Clinical trial results:
Efficacy and safety of gadopiclenol for body magnetic resonance imaging (MRI) (The PROMISE trial)

Summary

EudraCT number	2018-003946-18
Trial protocol	FR HU BG DE ES IT
Global end of trial date	09 December 2020

Results information

Result version number	v1 (current)
This version publication date	24 December 2021
First version publication date	24 December 2021

Trial information

Trial identification

Sponsor protocol code	GDX-44-011

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03986138
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Guerbet
Sponsor organisation address	B.P. 57400, CdG Cedex, France, 95943
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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	31 May 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	09 December 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary objective 1:
To demonstrate the superiority of gadopiclenol-enhanced MRI at 0.05 mmol/kg body weight compared to unenhanced MRI for patients referred for contrast-enhanced MRI of body regions, in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology and degree of contrast enhancement) using the patient as his/her own control.
Primary objective 2:
To demonstrate the non-inferiority of gadopiclenol at 0.05 mmol/kg compared to gadobutrol at 0.1 mmol/kg in terms of 3 lesion visualization co-primary criteria (border delineation, internal morphology, degree of contrast enhancement) for patients referred for contrast-enhanced MRI of body regions.

Protection of trial subjects:

This trial has been conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, that are consistent with Good Clinical Practice (GCP) according to International Conference on Harmonisation (ICH) guidelines and with the applicable regional/local regulations of the country in which the trial was conducted.
The safety of subjects was assessed over 1-day follow-up period after each MRI visit, for vital signs, injection site tolerance, clinical laboratory parameters and monitoring of adverse events. For patients enrolled in France: a safety follow-up contact between 7 and 14 days after the last IMP injection was performed.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	27 August 2019
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	Korea, Democratic People's Republic of: 46
Country: Number of subjects enrolled	Mexico: 31
Country: Number of subjects enrolled	Ukraine: 17
Country: Number of subjects enrolled	United States: 49
Country: Number of subjects enrolled	Poland: 75
Country: Number of subjects enrolled	Spain: 4
Country: Number of subjects enrolled	Bulgaria: 11
Country: Number of subjects enrolled	France: 11
Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Hungary: 51

Country: Number of subjects enrolled	Italy: 1
Worldwide total number of subjects	304
EEA total number of subjects	161

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	202
From 65 to 84 years	101
85 years and over	1

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	324[1]
Number of subjects completed	304

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Received first contrast agent but not randomized: 1
Reason: Number of subjects	screen failure: 19

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: The number of patients presented in the Pre-assignment period (324) is the number of screened patients. Among these patients, 304 were randomized.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Data analyst, Subject, Carer, Assessor

Arms

Arm title	Overall population

Arm description:

All patients who received at least one injection of one of the 2 contrast agents.

Arm type	Experimental
Investigational medicinal product name	gadopiclenol
Investigational medicinal product code	
Other name	P03277
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single intravenous bolus injection at 0.05 mmol/kg.
The injection rate was depending on scanned organ/region and a saline flush should follow, preferably via a power injector.

Investigational medicinal product name	gadobutrol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Single intravenous bolus injection at 0.1 mmol/kg.
The injection rate was depending on scanned organ/region and a saline flush should follow, preferably via a power injector.

Number of subjects in period 1	Overall population
Started	304
Completed	275
Not completed	29
Adverse event other than COVID-19	2
COVID-19 pandemic preventing protocol follow-up	2
Consent withdrawn by subject	11
COVID-19	1
Other reason	12
Discovery of an unacceptable risk to the patient	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	304	304	
Age categorical Units: Subjects			
Adults (18-64 years)	202	202	
From 65-84 years	101	101	
85 years and over	1	1	
Age continuous Units: years			
arithmetic mean	57.29		
standard deviation	± 12.93	-	
Gender categorical Units: Subjects			
Female	180	180	
Male	124	124	

End points

End points reporting groups

Reporting group title	Overall population
Reporting group description:	
All patients who received at least one injection of one of the 2 contrast agents.	
Subject analysis set title	FAS1 Paired images
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set 1 (FAS1): all patients who have both Pre and Paired images with gadopiclenol assessable for primary criteria 1 for at least one matching lesion for at least one off-site reader	
Subject analysis set title	FAS1 Pre images
Subject analysis set type	Full analysis
Subject analysis set description:	
Full analysis set 1 (FAS1): all patients who have both Pre and Paired images with gadopiclenol assessable for primary criteria 1 for at least one matching lesion for at least one off-site reader	
Subject analysis set title	PPS2 Gadopiclenol
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-Protocol Set 2 (PPS2): all patients from Full Analysis Set 2 (FAS 2) who have no major protocol deviations for primary criteria 2 FAS 2: all patients who have Paired images for both gadopiclenol and gadobutrol assessable for primary criteria 2 for at least one matching lesion for at least one off-site reader	
Subject analysis set title	PPS2 Gadobutrol
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-Protocol Set 2 (PPS2): all patients from Full Analysis Set 2 (FAS 2) who have no major protocol deviations for primary criteria 2 FAS 2: all patients who have Paired images for both gadopiclenol and gadobutrol assessable for primary criteria 2 for at least one matching lesion for at least one off-site reader	

Primary: Lesion visualization criteria for gadopiclenol-enhanced MRI compared to unenhanced MRI (off-site read)

End point title	Lesion visualization criteria for gadopiclenol-enhanced MRI compared to unenhanced MRI (off-site read)
End point description:	
The lesion visualization criteria were based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement, assessed on the images acquired during the MRI performed with gadopiclenol.	
End point type	Primary
End point timeframe:	
1 day procedure	

End point values	FAS1 Paired images	FAS1 Pre images		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	278	278		
Units: None				
least squares mean (standard error)				
Border delineation - Reader 1	3.79 (± 0.03)	2.26 (± 0.03)		
Border delineation - Reader 2	3.48 (± 0.06)	3.01 (± 0.06)		

Border delineation - Reader 3	3.49 (± 0.03)	1.78 (± 0.03)		
Internal morphology - Reader 1	3.80 (± 0.02)	1.99 (± 0.02)		
Internal morphology - Reader 2	3.75 (± 0.05)	3.22 (± 0.05)		
Internal morphology - Reader 3	3.72 (± 0.03)	1.69 (± 0.03)		
Degree of contrast enhancement - Reader 1	3.64 (± 0.03)	1.00 (± 0.03)		
Degree of contrast enhancement - Reader 2	2.82 (± 0.05)	1.00 (± 0.05)		
Degree of contrast enhancement - Reader 3	3.33 (± 0.03)	1.00 (± 0.03)		

Statistical analyses

Statistical analysis title	Border delineation - Reader 1
Statistical analysis description:	
The Null hypothesis is rejected if the difference ["Paired" scores mean – "Pre" scores mean] is significantly different from zero with a type 1 error set at 0.025.	
Comparison groups	FAS1 Paired images v FAS1 Pre images
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.46
upper limit	1.6
Variability estimate	Standard error of the mean
Dispersion value	0.04

Statistical analysis title	Border delineation - Reader 2
Statistical analysis description:	
The Null hypothesis is rejected if the difference ["Paired" scores mean – "Pre" scores mean] is significantly different from zero with a type 1 error set at 0.025.	
Comparison groups	FAS1 Paired images v FAS1 Pre images
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.47

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.36
upper limit	0.58
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	Border delineation - Reader 3

Statistical analysis description:

The Null hypothesis is rejected if the difference [“Paired” scores mean – “Pre” scores mean] is significantly different from zero with a type 1 error set at 0.025.

Comparison groups	FAS1 Paired images v FAS1 Pre images
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.71
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.65
upper limit	1.78
Variability estimate	Standard error of the mean
Dispersion value	0.04

Statistical analysis title	Internal morphology - Reader 1

Statistical analysis description:

The Null hypothesis is rejected if the difference [“Paired” scores mean – “Pre” scores mean] is significantly different from zero with a type 1 error set at 0.025.

Comparison groups	FAS1 Paired images v FAS1 Pre images
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.81
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.76
upper limit	1.87
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	Internal morphology - Reader 2
Statistical analysis description:	
The Null hypothesis is rejected if the difference ["Paired" scores mean – "Pre" scores mean] is significantly different from zero with a type 1 error set at 0.025.	
Comparison groups	FAS1 Paired images v FAS1 Pre images
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.53
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.42
upper limit	0.64
Variability estimate	Standard error of the mean
Dispersion value	0.06

Statistical analysis title	Internal morphology - Reader 3
Comparison groups	FAS1 Paired images v FAS1 Pre images
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.95
upper limit	2.11
Variability estimate	Standard error of the mean
Dispersion value	0.04

Statistical analysis title	Degree of contrast enhancement - Reader 1
Comparison groups	FAS1 Paired images v FAS1 Pre images

Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.64
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.56
upper limit	2.72
Variability estimate	Standard error of the mean
Dispersion value	0.04

Statistical analysis title	Degree of contrast enhancement - Reader 2
Comparison groups	FAS1 Paired images v FAS1 Pre images
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	1.82
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.68
upper limit	1.96
Variability estimate	Standard error of the mean
Dispersion value	0.07

Statistical analysis title	Degree of contrast enhancement - Reader 3
Comparison groups	FAS1 Paired images v FAS1 Pre images
Number of subjects included in analysis	556
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	2.33
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.26
upper limit	2.41

Variability estimate	Standard error of the mean
Dispersion value	0.04

Primary: Lesion visualization criteria for gadopiclenol compared to gadobutrol (offsite read)

End point title	Lesion visualization criteria for gadopiclenol compared to gadobutrol (offsite read)

End point description:

The lesion visualization criteria were based on 3 co-primary criteria: border delineation, internal morphology and degree of contrast enhancement, assessed on the images acquired during the MRI performed with gadopiclenol and those performed with gadobutrol.

End point type	Primary

End point timeframe:

Data from two different MRI (with gadopiclenol and gadobutrol) performed at an interval of 2 to 14 days

End point values	PPS2 Gadopiclenol	PPS2 Gadobutrol		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	260	260		
Units: None				
least squares mean (standard error)				
Border delineation - Reader 1	3.82 (± 0.02)	3.81 (± 0.02)		
Border delineation - Reader 2	3.56 (± 0.05)	3.53 (± 0.05)		
Border delineation - Reader 3	3.53 (± 0.03)	3.57 (± 0.03)		
Internal morphology - Reader 1	3.83 (± 0.02)	3.83 (± 0.02)		
Internal morphology - Reader 2	3.75 (± 0.04)	3.75 (± 0.04)		
Internal morphology - Reader 3	3.74 (± 0.03)	3.77 (± 0.03)		
Degree of contrast enhancement - Reader 1	3.69 (± 0.04)	3.68 (± 0.04)		
Degree of contrast enhancement - Reader 2	2.88 (± 0.07)	2.86 (± 0.07)		
Degree of contrast enhancement - Reader 3	3.35 (± 0.04)	3.37 (± 0.04)		

Statistical analyses

Statistical analysis title	Border delineation - Reader 1

Statistical analysis description:

The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference

Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol

Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	Border delineation - Reader 2
Statistical analysis description:	
The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference.	
Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol
Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.05
upper limit	0.1
Variability estimate	Standard error of the mean
Dispersion value	0.04

Statistical analysis title	Border delineation - Reader 3
Statistical analysis description:	
The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference.	
Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol
Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.04

Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.1
upper limit	0.01
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	Internal morphology - Reader 1
Statistical analysis description:	
The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference.	
Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol
Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.05
Variability estimate	Standard error of the mean
Dispersion value	0.03

Statistical analysis title	Internal morphology - Reader 2
Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol
Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.07
Variability estimate	Standard error of the mean
Dispersion value	0.04

