

## Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

## eAppendix 1. Exclusion Criteria

1. Inability to swallow medication.
2. CVT associated with central nervous system infection.
3. CVT due to head trauma.
4. Planned surgical treatment for CVT (eg, decompressive surgery, ear-nose-throat surgery).
5. Conditions associated with increased risk of bleeding, such as:
  - a) Major surgery in the month prior to Visit 1
  - b) Planned major surgery or intervention in the next 6 months
  - c) History of intraocular, spinal, retroperitoneal, or atraumatic intra-articular bleeding, unless the causative factor has been permanently eliminated or repaired
  - d) Gastrointestinal hemorrhage within the past 6 months (prior to Visit 1), unless the cause has been permanently eliminated or repaired, or endoscopically documented gastroduodenal ulcer disease in the previous 30 days prior to Visit 1
  - e) Hemorrhagic disorder or bleeding diathesis, eg, history of thrombocytopenia or platelet count <100 000/mL at screening, von Willebrand disease, hemophilia A or B or other hereditary bleeding disorder, history of prolonged bleeding after surgery/intervention
  - f) Fibrinolytic agents within 48 hours of starting trial medication. Pre-randomization interventional treatment (i.v. r-tPA or urokinase and/or stenting) is neither required nor excluded provided that the start of trial medication is at least 48 hours after the application of any fibrinolytic agent
  - g) Uncontrolled hypertension (systolic blood pressure >180 mmHg and/or diastolic blood pressure >100 mmHg)
  - h) History of intracranial aneurysm (unless it was permanently resolved with either clipping or coiling at least 1 year prior to the study entry).
6. Life-threatening or major bleeding (per International Society for Thrombosis and Haemostasis criteria), other than intracerebral hemorrhage due to the index CVT, during the 6 months prior to, or while on anticoagulants during the acute phase of CVT.
7. History of symptomatic non-traumatic intracerebral hemorrhage with risk of recurrence (including hemorrhagic stroke within 6 months prior to screening, but other than intracerebral hemorrhage during the acute phase of CVT).
8. Severe renal impairment defined as creatinine clearance (calculated by Cockcroft–Gault equation) <30 mL/min at screening, or if the Investigator expects creatinine clearance is likely to drop below 30 mL/min during the course of the study.
9. Patients who require taking GPIIb/IIIa antagonists, rivaroxaban, apixaban, and edoxaban, or other oral anticoagulants, systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus and dronedarone, rifampicin, carbamazepine, phenytoin, and St John's Wort.
10. Patients receiving treatment with warfarin, dabigatran etexilate, or other antithrombotic regimen (ie, anticoagulants or antiplatelet medication) for an indication other than CVT and requiring continuation of that treatment for the original diagnosis without change in the regimen.
11. Patients with prosthetic heart valves.
12. Known hypersensitivity to dabigatran etexilate or warfarin, or to any of the excipients of either product.
13. Any current or recent malignancy (≤6 months prior to Visit 1) unless the malignancy was a basal cell carcinoma that was completely removed.
14. Concomitant disease that increases the risk of an adverse reaction to study interventions or that has life expectancy <6 months.
15. Premenopausal women (last menstruation ≤1 year prior to Visit 1) who are pregnant or breastfeeding, or who plan to become pregnant while in the trial.
16. Patients who have participated in another trial with an investigational drug or device within the 14 days preceding Visit 1, or who currently are participating in another trial. Patients who are still experiencing a clinical effect from an investigational drug.
17. Patients considered unreliable by the investigator concerning the requirements for follow-up during the study or at the end of the study.
18. Any condition the Investigator believes would not allow safe participation in the study.
19. Active liver disease, as indicated by ≥1 of the following:
  - a) Prior and persistent alanine aminotransferase or aspartate transaminase, or alkaline phosphatase >3× upper limit of normal

- b) Known active hepatitis C
  - c) Known active hepatitis B
  - d) Known active hepatitis A.
20. Previous randomization in this trial.

## eAppendix 2. MRI Protocol

Measurements at the end of treatment were performed at a minimum field strength of 1.5 T.

- For any parallel imaging technique (GRAPPA, ASSET ...), an acceleration factor of 2 was used
- Wherever “Slice orientation: transverse” was indicated, this was according to bicommissural line

### Localizer/Scout

3D T1w pre-contrast (MPRAGE, 3D IR FSPGR T1w)

- Minimum TE
- TI, TR, and flip angle according to manufacturer specific/field strength specific recommendations for optimum image quality
- SENSE/SMASH/GRAPPA/ASSET allowed
- Slice/3D slab orientation: sagittal or transverse
- FOV: 256 × 256 mm
- Matrix: 256 × 256
- Slice thickness: ≤1.5 mm
- Full brain coverage

### DWI

- Single-shot EPI sequence
- Minimum TE
- TR >3000 ms
- Spectral fat suppression
- b: 0 and 1000 s/mm<sup>2</sup> (3 directions)
- SENSE/SMASH/GRAPPA/ASSET: optional for 1.5 T, obligatory for 3 T
- Slice orientation: transverse
- Slice thickness: 5 mm
- Slice gap: 0
- Number of slices: Full brain coverage
- FOV: 240 × 240 mm
- Matrix: 128 × 128 or higher
- Post-processing: calculation of ADC maps (diffusion trace maps)

### 2D FLAIR

- Turbo Spin Echo (TSE)/Fast Spin Echo (FSE) sequence
- TE: 90-140 ms
- TR: 6000-10 000 ms
- TI: 2000-2500 ms (use TI according to optimized protocol for specific inversion pulses and field strength)
- SENSE/SMASH/GRAPPA/ASSET allowed
- Slice orientation: transverse
- Slice thickness: 5 mm
- Slice gap: 0
- Number of slices: same as sequence 3 (DWI)
- Slice positioning as in sequence 3 (DWI)
- FOV: 240 × 240 mm
- Matrix: 256 × 256 or higher
- Flow compensation applied

### Susceptibility weighted imaging (SWI)

- TE: ≥15 ms
- TR: ≥20 ms
- Flip angle ≤20°
- 3D block: 1

- Slices in 3D block:  $\geq 50$
- SENSE/SMASH/GRAPPA/ASSET allowed
- Slice orientation: transverse
- 3D slab should cover the same volume as sequence 3 (DWI)
- FOV:  $240 \times 240$  mm
- FOV phase:  $\geq 75\%$
- Matrix:  $256 \times 256$  or higher

If SWI was not available:

T2\*-weighted imaging (2D-FLASH)

- TE:  $\geq 20$  ms
- TR:  $\geq 500$  ms
- Flip angle  $\leq 20^\circ$
- Slice thickness: 2.5 mm
- Number of slices: full brain coverage (about twice the number of slices that is used in DWI, FLAIR, and T2w imaging)
- SENSE/SMASH/GRAPPA/ASSET allowed
- Slice orientation: transverse
- Phase coding: right–left
- Block of slices should cover the same volume as sequence 3 (DWI)
- FOV:  $240 \times 240$  mm
- FOV phase:  $\geq 75\%$
- Matrix:  $256 \times 256$  or higher
- Flow compensation not applied

Venous 3D time of flight angiography

- 3D block: 1
- Slices: 128
- Orientation: coronal
- Full brain coverage
- Phase coding: right–left
- FOV 200-240 mm
- FOV phase: 100%
- Slice thickness: 2-3 mm
- TR:  $\geq 20$  ms
- TE:  $\geq 5$  ms
- Averages: 1
- Matrix:  $\geq 256 \times 192$
- SENSE/SMASH/GRAPPA/ASSET allowed
- F flow compensation not applied

Contrast agent injection

- 0.1 mmol/kg BW of a GAD-based contrast agent

3D contrast-enhanced MRA (3D FLASH, SPGR, FFE)

- 3D block: 1
- Slices: 400-440
- Orientation: sagittal
- Phase coding: anterior–posterior
- FOV 250-280 mm
- FOV phase: 75%
- Slice thickness: 0.4-0.6 mm
- TR:  $\geq 4.1$  ms
- TE:  $\geq 1.5$  ms
- Flip angle: 10-15°

- Averages: 1
- Measurements: 2, without delay (with subtraction before, vs after, GAD)
- Matrix:  $384 \times 288$
- SENSE/SMASH/GRAPPA/ASSET allowed

#### T2w-TSE

- Turbo Spin Echo (TSE)/Fast Spin Echo (FSE) sequence
- TE: 80-120 ms
- TR:  $\geq 2500$  ms
- SENSE/SMASH/GRAPPA/ASSET allowed
- Slice orientation: transverse
- Slice thickness: 5 mm
- Slice gap: 0
- Number of slices: same as sequence 3 (DWI)
- Slice positioning as in sequence 3 (DWI)
- FOV:  $240 \times 240$  mm
- Matrix:  $256 \times 256$  or higher

#### 3D T1w post-contrast (MPRAGE, 3D IR FSPGR T1w)

- Sequence parameters and slice positioning as in sequence 1 (3D T1w pre-contrast)

### eAppendix 3. Study Flowchart

Trial Periods	Screening Period	Randomized Treatment Period				Follow-Up Period	Extended Follow-Up for Early Discontinuations
	1 <sup>a</sup>	2 <sup>b</sup>	3	4	5 EOT	6 <sup>c</sup>	7 <sup>d</sup>
Visit	1 <sup>a</sup>	2 <sup>b</sup>	3	4	5 EOT	6 <sup>c</sup>	7 <sup>d</sup>
Study Day	-1	Day 1	Day 29	Day 85	Day 169	Day 7 after Visit 5	Day 176
Time window for visits	Up to -15 days	none	±7 days	±7 days	±7 days	+7 days	+7 days
Informed consent <sup>a,e</sup>	X						
Demographics	X						
Medical history	X						
CVT risk score	X						
Physical examination	X	X			X		
NIHSS <sup>f</sup>	X						
Vital signs	X	X	X	X	X		
Weight and height <sup>g</sup>	X		X	X	X		
Safety laboratory tests	X		X	X	X		
D-dimer	X		X		X		
Pregnancy test <sup>h</sup>	X <sup>i</sup>		X	X	X		
12-lead ECG	X						
Modified Rankin scale (mRS)			X		X		
Assessment of venous occlusion/recanalization by imaging	X <sup>j</sup>				X <sup>k</sup>		
Assessment of intracranial hemorrhage by CT or MRI <sup>l,l</sup>	X	X <sup>m</sup>					
Review of inclusion/exclusion criteria	X	X					
Randomization		X					
Dispense trial drugs		X	X	X			
First administration of trial medication		X					
INR/warfarin dose adjustment <sup>n,o</sup>		X		X			
Adverse events	X	X	X	X	X	X	X
Assessment of bleeding	X	X	X	X	X	X	X
Collection of data of new venous thrombotic events (CVT, DVT, PE, splanchnic vein thrombosis)		X <sup>p</sup>	X	X	X	X	X
Compliance check			X	X	X		
Termination of trial medication					X		
Concomitant therapy	X	X	X	X	X	X	

<b>Trial Periods</b>	<b>Screening Period</b>	<b>Randomized Treatment Period</b>				<b>Follow-Up Period</b>	<b>Extended Follow-Up for Early Discontinuations</b>
<b>Visit</b>	<b>1<sup>a</sup></b>	<b>2<sup>b</sup></b>	<b>3</b>	<b>4</b>	<b>5 EOT</b>	<b>6<sup>c</sup></b>	<b>7<sup>d</sup></b>
<b>Study Day</b>	<b>-1</b>	<b>Day 1</b>	<b>Day 29</b>	<b>Day 85</b>	<b>Day 169</b>	<b>Day 7 after Visit 5</b>	<b>Day 176</b>
Collection of post-study anticoagulation information							X
Vital status collection							X
Completion of patient participation <sup>q,r</sup>						X	X

<sup>a</sup> Signing of informed consent and subsequent screening was done after the diagnosis of CVT had been established, treatment with parenteral anticoagulation had started, and the patient was considered to be stable. A fictitious day number (Day -1) has been assigned to the screening visit (Visit 1).

<sup>b</sup> Day of randomization. Could be performed on the same day as Visit 1. In that case, Visit 2 procedures that were performed as part of Visit 1 were not repeated.

<sup>c</sup> EOT and follow-up procedures (Visits 5 and 6) were performed for all patients at the time of discontinuation of trial medication. This included patients who discontinued trial medication prior to Day 169.

<sup>d</sup> Extended follow-up applied only to patients who discontinued trial medication early.

<sup>e</sup> Re-consenting might have been necessary when new relevant information became available and was conducted according to the instructions of the sponsor (Boehringer Ingelheim).

<sup>f</sup> National Institute of Health Stroke Scale (NIHSS).

<sup>g</sup> Height was measured at screening only.

<sup>h</sup> Pregnancy tests required for all women of childbearing potential. The test at Visit 1 was performed after informed consent had been obtained.

<sup>i</sup> In addition to the tests performed at the visits, women of childbearing potential were supplied with pregnancy tests and instructed to perform pregnancy testing every 4 weeks when visits were more than 4 weeks apart.

<sup>j</sup> At screening, imaging was not performed specifically for the trial. The imaging that was done for diagnosis of the cerebral venous or dural sinus thrombosis was used and was submitted for review by the trial's AC.

<sup>k</sup> At EOT, the assessment of recanalization was done by MRI and MR venography. An MRI protocol was provided as part of the ISF and was followed for the EOT imaging. The EOT images were submitted for review by the AC.

<sup>l</sup> Throughout the trial, whenever routine imaging was performed due to worsening of the patient's condition, a suspected new intracranial hemorrhage, or a new VTE, those images were made available to the trial's AC for independent blinded review.

<sup>m</sup> EOT assessment of intracranial hemorrhage was done by MRI.

<sup>n</sup> Assessment of INR for patients who were on a VKA prior to randomization. At least 1 measurement prior to start of trial treatment was done in order to determine when to stop initial parenteral therapy and when to start trial treatment.

<sup>o</sup> Assessment of INR for patients randomized to warfarin. Daily INR measurements were performed from just prior to start of treatment until concomitant heparin treatment was stopped. INR measurements were then taken at least every 2 weeks for the first 3 months and monthly thereafter.

<sup>p</sup> At Visit 2, information is collected on any new VTEs since signing of consent.

<sup>q</sup> Completion of patient participation. Patients who completed the full treatment period of 169 days completed their participation at the follow-up visit (Visit 6).

<sup>r</sup> Completion of patient participation. Patients who discontinued trial medication early after the follow-up visit were followed for survival, for major bleeding events, VTE events and any other adverse events until Day 176 (25 weeks) after randomization. They completed participation at that moment.

Abbreviations: AC, Adjudication Committee; CVT, cerebral venous thrombosis; DVT, deep vein thrombosis; ECG, electrocardiography; EOT, end of treatment; INR, international normalized ratio; ISF, investigator site file; MR, magnetic resonance; MRI, magnetic resonance imaging; VKA, vitamin K antagonist; VTE, venous thrombotic event.



## eAppendix 4. Definitions of Outcomes

- Venous thrombotic events (VTE)
- Cerebral venous thrombosis (CVT)
  - New neurological signs/symptoms or worsening of previous signs/symptoms with new CVT on neuroimaging
- Deep venous thrombosis (DVT) (of any limb)
  - Documented by venous compression ultrasonography, venography, or at autopsy
- Splanchnic vein thrombosis
  - Thrombus or absence of flow in the extrahepatic portal veins or mesenteric veins as shown by duplex-Doppler ultrasound, or contrast-enhanced CT scan, or MRI
- Pulmonary embolism
  - Intraluminal filling defect in segmental or more proximal branches on spiral CT scan or an intraluminal filling defect or an extension of an existing defect or a sudden cut-off of vessels more than 2.5 mm in diameter on the pulmonary angiogram or a perfusion defect of at least 75% of a segment with a local normal ventilation result (high-probability) on ventilation/perfusion lung scan or inconclusive spiral CT, pulmonary angiography or lung scintigraphy with demonstration of DVT in the lower extremities by compression ultrasonography or venography, or at autopsy

### Cerebral venous recanalization

Cerebral venous recanalization was assessed following the thrombus load concept:<sup>1</sup>

1. At baseline and at the end of treatment, occlusion of individual cerebral veins and sinuses were scored as follows: 1 = full occlusion; 0 = no occlusion or partial occlusion.
2. This score was applied to each of the veins and sinuses: superior sagittal sinus, straight sinus, cavernous sinus, left jugular vein, and right jugular vein were each scored individually (ie, each was scored as either 0 or 1); right lateral transverse and sigmoid sinus were scored together (ie, 0 points if neither is fully occluded; 1 point if at least 1 of them is fully occluded); left lateral transverse and sigmoid sinus were scored together; superior petrous sinus and inferior petrous sinus were scored together; deep venous system was scored as a group, irrespective of the number of occluded veins (ie, 0 points if none is fully occluded; 1 point if at least 1 is fully occluded); superficial cortical veins were scored as a group, irrespective of the number of occluded veins; cerebellar veins were scored as a group system, irrespective of the number of occluded veins.
3. For each individual patient a total score (thrombus load) was calculated at baseline and at the end of treatment.
4. A recanalization score was calculated for each patient as the difference between the baseline total score and the end-of-treatment total score.

### New hemorrhagic brain lesion or worsening of the hemorrhagic component of a baseline lesion

- This was assessed by comparing repeated neuroimaging that is routinely performed if the patient has a neurological worsening during the trial, or at the end-of-treatment visit, to the baseline image (ie, to the neuroimaging that established the diagnosis of CVT). The comparison of images and the categorization of the lesions was done by the adjudication committee.
- Hemorrhagic brain lesions at baseline and during treatment/at end-of-treatment visit were categorized as indicated on p.10, according to the definitions as recommended by von Kummer et al (2015).<sup>2</sup> Any new hemorrhagic brain lesion was categorized as Class 3 (intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage). If there was more than 1 hemorrhagic lesion present on imaging, the category of the most severe lesion was assigned.

### Major bleed

- Major bleed was defined according to the ISTH definition<sup>3</sup> as:
  - Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome and/or

bleeding associated with a reduction in hemoglobin of at least 2 g/dL (1.24 mmol/L) within 24 hours, or leading to transfusion of 2 or more units of blood or packed red cells and/or fatal bleed.

### **Life-threatening bleed**

- Life-threatening bleed was defined as:
  - Symptomatic intracranial bleed and/or reduction in hemoglobin of at least 5 g/dL and/or transfusion of at least 4 units of blood or packed cells, associated with hypotension requiring the use of i.v. inotropic agents and/or necessitating surgical intervention.

### **Intracranial hemorrhage**

- Intracerebral, subdural, epidural, or subarachnoid hemorrhages.

### **Fatal bleeding**

- Bleeding event that is the primary cause of death or contributing directly to death (as adjudicated by the adjudication committee).

### **Clinically relevant non-major bleeding events**

- A clinically overt bleed that does not meet the criteria for a major bleed but prompts a clinical response, leading to at least 1 of the following: a hospital admission (at least 1 overnight stay) for bleeding; a physician-guided medical or surgical treatment for bleeding; a physician-guided change, interruption, or discontinuation of trial medication.

### **Any bleed**

- Sum of all major and non-major bleeds.

### **References**

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2. von Kummer R, Broderick JP, Campbell BCV, et al. The Heidelberg Bleeding Classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46(10):2981-2986.
3. Schulman S, Kearon C; Subcommittee on Control of Anticoagulation of the Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis. Definition of major bleeding in clinical investigations of antihaemostatic medicinal products in non-surgical patients. *J Thromb Haemost*. 2005;3(4):692-694.

## **eAppendix 5. Committees**

### **STEERING COMMITTEE**

José M Ferro (Chair), Jonathan M Coutinho, Francesco Dentali, Hans-Christoph Diener, Adam Kobayashi, Paul Reilly (replaced Marc Desch on April 24, 2017), Mandy Frässdorf, Holger Huisman

### **OUTCOME ADJUDICATION COMMITTEE**

Prof. Saskia Middeldorp, Amsterdam, Netherlands; Prof. Martin Grond, Siegen, Germany (efficacy and safety events)

Prof. Olav Jansen, Kiel, Germany; Prof. Martin Bendszus, Heidelberg, Germany (neuroimaging outcomes)

### **DATA MONITORING SAFETY COMMITTEE**

Prof. Kennedy Lees, Glasgow, UK; Prof. Rüdiger von Kummer, Dresden, Germany; Prof. JGP Tijssen, Naarden, the Netherlands; Prof. Paulus Kirchhof, Birmingham, UK

## eAppendix 6. Categorization of Hemorrhagic Brain Lesions

Class	Type	Description
1		Hemorrhagic transformation of infarcted brain tissue
1a	HI-1	Scattered small petechiae, no mass effect
1b	HI-2	Confluent petechiae, no mass effect
1c	PH-1	Hematoma within infarcted tissue, occupying <30%, no substantive mass effect
2		Intracerebral hemorrhage within and beyond infarcted brain tissue
	PH-2	Hematoma occupying 30% or more of the infarcted tissue, with obvious mass effect
3		Intracerebral hemorrhage outside the infarcted brain tissue or intracranial-extracerebral hemorrhage
3a		Parenchymal hematoma remote from infarcted brain tissue
3b		Intraventricular hemorrhage
3c		Subarachnoid hemorrhage
3d		Subdural hemorrhage

Abbreviations: HI, hemorrhagic infarction; PH, parenchymatous hematoma.

### Reference

von Kummer R, Broderick JP, Campbell BCV, et al. The Heidelberg Bleeding Classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke*. 2015;46(10):2981-2986.