



## Clinical trial results:

### Effects of perioperative administration of dexamethasone on postoperative complications and mortality after non-cardiac major surgery : a randomized, multicentre, double blind, study

#### Summary

EudraCT number	2017-000442-21
Trial protocol	FR
Global end of trial date	16 April 2019

#### Results information

Result version number	v1 (current)
This version publication date	20 April 2022
First version publication date	20 April 2022
Summary attachment (see zip file)	Summary (MEDICAMENT Résumé du rapport final.pdf)

#### Trial information

##### Trial identification

Sponsor protocol code	RC17_0029
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03218553
WHO universal trial number (UTN)	-

Notes:

##### Sponsors

Sponsor organisation name	CHU de Nantes
Sponsor organisation address	5,Allée de l'île Gloriette, Nantes, France,
Public contact	June FORTIN, CHU de Nantes, 0033 253482844, bp-prom-reglu@chu-nantes.fr
Scientific contact	June FORTIN, CHU de Nantes, 0033 253482844, bp-prom-regl@chu-nantes.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:

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**Results analysis stage**

Analysis stage	Final
Date of interim/final analysis	05 November 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	16 April 2019
Global end of trial reached?	Yes
Global end of trial date	16 April 2019
Was the trial ended prematurely?	No

Notes:

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**General information about the trial**

Main objective of the trial:

Evaluate the effectiveness of perioperative administration of corticosteroid to reduce postoperative morbidity and mortality in patients undergoing major non-cardiac surgery

Protection of trial subjects:

Patients were informed in complete and faithful terms and in understandable language of the objectives and constraints of the study, the potential risks, the required observation and safety measures, and their right to refuse to participate in the study or to revoke their consent at any time.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	06 November 2017
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

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**Population of trial subjects****Subjects enrolled per country**

Country: Number of subjects enrolled	France: 1222
Worldwide total number of subjects	1222
EEA total number of subjects	1222

Notes:

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**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)	289
From 65 to 84 years	885
85 years and over	48

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

All consecutive adult patients requiring major surgery with an expected duration  $\geq 90$  minutes, provided they satisfied at least 1 of the high-risk criteria will be assessed for eligibility.

### Period 1

Period 1 title	Period 1 (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator

Blinding implementation details:

All members of the surgical unit, including the anesthesiologist and the surgeon, will remain blinded to the allocated treatment group.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Experimental group

Arm description:

dexamethasone: first dose: 0,2mg.kg-1 at the end of the surgical procedure, second dose (0,2mg.kg-1) 24 hours after the surgery

Arm type	Experimental
Investigational medicinal product name	DEXAMETHASONE
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

DESAMETHASONE MYLAN 20 mg/ml

2 times in 24 Hours : the first one at the end of surgery and the second one 24 Hours after the surgery

<b>Arm title</b>	Control group : placebo
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Arm description:

administration of a first dose of placebo dexamethasone given intravenously just after surgery. A second dose (0.2 mg.kg-1) is given intravenously at day +1

Arm type	Placebo
Investigational medicinal product name	CHLORURE DE SODIUM
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

CHLORURE DE SODIUM LAVOISIER 0.9 POUR CENT

2 times in 24 Hours : the first one at the end of surgery and the second one 24 Hours after the surgery

<b>Number of subjects in period 1</b>	Experimental group	Control group : placebo
Started	613	609
Completed	601	593
Not completed	12	16
Surgery Cancelled	-	3
Did not receive injection	-	4
UNKNOWN	5	-
FORGET	1	-
Protocol deviation	6	9

## Baseline characteristics

### Reporting groups

Reporting group title	Experimental group
Reporting group description: dexamethasone: first dose: 0,2mg.kg-1 at the end of the surgical procedure, second dose (0,2mg.kg-1) 24 hours after the surgery	
Reporting group title	Control group : placebo
Reporting group description: administration of a first dose of placebo dexamethasone given intravenously just after surgery. A second dose (0.2 mg.kg-1) is given intravenously at day +1	

Reporting group values	Experimental group	Control group : placebo	Total
Number of subjects	613	609	1222
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)	155	134	289
From 65-84 years	435	450	885
85 years and over	23	25	48
Gender categorical Units: Subjects			
Female	223	227	450
Male	390	382	772

### Subject analysis sets

Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The main analysis of the primary outcome was conducted in the modified intention-to-treat population, defined as all randomised participants except those who would have no longer been considered eligible for randomisation at the time of first treatment injection or who would never had any injection of the study treatment.	

Reporting group values	mITT		
Number of subjects	1184		
Age categorical Units: Subjects			
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) From 65-84 years 85 years and over			
Gender categorical Units: Subjects			
Female	436		
Male	748		

## End points

### End points reporting groups

Reporting group title	Experimental group
Reporting group description: dexamethasone: first dose: 0,2mg.kg-1 at the end of the surgical procedure, second dose (0,2mg.kg-1) 24 hours after the surgery	
Reporting group title	Control group : placebo
Reporting group description: administration of a first dose of placebo dexamethasone given intravenously just after surgery. A second dose (0.2 mg.kg-1) is given intravenously at day +1	
Subject analysis set title	mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description: The main analysis of the primary outcome was conducted in the modified intention-to-treat population, defined as all randomised participants except those who would have no longer been considered eligible for randomisation at the time of first treatment injection or who would never had any injection of the study treatment.	

### Primary: All cause mortality or major postoperative complications within 14 days after surgery

End point title	All cause mortality or major postoperative complications within 14 days after surgery
End point description: The primary outcome was a composite of postoperative complications or all cause mortality within 14 days after surgery, assessed in the modified intention-to-treat population (at least one treatment administered).	
End point type	Primary
End point timeframe: 14 DAYS	

End point values	Experimental group	Control group : placebo	mITT	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	595	589	1184	
Units: number of subjects				
number (not applicable)	101	117	218	

### Statistical analyses

Statistical analysis title	Primary analysis
Statistical analysis description: Data are analyzed with the use of logistic regression adjusted for stratification factors (cancer and type of surgery).	
Comparison groups	Control group : placebo v Experimental group

Number of subjects included in analysis	1184
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.05 <sup>[1]</sup>
Method	Regression, Logistic

Notes:

[1] - All statistical analyzes will take into account stratified randomization (cancer and type of surgery) as recommended in the CONSORT 2010 statement and in the literature [Moher D, Hopewell S, Schulz KF, Montori V, Gotzsche PC, Devereaux PJ, et al. C



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

28 Days

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	22.0
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### Reporting groups

Reporting group title	Experimental
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Reporting group description: -

Reporting group title	Placebo
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Reporting group description: -

Serious adverse events	Experimental	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	110 / 601 (18.30%)	108 / 593 (18.21%)	
number of deaths (all causes)	10	12	
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified			
subjects affected / exposed	0 / 601 (0.00%)	1 / 593 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	14 / 601 (2.33%)	11 / 593 (1.85%)	
occurrences causally related to treatment / all	1 / 14	2 / 12	
deaths causally related to treatment / all	0 / 1	0 / 3	
General disorders and administration site conditions			
General disorders and administration site conditions			
subjects affected / exposed	9 / 601 (1.50%)	4 / 593 (0.67%)	
occurrences causally related to treatment / all	2 / 10	0 / 4	
deaths causally related to treatment / all	0 / 2	0 / 0	
Reproductive system and breast disorders			

Reproductive system and breast disorders			
subjects affected / exposed	0 / 601 (0.00%)	1 / 593 (0.17%)	
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			
Respiratory, thoracic and mediastinal disorders			
subjects affected / exposed	24 / 601 (3.99%)	21 / 593 (3.54%)	
occurrences causally related to treatment / all	2 / 26	1 / 26	
deaths causally related to treatment / all	0 / 2	0 / 2	
Psychiatric disorders			
Psychiatric disorders			
subjects affected / exposed	0 / 601 (0.00%)	2 / 593 (0.34%)	
occurrences causally related to treatment / all	0 / 0	1 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Product issues			
subjects affected / exposed	1 / 601 (0.17%)	0 / 593 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Injury, poisoning and procedural complications			
subjects affected / exposed	19 / 601 (3.16%)	27 / 593 (4.55%)	
occurrences causally related to treatment / all	2 / 22	3 / 28	
deaths causally related to treatment / all	0 / 1	0 / 0	
Congenital, familial and genetic disorders			
Congenital , familial and genetic disorders			
subjects affected / exposed	0 / 601 (0.00%)	1 / 593 (0.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac disorder			

subjects affected / exposed	7 / 601 (1.16%)	2 / 593 (0.34%)	
occurrences causally related to treatment / all	0 / 7	0 / 2	
deaths causally related to treatment / all	0 / 2	0 / 1	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	4 / 601 (0.67%)	0 / 593 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Blood and lymphatic system disorders			
subjects affected / exposed	2 / 601 (0.33%)	1 / 593 (0.17%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Gastrointestinal disorders			
subjects affected / exposed	19 / 601 (3.16%)	21 / 593 (3.54%)	
occurrences causally related to treatment / all	4 / 22	1 / 27	
deaths causally related to treatment / all	0 / 0	0 / 3	
Hepatobiliary disorders			
Hepatobiliary disorder			
subjects affected / exposed	3 / 601 (0.50%)	3 / 593 (0.51%)	
occurrences causally related to treatment / all	0 / 3	2 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Skin and subcutaneous tissue disorders			
Skin and subcutaneous tissue disorders			
subjects affected / exposed	1 / 601 (0.17%)	2 / 593 (0.34%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Renal and urinary disorders			
subjects affected / exposed	4 / 601 (0.67%)	7 / 593 (1.18%)	
occurrences causally related to treatment / all	0 / 4	0 / 7	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Musculoskeletal and connective tissue disorders			

Musculoskeletal and connective tissue disorders			
subjects affected / exposed	2 / 601 (0.33%)	1 / 593 (0.17%)	
occurrences causally related to treatment / all	0 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infections and Infestations			
subjects affected / exposed	37 / 601 (6.16%)	31 / 593 (5.23%)	
occurrences causally related to treatment / all	13 / 42	9 / 34	
deaths causally related to treatment / all	0 / 2	0 / 2	
Metabolism and nutrition disorders			
Metabolism and nutrition disorders			
subjects affected / exposed	2 / 601 (0.33%)	5 / 593 (0.84%)	
occurrences causally related to treatment / all	0 / 3	1 / 5	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

<b>Non-serious adverse events</b>	Experimental	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	202 / 601 (33.61%)	212 / 593 (35.75%)	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
subjects affected / exposed	0 / 601 (0.00%)	1 / 593 (0.17%)	
occurrences (all)	0	1	
Vascular disorders			
Vascular disorders			
subjects affected / exposed	25 / 601 (4.16%)	17 / 593 (2.87%)	
occurrences (all)	25	17	
Surgical and medical procedures			
Surgical and medical procedures			
subjects affected / exposed	1 / 601 (0.17%)	1 / 593 (0.17%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
General disorders and administration site conditions			

subjects affected / exposed occurrences (all)	6 / 601 (1.00%) 6	14 / 593 (2.36%) 14	
Immune system disorders Immune system disorders subjects affected / exposed occurrences (all)	3 / 601 (0.50%) 3	0 / 593 (0.00%) 0	
Reproductive system and breast disorders Reproductive system and breast disorders subjects affected / exposed occurrences (all)	2 / 601 (0.33%) 2	1 / 593 (0.17%) 1	
Respiratory, thoracic and mediastinal disorders Respiratory, thoracic and mediastinal disorders subjects affected / exposed occurrences (all)	19 / 601 (3.16%) 19	19 / 593 (3.20%) 19	
Psychiatric disorders Psychiatric disorders subjects affected / exposed occurrences (all)	8 / 601 (1.33%) 8	5 / 593 (0.84%) 5	
Investigations Investigations subjects affected / exposed occurrences (all)	2 / 601 (0.33%) 2	5 / 593 (0.84%) 5	
Injury, poisoning and procedural complications Injury, poisoning and procedural complications subjects affected / exposed occurrences (all)	20 / 601 (3.33%) 20	24 / 593 (4.05%) 24	
Cardiac disorders Cardiac disorders subjects affected / exposed occurrences (all)	3 / 601 (0.50%) 3	6 / 593 (1.01%) 6	
Nervous system disorders Nervous system disorders subjects affected / exposed occurrences (all)	2 / 601 (0.33%) 2	3 / 593 (0.51%) 3	
Blood and lymphatic system disorders			

Blood and lymphatic system disorders subjects affected / exposed occurrences (all)	7 / 601 (1.16%) 7	7 / 593 (1.18%) 7	
Eye disorders Eye disorders subjects affected / exposed occurrences (all)	1 / 601 (0.17%) 1	0 / 593 (0.00%) 0	
Gastrointestinal disorders Gastrointestinal disorders subjects affected / exposed occurrences (all)	31 / 601 (5.16%) 31	36 / 593 (6.07%) 36	
Hepatobiliary disorders Hepatobiliary disorders subjects affected / exposed occurrences (all)	8 / 601 (1.33%) 8	5 / 593 (0.84%) 5	
Skin and subcutaneous tissue disorders Skin and subcutaneous tissue disorders subjects affected / exposed occurrences (all)	2 / 601 (0.33%) 2	0 / 593 (0.00%) 0	
Renal and urinary disorders Renal and urinary disorders subjects affected / exposed occurrences (all)	8 / 601 (1.33%) 8	16 / 593 (2.70%) 16	
Musculoskeletal and connective tissue disorders Musculoskeletal and connective tissue disorders subjects affected / exposed occurrences (all)	7 / 601 (1.16%) 7	5 / 593 (0.84%) 5	
Infections and infestations Infections and infestations subjects affected / exposed occurrences (all)	42 / 601 (6.99%) 42	38 / 593 (6.41%) 38	
Metabolism and nutrition disorders Metabolism and nutrition disorders subjects affected / exposed occurrences (all)	14 / 601 (2.33%) 14	15 / 593 (2.53%) 15	



## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
04 May 2018	Modification of the list of investigators with the deletion of investigator centres Modification of principal investigators and the addition of centers Modification of the pharmacovigilance part of the protocol with clarifications on the notification of SAEs. Clarifications of the statistical part Modification of the DSMB following the death of one of the members Details on the inclusion and non-inclusion criteria and the maximum dosage of dexamethasone used

Notes:

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported

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### Online references

<http://www.ncbi.nlm.nih.gov/pubmed/34078591>