Clinical trial results:
Clinical Study to Investigate the Pharmacokinetics, Efficacy, Safety, and Immunogenicity of Wilate in Previously Treated Patients with Severe Hemophilia A

Summary

EudraCT number	2016-003681-34
Trial protocol	HU BG PL
Global end of trial date	29 March 2018

Results information

Result version number	v1 (current)
This version publication date	02 May 2019
First version publication date	02 May 2019

Trial information

Trial identification

Sponsor protocol code	WIL-27

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02954575
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Octapharma AG
Sponsor organisation address	Seidenstrasse 2, Lachen, Switzerland, CH-8853
Public contact	Clinical Trial Manager, Octapharma AG, +41 554512180, Cristina.Solomon@octapharma.ch
Scientific contact	Clinical Trial Manager, Octapharma AG, +41 554512180, Cristina.Solomon@octapharma.ch

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	22 August 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this study is to determine the efficacy of Wilate in the prophylactic treatment of previously treated patients (PTP) with severe hemophilia A.

Protection of trial subjects:

This trial was conducted in accordance to the principles of ICH- GCP, ensuring that the rights, safety and well-being of patients are protected and in consistency with the Declaration of Helsinki and national regulatory requirements.
Inclusion and exclusion criteria were carefully defined in order to protect subjects from contraindications, interactions with other medication and risk factors associated with the investigational medicinal product. Throughout the study safety was assessed, such as occurrence of AEs and concomitant medications.

Background therapy: -
Evidence for comparator: -

Actual start date of recruitment	21 December 2016
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	Russian Federation: 7
Country: Number of subjects enrolled	Poland: 17
Country: Number of subjects enrolled	Bulgaria: 27
Country: Number of subjects enrolled	Hungary: 4
Worldwide total number of subjects	55
EEA total number of subjects	48

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)	5
Adults (18-64 years)	50
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients with documented severe hemophilia A, who had previous treatment with a FVIII concentrate for at least 150 exposure days (EDs) were screened according to predefined in- and exclusion criteria.

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	Wilate

Arm description:

All patients will received Wilate for prophylactic treatment according to the guidelines given in the clinical study protocol and the patient's clinical condition.

Arm type	Experimental
Investigational medicinal product name	Wilate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solvent for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

Dose and frequency of Wilate was determined according to detailed guidelines given in the clinical study protocol and to the patient's clinical condition.
The dose used for PK assessment, i.e., 50 ± 5 IU/kg, was in line with the current recommendations of the EMA ,which recommends a dose of 25–50 IU/kg.
The doses for prophylaxis (20–40 IU/kg Wilate/kg BW given at intervals of 2 to 3 days), the treatment of bleeding episodes and perioperative prophylaxis, were given as indicated in the European Summary of Product Characteristics. The body weight measurement obtained at the visit prior to the prophylactic treatments was used in the calculations of dose.

Number of subjects in period 1	Wilate
Started	55
Completed	54
Not completed	1
Adverse event, non-fatal	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall Trial

Reporting group description: -

Reporting group values	Overall Trial	Total	
Number of subjects	55	55	
Age categorical Units: Subjects			
< 16 years	5	5	
>= 16 years	50	50	
Age continuous Units: years			
arithmetic mean	35.0		
standard deviation	± 12.3	-	
Gender categorical Units: Subjects			
Female	0	0	
Male	55	55	

End points

End points reporting groups

Reporting group title	Wilate
Reporting group description:	
All patients will received Wilate for prophylactic treatment according to the guidelines given in the clinical study protocol and the patient's clinical condition.	
Subject analysis set title	Per-protocol population (PP)
Subject analysis set type	Per protocol
Subject analysis set description:	
The per-protocol (PP) set, i.e. a subset of the full analysis set excludes subjects with major protocol deviations which may have an impact on the evaluation of the primary study outcome parameter (major protocol deviations as defined during the data review meeting.	
Subject analysis set title	Safety population (SAF)
Subject analysis set type	Safety analysis
Subject analysis set description:	
The safety (SAF) set includes all subjects who received at least one infusion of IMP	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
The full analysis set (FAS) defined according to the intention-to-treat (ITT) principle will include all enrolled subjects who received at least one infusion of IMP after the initial PK or at Non-PK Visit.	
Subject analysis set title	Pharmacokinetic population (PK)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
The pharmacokinetic (PK) set will include all subjects for which at least one valid Wilate PK profile has been obtained.	
Subject analysis set title	N (BE)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Number of bleeding events (PP -data set)	
Subject analysis set title	% (BE)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Percentage of bleeding events (PP -data set)	
Subject analysis set title	Initial PK
Subject analysis set type	Safety analysis
Subject analysis set description:	
Initial PK Assessment of FVIII:C	
Subject analysis set title	PK completion 6 months
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
PK Assessment of FVIII:C at 6 months	
Subject analysis set title	Number of patients
Subject analysis set type	Safety analysis
Subject analysis set description:	
Number of patients	
Subject analysis set title	% of patients
Subject analysis set type	Safety analysis
Subject analysis set description:	
percentage of patients	
Subject analysis set title	Overall efficacy assessment (n)

