Clinical trial results:
Efficacy, safety and pharmaco-economic assessment of secondary long term prophylaxis with highly purified, standardized, doubly virus inactivated FVIII/VWF concentrates in patients with severe, inherited VWD and frequent bleedings

Summary

EudraCT number	2006-001383-23
Trial protocol	IT GB ES DE
Global end of trial date	24 August 2016

Results information

Result version number	v1 (current)
This version publication date	07 August 2021
First version publication date	07 August 2021
Summary attachment (see zip file)	Pro.Will CSR Synopsis (PRO.WILL CSR synopsis (002).pdf)

Trial information

Trial identification

Sponsor protocol code	Pro.Will

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico di Milano
Sponsor organisation address	Via Pace 9 , Milan, Italy, 20122
Public contact	Prof. Flora Peyvandi, Fondazione Luigi Villa Fondazione IRCCS Cà Granda Ospedale Maggiore Polic, flora.peyvandi@unimi.it
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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	30 June 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 August 2016
Global end of trial reached?	Yes
Global end of trial date	24 August 2016
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate if long term, secondary prophylaxis with highly purified FVIII/VWF concentrates, with respect to on demand treatment with the same pharmacological agent, prevents spontaneous bleedings onset in patients with severe inherited VWD unresponsive to DDAVP and with frequent bleedings

Protection of trial subjects:

Patients were evaluated for recruitment by a medical visit and a laboratory investigation (including complete blood analysis) to verify general health conditions, the fulfilment of the inclusion criteria and to rule out the presence of any exclusion criteria. At enrolment patients had to be in stable conditions (no bleeding in act).
Being the baseline clinical condition an important prognostic factor, the randomisation was stratified according to the following three types of bleeding: gastrointestinal, hemarthrosis, and epistaxis/other bleedings.
In general any medication needed to treat concomitant pathologies or to control and ameliorate the general conditions of the patients were allowed.
Every patient had the right to discontinue study participation at any time, and every patient may have been discontinued from the study for any reason beneficial to her wellbeing.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 October 2006
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	Germany: 1
Country: Number of subjects enrolled	Spain: 2
Country: Number of subjects enrolled	Italy: 16
Worldwide total number of subjects	19
EEA total number of subjects	19

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)	2
Adolescents (12-17 years)	2
Adults (18-64 years)	11
From 65 to 84 years	3
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment started in 2006 for all study centres (Germany, Italy and Spain). Recruitment ended in 2015

Pre-assignment

Screening details:

Before enter the study a wash out of 10 days from last FVIII/VWF concentrate infusion is mandatory. Being the baseline clinical condition an important prognostic factor, the randomisation will be stratified according to the following three types of bleeding: gastrointestinal, hemarthrosis, and epistaxis/other bleedings.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	on demand -group

Arm description:

On demand treatment (intended as replacement therapy with FVIII/VWF concentrates) was given only in case of bleeding

Arm type	Active comparator
Investigational medicinal product name	Fanhdi/Alphanate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Suspension for injection
Routes of administration	Intravenous use

Dosage and administration details:

dosage followed standard recommendations as in SmPC. The amount to be administered and the frequency of administration should always be oriented to the clinical effectiveness in the individual case.

Arm title	prophylaxix group

Arm description:

Prophylaxis was given for 12 consecutive months. Two different schedules were foreseen, according to the individual prominent symptoms and the type of haemorrhagic manifestations to be prevented:
- for patients presenting with recurrent hemarthroses or haematomas 60 IU VWF:RCo/kg b.w. was given every third day;
- for patients presenting with recurrent mucosal bleeding (gastrointestinal, epistaxis, other) 60 IU VWF:RCo/kg b.w. wase given every second day.

Arm type	Active comparator
Investigational medicinal product name	Fanhdi/Alphanate
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Number of subjects in period 1	on demand -group	prophylaxix group
Started	9	10
Completed	7	5
Not completed	2	5
Consent withdrawn by subject	-	2
Treatment failure	1	-
Lost to follow-up	1	2
Protocol deviation	-	1

Baseline characteristics

Reporting groups	
Reporting group title	all study

Reporting group description: -

Reporting group values	all study	Total	
Number of subjects	19	19	
Age categorical Units: Subjects			
Children (2-11 years)	2	2	
Adolescents (12-17 years)	2	2	
Adults (18-64 years)	11	11	
From 65-84 years	3	3	
85 years and over	1	1	
Gender categorical Units: Subjects			
Female	5	5	
Male	14	14	

End points

End points reporting groups

Reporting group title	on demand -group

Reporting group description:

On demand treatment (intended as replacement therapy with FVIII/VWF concentrates) was given only in case of bleeding

Reporting group title	prophylaxix group

Reporting group description:

Prophylaxis was given for 12 consecutive months. Two different schedules were foreseen, according to the individual prominent symptoms and the type of haemorrhagic manifestations to be prevented:
- for patients presenting with recurrent hemarthroses or haematomas 60 IU VWF:RCo/kg b.w. was given every third day;
- for patients presenting with recurrent mucosal bleeding (gastrointestinal, epistaxis, other) 60 IU VWF:RCo/kg b.w. wase given every second day.

Primary: prevention of spontaneous bleeding

End point title	prevention of spontaneous bleeding[1]

End point description:

The primary end point was the prevention of spontaneous bleeding onset, expressed as proportion of patients who did not present any spontaneous bleeding episode during the study period.
A bleeding episode was defined as spontaneous when occurring in absence of concomitant trauma, local injury, invasive diagnostic or surgical procedures.

End point type	Primary

End point timeframe:

all time of participation in 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: some of the requested statistical data are not available and incomplete data set is not allowed

End point values	on demand - group	prophylaxix group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	9	6		
Units: bleeding episodes				
bleeding episode	9	10		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Time in which patients were participating in the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

Reporting groups	
Reporting group title	on demand -group
Reporting group description:	
On demand treatment (intended as replacement therapy with FVIII/VWF concentrates) was given only in case of bleeding	
Reporting group title	prophylaxix group
Reporting group description:	
Prophylaxis was given for 12 consecutive months. Two different schedules were foreseen, according to the individual prominent symptoms and the type of haemorrhagic manifestations to be prevented: - for patients presenting with recurrent hemarthroses or haematomas 60 IU VWF:RCo/kg b.w. was given every third day; - for patients presenting with recurrent mucosal bleeding (gastrointestinal, epistaxis, other) 60 IU VWF:RCo/kg b.w. wase given every second day.	

Serious adverse events	on demand -group	prophylaxix group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Intestinal perforation	Additional description: It resolved with a combination of adjustment to study drug dose, use of concomitant medication and hospitalization		
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
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: 0 %

Non-serious adverse events	on demand -group	prophylaxix group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	3 / 9 (33.33%)	5 / 10 (50.00%)	
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Orthostatic hypertension			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Chest pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 9 (0.00%)	2 / 10 (20.00%)	
occurrences (all)	0	2	
Cardiac disorders			
Left ventricular failure			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Tachycardia			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Nervous system disorders			
Dizziness postural			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
occurrences (all)	1	1	

Iron deficiency anaemia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Lymphadenopathy			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Ear and labyrinth disorders			
Hypoacusis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Eye disorders			
Eye haemorrhage			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Flatulence			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Haemorrhoids			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Intestinal perforation			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Psoriasis			
subjects affected / exposed	2 / 9 (22.22%)	0 / 10 (0.00%)	
occurrences (all)	2	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 9 (11.11%)	1 / 10 (10.00%)	
occurrences (all)	1	1	
Back pain			

subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Rotator cuff syndrome			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Infection			
subjects affected / exposed	1 / 9 (11.11%)	0 / 10 (0.00%)	
occurrences (all)	1	0	
Rhinitis			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	0 / 9 (0.00%)	1 / 10 (10.00%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 November 2011	Specification of substantial amendments: Anti-fibrinogen agents were removed from the prohibited medication list. The protocol was amended in order to include also Spain among the participating Countries, and the fact that the web based system used for the study was updated accordingly. Inclusion criteria relevant to patient's age was modified to include only patients aged 2: 6 years. Moreover, on demand treatment dosage was expressed in a different manner, albeit substantially unchanged, in order to attain international specifications as in the Summary of Product Characteristics (SPCs) of Fanhdi and Alphanate. Finally, QoL generic questionnaires were removed and only specific questionnaires were maintained to assess the patients QoL

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/30747707