Statistical analysis title	Internal morphology - Reader 3
Statistical analysis description:	
The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference.	
Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol
Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.02
Variability estimate	Standard error of the mean
Dispersion value	0.02

Statistical analysis title	Degree of contrast enhancement - Reader 1
Statistical analysis description:	
The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference.	
Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol
Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.01
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.06
upper limit	0.09
Variability estimate	Standard error of the mean
Dispersion value	0.04

Statistical analysis title	Degree of contrast enhancement - Reader 2
Statistical analysis description:	
The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference.	
Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol

Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.07
upper limit	0.12
Variability estimate	Standard error of the mean
Dispersion value	0.05

Statistical analysis title	Degree of contrast enhancement - Reader 3
Statistical analysis description:	
The Null hypothesis is rejected if the 2-sided 95% Confidence Interval (CI) for the difference.	
Comparison groups	PPS2 Gadopiclenol v PPS2 Gadobutrol
Number of subjects included in analysis	520
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.0001
Method	t-test, 2-sided
Parameter estimate	Mean difference (final values)
Point estimate	-0.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.08
upper limit	0.04
Variability estimate	Standard error of the mean
Dispersion value	0.03

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were recorded from informed consent signature up to one day after the second MRI. For patients enrolled in France: a safety follow-up contact between 7 and 14 days after the last IMP injection was performed.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

Reporting groups

Reporting group title	Safety Set - Gadopiclenol

Reporting group description:

All patients having received at least one injection of gadopiclenol regardless of the quantity

Reporting group title	Safety Set - Gadobutrol

Reporting group description:

All patients having received at least one injection of gadobutrol regardless of the quantity

Serious adverse events	Safety Set - Gadopiclenol	Safety Set - Gadobutrol	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 288 (1.04%)	0 / 290 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Nervous system disorders			
Depressed level of consciousness			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (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			
Condition aggravated			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
COVID-19			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (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: 0 %

Non-serious adverse events	Safety Set - Gadopiclenol	Safety Set - Gadobutrol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	49 / 288 (17.01%)	58 / 290 (20.00%)	
Surgical and medical procedures			
Central venous catheterisation			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Injection site pain			
subjects affected / exposed	5 / 288 (1.74%)	7 / 290 (2.41%)	
occurrences (all)	5	7	
Injection site bruising			
subjects affected / exposed	3 / 288 (1.04%)	1 / 290 (0.34%)	
occurrences (all)	3	1	
Fatigue			
subjects affected / exposed	1 / 288 (0.35%)	1 / 290 (0.34%)	
occurrences (all)	1	1	
Injection site discomfort			
subjects affected / exposed	1 / 288 (0.35%)	1 / 290 (0.34%)	
occurrences (all)	1	1	
Injection site erythema			
subjects affected / exposed	0 / 288 (0.00%)	2 / 290 (0.69%)	
occurrences (all)	0	2	
Injection site haemorrhage			
subjects affected / exposed	0 / 288 (0.00%)	2 / 290 (0.69%)	
occurrences (all)	0	2	
Pain			
subjects affected / exposed	0 / 288 (0.00%)	2 / 290 (0.69%)	
occurrences (all)	0	2	
Asthenia			

subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Extravasation			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Infusion site pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Injection site haematoma			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Injection site inflammation			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Injection site pruritus			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Injection site warmth			
subjects affected / exposed	1 / 288 (0.35%)	1 / 290 (0.34%)	
occurrences (all)	1	1	
Oedema peripheral			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Pyrexia			
subjects affected / exposed	1 / 288 (0.35%)	1 / 290 (0.34%)	
occurrences (all)	1	1	
Swelling			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Contrast media reaction			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	

Drug hypersensitivity			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 288 (0.69%)	1 / 290 (0.34%)	
occurrences (all)	2	1	
Epistaxis			
subjects affected / exposed	0 / 288 (0.00%)	2 / 290 (0.69%)	
occurrences (all)	0	2	
Dyspnoea			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Nasal congestion			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Product issues			
Device malfunction			
subjects affected / exposed	0 / 288 (0.00%)	2 / 290 (0.69%)	
occurrences (all)	0	2	
Investigations			
Blood pressure increased			
subjects affected / exposed	2 / 288 (0.69%)	2 / 290 (0.69%)	
occurrences (all)	2	2	
Cystatin C increased			
subjects affected / exposed	1 / 288 (0.35%)	1 / 290 (0.34%)	
occurrences (all)	1	1	
Blood creatinine increased			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Glomerular filtration rate decreased			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Neutrophil count increased			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	

Paracentesis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
White blood cell count increased			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Incorrect dosage administered			
subjects affected / exposed	5 / 288 (1.74%)	4 / 290 (1.38%)	
occurrences (all)	5	4	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Nervous system disorders			
Headache			
subjects affected / exposed	16 / 288 (5.56%)	4 / 290 (1.38%)	
occurrences (all)	17	4	
Dizziness			
subjects affected / exposed	1 / 288 (0.35%)	1 / 290 (0.34%)	
occurrences (all)	1	1	
Dysgeusia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 288 (0.69%)	3 / 290 (1.03%)	
occurrences (all)	2	3	
Neutropenia			
subjects affected / exposed	1 / 288 (0.35%)	4 / 290 (1.38%)	
occurrences (all)	1	4	
Leukopenia			
subjects affected / exposed	0 / 288 (0.00%)	3 / 290 (1.03%)	
occurrences (all)	0	3	
Thrombocytopenia			

subjects affected / exposed	0 / 288 (0.00%)	3 / 290 (1.03%)	
occurrences (all)	0	3	
Lymphopenia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Monocytopenia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Tinnitus			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Eye disorders			
Swelling of eyelid			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Nausea			
subjects affected / exposed	5 / 288 (1.74%)	4 / 290 (1.38%)	
occurrences (all)	5	4	
Dry mouth			
subjects affected / exposed	3 / 288 (1.04%)	3 / 290 (1.03%)	
occurrences (all)	3	3	
Diarrhoea			
subjects affected / exposed	2 / 288 (0.69%)	2 / 290 (0.69%)	
occurrences (all)	2	2	
Vomiting			
subjects affected / exposed	1 / 288 (0.35%)	2 / 290 (0.69%)	
occurrences (all)	1	2	
Abdominal pain			
subjects affected / exposed	1 / 288 (0.35%)	1 / 290 (0.34%)	
occurrences (all)	1	1	
Abdominal distension			

subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Abdominal pain upper			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Constipation			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Enteritis			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Angioedema			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Dermatitis allergic			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Dermatitis contact			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Erythema			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Pruritus			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Nephropathy			
subjects affected / exposed	1 / 288 (0.35%)	1 / 290 (0.34%)	
occurrences (all)	1	1	
Renal impairment			

subjects affected / exposed	0 / 288 (0.00%)	2 / 290 (0.69%)	
occurrences (all)	0	2	
Acute kidney injury			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Renal failure			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 288 (0.69%)	1 / 290 (0.34%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	0 / 288 (0.00%)	3 / 290 (1.03%)	
occurrences (all)	0	3	
Muscle spasms			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Pain in jaw			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	0 / 288 (0.00%)	1 / 290 (0.34%)	
occurrences (all)	0	1	
Hypokalaemia			
subjects affected / exposed	1 / 288 (0.35%)	0 / 290 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
30 June 2020	The anticipated actual rate of non-evaluable patients was estimated to be higher than initially planned: the revised hypothesis for the non-evaluable patient rate was about 33% instead of 20%. This increase in drop-out rate was due in part to the Covid-19 pandemic impact on enrollment of patients and/or compliance with protocol, but also to the variety and complexity of organs in this study. Therefore, to secure the target 200 evaluable patients needed for sufficient statistical power to meet both study primary objectives, the sample size had to be increased from 250 to 300 enrolled patients.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported