



Clinical trial results:

Réversion préventive systématique versus réversion en cas d'hémorragie intracrânienne chez les patients prenant un traitement antivitamine K et venant de subir un traumatisme crânien léger

Summary

EudraCT number	2013-000421-31
Trial protocol	FR
Global end of trial date	03 September 2020

Results information

Result version number	v1 (current)
This version publication date	07 January 2024
First version publication date	07 January 2024

Trial information

Trial identification

Sponsor protocol code	PHRC2012-02
-----------------------	-------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01961804
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU Angers
Sponsor organisation address	4 Rue Larrey, ANGERS, France,
Public contact	Direction de la Recherche, CHU d'Angers, +33 0241356825, begable@chu-angers.fr
Scientific contact	Direction de la Recherche, CHU d'Angers, +33 0241356825, begable@chu-angers.fr

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	12 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	28 February 2020
Global end of trial reached?	Yes
Global end of trial date	03 September 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Démontrer que la réalisation d'une réversion systématique préventive des patients traumatisés crâniens légers (CGS de 13 à 15), permet une diminution significative des hémorragies intracrâniennes comparativement à une réversion réalisée qu'après constatation d'une hémorragie post-traumatique sur une imagerie cérébrale.

Protection of trial subjects:

no specific protection, patient with suspected intracranial bleeding

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 March 2014
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	France: 202
Worldwide total number of subjects	202
EEA total number of subjects	202

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)	0
Adults (18-64 years)	2
From 65 to 84 years	49
85 years and over	151

Subject disposition

Recruitment

Recruitment details:

patients admitted in the emergency department for head trauma under VKA treatment

Pre-assignment

Screening details:

VKA treatment

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

Routine care

Arm type	No intervention
No investigational medicinal product assigned in this arm	
Arm title	Interventionnal

Arm description:

Kanokad before CT-Scan

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

Dosage and administration details:

25UI/kg

Number of subjects in period 1	Control	Interventionnal
Started	101	101
Completed	99	98
Not completed	2	3
Consent withdrawn by subject	-	2
Protocol deviation	2	1

Baseline characteristics

Reporting groups

Reporting group title	Control
Reporting group description: Routine care	
Reporting group title	Interventionnal
Reporting group description: Kanokad before CT-Scan	

Reporting group values	Control	Interventionnal	Total
Number of subjects	101	101	202
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	1	1	2
From 65-84 years	22	27	49
85 years and over	78	73	151
Age continuous Units: years			
arithmetic mean	91	90	-
standard deviation	± 7.9	± 8.2	-
Gender categorical Units: Subjects			
male	46	52	98
female	55	49	104

Subject analysis sets

Subject analysis set title	Control arm
Subject analysis set type	Intention-to-treat
Subject analysis set description: Groups don't show significant differences in the characteristics of inclusion or compliance with the assigned intervention and other aspects of managing	
Subject analysis set title	Interventional arm
Subject analysis set type	Intention-to-treat
Subject analysis set description: Groups don't show significant differences in the characteristics of inclusion or compliance with the assigned intervention and other aspects of managing	

Reporting group values	Control arm	Interventional arm	
Number of subjects	99	98	
Age categorical			
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)	1	1	
From 65-84 years	26	22	
85 years and over	71	76	
Age continuous			
Units: years			
arithmetic mean	90	91	
standard deviation	± 8.2	± 7.9	
Gender categorical			
Units: Subjects			
male	51	44	
female	47	55	

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
Routine care	
Reporting group title	Interventional
Reporting group description:	
Kanokad before CT-Scan	
Subject analysis set title	Control arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Groups don't show significant differences in the characteristics of inclusion or compliance with the assigned intervention and other aspects of managing	
Subject analysis set title	Interventional arm
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Groups don't show significant differences in the characteristics of inclusion or compliance with the assigned intervention and other aspects of managing	

Primary: intracranial hemorrhage

End point title	intracranial hemorrhage
End point description:	
End point type	Primary
End point timeframe:	
between +20h and +28h after inclusion	

End point values	Control	Interventional	Control arm	Interventional arm
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	99	98	99	98
Units: individual	99	98	99	98

Statistical analyses

Statistical analysis title	statistical analysis
Comparison groups	Control arm v Interventional arm
Number of subjects included in analysis	197
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.215
Method	Fisher exact
Parameter estimate	Odds ratio (OR)
Point estimate	0.48

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.14
upper limit	1.44
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

7 March 2014 to 7 September 2020

Assessment type	Systematic
-----------------	------------

Dictionary used

Dictionary name	MedDRA
-----------------	--------

Dictionary version	8.1
--------------------	-----

Reporting groups

Reporting group title	Control
-----------------------	---------

Reporting group description: -

Reporting group title	Kanokad
-----------------------	---------

Reporting group description: -

Serious adverse events	Control	Kanokad	
Total subjects affected by serious adverse events			
subjects affected / exposed	36 / 101 (35.64%)	28 / 98 (28.57%)	
number of deaths (all causes)	24	13	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lymphoma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Prostate cancer metastatic			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Haematoma			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma muscle			

subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemothorax			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Ischaemic stroke			
subjects affected / exposed	2 / 101 (1.98%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 2	1 / 1	
deaths causally related to treatment / all	0 / 0	1 / 1	
Myocardial infarction			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peripheral ischaemia			
subjects affected / exposed	0 / 101 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Rectal haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Shock haemorrhagic			

subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 101 (0.99%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Wound haematoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Death			
subjects affected / exposed	2 / 101 (1.98%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 2	
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Oedema peripheral			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			

Acute pulmonary oedema			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bronchopneumopathy			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lung disorder			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			
subjects affected / exposed	3 / 101 (2.97%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory distress			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Craniocerebral injury			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Fall			
subjects affected / exposed	4 / 101 (3.96%)	4 / 98 (4.08%)	
occurrences causally related to treatment / all	0 / 4	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 0	

Femoral neck fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Head injury			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hip fracture			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Bradyarrhythmia			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac arrest			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	4 / 101 (3.96%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardio-respiratory arrest			

subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Right ventricular failure			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Altered state of consciousness			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebellar syndrome			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Coma			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Epilepsy			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Generalised tonic-clonic seizure			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Neurological decompensation			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Seizure			

subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Cutaneous vasculitis			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 101 (0.00%)	2 / 98 (2.04%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthritis			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Bone lesion			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Epiglottitis			

subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyelonephritis acute			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	Control	Kanokad	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 101 (11.88%)	7 / 98 (7.14%)	
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 101 (0.00%)	1 / 98 (1.02%)	
occurrences (all)	0	1	
Vascular disorders			
epistaxis			
subjects affected / exposed	1 / 101 (0.99%)	1 / 98 (1.02%)	
occurrences (all)	1	1	
Haematoma			
subjects affected / exposed	2 / 101 (1.98%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Soft tissue haemorrhage			
subjects affected / exposed	1 / 101 (0.99%)	0 / 98 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	2 / 101 (1.98%)	0 / 98 (0.00%)	
occurrences (all)	2	0	
Cardiac disorders			

Cardiac failure subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	1 / 98 (1.02%) 1	
Nervous system disorders Neurological examination abnormal subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	0 / 98 (0.00%) 0	
Myositis subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	1 / 98 (1.02%) 1	
Blood and lymphatic system disorders Anaemia subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	0 / 98 (0.00%) 0	
General disorders and administration site conditions Discomfort subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	0 / 98 (0.00%) 0	
Musculoskeletal and connective tissue disorders Arthritis subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	0 / 98 (0.00%) 0	
Infections and infestations Urinary tract infection bacterial subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	1 / 98 (1.02%) 1	
Urinary tract infection subjects affected / exposed occurrences (all)	0 / 101 (0.00%) 0	1 / 98 (1.02%) 1	
Urinary retention subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	1 / 98 (1.02%) 1	
Bronchitis subjects affected / exposed occurrences (all)	1 / 101 (0.99%) 1	0 / 98 (0.00%) 0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 December 2013	addition of ANSM requests and clarification on randomization
21 July 2014	primary outcome deadline updated
17 July 2015	Inclusion and non-inclusion criteria updated
25 September 2015	Updated list of associated centers and modified consent formatting
02 February 2016	extended inclusion period
26 April 2016	New study site
20 September 2016	Update of investigator centers (opening and closing), change of principal investigator
28 February 2017	Increased inclusion period and updated list of associated centers
13 June 2017	Closure of investigator center
27 December 2017	Closure of investigator centers and change in inclusion criteria for head injury
27 November 2018	Increased inclusion period, RGPD compliance, update of investigator centers (opening and closing) and change of principal investigator
11 September 2019	Change of principal investigators, closure of investigating centers

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported