	0	0	0
	BRONCHIAL OBSTRUCTION	0	0	1	0	0	0
	BRONCHOSPASM	0	2	0	0	0	0
	COUGH	1	0	3	7	1	2
	SPUTUM RETENTION	0	0	1	0	0	0
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		1	1	0	4	1	0
	ERYTHEMA	0	0	0	1	0	0
	PRURITUS	0	0	0	2	0	0
	PRURITUS GENITAL	0	1	0	0	0	0
	SKIN IRRITATION	1	0	0	0	0	0
	SKIN REACTION	0	0	0	1	0	0
	URTICARIA	0	0	0	0	1	0
VASCULAR DISORDERS		3	1	0	4	1	1

SOC	MEDDRA	Group 1 Placebo	Group 1 Roscovitine 200mg	Group 2 Placebo	Group 2 Roscovitine 400mg	Group 3 Placebo	Group 3 Roscovitine 800mg
	EPISTAXIS	0	0	0	1	0	0
	HAEMATOMA	0	1	0	0	0	0
	HAEMOPTYSIS	3	0	0	3	1	1