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 Résume du rapport final.pdf)

Trial information

Trial identification

Sponsor protocol code	RC17_0029

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:

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:

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:

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:

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 ≥ 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
Arm title	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

Arm title	Control group : placebo

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

Number of subjects in period 1	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 [1]
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

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Experimental
Reporting group description: -	
Reporting group title	Placebo
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			
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 Infestions			
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 %

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

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

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