Clinical trial results:
A phase III, multicentre, randomized, open label clinical trial comparing azacytidine (Vidaza®) versus fludarabine plus cytarabine in elderly patients with newly diagnosed acute myeloid leukemia.

Summary

EudraCT number	2014-000319-15
Trial protocol	ES
Global end of trial date	28 October 2019

Results information

Result version number	v1 (current)
This version publication date	23 December 2021
First version publication date	23 December 2021

Trial information

Trial identification

Sponsor protocol code	FLUGAZA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02319135
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Fundación PETHEMA
Sponsor organisation address	C/ Profesor Martín Lagos s/n, Madrid, Spain, 28040
Public contact	Gerencia Fundación Pethema, Fundación PETHEMA, +34 91 6266232, gerencia@fundacionpethema.es
Scientific contact	Gerencia Fundación Pethema, Fundación PETHEMA, +34 91 6266232, gerencia@fundacionpethema.es

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	28 July 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	14 November 2018
Global end of trial reached?	Yes
Global end of trial date	28 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the overall survival (OS) in one year treatment with 2 first-line regimens in newly diagnosed elderly patients: 3 cycles of induction chemotherapy based on fludarabine and cytarabine (FLUGA scheme) followed by maintenance with reduced doses (Mini-FLUGA) (standard treatment arm) versus subcutaneous azacitidine cycles (experimental treatment arm).

Protection of trial subjects:

This study was conducted in compliance with the ethical principles originating in or derived from the Declaration of Helsinki and in compliance with all International Council for Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. In addition, all local regulatory requirements were followed, in particular, those affording greater protection to the safety of trial subjects.

Background therapy: -

Evidence for comparator:

Evaluate the overall survival (OS) in one year treatment with 2 first-line regimens in newly diagnosed elderly patients: 3 cycles of induction chemotherapy based on fludarabine and cytarabine (FLUGA scheme) followed by maintenance with reduced doses(Mini-FLUGA) (standard treatment arm) versus subcutaneous azacitidine cycles (experimental treatment arm).

Actual start date of recruitment	28 October 2014
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: 283
Worldwide total number of subjects	283
EEA total number of subjects	283

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)	0
From 65 to 84 years	265
85 years and over	18

Subject disposition

Recruitment

Recruitment details:

Recruitment period started on 28/10/2014 and ended on 28/10/2017. All patients were recruited in Spain.

Pre-assignment

Screening details:

A total of 329 potential subjects were screened after signing an informed consent form, of whom 283 subjects were randomized to receive study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	fludarabine cytarabine

Arm description:

Daily administration of subcutaneous G-CSF (lenograstim or filgrastim 5 mcg /kg / day, days -1, 1 and 2) (not given if hyperleukocytosis> 25 x 109/l), followed by:

- Oral fludarabine (40 mg/m2/day, days 1 to 5) and subcutaneous cytarabine (75mg/m2/day, days 1 to 5) (FLUGA scheme) (fludarabine and cytarabine only days 1 to 4 if age ≥75 years), OR

- Fludarabine (25 mg/m2/day) and cytarabine (75 mg/m2/day infusion of 6 hours) on their intravenous formulations if the patient is hospitalized (patients with hyperleukocytosis or other unfavourable conditions).

Treatment cycles every 28 days

Arm type	Active comparator
Investigational medicinal product name	Fludarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion, Film-coated tablet
Routes of administration	Intravenous use, Oral use

Dosage and administration details:

- Oral fludarabine (40 mg/m2/day, days 1 to 5) (fludarabine only days 1 to 4 if age ≥75 years), OR

- Fludarabine (25 mg/m2/day) on its intravenous formulations if the patient is hospitalized (patients with hyperleukocytosis or other unfavourable conditions).

Treatment cycles every 28 days

Investigational medicinal product name	Cytarabine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Subcutaneous use, Intracavernous use

Dosage and administration details:

- Subcutaneous cytarabine (75mg/m2/day, days 1 to 5) (cytarabine only days 1 to 4 if age ≥75 years), OR

- Cytarabine (75 mg/m2/day infusion of 6 hours) on its intravenous formulation if the patient is hospitalized (patients with hyperleukocytosis or other unfavourable conditions).

Treatment cycles every 28 days

Arm title	Azacitidine
Arm description: Subcutaneous Azacitidine 75 mg/m2/day, days 1 to 7. Treatment cycles every 28 days.	
Arm type	Experimental
Investigational medicinal product name	Azacitidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection
Routes of administration	Subcutaneous use
Dosage and administration details: Subcutaneous Azacitidine 75 mg/m2/day, days 1 to 7. Treatment cycles every 28 days.	

Number of subjects in period 1	fludarabine cytarabine	Azacitidine
Started	141	142
Completed	25	46
Not completed	116	96
Adverse event, serious fatal	50	47
Consent withdrawn by subject	6	3
Physician decision	-	2
Adverse event, non-fatal	9	6
Lost to follow-up	1	-
Second neoplasm	-	1
Lack of efficacy	50	37

Baseline characteristics

Reporting groups	
Reporting group title	fludarabine cytarabine

Reporting group description:

Daily administration of subcutaneous G-CSF (lenograstim or filgrastim 5 mcg /kg / day, days -1, 1 and 2) (not given if hyperleukocytosis> 25 x 109/l), followed by:

- Oral fludarabine (40 mg/m2/day, days 1 to 5) and subcutaneous cytarabine (75mg/m2/day, days 1 to 5) (FLUGA scheme) (fludarabine and cytarabine only days 1 to 4 if age ≥75 years), OR

- Fludarabine (25 mg/m2/day) and cytarabine (75 mg/m2/day infusion of 6 hours) on their intravenous formulations if the patient is hospitalized (patients with hyperleukocytosis or other unfavourable conditions).

Treatment cycles every 28 days

Reporting group title	Azacitidine

Reporting group description:

Subcutaneous Azacitidine 75 mg/m2/day, days 1 to 7. Treatment cycles every 28 days.

Reporting group values	fludarabine cytarabine	Azacitidine	Total
Number of subjects	141	142	283
Age categorical Units: Subjects			
From 65-69 years	26	23	49
From 70-74 years	35	49	84
75 years and over	80	70	150
Age continuous Units: years			
median	76	74	
full range (min-max)	65 to 88	65 to 90	-
Gender categorical Units: Subjects			
Female	62	57	119
Male	79	85	164
ECOG PS Units: Subjects			
0 or 1	114	105	219
2 or 3	26	36	62
UNK	1	1	2
WBC x10^9/L Units: Subjects			
<15x10^9/L	87	96	183
15-50x10^9/L	36	33	69
>50x10^9/L	18	13	31
WBC x10^9/L Units: x10^9/L			
median	7.9	4.5	
full range (min-max)	0.8 to 203.4	0.6 to 235.5	-

End points

End points reporting groups

Reporting group title	fludarabine cytarabine

Reporting group description:

Daily administration of subcutaneous G-CSF (lenograstim or filgrastim 5 mcg /kg / day, days -1, 1 and 2) (not given if hyperleukocytosis> 25 x 109/l), followed by:

- Oral fludarabine (40 mg/m2/day, days 1 to 5) and subcutaneous cytarabine (75mg/m2/day, days 1 to 5) (FLUGA scheme) (fludarabine and cytarabine only days 1 to 4 if age ≥75 years), OR

- Fludarabine (25 mg/m2/day) and cytarabine (75 mg/m2/day infusion of 6 hours) on their intravenous formulations if the patient is hospitalized (patients with hyperleukocytosis or other unfavourable conditions).

Treatment cycles every 28 days

Reporting group title	Azacitidine

Reporting group description:

Subcutaneous Azacitidine 75 mg/m2/day, days 1 to 7. Treatment cycles every 28 days.

Primary: Efficacy (overall survival (OS) attained without increasing the therapy-related toxicity or decreasing the patients QoL

End point title	Efficacy (overall survival (OS) attained without increasing the therapy-related toxicity or decreasing the patients QoL

End point description:

To evaluate the overall survival (OS) in one year treatment with 2 first-line regimens in newly diagnosed elderly patients: 3 cycles of induction chemotherapy based on fludarabine and cytarabine (FLUGA scheme) followed by maintenance with reduced doses(Mini-FLUGA) (standard treatment arm) versus subcutaneous azacitidine cycles (experimental treatment arm).

End point type	Primary

End point timeframe:

1 year.

End point values	fludarabine cytarabine	Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	142		
Units: month				
number (confidence interval 95%)	27 (20 to 34)	47 (39 to 55)		

Statistical analyses

Statistical analysis title	1-year OS between AZA and FLUGA regimens

Statistical analysis description:

To analyze these variables, survival curves were estimated by Kaplan-Meier method and log-rank test was performed for comparison between groups.

Comparison groups	fludarabine cytarabine v Azacitidine

Number of subjects included in analysis	283
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Logrank

Secondary: Efficacy Event free survival (EFS)

End point title	Efficacy Event free survival (EFS)
End point description: Event free survival (EFS)	
End point type	Secondary
End point timeframe: 4 years	

End point values	fludarabine cytarabine	Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	142		
Units: month				
median (confidence interval 95%)	3 (2.5 to 3.5)	4.9 (2.8 to 7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy (Duration of remission.)

End point title	Efficacy (Duration of remission.)
End point description: Duration of remission.	
End point type	Secondary
End point timeframe: 4 years	

End point values	fludarabine cytarabine	Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	142		
Units: month				
median (confidence interval 95%)	9 (6.2 to 16.4)	12.3 (9.8 to 17)		

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy (Overall survival)

End point title	Efficacy (Overall survival)
End point description: Overall survival	
End point type	Secondary
End point timeframe: 4 years	

End point values	fludarabine cytarabine	Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	142		
Units: month				
median (confidence interval 95%)	4.1 (2.7 to 5.5)	9.8 (5.6 to 14)		

Statistical analyses

No statistical analyses for this end point

Secondary: Safety (Compare hematologic and non-hematologic toxicity)

End point title	Safety (Compare hematologic and non-hematologic toxicity)
End point description: Compare hematologic and non-hematologic toxicity in both arms (adverse events grades ≥3)	
End point type	Secondary
End point timeframe: 4 years	

End point values	fludarabine cytarabine	Azacitidine		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	141	142		
Units: adverse events grade ≥ 3	346	311		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

4 years

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17

Reporting groups

Reporting group title	Fludarabine Cytarabine

Reporting group description:

Daily administration of subcutaneous G-CSF (lenograstim or filgrastim 5 mcg /kg / day, days -1, 1 and 2) (not given if hyperleukocytosis> 25 x 109/l), followed by:

- Oral fludarabine (40 mg/m2/day, days 1 to 5) and subcutaneous cytarabine (75mg/m2/day, days 1 to 5) (FLUGA scheme) (fludarabine and cytarabine only days 1 to 4 if age ≥75 years), OR

- Fludarabine (25 mg/m2/day) and cytarabine (75 mg/m2/day infusion of 6 hours) on their intravenous formulations if the patient is hospitalized (patients with hyperleukocytosis or other unfavourable conditions).

Treatment cycles every 28 days

Reporting group title	Azacitidine

Reporting group description:

Subcutaneous Azacitidine 75 mg/m2/day, days 1 to 7. Treatment cycles every 28 days.

Serious adverse events	Fludarabine Cytarabine	Azacitidine	
Total subjects affected by serious adverse events			
subjects affected / exposed	109 / 141 (77.30%)	128 / 142 (90.14%)	
number of deaths (all causes)	133	127	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Adenocarcinoma			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nodule			
subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			

Hypotension			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
multi-organ failure			
subjects affected / exposed	3 / 141 (2.13%)	2 / 142 (1.41%)	
occurrences causally related to treatment / all	0 / 3	0 / 2	
deaths causally related to treatment / all	0 / 3	0 / 2	
Diarrhoea			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pain			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fever			
subjects affected / exposed	6 / 141 (4.26%)	5 / 142 (3.52%)	
occurrences causally related to treatment / all	3 / 6	0 / 5	
deaths causally related to treatment / all	0 / 2	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory			
subjects affected / exposed	9 / 141 (6.38%)	9 / 142 (6.34%)	
occurrences causally related to treatment / all	3 / 9	2 / 14	
deaths causally related to treatment / all	1 / 6	0 / 3	
Pneumonia			
subjects affected / exposed	26 / 141 (18.44%)	21 / 142 (14.79%)	
occurrences causally related to treatment / all	12 / 32	5 / 24	
deaths causally related to treatment / all	3 / 9	1 / 6	
Psychiatric disorders			
Confusional state			

subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Investigations			
Laboratory test abnormal			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	1 / 141 (0.71%)	3 / 142 (2.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Toxicity to various agents			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiological			
subjects affected / exposed	5 / 141 (3.55%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 5	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 1	
Nervous system disorders			
Coordination abnormal			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	1 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			

subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Neutropenia			
subjects affected / exposed	4 / 141 (2.84%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	4 / 5	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Thrombocytopenia			
subjects affected / exposed	4 / 141 (2.84%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	5 / 5	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Febrile neutropenia			
subjects affected / exposed	40 / 141 (28.37%)	30 / 142 (21.13%)	
occurrences causally related to treatment / all	52 / 52	43 / 43	
deaths causally related to treatment / all	1 / 2	0 / 2	
Hemorrhage			
subjects affected / exposed	10 / 141 (7.09%)	9 / 142 (6.34%)	
occurrences causally related to treatment / all	6 / 14	1 / 9	
deaths causally related to treatment / all	3 / 5	1 / 4	
Thrombotic			
subjects affected / exposed	2 / 141 (1.42%)	7 / 142 (4.93%)	
occurrences causally related to treatment / all	0 / 2	1 / 7	
deaths causally related to treatment / all	0 / 1	0 / 2	
Splenomegaly			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Hepatobiliary disorders			
Hepatic			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 1	1 / 1	
deaths causally related to treatment / all	0 / 1	0 / 0	
Skin and subcutaneous tissue disorders			

Skin disorder			
subjects affected / exposed	2 / 141 (1.42%)	0 / 142 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal			
subjects affected / exposed	0 / 141 (0.00%)	6 / 142 (4.23%)	
occurrences causally related to treatment / all	0 / 0	2 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	8 / 141 (5.67%)	14 / 142 (9.86%)	
occurrences causally related to treatment / all	3 / 8	4 / 18	
deaths causally related to treatment / all	1 / 2	0 / 1	
Sepsis			
subjects affected / exposed	18 / 141 (12.77%)	18 / 142 (12.68%)	
occurrences causally related to treatment / all	14 / 21	3 / 19	
deaths causally related to treatment / all	2 / 5	3 / 8	
Metabolism and nutrition disorders			
Tumour lysis syndrome			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences causally related to treatment / all	1 / 1	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	

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

Non-serious adverse events	Fludarabine Cytarabine	Azacitidine	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	125 / 141 (88.65%)	108 / 142 (76.06%)	

Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences (all)	2	1	
General disorders and administration site conditions			
Diarrhoea			
subjects affected / exposed	3 / 141 (2.13%)	0 / 142 (0.00%)	
occurrences (all)	3	0	
Pain			
subjects affected / exposed	3 / 141 (2.13%)	4 / 142 (2.82%)	
occurrences (all)	4	4	
Edema			
subjects affected / exposed	2 / 141 (1.42%)	1 / 142 (0.70%)	
occurrences (all)	2	2	
Fever			
subjects affected / exposed	6 / 141 (4.26%)	4 / 142 (2.82%)	
occurrences (all)	7	4	
Fatigue			
subjects affected / exposed	10 / 141 (7.09%)	7 / 142 (4.93%)	
occurrences (all)	10	8	
General symptom			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			
Arthralgia			
subjects affected / exposed	2 / 141 (1.42%)	7 / 142 (4.93%)	
occurrences (all)	2	7	
Transfusion reaction			
subjects affected / exposed	0 / 141 (0.00%)	2 / 142 (1.41%)	
occurrences (all)	0	2	
Respiratory, thoracic and mediastinal disorders			
Respiratory			
subjects affected / exposed	6 / 141 (4.26%)	5 / 142 (3.52%)	
occurrences (all)	7	5	
Pneumonia			

subjects affected / exposed	9 / 141 (6.38%)	6 / 142 (4.23%)	
occurrences (all)	9	7	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	2 / 141 (1.42%)	2 / 142 (1.41%)	
occurrences (all)	2	2	
Investigations			
Laboratory test abnormal			
subjects affected / exposed	6 / 141 (4.26%)	6 / 142 (4.23%)	
occurrences (all)	6	10	
Injury, poisoning and procedural complications			
Fracture			
subjects affected / exposed	0 / 141 (0.00%)	3 / 142 (2.11%)	
occurrences (all)	0	3	
Cardiac disorders			
cardiological			
subjects affected / exposed	1 / 141 (0.71%)	3 / 142 (2.11%)	
occurrences (all)	1	3	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	16 / 141 (11.35%)	13 / 142 (9.15%)	
occurrences (all)	29	14	
leukocytosis			
subjects affected / exposed	3 / 141 (2.13%)	0 / 142 (0.00%)	
occurrences (all)	3	0	
Neutropenia			
subjects affected / exposed	10 / 141 (7.09%)	16 / 142 (11.27%)	
occurrences (all)	14	23	
Thrombocytopenia			
subjects affected / exposed	14 / 141 (9.93%)	3 / 142 (2.11%)	
occurrences (all)	22	7	
hemorrhage			
subjects affected / exposed	4 / 141 (2.84%)	2 / 142 (1.41%)	
occurrences (all)	4	3	
thrombotic			

subjects affected / exposed	0 / 141 (0.00%)	1 / 142 (0.70%)	
occurrences (all)	0	1	
Febrile neutropenia			
subjects affected / exposed	12 / 141 (8.51%)	6 / 142 (4.23%)	
occurrences (all)	16	7	
Skin and subcutaneous tissue disorders			
Skin disorder			
subjects affected / exposed	1 / 141 (0.71%)	1 / 142 (0.70%)	
occurrences (all)	1	1	
Renal and urinary disorders			
Renal			
subjects affected / exposed	3 / 141 (2.13%)	2 / 142 (1.41%)	
occurrences (all)	3	2	
Infections and infestations			
Infection			
subjects affected / exposed	4 / 141 (2.84%)	11 / 142 (7.75%)	
occurrences (all)	5	16	
Sepsis			
subjects affected / exposed	4 / 141 (2.84%)	2 / 142 (1.41%)	
occurrences (all)	5	3	
Metabolism and nutrition disorders			
Anorexia			
subjects affected / exposed	1 / 141 (0.71%)	0 / 142 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
13 June 2014	Version 2 UPDATE CRF INCLUDING THE QUESTIONARY EQ-5D
26 October 2016	Version 3 THE TRIAL RECRUITMENT PERIOD WAS EXTENDED ONE YEAR

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/33626197