Subject analysis set type	Full analysis
Subject analysis set description: Result of overall efficacy assessment (n)	
Subject analysis set title	Overall efficacy assessment (%)
Subject analysis set type	Full analysis
Subject analysis set description: Overall efficacy assessment (%)	
Subject analysis set title	ABRs during Wilate Prophylaxis
Subject analysis set type	Full analysis
Subject analysis set description: ABRs during Wilate Prophylyxis	
Subject analysis set title	Incremental IVR (kg/dL) over time
Subject analysis set type	Full analysis
Subject analysis set description: IVR from FVIII:C plasma levels from all patients at each visit	
Subject analysis set title	ANOVA assessed association between blood group &IMP half-life
Subject analysis set type	Full analysis
Subject analysis set description: ANOVA assessed association between blood group and Wilate half-life	
Subject analysis set title	ANOVA assessed association between VWF:Ag and IMP half-life
Subject analysis set type	Full analysis
Subject analysis set description: ANOVA assessed association between VWF:Ag and Wilate half-life	
Subject analysis set title	Number of patients Pearson Clopper CI (2-sided) 95%
Subject analysis set type	Full analysis
Subject analysis set description: 95% Pearson Clopper interval	

Primary: Reduction of total annualized bleeding rate (TABR) under Prophylaxis

End point title	Reduction of total annualized bleeding rate (TABR) under Prophylaxis[1]

End point description:

The efficacy of prophylactic treatment with Wilate was statistically evaluated by comparing the primary endpoint, i.e., TABR under prophylaxis, with a predefined threshold of 29 BEs per patient per year. This threshold corresponds to 50% of the TABR reported in GENA-01 study which had a TABR of 58.1 per patient per year. A confirmative one-sided, one-sample Poisson test was used to test whether the mean annualised bleeding rate (ABR) in patients treated prophylactically with Wilate was below the threshold of 29 BEs per patient year (alpha = 2.5%). A corresponding two-sided 95% CI for the TABR was also provided.

In the per-protocol population (N=52) the one-sample Poisson test estimate was 2.13 (95% CI 1.64, 2.76) p<0.0001 vs mean TABR >29

End point type	Primary

End point timeframe:

6 months

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: Trial includes one arm only. For specifying statistical analysis in the system at least 2 arms are required, so no statistical analysis can be entered. Therefore only results for this endpoint are provided.

84.2% of all BEs were treated successfully (95% CI 72.13%, 92.52%; p=0.0096 for proportion of success ≤70%)

End point values	ABRs during Wilate Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: bleeding events				
arithmetic mean (confidence interval 95%)				
Bleeding Rate	2.13 (1.64 to 2.76)			

Statistical analyses

No statistical analyses for this end point

Secondary: Spontaneous annualized bleeding rate (SABR)

End point title	Spontaneous annualized bleeding rate (SABR)

End point description:

SABR was analysed in the same way as TABR, the only exception being that, for the comparison of mean SABRs, a predefined threshold of 19.1 per patient per year was chosen; this threshold corresponds to 50% of the SABR in GENA-01.

For the spontaneous BEs in the PP population, the one-sample Poisson test estimate was 1.53 (95% CI 1.13, 2.08; p<0.0001 vs mean SABR >19.1).

End point type	Secondary

End point timeframe:

6 months

End point values	ABRs during Wilate Prophylaxis			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: Bleeding Events				
geometric mean (confidence interval 95%)				
Bleeding Rate	1.53 (1.13 to 2.08)			

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Wilate in the treatment of breakthrough bleeding events

End point title	Efficacy of Wilate in the treatment of breakthrough bleeding events

End point description:

The proportion of bleeding events (BEs) successfully treated with Wilate were documented by the

patient (together with the investigator in case of on-site treatments) in the patient diary for all BEs according to a 4 point hemostatic efficacy scales including the four items: 'excellent,' 'good,' moderate,' and 'none'.
All efficacy ratings assessed as either ‘excellent’ or ‘good’ were considered ‘successfully treated.’

End point type	Secondary

End point timeframe:

6 months

End point values	N (BE)	% (BE)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	25[2]	25[3]		
Units: Bleeding Events				
number (not applicable)				
Excellent	16	28.1		
Good	32	56.1		
Moderate	9	15.8		
Treated sucessfully (all BEs)	48	84.2		

Notes:

[2] - Number of patients with BEs

[3] - Number of patients with BEs

Statistical analyses

No statistical analyses for this end point

Secondary: Wilate consumption for prophylaxis

End point title	Wilate consumption for prophylaxis

End point description:

The total consumption of Wilate for all patients receiving prophylaxis (IU/kg)

End point type	Secondary

End point timeframe:

6 months

End point values	Per-protocol population (PP)			
Subject group type	Subject analysis set			
Number of subjects analysed	52			
Units: Total Dose IU/kg				
number (not applicable)				
Prophylaxis	1300017.1			

Statistical analyses

No statistical analyses for this end point

Secondary: Pharmacokinetic (PK) assessment area under the curve [AUCnorm] of FVIII:C

End point title	Pharmacokinetic (PK) assessment area under the curve [AUCnorm] of FVIII:C

End point description:

PK assessments of FVIII:C were conducted using the one-stage (OS) assay. The value of the area under the curve [AUC]) of FVIII:C was calculated based on the FVIII:C values measured in the patients participating in the PK study.

End point type	Secondary

End point timeframe:

at baseline and 6 months

End point values	Initial PK	PK completion 6 months		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: AUCnorm (h*kg*IU/dL/IU)				
geometric mean (standard deviation)				
AUCnorm	28.61 (± 9.31)	30.75 (± 11.32)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK OS assay assessment (in vivo half-life) of FVIII:C

End point title	PK OS assay assessment (in vivo half-life) of FVIII:C

End point description:

PK assessments of FVIII:C were conducted using the OS assay. The in vivo half-life of FVIII:C was calculated based on the FVIII:C values measured in the patients participating in the PK study

End point type	Secondary

End point timeframe:

at baseline and 6 months

End point values	Initial PK	PK completion 6 months		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Half-life (h)				
geometric mean (standard deviation)				
Half-life (h)	10.82 (± 2.5)	11.5 (± 2.3)		

Statistical analyses

No statistical analyses for this end point

Secondary: PK assessment (Maximum plasma concentration [Cmax]) of FVIII:C

End point title	PK assessment (Maximum plasma concentration [Cmax]) of FVIII:C

End point description:

PK assessments of FVIII:C were conducted using the one-stage (OS) assay. The Maximum plasma concentration of FVIII:C was calculated based on the FVIII:C values measured in the patients participating in the PK study.

End point type	Secondary

End point timeframe:

at baseline and 6 months

End point values	Initial PK	PK completion 6 months		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	21	21		
Units: Cmax (IU/dL)				
geometric mean (standard deviation)				
Cmax (IU/dL)	106.7 (± 22.45)	103.49 (± 26.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Incremental in vivo recovery (IVR) of Wilate over time

End point title	Incremental in vivo recovery (IVR) of Wilate over time

End point description:

IVR was determined from FVIII:C plasma levels from all patients at each visit using OS assay

End point type	Secondary

End point timeframe:

At baseline, and at 3 and 6 months of treatment

End point values	Incremental IVR (kg/dL) over time			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: kg/dL				
geometric mean (standard deviation)				
First PK/non-PK visit	2.14 (± 0.51)			
3 months	2.14 (± 0.49)			
PK/non-PK completion 6 months	1.97 (± 0.64)			

Statistical analyses

No statistical analyses for this end point

Secondary: Association between ABO blood type and the FVIII:C half-life of Wilate

End point title	Association between ABO blood type and the FVIII:C half-life of Wilate

End point description:

Analysis of variance (ANOVA) was used in an exploratory sense to assess an association between AB0 blood type and the FVIII:C half-life of Wilate.

End point type	Secondary

End point timeframe:

6 months

End point values	ANOVA assessed association between blood group &IMP half-life			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: p-value				
number (not applicable)				
One-Stage Assay (OS assay)	0.0346			

Statistical analyses

No statistical analyses for this end point

Secondary: Association between VWF:Ag concentration and the FVIII:C half-life of Wilate

End point title	Association between VWF:Ag concentration and the FVIII:C half-life of Wilate

End point description:

ANOVA was used in an exploratory sense to assess an association between VWF:Ag with the FVIII:C half-life of Wilate.

End point type	Secondary

End point timeframe:

6 months

End point values	ANOVA assessed association between VWF:Ag and IMP half-life			
Subject group type	Subject analysis set			
Number of subjects analysed	21			
Units: p-value				
number (not applicable)				
One-Stage Assay (OS assay)	0.4244			

Statistical analyses

No statistical analyses for this end point

Secondary: Immunogenicity of Wilate by testing for FVIII inhibitors

End point title	Immunogenicity of Wilate by testing for FVIII inhibitors

End point description:

FVIII inhibitor activity was determined at each study visit before the injection of Wilate using the modified Bethesda assay (Nijmegen modification).

End point type	Secondary

End point timeframe:

6 months

End point values	Number of patients Pearson Clopper CI (2-sided) 95%			
Subject group type	Subject analysis set			
Number of subjects analysed	55			
Units: patients				
number (confidence interval 95%)				
FVIII inhibitors developed	0 (0 to 16.11)			

Statistical analyses

No statistical analyses for this end point

Secondary: Virus safety to be measured by the incidence of parvovirus B19 seroconversions between baseline (BL) and end of study

End point title	Virus safety to be measured by the incidence of parvovirus B19

	seroconversions between baseline (BL) and end of study

End point description:

Virus safety was evaluated by taking a plasma sample for parvovirus B19 antibody testing before the first injection of Wilate. All patients negative at screening were tested again at the study completion visit.

End point type	Secondary

End point timeframe:

6 months

End point values	Number of patients	% of patients		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55[4]	55[5]		
Units: % of patients				
number (not applicable)				
Positive for parvovirus B19 IgG antibodies at BL	53	96.4		
Positive for parvovirus B19 IgM antibodies at BL	1	1.82		
Negative for B19 IgM&IgG at BL and end of study	2	3.64		

Notes:

[4] - refers to percentage from the total 55 subjects in SAF

[5] - refers to percentage from the total 55 subjects in SAF

Statistical analyses

No statistical analyses for this end point

Secondary: Efficacy of Wilate in surgical prophylaxis assessed by surgeon and hematologist using predefined assessment criteria

End point title	Efficacy of Wilate in surgical prophylaxis assessed by surgeon and hematologist using predefined assessment criteria

End point description:

Hemostatic efficacy was assessed at the end of surgery by the surgeon and at end of the postoperative period by the haematologist, using 4 point hemostatic efficacy scales including the four items: 'excellent,' 'good,' moderate,' and 'none'. Overall efficacy was assessed by the investigator, taking both the intra and postoperative assessments into account, and using the ‘excellent,’ ‘good,’ moderate,’ and ‘none’ scale.

End point type	Secondary

End point timeframe:

6 months

End point values	Overall efficacy assessment (n)	Overall efficacy assessment (%)		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	55	55		
Units: Efficacy Rating				
number (not applicable)				

Excellent	0	0		
Good	1	100		
Moderate	0	0		
None	0	0		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: Throughout the observation period until study completion.	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	20.0
Reporting groups	
Reporting group title	SAF Population

Reporting group description: -

Serious adverse events	SAF Population		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 55 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	SAF Population		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 55 (21.82%)		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 55 (1.82%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Thrombocytosis			
subjects affected / exposed	2 / 55 (3.64%)		
occurrences (all)	2		
General disorders and administration site conditions			

Pain subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Immune system disorders Seasonal allergy subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 2		
Skin and subcutaneous tissue disorders Eczema subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	2 / 55 (3.64%) 5		
Infections and infestations Erysipelas subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 55 (1.82%) 1 1 / 55 (1.82%) 1 1 / 55 (1.82%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
16 January 2017	Protocol amendment has been prepared in response to the FDA information request: - a second PK Assessment Phase after 6 months of prophylactic treatment which is included in the PK Study Completion Visit has been added - study duration for patients undergoing PK assessment has been corrected from 1 week to 2 days per PK Assessment Phase. - thromboembolic events have been defined as events subject to expedited reporting throughout the duration of the study. Also, to actively monitor patients for signs and symptoms of thromboembolic events after the end of study treatment, a Follow-up Contact 30 days after the end of study treatment has been included. - specification that, of the 20 patients undergoing PK assessment, 4 patients should be between ≥12 and <17 years of age has been added - the time period for recording bleeding events that will count towards the primary and relevant secondary endpoint has been more clearly defined. - determination of VWF:Ag and VWF:Ac has been dropped from the Screening Visit - further instruction whow to proceed in case the interval between screening and treatment initiation is longer than 30 days have been added - information on how to deal with patients who develop FVIII inhibitors have been specified - details which bleeding frequency during prophylactic treatment should be considered 'unacceptable' for a dose adjustment to be triggered have been added - a retention sample being taken for possible virus marker testing in addition to parvovirus B19 antibody testing - the use of Wilate in surgical prophylaxis has been defined as additional (i.e., exploratory) rather than a secondary endpoint. - continuous infusion of Wilate during surgical prophylaxis has been disallowed - The possibility of 'severe hemorrhage' during surgery was deleted as a defining criterion for major surgeries

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported