Clinical trial results:
A phase II, multicenter, open-label, randomized two-year study to evaluate the efficacy and safety of deferasirox film-coated tablet versus phlebotomy in patients with Hereditary Hemochromatosis.

Summary

EudraCT number	2016-002529-12
Trial protocol	ES SK DE BE RO
Global end of trial date	17 April 2023

Results information

Result version number	v1 (current)
This version publication date	27 April 2024
First version publication date	27 April 2024

Trial information

Trial identification

Sponsor protocol code	CICL670F2203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03203850
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharmaceuticals
Sponsor organisation address	Novartis Campus, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	17 April 2023
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to assess the response rate in the deferasirox FCT and phlebotomy treatment arms where response is defined by achieving target serum ferritin (SF) ≤ 100 µg/L on or before 24 months.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 January 2018
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Romania: 1
Country: Number of subjects enrolled	Belgium: 5
Country: Number of subjects enrolled	Spain: 22
Country: Number of subjects enrolled	Switzerland: 2
Country: Number of subjects enrolled	Russian Federation: 8
Country: Number of subjects enrolled	Slovakia: 2
Country: Number of subjects enrolled	France: 5
Worldwide total number of subjects	45
EEA total number of subjects	35

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23	0

months)	
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	43
From 65 to 84 years	2
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Participants took part in 11 investigative sites in 7 countries.

Pre-assignment

Screening details:

There was a screening period of 4 weeks to assess participants eligibility.

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Deferasirox FCT 7mg/kg

Arm description:

Deferasirox film-coated tablet 7mg/kg, oral dose daily (starting dose for the first 12 weeks)

Arm type	Experimental
Investigational medicinal product name	Deferasirox film-coated tablet
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Deferasirox film-coated tablet 7mg/kg, oral dose daily (starting dose for the first 12 weeks)

Arm title	Phlebotomy

Arm description:

Phlebotomy - standard of care

Arm type	No intervention

No investigational medicinal product assigned in this arm

Number of subjects in period 1	Deferasirox FCT 7mg/kg	Phlebotomy
Started	30	15
Completed	22	12
Not completed	8	3
Adverse event, serious fatal	1	-
Adverse events	3	-
Subject/guardian decision	4	3

Baseline characteristics

Reporting groups	
Reporting group title	Deferasirox FCT 7mg/kg
Reporting group description:	
Deferasirox film-coated tablet 7mg/kg, oral dose daily (starting dose for the first 12 weeks)	
Reporting group title	Phlebotomy
Reporting group description:	
Phlebotomy - standard of care	

Reporting group values	Deferasirox FCT 7mg/kg	Phlebotomy	Total
Number of subjects	30	15	45
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	29	14	43
From 65-84 years	1	1	2
85 years and over	0	0	0
Age Continuous Units: years			
arithmetic mean	51.6	52.1	
standard deviation	± 8.20	± 8.13	-
Sex: Female, Male Units: participants			
Female	4	3	7
Male	26	12	38
Race/Ethnicity, Customized Units: Subjects			
Caucasian	30	15	45

End points

End points reporting groups

Reporting group title	Deferasirox FCT 7mg/kg
Reporting group description:	
Deferasirox film-coated tablet 7mg/kg, oral dose daily (starting dose for the first 12 weeks)	
Reporting group title	Phlebotomy
Reporting group description:	
Phlebotomy - standard of care	

Primary: Proportion of patients achieving target SF ≤ 100 µg/L for the first time

End point title	Proportion of patients achieving target SF ≤ 100 µg/L for the first time[1]
End point description:	
Proportion of participants achieving target serum ferritin (SF) ≤ 100 µg/L on or before Month 24. Participants were considered responders if they met response criteria (target SF ≤100 µg/L) on or before Month 24 (Week 104) during the treatment phase. Any participant who discontinued treatment prematurely before meeting such criterion and participants with unknown or missing SF by Month 24 were counted as non-responder.	
End point type	Primary
End point timeframe:	
Up to Month 24	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: only analyzed descriptively.

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: percentage of participants				
number (confidence interval 95%)				
Responder	40 (22.7 to 59.4)	80 (51.9 to 95.7)		
Non-Responder	60 (40.6 to 77.3)	20 (4.3 to 48.1)		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with ocular treatment emergent adverse events (AEs)

End point title	Number of participants with ocular treatment emergent adverse events (AEs)
End point description:	
Number of participants with at least one ocular treatment emergent adverse event (new or worsening from baseline).	

End point type	Secondary

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 108 weeks.

