Clinical trial results:
Phase Ib/II clinical trial of ruxolitinib in combination with nilotinib and prednisona for myelofibrosis: RuNiC study

Summary

EudraCT number	2016-005214-21
Trial protocol	ES
Global end of trial date	30 June 2020

Results information

Result version number	v1 (current)
This version publication date	01 March 2023
First version publication date	01 March 2023

Trial information

Trial identification

Sponsor protocol code	RuNiC

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Grupo Español de Enfermedades Mieloproliferativas Crónicas Filadelfia Negativas (GEMFIN)
Sponsor organisation address	Carrer del Secretari Coloma, 64-68, Barcelona, Spain, 08024
Public contact	Departamento de Ensayos Clínicos, Dynamic Solutions S.L, 34 914561125, a.tello@dynasolutions.com
Scientific contact	Departamento de Ensayos Clínicos, Dynamic Solutions S.L, 34 914561125, a.tello@dynasolutions.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	18 October 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	30 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the study is to determine the maximum tolerated dose (MTD) and the recommended phase III dose (RP3D) of ruxolitinib when administered in combination with nilotinib 300mg twice a day (BID) and prednisone 50mg every other day (EOD).

Protection of trial subjects:

This clinical trial was conducted in accordance with the protocol, the principles established in the current revised version of the Declaration of Helsinki on medical research in human subjects (60th WMA General Assembly, Fortaleza, Brazil, 2013), and in accordance with applicable regulatory requirements, in particular the 1996 ICH Harmonised Tripartite Guidelines For Good Clinical Practice and local legislation on Clinical Trials (Royal Decree 1090/2015 that rules clinical drug trials in Spain, Ethics Committees of medicines research and the Spanish Clinical Trials Register), as well as Act No. 14/2007 of 3 July on biomedical research and Royal Decree 1716/2011 of 18 November in all applicable matters. At the time of study initiation, and incorporating the specific provisions for application in Spain of Regulation (EU) No 536/2014 of the European Parliament and of the Council on clinical trials on medicinal products for human use.
By signing the protocol, the investigators agreed to follow the instructions and procedures described in the protocol and therefore to comply with the principles of GCP on which it is based.
In compliance with Royal Decree 1090/2015, the sponsor submitted the pertinent documentation to the ethics committee. The study did not start until approval by the IEC and the AEMPS has been obtained.

Background therapy: -	
Evidence for comparator: -	
Actual start date of recruitment	30 June 2017
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	Spain: 21
Worldwide total number of subjects	21
EEA total number of subjects	21

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)	8
From 65 to 84 years	13
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Between November 2017 and June 2020, a total of 21 patients were included in the study at 6 Spanish sites. Six patients were considered screening failures and did not receive treatment, and were thus not included in the ITT or the PP populations

Pre-assignment

Screening details:

Patients must be > 18 years, diagnosed with PMF, PPV-MF or PET-MF irrespective of JAK2 mutation status, classified as intermediate risk level 1 (1 or more prognostic factors defined by the International Working Group) with at least one criterion other than age, have palpable spleen of at least 5 cm and active symptoms of MF measured by MPN-SAF TSS.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Arm A

Arm description:

Patients naïve to JAK inhibitors treatment.

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose levels of ruxolitinib ranging from 5 mg twice a day (BID) to 20 mg BID in 28-day treatment cycles in combination with nilotinib and prednisone.

Investigational medicinal product name	Nilotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nilotinib dose of 300 mg of nilotinib twice a day in 28-day treatment cycles.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone dose of 50 mg every other day in 28-day treatment cycles.

Arm title	Arm B

Arm description:

Patients non-responding to or relapsed after JAK inhibitors treatment. Patients non- responding to or relapsed after JAK inhibitors treatment met one of the following criteria at screening to be eligible for treatment arm B (patients with prior ruxolitinib treatment must meet one of the criteria below after at

least 12 weeks on ruxolitinib treatment):
• Patients with no improvement in spleen length and may or may not have a corresponding symptomatic improvement.
• Patients with less than a 25% spleen length reduction by palpation and may or may not have a corresponding symptomatic improvement.
• Patients that have had a 25% to 49% reduction in spleen length by palpation and without symptomatic improvement.
• Patients who have lost benefit from prior treatment with a JAK inhibitor as per investigator (i.e., increased spleen length from nadir >40% as measured by palpation and/or return of symptoms as per investigator's assessment).

