

Template for reporting of results in EudraCT

1. Trial Information

1.1 Sponsor details

EudraCT number	2012-001039-30
Full title of the trial	BethHäm2012: A monocenter, single-blind, randomized, 2-armed, placebo-controlled, cross-over study to investigate coagulation markers in patients with haemophilia A after administration of Betain
Responsible researcher (point of contact) - Name - Email address	- Prof. Dr. Wolfgang Miesbach - Wolfgang.miesbach@unimedizin-ffm.de

1.2 Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
- If yes, enter EMA paediatric investigation plan (EMA PIP code)		
Does article 45 of Regulation (EC) No 1901/2006 apply to this trial?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
Does article 46 of Regulation (EC) No 1901/2006 apply to this trial?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

1.3 Results analysis stage

Date of interim/final analysis (dd/mm/yy):	02/01/26	
Is this the analysis of the primary completion data?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
Primary completion date (dd/mm/yy): <i>(The primary completion date is the date that the final subject was examined or received an intervention for the purposes of final collection of data for the primary end point.)</i>	24/01/2025	

Global end of trial date reached? <i>(The global end of trial date is when the last subject in the trial was examined or received an intervention globally.)</i>	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
	Date (dd/mm/yy): 24/01/2025	
Was the trial ended prematurely?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No

1.4 General information about the trial

Actual start date of recruitment (dd/mm/yy):	23/01/24	
Long term follow-up planned?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
- If yes, enter rationale (Select main reason(s) for long-term follow up)	<input type="checkbox"/> Safety <input type="checkbox"/> Efficacy <input type="checkbox"/> Ethical reason <input type="checkbox"/> Regulatory reason <input type="checkbox"/> Scientific research	
Long term follow-up duration (number of months/years)		
Independent data monitoring committee (IDMC) involvement?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No

1.5 Population of trial subjects

Subject number per country	
Country	Actual number of subjects enrolled
a) Germany	a) 8
b)	b)
c)	c)
Age group breakdown for trial	
Age range	Actual number of subjects enrolled
In utero	
Preterm newborn infants (gestational age < 37 wks)	
Newborns (0-27 days)	
Infants and toddlers (28 days-23 months)	
Children (2-11 years)	
Adolescents (12-17 years)	

Adults (18-64 years)	5
From 65-84 years	3
85 years and over	

2. Subject Disposition

2.1 Period details

Allocation method (choose one)	<input checked="" type="checkbox"/> Randomized – controlled <input type="checkbox"/> Non-randomized – controlled <input type="checkbox"/> Not applicable
Blinding used (choose one)	<input type="checkbox"/> Double blind <input checked="" type="checkbox"/> Single blind <input type="checkbox"/> Not blinded
- If blinded, choose roles that were blinded	<input checked="" type="checkbox"/> Subject <input type="checkbox"/> Investigator <input type="checkbox"/> Monitor <input type="checkbox"/> Data analyst <input type="checkbox"/> Carer <input type="checkbox"/> Assessor

2.2 Arm Information

Total number of study arms	2
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Arm 1:

Arm Title	Group I: Betain > Placebo
Arm description	Group I receives two oral doses of betaine daily (2 x 3 g Cystadane [®]) for 15 days, followed by a washout period of 7 days and placebo for 15 days.
Arm type (choose one)	<input checked="" type="checkbox"/> Experimentell <input type="checkbox"/> Active comparator <input type="checkbox"/> Placebo <input type="checkbox"/> No intervention <input type="checkbox"/> Other

Number of subjects started:	4
Number of subjects completed:	4
Subject non-completion reason	
Reason	Number of subjects
a) <input type="checkbox"/> Adverse event, non-fatal	a)
b) <input type="checkbox"/> Adverse event, serious fatal	b)
c) <input type="checkbox"/> Consent withdrawn by subject	c)
d) <input type="checkbox"/> Lack of efficacy	d)
e) <input type="checkbox"/> Lost to follow-up	e)
f) <input type="checkbox"/> Physician decision	f)
g) <input type="checkbox"/> Pregnancy	g)
h) <input type="checkbox"/> Protocol deviation	h)
i) <input type="checkbox"/> Transferred to another arm/group	i)
j) <input type="checkbox"/> Other (please specify)	j)
Subject joining reason	
Number of subjects	
Reason	<input type="checkbox"/> Late recruitment <input type="checkbox"/> Transferred from another arm/group <input type="checkbox"/> Other (please specify)

Arm 2 (only fill in if a 2nd arm was used in the study):

Arm Title	Group II: Placebo > Betain
Arm description	Group I receives two oral doses of placebo daily (2 x 3 g Cystadane [®]) for 15 days, followed by a washout period of 7 days, cross over to betaine for 15 days.
Arm type (choose one)	<input checked="" type="checkbox"/> Experimentell <input type="checkbox"/> Active comparator <input type="checkbox"/> Placebo <input type="checkbox"/> No intervention <input type="checkbox"/> Other
Number of subjects started:	4
Number of subjects completed:	3

Subject non-completion reason	
Reason	Number of subjects
a) <input type="checkbox"/> Adverse event, non-fatal	a)
b) <input type="checkbox"/> Adverse event, serious fatal	b)
c) <input checked="" type="checkbox"/> Consent withdrawn by subject	c) 1
d) <input type="checkbox"/> Lack of efficacy	d)
e) <input type="checkbox"/> Lost to follow-up	e)
f) <input type="checkbox"/> Physician decision	f)
g) <input type="checkbox"/> Pregnancy	g)
h) <input type="checkbox"/> Protocol deviation	h)
i) <input type="checkbox"/> Transferred to another arm/group	i)
j) <input type="checkbox"/> Other (please specify)	j)
Subject joining reason	
Number of subjects	
Reason	<input type="checkbox"/> Late recruitment <input type="checkbox"/> Transferred from another arm/group <input type="checkbox"/> Other (please specify)

3. Baseline Characteristics

Age and gender are always included as baseline characteristics. Are there other study specific baseline characteristics you would like to report?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
- If yes, which baseline characteristics	- Residual FVIII activity	

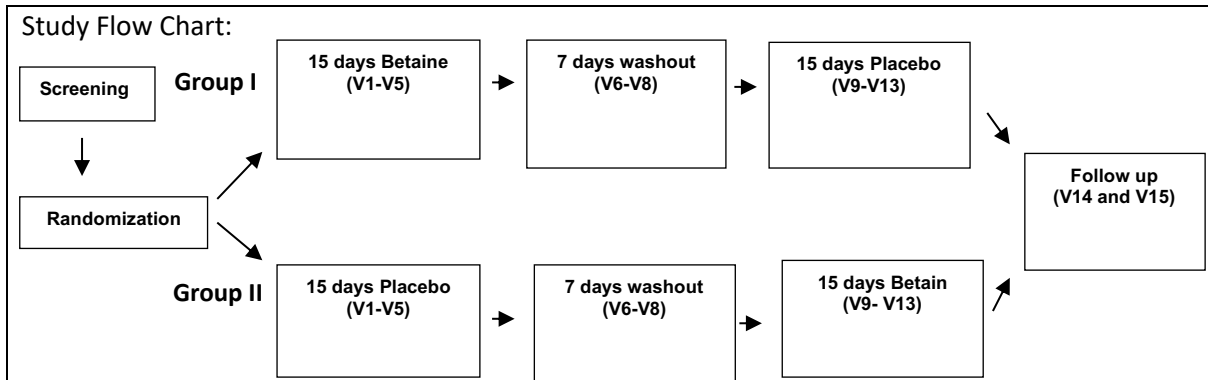


Table 1

Parameter	Group I (n=4, betaine>placebo)	Group II (n=3, placebo > betaine)
Sex (female)	4 (0)	3 (0)
Age [years] (mean±SD)	63.8±7.3	51.7±10.0
Res. FVIII activity [%] (one stage, mean±SD)	27.4 ± 11.1	20.5±16.8

4. End point definition

End point 1:

End point title	Factor VIII activity (one stage)		
End point type	<input checked="" type="checkbox"/> Primary <input type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		
Data can be found here:	Table	Row	Column
(mean ± SD)	2	1	2-5
Statistical Analysis: No statistical analyses for this end point			

End point 2:

End point title	Factor VIII activity (chromogenic)		
End point type	<input checked="" type="checkbox"/> Primary <input type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		
Data can be found here:	Table	Row	Column
(mean ± SD)	2	2	2-5
Statistical Analysis: No statistical analyses for this end point			

End point 3:

End point title	Factor VIII antigen		
End point type	<input type="checkbox"/> Primary <input checked="" type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		
Data can be found here:	Table	Row	Column
<i>(mean ± SD)</i>	2	3	2-5
Statistical Analysis: No statistical analyses for this end point			

End point 4:

End point title	aPTT		
End point type	<input type="checkbox"/> Primary <input checked="" type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		
Data can be found here:	Table	Row	Column
<i>(mean ± SD)</i>	2	4	2-5
Statistical Analysis: No statistical analyses for this end point			

End point 5:

End point title	Factor IX activity		
End point type	<input type="checkbox"/> Primary <input checked="" type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		
Data can be found here:	Table	Row	Column
<i>(mean ± SD)</i>	2	5	2-5
Statistical Analysis: No statistical analyses for this end point			

End point 6:

End point title	VWF activity (VWF:RCo)		
End point type	<input type="checkbox"/> Primary <input checked="" type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		

Data can be found here: <i>(mean ± SD)</i>	Table	Row	Column
	2	6	2-5
Statistical Analysis: No statistical analyses for this end point			

End point 7:

End point title	VWF antigen		
End point type	<input type="checkbox"/> Primary <input checked="" type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		
Data can be found here: <i>(mean ± SD)</i>	Table	Row	Column
	2	7	2-5
Statistical Analysis: No statistical analyses for this end point			

End point 8:

End point title	Methionine plasma level		
End point type	<input type="checkbox"/> Primary <input checked="" type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		
Data can be found here: <i>(mean ± SD)</i>	Table	Row	Column
	2	8	2-5
Statistical Analysis: No statistical analyses for this end point			

End point 9:

End point title	Factor VIII inhibitor		
End point type	<input type="checkbox"/> Primary <input checked="" type="checkbox"/> Secondary <input type="checkbox"/> Other pre-specified <input type="checkbox"/> Post-hoc		
Data can be found here: <i>(mean ± SD)</i>	Table	Row	Column
	2	9	2-5
Statistical Analysis: No statistical analyses for this end point			

Table 2

Parameter (mean±SD)	Group I (n=4)		Group II (n=3)	
	Treatment period		Treatment period*	
	Betaine*	Placebo**	Placebo ^a	Betaine**
FVIII activity [%] (one stage)	27.5±2.1	30.7±1.8	19.0±3.3	22.1±1.4
FVIII activity [%] (chromogenic)	25.4±1.0	26.4±4.4	13.3±4.8	16.8±2.3
FVIII antigen[%]	25.8±1.5	26.5±1.4	21.3±1.7	23.9±1.4
aPTT [sec]	42.0±1.0	40.5±1.0	38.8±0.9	37.6±0.5
FIX activity[%]	103.3±3.6	113.3±3.6	96.8±4.1	100.2±2.7
VWF activity [%] (VWF:RCo)	116.1±7.7	127.9±2.7	113.5±7.1	118.1±5.2
VWF antigen [%]	125.4±4.6	134.9±3.9	123.8 ±4.3	126.1 ±6.1
Methionine plasma level [micromol/L][min-max]	46.1±9.9 [min-max]	28.4±3.1 [min-max]	28.3±6.0 [min-max]	32.2±6.8 [min-max]
FVIII inhibitor [BU/ml]	<0.4	<0.4	<0.4	<0.4

*data of V1 (2 h after first IMP1-intake) until V5 (day 14 after start of IMP1-intake) are shown as arithmetic mean ±SD; **data of V9 (2 h after first IMP2-intake) until V13 (day 14 after start of IMP2-intake) are shown as arithmetic mean ±SD; ^aV5 data missing for one patient.

5. Adverse events

5.1 Overview

Timeframe for adverse event reporting (Enter the time point(s) or time period for adverse events assessment)	23/01/24 - 24/01/25	
Assessment type	<input checked="" type="checkbox"/> Systematic	<input type="checkbox"/> Non-systematic
Adverse events dictionary name	<input checked="" type="checkbox"/> MedDRA <input type="checkbox"/> SNOMED CT <input type="checkbox"/> Other (specify):	
Dictionary version		

5.2 Adverse event reporting

Summary

How do you wish to report adverse events?	<input type="checkbox"/> Per arm	<input checked="" type="checkbox"/> For all study subjects
Number of subjects affected by serious adverse events	0	
Number of subjects affected by non-serious adverse events	0	
Total number of deaths (all causes)	0	
Total number of deaths resulting from adverse events	0	

6. More information

Were there any global substantial amendments to the protocol?	<input checked="" type="checkbox"/> Yes	<input type="checkbox"/> No
<ul style="list-style-type: none"> - If yes, please provide <u>Amendment date</u> - If yes, please provide <u>Amendment description</u> 	<ul style="list-style-type: none"> - 30.06.2014: correction of safety parameters - 05.11.2015: change of study duration to 40 days because of wash out period shortening - 09.05.2016: change of deputy of PI - 12.06.2018: change of deputy of PI - 07.06.2023: adaptation of IMP labeling and name of Cystadane MAH - 13.02.2024: change of deputy of PI 	
Were there any global interruptions to the trial?	<input type="checkbox"/> Yes	<input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> - If yes, please provide <u>Interruption date</u> - If yes, please provide <u>Interruption description</u> - If yes, please provide <u>Restart date</u> (if applicable) 	<ul style="list-style-type: none"> - - - 	

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed leading to unreliable data. It had been planned to include 30 patients, but the study has prematurely ended (n=8) due to stagnant recruitment.