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
At least one ocular AE	9	0		
Treatment-related ocular AEs	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with ocular treatment emergent adverse events (AEs) by preferred term

End point title	Number of participants with ocular treatment emergent adverse events (AEs) by preferred term

End point description:

Number of participants with at least one ocular treatment emergent adverse event (new or worsening from baseline). Preferred terms are based on Medical Dictionary of Regulatory Activities (MedDRA) version 26.0.

End point type	Secondary

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 108 weeks.

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
Cataract nuclear	2	0		
Glaucoma	2	0		
Blepharitis	1	0		
Cellulitis orbital	1	0		
Dry eye	1	0		
Eye pain	1	0		
Eye ulcer	1	0		
Macular oedema	1	0		
Open angle glaucoma	1	0		
Optic nerve disorder	1	0		
Panophthalmitis	1	0		

Retinal degeneration	1	0		
Retinal haemorrhage	1	0		
Visual acuity reduced	1	0		
Vitreous haemorrhage	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

End point title	Number of participants with treatment emergent adverse events (AEs) and serious adverse events (SAEs)

End point description:

Number of participants with treatment emergent AEs (any AE regardless of seriousness), AEs leading to study treatment discontinuation, SAEs and SAEs leading to study treatment discontinuation.

End point type	Secondary

End point timeframe:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 108 weeks.

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
At least one AE	28	12		
At least one SAE	7	0		
AEs leading to discontinuation	3	0		
SAEs leading to discontinuation	0	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of adverse events in participants who had study treatment interrupted due to SF ≤ 100 µg/L and re-initiated study treatment when ≥ 300 µg/L

End point title	Number of adverse events in participants who had study treatment interrupted due to SF ≤ 100 µg/L and re-initiated study treatment when ≥ 300 µg/L

End point description:

Number of participants who interrupt deferasirox FCT at least once due to SF level ≤ 100 µg/L and re-initiate therapy at SF level ≥ 300 µg/L.
There were no participants that re-initiated therapy when reached 300 ug/L.

End point type	Secondary

End point timeframe:

Up to 24 months

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	0[2]	0[3]		
Units: participants				

Notes:

[2] - There were no participants that re-initiated therapy when reached 300 ug/L.

[3] - There were no participants that re-initiated therapy when reached 300 ug/L.

Statistical analyses

No statistical analyses for this end point

Secondary: Categorical analysis of logMAR score changes from baseline to best/worst post-baseline changes in one eye with more extreme change

End point title	Categorical analysis of logMAR score changes from baseline to best/worst post-baseline changes in one eye with more extreme change

End point description:

Visual acuity was measured using an Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A letter score was calculated based on the number of letters that could correctly be identified from specified distances. For low luminance and standard acuity measures, visual acuity was described on a logMAR scale for all measures. For including acuity obtained with the ETDRS letter score, the values were converted to a logMAR scale, using the following formula: logMAR = 1.7-0.02*ETDRS score. With this conversion, a difference from baseline of 0.1 logMAR = 5-letter difference in visual acuity, 0.2 logMAR = 10-letter difference, 0.3 logMAR = 15-letter difference, 0.4 logMAR = 20-letter difference, 0.5 logMAR = 25-letter difference and 0.6 logMAR = 30-letter difference. Increase in logMAR score from baseline indicates worsening in visual acuity. Decrease in logMAR score category from baseline indicates improvement in visual acuity.

End point type	Secondary

End point timeframe:

Baseline, up to Week 104

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
Best change: Decrease <0.1	9	4		
Best change: Decrease >=0.1 - <0.2	9	5		
Best change: Decrease >=0.2 - <0.3	1	0		
Best change: Decrease >=0.3 - <0.6	0	0		
Best change: Decrease >=0.6	1	0		
Best change: Decrease Missing baseline assessment	2	0		
Best change: Decrease No decrease from baseline	8	6		
Worst change: Increase <0.1	11	11		
Worst change: Increase >=0.1 - <0.2	10	2		
Worst change: Increase >=0.2 - <0.3	1	2		

Worst change: Increase >=0.3 - <0.6	3	0		
Worst change: Increase >=0.6	0	0		
Worst change: Increase Missing baseline assessment	2	0		
Worst change: Increase No increase from baseline	3	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Categorical analysis of worst post-baseline values of intraocular pressure in one eye with more extreme change

End point title	Categorical analysis of worst post-baseline values of intraocular pressure in one eye with more extreme change

End point description:

Intraocular pressure was measured by tonometry. Intraocular pressure values >5 to ≤21 mmHg were considered normal.

End point type	Secondary

End point timeframe:

Baseline, up to Week 104

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
Worst post-baseline value- <=5 mmHg	0	0		
Worst post-baseline value- >5 to <=21 mmHg	27	12		
Worst post-baseline value- >21 to <=30 mmHg	1	3		
Worst post-baseline value- >30 mmHg	0	0		
missing post-baseline assessment	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Categorical analysis of changes in intraocular pressure from baseline to best/worst post-baseline changes in one eye with more extreme change

End point title	Categorical analysis of changes in intraocular pressure from baseline to best/worst post-baseline changes in one eye with more extreme change

End point description:

Intraocular pressure was measured by tonometry. A decrease in intraocular pressure from baseline indicated improvement.

End point type	Secondary
End point timeframe: Baseline, up to Week 104	

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
Increase from baseline >=5 mmHg and <10 mmHg	4	2		
Increase from baseline >=10 mmHg	0	1		
Decrease from baseline >=5 mmHg and <10 mmHg	6	3		
Decrease from baseline >=10 mmHg	1	0		
No change from baseline or min. change (>5 mmHg)	17	9		
Missing post-baseline values	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with slit lamp results for any evaluation and worst eye

End point title	Number of participants with slit lamp results for any evaluation and worst eye

End point description:

Slit lamp examination was used to evaluate lids, cornea, conjunctiva, iris, anterior chamber, aqueous flare, aqueous inflammatory cells and lens. Any post-baseline abnormalities (not present at baseline) in slit lamp examination were assesses by the investigator and classified as insignificant or clinically significant. Number of participants with slit lamp results (normal, insignificant, significant, missing) for any evaluation and worst eye are reported.

End point type	Secondary
End point timeframe: Baseline, up to Week 104	

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
Baseline|Normal	12	6		
Any post-baseline|Normal	7	3		
Baseline|Insignificant	14	9		
Any post-baseline|Insignificant	18	12		
Baseline|Significant	2	0		

Any post-baseline|Significant	3	0		
Baseline|Missing	2	0		
Any post-baseline|Missing	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with an increase from baseline of ≥1 and ≥2 in LOCS III grades

End point title	Number of participants with an increase from baseline of ≥1 and ≥2 in LOCS III grades

End point description:

Lens Opacities Classification System III (LOCS III) grading scales include lens opacities defined as nuclear opalescence (NO), nuclear color (NC), cortical (C) cataract and posterior subcapsular (P) cataract with several degrees of extend, i.e. severity. The LOCS III scale for nuclear opalescence and for nuclear color ranges from 0 to 6. The LOCS III scale for cortical cataract and posterior subcapsular cataract opacity ranges from 0 to 5. For all scales, higher values indicate higher opacity, opalescence, or color (range: NO0/NC0/C0/P0 to NO6/NC6/C5/P5).
Number of participants with an increase from baseline of ≥1 and increase of ≥2 in LOCS III grades is reported.

End point type	Secondary

End point timeframe:

Baseline, up to Week 104

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
≥1 grade increase from baseline	10	5		
≥2 grade increase from baseline	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with fundus oculi results for any evaluation and worst eye

End point title	Number of participants with fundus oculi results for any evaluation and worst eye

End point description:

Fundus oculi examination was used to evaluate peripheral retina, macula, optic nerve, and vitreous hemorrhage. Any post-baseline abnormalities (not present at baseline) in fundus oculi examination were assessed by the investigator and classified as insignificant or clinically significant. Number of participants with fundus oculi results (normal, insignificant, significant, missing) for any evaluation and worst eye are reported.

End point type	Secondary

End point timeframe:

Baseline, up to Week 104

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: participants				
Baseline|Normal	15	10		
Any post-baseline|Normal	12	10		
Baseline|Insignificant	12	5		
Any post-baseline|Insignificant	14	5		
Baseline|Significant	1	0		
Any post-baseline|Significant	2	0		
Baseline|Missing	2	0		
Any post-baseline|Missing	2	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Time to response (TTR)

End point title	Time to response (TTR)

End point description:

Time to response (TTR) is defined as the time from the date of randomization to the date of the first time the SF achieved a value ≤ 100 µg/L during the treatment phase. Participants who did not achieve SF ≤ 100 µg/L were censored as follows: at the last serum ferritin assessment date on or before month 24 (week 104), at the day of randomization if a subject does not have any post-baseline serum ferritin value or at the death date. TTR was analyzed using the Kaplan-Meier method. Due to EudraCT system limitations, data fields in the table cannot contain letters (eg. NA indicating 'not applicable'). Therefore, not applicable values are indicated as '999'.

End point type	Secondary

End point timeframe:

Up to Month 24

End point values	Deferasirox FCT 7mg/kg	Phlebotomy		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	15		
Units: months				
median (confidence interval 95%)	999 (19.4 to 999)	13.6 (4.0 to 22.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were reported from first dose of study treatment until end of study treatment plus 30 days post treatment, up to a maximum duration of approximately 108 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	26.0

Reporting groups

Reporting group title	DFX FCT

Reporting group description:

DFX FCT

Reporting group title	Phlebotomy

Reporting group description:

Phlebotomy

Serious adverse events	DFX FCT	Phlebotomy	
Total subjects affected by serious adverse events			
subjects affected / exposed	7 / 30 (23.33%)	0 / 15 (0.00%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transaminases increased			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder neoplasm			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			

Lower limb fracture			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Thoracic outlet syndrome			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Sudden death			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cellulitis			
subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			

subjects affected / exposed	1 / 30 (3.33%)	0 / 15 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	DFX FCT	Phlebotomy	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	23 / 30 (76.67%)	12 / 15 (80.00%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hypertension			
subjects affected / exposed	3 / 30 (10.00%)	3 / 15 (20.00%)	
occurrences (all)	4	3	
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Fatigue			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Asthenia			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vaccination site pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Oropharyngeal pain			

subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Nasal congestion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 30 (3.33%)	3 / 15 (20.00%)	
occurrences (all)	1	3	
Catarrh			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Asthma			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Investigations			
Blood uric acid increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood urea increased			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Blood lactate dehydrogenase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood creatinine increased			
subjects affected / exposed	10 / 30 (33.33%)	1 / 15 (6.67%)	
occurrences (all)	13	1	
Blood creatine phosphokinase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Blood cholesterol increased			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Aspartate aminotransferase increased			

subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Alanine aminotransferase increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Glycosylated haemoglobin increased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vitamin D decreased			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Road traffic accident			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Procedural pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			
Sinus bradycardia			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Nervous system disorders			
Taste disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	4 / 30 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	8	3	
Dizziness			

subjects affected / exposed	0 / 30 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	4	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 15 (13.33%)	
occurrences (all)	1	2	
Ear and labyrinth disorders			
Deafness unilateral			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Ear pain			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Phobic postural vertigo			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Middle ear inflammation			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Eye disorders			
Glaucoma			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Cataract nuclear			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Abdominal distension			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Gastrointestinal disorder			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Diarrhoea			

subjects affected / exposed	6 / 30 (20.00%)	2 / 15 (13.33%)	
occurrences (all)	8	3	
Constipation			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Nausea			
subjects affected / exposed	5 / 30 (16.67%)	0 / 15 (0.00%)	
occurrences (all)	8	0	
Haemorrhoids			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Gastrointestinal pain			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	3	0	
Renal and urinary disorders			
Haematuria			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 30 (3.33%)	2 / 15 (13.33%)	
occurrences (all)	1	3	
Arthritis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Back pain			
subjects affected / exposed	4 / 30 (13.33%)	2 / 15 (13.33%)	
occurrences (all)	4	2	
Neck pain			
subjects affected / exposed	0 / 30 (0.00%)	2 / 15 (13.33%)	
occurrences (all)	0	2	
Infections and infestations			

Wound infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Urinary tract infection			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Suspected COVID-19			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Nasopharyngitis			
subjects affected / exposed	2 / 30 (6.67%)	3 / 15 (20.00%)	
occurrences (all)	2	5	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Ear infection			
subjects affected / exposed	1 / 30 (3.33%)	1 / 15 (6.67%)	
occurrences (all)	1	1	
Cystitis			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
COVID-19			
subjects affected / exposed	2 / 30 (6.67%)	0 / 15 (0.00%)	
occurrences (all)	2	0	
Bone abscess			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Folate deficiency			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Hyperglycaemia			

subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	
Vitamin B12 deficiency			
subjects affected / exposed	0 / 30 (0.00%)	1 / 15 (6.67%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 August 2018	The purpose of this amendment is to modify the inclusion and exclusion criteria, to correct inconsistencies, typos, add some clarifications and to update withdrawal of consent language. Additionally, the local French amendment text is formally integrated in this global amendment. However, the French specific requirements remain valid for France only.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported