Clinical trial results:
Clinical Phase II Trial to evaluate efficacy and safety of CD34+ cells mobilization and collection after treatment with plerixafor and filgrastim in patients with Fanconi anemia for subsequent transduction with a lentiviral vector carring FANCA gene and reinfusion in the patient

Summary

EudraCT number	2011-006197-88
Trial protocol	ES
Global end of trial date	30 November 2018

Results information

Result version number	v1 (current)
This version publication date	04 October 2021
First version publication date	04 October 2021

Trial information

Trial identification

Sponsor protocol code	FANCOSTEM-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02931071
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall Hebron 119-129, Barcelona, Spain, 08035
Public contact	Joaquin Lopez Soriano, VHIR, 0034 934894865, joaquin.lopez.soriano@vhir.org
Scientific contact	Cristina Díaz de Heredia Rubio, VHIR, 0034 934893093, crdiaz@vhebron.net

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	30 November 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 November 2018
Global end of trial reached?	Yes
Global end of trial date	30 November 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective is to assess the safety of cell mobilization after treatment with filgrastim and plerixafor in patients with Fanconi Anemia.

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: -

Actual start date of recruitment	01 September 2012
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: 11
Worldwide total number of subjects	11
EEA total number of subjects	11

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)	9
Adolescents (12-17 years)	2
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment	
Recruitment details: -	
Pre-assignment	
Screening details: -	
Pre-assignment period milestones	
Number of subjects started	11
Number of subjects completed	11

Period 1	
Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded
Arms	
Arm title	CD34+ cells mobilization, collection and immunoselection
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Filgrastim
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use
Dosage and administration details: 12 microgram/Kg/12 hours, subcutaneous days 0 to 5	
Investigational medicinal product name	Plerixafor
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection in vial
Routes of administration	Subcutaneous use
Dosage and administration details: 240 microgram/kg/day subcutaneous at days 5 to 8	

Number of subjects in period 1	CD34+ cells mobilization, collection and immunoselection
Started	11
Mobilization of CD34+ cells	11
Collection of CD34+ cells	11
Immunoselection of PB HSPCs	11

Completed	11

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	11	11	
Age categorical Units: Subjects			
Children	9	9	
Adolescent	2	2	
Age continuous Units: years			
median	5		
full range (min-max)	2 to 16	-	
Gender categorical Units: Subjects			
Female	1	1	
Male	10	10	
Chromosome fragility test			
Test with diepoxybutane or mitomycin C to confirm chromosome fragility for Fanconi anemia, descarding mosaicism			
Units: Subjects			
Yes	11	11	
Neutrophils			
> or = 0.75 x 10^9 cells/L			
Units: cell/L			
median	1.26		
full range (min-max)	0.76 to 2.4	-	
Platelet			
> or = to 30 x 10^9 cell/L			
Units: cells/L			
median	76		
full range (min-max)	27 to 191	-	
Haemoglobin levels			
> or = to 8g/dL			
Units: g/dL			
median	11.3		
full range (min-max)	10.4 to 12.8	-	

Subject analysis sets

Subject analysis set title	Efficacy and safety of cell yield
Subject analysis set type	Full analysis

Subject analysis set description:

After screening, 11 patients were treated with filgrastim and plerixafor for mobilization of CD34+ cells. 9 patients satisfactorily mobilized cells and underwent cell collection. After collection, cells were sorted

Reporting group values	Efficacy and safety of cell yield		
Number of subjects	11		
Age categorical Units: Subjects			
Children	9		
Adolescent	2		
Age continuous Units: years			
median	5		
full range (min-max)	2 to 16		
Gender categorical Units: Subjects			
Female	1		
Male	10		
Chromosome fragility test			
Test with diepoxybutane or mitomycin C to confirm chromosome fragility for Fanconi anemia, descarding mosaicism			
Units: Subjects			
Yes	11		
Neutrophils			
> or = 0.75 x 10^9 cells/L			
Units: cell/L			
median	1.26		
full range (min-max)	0.76 to 2.4		
Platelet			
> or = to 30 x 10^9 cell/L			
Units: cells/L			
median	76		
full range (min-max)	27 to 191		
Haemoglobin levels			
> or = to 8g/dL			
Units: g/dL			
median	11.3		
full range (min-max)	10.4 to 12.8		

End points

End points reporting groups

Reporting group title	CD34+ cells mobilization, collection and immunoselection
Reporting group description: -	
Subject analysis set title	Efficacy and safety of cell yield
Subject analysis set type	Full analysis
Subject analysis set description:	
After screening, 11 patients were treated with filgrastim and plerixafor for mobilization of CD34+ cells. 9 patients satisfactorily mobilized cells and underwent cell collection. After collection, cells were sorted	

Primary: Safety

End point title	Safety[1]
End point description:	
End point type	Primary
End point timeframe:	
12 months follow-up after cell mobilization	

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: Goal of the study was to evaluate the safety of the procedure for mobilizing and collecting CD34 cells. There were no treatments in separate arms or periods to justify an statistical analysis.
No procedure-associated serious adverse events were observed. Safety of the procedure is included in the adverse events section

End point values	CD34+ cells mobilization, collection and immunoselection			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Lack of severe adverse effects	11			

Statistical analyses

No statistical analyses for this end point

Secondary: Patients with CD34 cell threshold mobilized

End point title	Patients with CD34 cell threshold mobilized
End point description:	
> or = to 5 CD34 cell/microliter	
End point type	Secondary
End point timeframe:	
After tretament with filgrastim and plerixafor	

End point values	CD34+ cells mobilization, collection and immunoselectio n			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: cells/microL				
Yes	9			

Statistical analyses

No statistical analyses for this end point

Secondary: CD34 cell collected

End point title	CD34 cell collected

End point description:

Number of patients with efficient collection of cells after apheresis, > or = to 4x10^6 cells/kg body weight (projections of body weight after 5 years)

End point type	Secondary

End point timeframe:

After apheresis collection

End point values	CD34+ cells mobilization, collection and immunoselectio n			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Cells/Kg				
Yes	4			

Statistical analyses

No statistical analyses for this end point

Secondary: CD34 cell immunoselected

End point title	CD34 cell immunoselected

End point description:

Recovery of CD34 cells after immunoselection has to be > or = to 50%

End point type	Secondary

End point timeframe:

After mobiliation, collection, and immunoselection

End point values	CD34+ cells mobilization, collection and immunoselection			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percentage of cells				
Yes	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Global efficacy of the procedure

End point title	Global efficacy of the procedure

End point description:

Patients achieving > or = 4x10^6 CD34 cells/kg, projecting body weight at 5 years

End point type	Secondary

End point timeframe:

After completing the procedure

End point values	CD34+ cells mobilization, collection and immunoselection			
Subject group type	Reporting group			
Number of subjects analysed	11			
Units: Cells/Kg				
Yes	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
The whole study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	2

Reporting groups	
Reporting group title	Drug-related
Reporting group description: -	
Reporting group title	Total adverse events
Reporting group description: -	

Serious adverse events	Drug-related	Total adverse events	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 11 (0.00%)	4 / 11 (36.36%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
General disorders and administration site conditions			
Fever of unknown origin			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Interstitial lung disease			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Varicella			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory infection			

subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Drug-related	Total adverse events	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 11 (63.64%)	9 / 11 (81.82%)	
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Cardiac disorders			
Tachycardia			
subjects affected / exposed	0 / 11 (0.00%)	2 / 11 (18.18%)	
occurrences (all)	0	2	
General disorders and administration site conditions			
Fever			
subjects affected / exposed	2 / 11 (18.18%)	4 / 11 (36.36%)	
occurrences (all)	2	4	
Pain at administration site			
subjects affected / exposed	1 / 11 (9.09%)	1 / 11 (9.09%)	
occurrences (all)	1	1	
Pain at central venous line access			
subjects affected / exposed	0 / 11 (0.00%)	3 / 11 (27.27%)	
occurrences (all)	0	3	
Bleeding at central venous line access			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Throat pain			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Headache			

subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anemia			
subjects affected / exposed	2 / 11 (18.18%)	3 / 11 (27.27%)	
occurrences (all)	2	3	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	2 / 11 (18.18%)	5 / 11 (45.45%)	
occurrences (all)	2	5	
Vomiting			
subjects affected / exposed	2 / 11 (18.18%)	4 / 11 (36.36%)	
occurrences (all)	2	4	
Nausea			
subjects affected / exposed	1 / 11 (9.09%)	2 / 11 (18.18%)	
occurrences (all)	1	2	
Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	0 / 11 (0.00%)	1 / 11 (9.09%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	1 / 11 (9.09%)	2 / 11 (18.18%)	
occurrences (all)	1	2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 March 2015	Change of sponsor from Cristina Díaz de Heredia to VHIR Change of CRO from Quantum to Sermes Modification of hour of administration of plerixafor, closer to the apheresis procedure Modification of consent forms Modification in pharmaceutical form of filgrastrim to vials for injection Filgrastim datasheet was added to documentation
06 September 2017	Sample size and recruitment period were expanded

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Although the threshold of CD34 immunoselected cells was not achieved, enough number of cells were obtained for gene correction and engraftment.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34485595