Arm type	Experimental
Investigational medicinal product name	Ruxolitinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Dose levels of ruxolitinib ranging from 5 mg twice a day (BID) to 20 mg BID in 28-day treatment cycles in combination with nilotinib and prednisone.

Investigational medicinal product name	Nilotinib
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Nilotinib dose of 300 mg of nilotinib twice a day in 28-day treatment cycles.

Investigational medicinal product name	Prednisone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Prednisone dose of 50 mg every other day in 28-day treatment cycles.

Number of subjects in period 1[1]	Arm A	Arm B
Started	5	10
Completed	1	5
Not completed	4	5
Spleen regrowth and presence of some toxicities	1	-
Consent withdrawn by subject	1	1
Physician decision	1	-
Disease progression	-	1
Adverse event	1	-
Disease progression and physician decision	-	1
Lack of efficacy and worsening of the patient	-	1
Lack of efficacy	-	1

Notes:

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

Justification: Six patients were considered screening failures and did not receive treatment, and thus were excluded.

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	15	15	
Age categorical Units: Subjects			
Age continuous Units: years			
median	66.5		
full range (min-max)	53.4 to 70.8	-	
Gender categorical Units: Subjects			
Female	6	6	
Male	9	9	
Ethnicity Units: Subjects			
Caucasian	14	14	
Arabic	1	1	
Hematologic diseases Units: Subjects			
Yes	7	7	
No	8	8	
Cardiovascular diseases Units: Subjects			
Yes	6	6	
No	9	9	
Musculoskeletal disorders Units: Subjects			
Yes	5	5	
No	10	10	
Neurologic or psychiatric disorders Units: Subjects			
Yes	3	3	
No	12	12	
Gastrointestinal disorders Units: Subjects			
Yes	2	2	
No	13	13	
Endocrine disorders Units: Subjects			
Yes	2	2	
No	13	13	
Autoimmune disease			

Units: Subjects			
Yes	1	1	
No	14	14	
Respiratory diseases Units: Subjects			
Yes	1	1	
No	14	14	
Hepatic diseases Units: Subjects			
Yes	1	1	
No	14	14	
Other diseases Units: Subjects			
Yes	8	8	
No	7	7	
Patients with transfusion 12 weeks prior screening Units: Subjects			
Yes	4	4	
No	11	11	
Abnormal megakaryocyte morphology Units: Subjects			
Yes	7	7	
No	8	8	
Physical examination abnormalities Units: Subjects			
Bilateral lymphedema in legs	1	1	
Massive splenomegaly	1	1	
Splenomegaly of around 21 cm	1	1	
Splenomegaly of around 13 cm	1	1	
Splenomegaly of at least 5 cm	11	11	
ECOG performance status Units: Subjects			
Zero	5	5	
One	7	7	
Two	3	3	
Type of myelofibrosis Units: Subjects			
Primary MF	6	6	
Post-polycythemia vera MF	4	4	
Post-essential thrombocythemia MF	4	4	
Not available	1	1	
IPSS risk category Units: Subjects			
Low	1	1	
Intermediate 1	5	5	
Intermediate 2	4	4	
High	1	1	
Not available	4	4	
DIPSS risk category Units: Subjects			

Intermediate 1	8	8	
Intermediate 2	3	3	
High	1	1	
Not available	3	3	
DIPSS-Plus risk category Units: Subjects			
Intermediate 1	5	5	
Intermediate 2	4	4	
Not available	6	6	
Mutations at diagnosis: JAK2 V617F Units: Subjects			
Yes	9	9	
No	6	6	
Mutations at diagnosis: CALR Type 1 Units: Subjects			
Yes	4	4	
No	11	11	
Mutations at diagnosis: TET2 T1884P Units: Subjects			
Yes	2	2	
No	13	13	
Other mutations at diagnosis Units: Subjects			
Exon 12	1	1	
Allele frequency P.V617F	1	1	
MPL W515L/K	1	1	
TET H1778R	1	1	
None of these	11	11	
Patients undergone Biopsy Units: Subjects			
Grade 2	1	1	
Grade 3	2	2	
Unknown	2	2	
None	10	10	
Patients undergone Aspirate Units: Subjects			
Grade 1	1	1	
Unknown	2	2	
None	12	12	
Patients undergone Both Units: Subjects			
Grade 0	1	1	
Grade 1	1	1	
Grade 3	3	3	
Unknown	2	2	
None	8	8	
Abnormal erythrocyte morphology Units: Subjects			
Yes	4	4	
No	4	4	
Not available	7	7	

Abnormal megakaryocyte morphology Units: Subjects			
Yes	7	7	
No	2	2	
Not available	6	6	
Diagnostic interpretation Units: Subjects			
Absence of infiltrative or granulomatous process	2	2	
Medullary hypoplasia, without evidence of MF	1	1	
Primary MF	1	1	
smPCR type PV/ET without signs of transformation	1	1	
Not available	10	10	
Patients with prior anti-neoplastic therapy Units: Subjects			
Yes	13	13	
No	2	2	
Anti-neoplastic therapy type: Hydroxyurea Units: Subjects			
Yes	11	11	
No	4	4	
Anti-neoplastic therapy type: Ruxolitinib Units: Subjects			
Yes	10	10	
No	5	5	
Other anti-neoplastic therapy types Units: Subjects			
Melphalan	1	1	
Adiro, Interferon, Clopidogrel, Vitamin B12	1	1	
Anagrelide, alpha-Interferon, Adiro	1	1	
BKM120	1	1	
Imetelstat	1	1	
Mercaptopurine	1	1	
None of them	9	9	
Patients with prior anti-neoplastic radiotherapy Units: Subjects			
Yes	1	1	
No	14	14	
Median peripheral-blood blast count Units: Percentage			
median	4		
inter-quartile range (Q1-Q3)	2 to 9	-	
Hemoglobin Units: g/dL			
median	10.8		
inter-quartile range (Q1-Q3)	9.2 to 11.7	-	
Platelet count Units: x10-9/L			

median	230		
inter-quartile range (Q1-Q3)	92 to 467	-	
Absolute neutrophil count Units: x10-9/L			
median	7.6		
inter-quartile range (Q1-Q3)	6.2 to 13.8	-	
White-cell count Units: x10-9/L			
median	10.6		
inter-quartile range (Q1-Q3)	4.61 to 13.5	-	
Median spleen length Units: cm			
median	8		
inter-quartile range (Q1-Q3)	6 to 20	-	
Time from diagnosis Units: Years			
median	2.91		
inter-quartile range (Q1-Q3)	0.59 to 3.98	-	

End points

End points reporting groups

Reporting group title	Arm A

Reporting group description:

Patients naïve to JAK inhibitors treatment.

Reporting group title	Arm B

Reporting group description:

Patients non-responding to or relapsed after JAK inhibitors treatment. Patients non- responding to or relapsed after JAK inhibitors treatment met one of the following criteria at screening to be eligible for treatment arm B (patients with prior ruxolitinib treatment must meet one of the criteria below after at least 12 weeks on ruxolitinib treatment):
• Patients with no improvement in spleen length and may or may not have a corresponding symptomatic improvement.
• Patients with less than a 25% spleen length reduction by palpation and may or may not have a corresponding symptomatic improvement.
• Patients that have had a 25% to 49% reduction in spleen length by palpation and without symptomatic improvement.
• Patients who have lost benefit from prior treatment with a JAK inhibitor as per investigator (i.e., increased spleen length from nadir >40% as measured by palpation and/or return of symptoms as per investigator’s assessment).

Subject analysis set title	ITT population
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Pooled analysis of patients

Primary: Percentage of participants experiencing study treatment-related adverse events

End point title	Percentage of participants experiencing study treatment-related adverse events[1]

End point description:

End point type	Primary

End point timeframe:

Through the study

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: This is a descriptive evaluation and no statistical analysis has been performed.

End point values	Arm A	Arm B		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	5	10		
Units: percentage				
number (not applicable)	100	100		

Statistical analyses

No statistical analyses for this end point

Secondary: ECOG performance status at cycle 4

End point title	ECOG performance status at cycle 4

End point description:

End point type	Secondary

End point timeframe:

At cycle 4 (day 1)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	13			
Units: score				
number (not applicable)				
ECOG 0	6			
ECOG 1	5			
Not available	2			

Statistical analyses

No statistical analyses for this end point

Secondary: ECOG performance status at cycle 7

End point title	ECOG performance status at cycle 7

End point description:

End point type	Secondary

End point timeframe:

At cycle 7 (day 1)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: score				
number (not applicable)				
ECOG 0	5			
ECOG 1	3			
ECOG 2	1			

Statistical analyses

No statistical analyses for this end point

Secondary: ECOG performance status at cycle 12

End point title	ECOG performance status at cycle 12

End point description:

End point type	Secondary

End point timeframe:

At cycle 12 (day 1)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	7			
Units: Score				
number (not applicable)				
ECOG 0	3			
ECOG 1	3			
Not available	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Spleen length reduction at cycle 7

End point title	Spleen length reduction at cycle 7

End point description:

End point type	Secondary

End point timeframe:

From Screening to Cycle 7 (Day 1)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed				
Units: percentage of reduction				
number (not applicable)				
Patient 2	100			
Patient 3	-25			
Patient 4	83.3			
Patient 5	100			
Patient 6	100			
Patient 7	0			
Patient 10	57.1			
Patient 12	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Spleen length reduction at cycle 12

End point title	Spleen length reduction at cycle 12

End point description:

End point type	Secondary

End point timeframe:

From Screening to Cycle 12 (Day 28)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: percentage of reduction				
number (not applicable)				
Patient 3	-5			
Patient 4	100			
Patient 5	100			
Patient 7	19			
Patient 10	100			

Statistical analyses

No statistical analyses for this end point

Secondary: Spleen length difference at cycle 7

End point title	Spleen length difference at cycle 7

End point description:

End point type	Secondary

End point timeframe:

From Screening to Cycle 7 (Day 1)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: cm				
number (not applicable)				
Patient 2	-5			
Patient 3	5			
Patient 4	-5			
Patient 5	-7			
Patient 6	-6			
Patient 7	0			
Patient 10	-4			
Patient 12	-13			

Statistical analyses

No statistical analyses for this end point

Secondary: Spleen length difference at cycle 12

End point title	Spleen length difference at cycle 12

End point description:

End point type	Secondary

End point timeframe:

From Screening to Cycle 12 (Day 28)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: cm				
number (not applicable)				
Patient 3	1			
Patient 4	-6			
Patient 5	-7			
Patient 7	-4			
Patient 10	-7			

Statistical analyses

No statistical analyses for this end point

Secondary: MPN-SAF TSS at cycle 4

End point title	MPN-SAF TSS at cycle 4

End point description:

End point type	Secondary

End point timeframe:
Cycle 4 (Day 1)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: score				
median (inter-quartile range (Q1-Q3))				
Fatigue	6.0 (5.0 to 8.0)			
Early satiety	4.0 (0.0 to 5.0)			
Abdominal discomfort	0.0 (0.0 to 4.0)			
Inactivity	3.0 (0.0 to 6.0)			
Concentration difficulties	3.0 (0.0 to 5.0)			
Night sweats	0.0 (0.0 to 4.0)			
Itching	2.0 (0.0 to 5.0)			
Bone pain	2.5 (0.0 to 6.0)			
Fever (>37ºC)	0.0 (0.0 to 0.0)			
Unintentional weight loss	0.0 (0.0 to 2.0)			
Total score	24.0 (14.0 to 33.8)			

Statistical analyses

No statistical analyses for this end point

Secondary: MPN-SAF TSS at cycle 7

End point title	MPN-SAF TSS at cycle 7

End point description:

End point type	Secondary

End point timeframe:
At Cycle 7 (Day 1)

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	8			
Units: score				
median (inter-quartile range (Q1-Q3))				
Fatigue	6.0 (5.0 to 7.0)			
Early satiety	4.0 (0.8 to 4.8)			

Abdominal discomfort	0.5 (0.0 to 4.3)			
Inactivity	1.0 (0.0 to 2.8)			
Concentration difficulties	1.0 (0.0 to 2.8)			
Night sweats	3.0 (0.5 to 5.0)			
Itching	1.0 (0.0 to 6.8)			
Bone pain	3.0 (0.0 to 5.8)			
Fever (>37ºC)	0.0 (0.0 to 0.0)			
Unintentional weight loss	0.0 (0.0 to 0.0)			
Total score	23.0 (21.0 to 25.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: MPN-SAF TSS at cycle 12

End point title	MPN-SAF TSS at cycle 12
End point description:	
End point type	Secondary
End point timeframe:	
At Cycle 12 (Day 28)	

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	5			
Units: score				
median (inter-quartile range (Q1-Q3))				
Fatigue	5.0 (3.5 to 8.5)			
Early satiety	4.0 (1.0 to 4.5)			
Abdominal discomfort	1.0 (0.0 to 4.5)			
Inactivity	1.0 (0.5 to 6.0)			
Concentration difficulties	2.0 (0.0 to 5.5)			
Night sweats	1.0 (0.0 to 2.0)			
Itching	3.0 (1.0 to 4.0)			
Bone pain	1.0 (0.0 to 9.0)			
Fever (>37ºC)	0.0 (0.0 to 3.0)			
Unintentional weight loss	0.0 (0.0 to 0.5)			
Total score	17.0 (10.0 to 44.0)			

Statistical analyses

No statistical analyses for this end point

Secondary: Ruxolitinib dose intensity

End point title	Ruxolitinib dose intensity

End point description:

End point type	Secondary

End point timeframe:

At cycles 4, 7 and 12

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	15[2]			
Units: mg/m2/week				
median (inter-quartile range (Q1-Q3))				
Cycle 4 (n=12)	0.427 (0.185 to 0.635)			
Cycle 7 (n=8)	0.536 (0.179 to 0.648)			
Cycle 12 (n=7)	0.417 (0.208 to 0.577)			

Notes:

[2] - At each time point the number of subjects is indicated.

Statistical analyses

No statistical analyses for this end point

Secondary: Nilotinib dose intensity

End point title	Nilotinib dose intensity

End point description:

End point type	Secondary

End point timeframe:

At cycles 4, 7 and 12

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	15[3]			
Units: mg/m2/week				
median (inter-quartile range (Q1-Q3))				
Cycle 4 (n=12)	10.9 (7.29 to 11.1)			
Cycle 7 (n=8)	11.1 (6.9 to 13.9)			

Cycle 12 (n=7)	11.1 (7.69 to 12.5)			

Notes:

[3] - At each time point the number of subjects is indicated.

Statistical analyses

No statistical analyses for this end point

Secondary: Prednisone dose intensity

End point title	Prednisone dose intensity

End point description:

End point type	Secondary

End point timeframe:

At cycles 4, 7 and 12

End point values	ITT population			
Subject group type	Subject analysis set			
Number of subjects analysed	15[4]			
Units: mg/m2/week				
median (inter-quartile range (Q1-Q3))				
Cycle 4 (n=11)	1 (0.926 to 1.79)			
Cycle 7 (n=8)	0.926 (0.678 to 1.67)			
Cycle 12 (n=6)	0.723 (0.185 to 1.92)			

Notes:

[4] - At each time point the number of subjects is indicated.

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE monitoring was continued for at least 30 days following the last dose of study treatment.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups

Reporting group title	Safety population

Reporting group description: -

Serious adverse events	Safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 15 (13.33%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Pericardial effusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac failure congestive			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Pulmonary hypertension			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Safety population		
Total subjects affected by non-serious adverse events subjects affected / exposed	15 / 15 (100.00%)		
Neoplasms benign, malignant and unspecified (incl cysts and polyps) Bowen's disease subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Squamous cell carcinoma subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Tumour associated fever subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Vascular disorders Flushing subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Haematoma subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 2		
General disorders and administration site conditions Asthenia subjects affected / exposed occurrences (all)	10 / 15 (66.67%) 14		
Chest pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Gait inability subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		

Oedema subjects affected / exposed occurrences (all)	2 / 15 (13.33%) 3		
Oedema peripheral subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Pyrexia subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 7		
Reproductive system and breast disorders			
Erectile dysfunction subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Catarrh subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Chest pain subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Cough subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Dyspnoea subjects affected / exposed occurrences (all)	3 / 15 (20.00%) 3		
Epistaxis subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Pleural effusion			

subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Pleuritic pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Productive cough			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Pulmonary hypertension			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Pulmonary thrombosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Upper-airway cough syndrome			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Disorientation			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Insomnia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Investigations			
Alanine aminotransferase			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	11		
Aspartate aminotransferase			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	4		
Blood bilirubin increased			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood creatine phosphokinase			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Blood folate decreased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gamma-glutamyltransferase			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Lipase increased			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Hip fracture			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Congenital, familial and genetic disorders			
Thalassaemia beta			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac disorders			
Cardiac failure acute			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cardiac failure congestive			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pericardial effusion			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Tachycardia			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nervous system disorders			
Cerebral small vessel ischaemic			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Cognitive disorder			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Headache			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Neuropathy peripheral			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	4		
Sciatica			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	22		
Leukocytosis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Splenomegaly			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Thrombocytopenia			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	18		
Ear and labyrinth disorders			

Ear pain			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Excessive cerumen production			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Abdominal pain upper			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Ascites			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Constipation			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Diarrhoea			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Dry mouth			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Flatulence			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Nausea			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Vomiting			

subjects affected / exposed occurrences (all)	1 / 15 (6.67%) 1		
Hepatobiliary disorders Biliary colic subjects affected / exposed occurrences (all) Cholelithiasis subjects affected / exposed occurrences (all) Cholestasis subjects affected / exposed occurrences (all) Hyperbilirubinaemia subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 4		
Skin and subcutaneous tissue disorders Ecchymosis subjects affected / exposed occurrences (all) Hyperhidrosis subjects affected / exposed occurrences (all) Pruritus subjects affected / exposed occurrences (all) Rash subjects affected / exposed occurrences (all) Skin plaque subjects affected / exposed occurrences (all)	 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1 1 / 15 (6.67%) 1		
Renal and urinary disorders Micturition urgency subjects affected / exposed occurrences (all) Pollakiuria	 1 / 15 (6.67%) 1		

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Renal impairment			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	2		
Urinary incontinence			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	4		
Arthritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Back pain			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	5		
Intervertebral disc disorder			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Muscle discomfort			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Muscle spasms			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Myopathy			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	2		
Spinal osteoarthritis			

subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Denture stomatitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Otosalpingitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Parapharyngeal space infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Pharyngitis			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Respiratory tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Upper respiratory tract infection			
subjects affected / exposed	3 / 15 (20.00%)		
occurrences (all)	3		
Urinary tract infection			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		

Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	2 / 15 (13.33%)		
occurrences (all)	3		
Hyperglycaemia			
subjects affected / exposed	5 / 15 (33.33%)		
occurrences (all)	27		
Hyperkalaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	3		
Hyperuricaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	1		
Hypocalcaemia			
subjects affected / exposed	1 / 15 (6.67%)		
occurrences (all)	7		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
10 January 2018	Change of principal investigator of Hospital del Mar (Barcelona).
28 June 2019	Change of principal investigator (Dr. Marcio Andrade) of Hospital del Mar (Barcelona).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported