



Clinical trial results:

Single dose, open label, uncontrolled, safety trial of intravenous administration of idarucizumab to paediatric patients enrolled from ongoing phase IIb/III clinical trials with dabigatran etexilate for the treatment and secondary prevention of venous thromboembolism.

Summary

EudraCT number	2015-002177-37
Trial protocol	SE LT CZ IT DE Outside EU/EEA GR HU BE ES BG AT FI FR
Global end of trial date	19 October 2019

Results information

Result version number	v1
This version publication date	16 April 2020
First version publication date	16 April 2020

Trial information

Trial identification

Sponsor protocol code	1321.7
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Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Boehringer Ingelheim
Sponsor organisation address	Binger Strasse 173, Ingelheim am Rhein, Germany, 55216
Public contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com
Scientific contact	Boehringer Ingelheim Call Center, Boehringer Ingelheim, +1 8002430127, clintriage.rdg@boehringer-ingelheim.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMA-001438-PIP01-13
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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	18 December 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	19 October 2019
Global end of trial reached?	Yes
Global end of trial date	19 October 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the safety of idarucizumab, as assessed by the occurrence of patients with drug related adverse events (including immune reactions) and all-cause mortality in paediatric venous thromboembolism (VTE) patients treated with dabigatran in ongoing clinical trials who require emergency surgery/urgent procedures or patients who have life-threatening or uncontrolled bleeding which requires urgent intervention, when rapid reversal of the anticoagulant effects of dabigatran is needed.

Protection of trial subjects:

Only subjects that met all the study inclusion and none of the exclusion criteria were to be entered in the study. All subjects were free to withdraw from the clinical trial at any time for any reason given. Close monitoring of all subjects was adhered to throughout the trial conduct. Rescue medication was allowed for all patients as required. The number 1 for age category 'In Utero' in trial population does not reflect the true age of this participant. The age information is not provide for protection of pediatric participant.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 March 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Russian Federation: 1
Worldwide total number of subjects	1
EEA total number of subjects	0

Notes:

Subjects enrolled per age group

In utero	1
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	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

An open-label, uncontrolled case series trial, with a single treatment arm of idarucizumab in patients with venous thromboembolism treated with dabigatran etexilate in ongoing Boehringer Ingelheim pediatric clinical trials (1160.106 and 1160.108). Treatment period was around 1 day followed by 29 days of safety follow-up period.

Pre-assignment

Screening details:

All subjects were screened for eligibility to participants in the trial. Subjects attended specialist sites which would then ensure that they met all strictly implemented inclusion/exclusion criteria. Subjects were not to be assigned to treatment groups if any one of the specific entry criteria were violated.

Period 1

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

Arms

Arm title	Idarucizumab
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Arm description:

2.5 gram (g) per 50 milliliter (mL) vial of Idarucizuma was administrated via intravenous injection (vial 1) with (in order of preference): a 5 minutes (min) infusion with an infusion pump, a 10 to 15 min drip, or intravenous push with a syringe followed by another injection (vial 2) of same dosage of Idarucizumab for participants who were treated with dabigatran and had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention or who required emergency surgery/urgent procedures where adequate haemostasis was required (total dosage: up to 5g based on the weight of participant). Two equal injection parts were administered no more than 15 min apart. The time between start of injection of the first vial and end of the second vial was 22 min followed by 24 hours post-dose observation period.

Arm type	Experimental
Investigational medicinal product name	Idarucizumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

2 injections of 2.5 gram (g) per 50 milliliter (mL) vial of Idarucizuma (total: up to 5g based on the weight of participant) were administrated via intravenous injection (vial 1) followed by another injection (vial 2) of same dosage of Idarucizumab for participants who were treated with dabigatran and had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention or who required emergency surgery/urgent procedures where adequate haemostasis was required. Two equal injection parts were administered no more than 15 minutes (min) apart. The time between start of injection of the first vial and end of the second vial was 22 min.

Number of subjects in period 1	Idarucizumab
Started	1
Completed	0
Not completed	1
Prematurely discontinued of the trial	1

Baseline characteristics

Reporting groups

Reporting group title	Idarucizumab
Reporting group description:	
2.5 gram (g) per 50 milliliter (mL) vial of Idarucizuma was administrated via intravenous injection (vial 1) with (in order of preference): a 5 minutes (min) infusion with an infusion pump, a 10 to 15 min drip, or intravenous push with a syringe followed by another injection (vial 2) of same dosage of Idarucizumab for participants who were treated with dabigatran and had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention or who required emergency surgery/urgent procedures where adequate haemostasis was required (total dosage: up to 5g based on the weight of participant). Two equal injection parts were administered no more than 15 min apart. The time between start of injection of the first vial and end of the second vial was 22 min followed by 24 hours post-dose observation period.	

Reporting group values	Idarucizumab	Total	
Number of subjects	1	1	
Age categorical			
Age was collected but not provided for protection of pediatric participant.			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Not available	1	1	
Age Continuous			
0 in Arithmetic Mean does not reflect the true value. Age information were collected but not provided for protection of pediatric participant. As single patient was entered, 0 in Standard Deviation stands for 'Not Applicable'.			
Units: years			
arithmetic mean	0		
standard deviation	± 0	-	
Sex: Female, Male			
Sex was collected but not provided for protection of pediatric participant.			
Units: Participants			
Female	0	0	
Male	0	0	
Not available	1	1	
Race/Ethnicity, Customized			
Race and Ethnicity were collected but not provided for protection of pediatric participant.			
Units: Subjects			
Not available	1	1	

End points

End points reporting groups

Reporting group title	Idarucizumab
Reporting group description: 2.5 gram (g) per 50 milliliter (mL) vial of Idarucizuma was administrated via intravenous injection (vial 1) with (in order of preference): a 5 minutes (min) infusion with an infusion pump, a 10 to 15 min drip, or intravenous push with a syringe followed by another injection (vial 2) of same dosage of Idarucizumab for participants who were treated with dabigatran and had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention or who required emergency surgery/urgent procedures where adequate haemostasis was required (total dosage: up to 5g based on the weight of participant). Two equal injection parts were administered no more than 15 min apart. The time between start of injection of the first vial and end of the second vial was 22 min followed by 24 hours post-dose observation period.	

Primary: Number of participants with drug-related adverse events (AEs)

End point title	Number of participants with drug-related adverse events
End point description: Number of participants with drug-related adverse events (AEs) including immune reactions and all cause mortality during the trial. Treated set (TS): including all patients who received any dose of Idarucizumab. The TS was used to assess safety, clinical endpoints, demographics and baseline characteristics, concomitant diagnosis/therapy and medical history, and antidrug antibodies (ADA).	
End point type	Primary
End point timeframe: From vial 1 of Idarucizumab until prematurely discontinued of the trial, up to 25 days	

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: This endpoint was evaluated only descriptively. Thus, no statistical hypothesis were tested.

End point values	Idarucizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percent change of coagulation time for diluted thrombin time (dTT) and ecarin clotting time (ECT) at 30 minutes post-dose compared with pre-dose

End point title	Percent change of coagulation time for diluted thrombin time (dTT) and ecarin clotting time (ECT) at 30 minutes post-dose compared with pre-dose
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End point description:

Percent change of coagulation time for diluted thrombin time (dTT) and ecarin clotting time (ECT) at 30 minutes (min) post-dose compared with pre-dose. Central blood sampling for dTT, ECT were to occur immediately prior to administration of each vial of Idarucizumab and post-dose at 30min, 4h, 12h and 24h. Pharmacodynamic (PD) set (PDS): comprising all patients in the TS who provided at least 1 evaluable pre-dose and at least 1 post-dose observation for PD endpoints or biomarker measures. The

PDS was used for the PD endpoint analyses. Note that for different PD endpoints or biomarkers, the number of evaluable patients could differ between endpoints.

End point type	Secondary
End point timeframe:	
At immediately prior to administration of vial 1 of Idarucizumab and 30 minutes (min) post vial 2 administration.	

End point values	Idarucizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Percentage of time in seconds				
number (not applicable)				
Diluted thrombin time (dTT)	-46.3			
Ecarin clotting time (ECT)	-67.8			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to achieve reversal of the dabigatran effect (based on the coagulation time for dTT and ECT)

End point title	Time to achieve reversal of the dabigatran effect (based on the coagulation time for dTT and ECT)
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End point description:

Idarucizumab administration resulted in normalisation of dTT and ECT. Time to achieve reversal of anticoagulant effect of dabigatran based on the coagulation time for dTT and ECT, at any time point from the end of the second injection (vial 2) up to 24 hours . Reversal of the dabigatran effect at time t was defined as the $100 \% \times (\text{pre-dose coagulation time} - \text{post-dose coagulation time at time t}) / (\text{pre-dose coagulation test} - \text{upper limit of normal})$. Values equal to or higher than 100% were interpreted as reversal. Central blood sampling for dTT, ECT were to occur immediately prior to administration of each vial of Idarucizumab and post-dose at 30min, 4h, 12h and 24h. PD set : comprising all patients in the TS who provided at least 1 evaluable pre-dose and at least 1 post-dose observation for PD endpoints or biomarker measures. The PDS was used for the PD endpoint analyses. Note that for different PD endpoints, the number of evaluable patients could differ between endpoints.

End point type	Secondary
End point timeframe:	
From end of vial 2 of Idarucizumab up to 24h.	

End point values	Idarucizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Minutes	30			

Statistical analyses

No statistical analyses for this end point

Secondary: Duration of reversal of the dabigatran effect sustained at 24 hours post-dose (based on the coagulation time for dTT and ECT)

End point title	Duration of reversal of the dabigatran effect sustained at 24 hours post-dose (based on the coagulation time for dTT and ECT)
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End point description:

Duration of reversal, defined as the time period a patient remained completely reversed based on dTT and ECT, up to 24 hours post-dose or restarting the treatment of anticoagulation. Central blood sampling for dTT, ECT were to occur immediately prior to administration of each vial of idarucizumab and post-dose at 30min, 4h, 12h and 24h. Pharmacodynamic (PD) set (PDS): comprising all patients in the TS who provided at least 1 evaluable pre-dose and at least 1 post-dose observation for PD endpoints or biomarker measures. The PDS was used for the PD endpoint analyses. Note that for different PD endpoints or biomarkers, the number of evaluable patients could differ between endpoints.

End point type	Secondary
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End point timeframe:

From end of vial 2 of Idarucizumab up to 24h.

End point values	Idarucizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Hours				
number (not applicable)	23.5			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with cessation of bleeding

End point title	Number of participants with cessation of bleeding
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End point description:

Treated set (TS): including all patients who received any dose of Idarucizumab. The TS was used to assess safety, clinical endpoints, demographics and baseline characteristics, concomitant diagnosis/therapy and medical history, and antidrug antibodies (ADA).

End point type	Secondary
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End point timeframe:

From vial 1 of Idarucizumab through vial 2 of Idarucizumab, up to 24h 30min.

End point values	Idarucizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants	1			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants per bleeding status during the trial

End point title	Number of participants per bleeding status during the trial
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End point description:

Numbers of participants whose bleeding had stopped, reduced, unchanged, worsened or not applicable during the trial were characterized. Treated set (TS): including all patients who received any dose of Idarucizumab. The TS was used to assess safety, clinical endpoints, demographics and baseline characteristics, concomitant diagnosis/therapy and medical history, and antidrug antibodies (ADA).

End point type	Secondary
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End point timeframe:

From vial 1 of Idarucizumab until prematurely discontinued of the trial, up to 25 days

End point values	Idarucizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants				
Stopped	1			
Reduced	0			
Unchanged	0			
Worsened	0			
Not applicable	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants with clinical conditions contributing to bleeding during the trial

End point title	Number of participants with clinical conditions contributing to bleeding during the trial
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End point description:

Number of participants with clinical conditions (trauma, surgery and use of antiplatelet) contributing to bleeding during the trial were characterized. Treated set (TS): including all patients who received any dose of Idarucizumab. The TS was used to assess safety, clinical endpoints, demographics and baseline characteristics, concomitant diagnosis/therapy and medical history, and antidrug antibodies (ADA).

End point type	Secondary
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End point timeframe:

From vial 1 of Idarucizumab until prematurely discontinued of the trial, up to 25 days

End point values	Idarucizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants				
Trauma	1			
Surgery	0			
Use of antiplatelet	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Number of participants developing treatment-emergent antidrug antibodies (ADA) with cross reactivity to Idarucizumab

End point title	Number of participants developing treatment-emergent antidrug antibodies (ADA) with cross reactivity to Idarucizumab
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End point description:

Treated set (TS): including all patients who received any dose of Idarucizumab. The TS was used to assess safety, clinical endpoints, demographics and baseline characteristics, concomitant diagnosis/therapy and medical history, and antidrug antibodies (ADA).

End point type	Secondary
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End point timeframe:

At day 25 post vial 2 of Idarucizumab administration, up to 1 day

End point values	Idarucizumab			
Subject group type	Reporting group			
Number of subjects analysed	1			
Units: Participants	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From vial 1 of Idarucizumab until prematurely discontinued of the trial, up to 25 days

Adverse event reporting additional description:

Treated set (TS): including all patients who received any dose of Idarucizumab. The TS was used to assess safety, clinical endpoints, demographics and baseline characteristics, concomitant diagnosis/therapy and medical history, and antidrug antibodies (ADA).

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.1
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Reporting groups

Reporting group title	Idarucizumab
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Reporting group description:

2.5 gram (g) per 50 milliliter (mL) vial of Idarucizuma was administrated via intravenous injection (vial 1) with (in order of preference): a 5 minutes (min) infusion with an infusion pump, a 10 to 15 min drip, or intravenous push with a syringe followed by another injection (vial 2) of same dosage of Idarucizumab for participants who were treated with dabigatran and had uncontrolled or life threatening bleeding that required urgent medical or surgical intervention or who required emergency surgery/urgent procedures where adequate haemostasis was required (total dosage: up to 5g based on the weight of participant). Two equal injection parts were administered no more than 15 min apart. The time between start of injection of the first vial and end of the second vial was 22 min.

Serious adverse events	Idarucizumab		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Idarucizumab		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

The patient had completed the treatment period, but the end-of-trial visit was by mistake scheduled 5 days earlier. Thus, the patient was formally considered as having prematurely discontinued the trial although all planned visits were performed.
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Notes: