Clinical trial results:
Correction of Neonatal Glutathione by N-acetylcysteine in Pregnant Women at Risk of Premature Birth (GSH MAP)

Summary

EudraCT number	2017-003999-31
Trial protocol	FR
Global end of trial date	01 November 2021

Results information

Result version number	v1 (current)
This version publication date	09 September 2023
First version publication date	09 September 2023

Trial information

Trial identification

Sponsor protocol code	RC15_0476

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03596125
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU Nantes
Sponsor organisation address	5 allée de l'île Gloriette, Nantes, France, 44000
Public contact	Direction Recherche CHU de Nantes, CHU de Nantes, 0033 2 40 08 49 8, soizic.boinet@chu-nantes.fr
Scientific contact	Direction Recherche CHU de Nantes, CHU de Nantes, 0033 2 40 08 49 8, soizic.boinet@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	03 July 2023
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	01 November 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this project is to determine whether N-acetyl-cysteine supplementation in women with moderate or severe Threatened Premature Delivery corrects fetal blood glutathione deficiency at birth.

Protection of trial subjects:

Eligible patients are mothers admitted to Nantes University Hospital with severe or moderate MAP between 24 and 34 weeks' gestation. Following information, informed maternal consent after sufficient time for reflection, and inclusion in the study, patients will receive the treatment determined by randomisation.
As part of the study, patients will be monitored for the duration of NAC supplementation and until delivery, with collection of a venous cord blood sample to measure GSH (primary endpoint).
However, for reasons of safety and vigilance, the patient will be monitored until 72 hours post-partum.
In the event of transfer to another neonatology unit, monitoring should be continued by regular telephone contact with the peripheral hospital centre. Overall neonatal follow-up (via the hospitalisation report) will then be carried out by the investigation team in order to collate pathologies of interest within the framework of GSH-MAP: ECUN, SDR/DBP, retinopathy, HIV, etc.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	05 November 2018
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: 39
Worldwide total number of subjects	39
EEA total number of subjects	39

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)	39
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Pregnant patients diagnosed with severe or moderate MAP between 24 and 34 weeks' gestation who are over 18 years of age and who are being followed in the obstetrics department of the CHU de Nantes will be recruited after receiving a full explanation of the aims of the GSH-MAP research, as well as the potential benefits and risks of the protocol.

Pre-assignment

Screening details:

Subjects were included in Nantes Hospital

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	N-Acetylcystéine

Arm description:

Injectable NAC was administered only for severe MAP.

Arm type	Experimental
Investigational medicinal product name	n-acetylcystéine 1.5g/250mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Injection

Dosage and administration details:

Severe MAP patients will receive N-acetylcysteine in the form of an IV test bolus (1.5 g) over 1 hour, followed by an IV loading dose (7.5 g) over 4 hours and, finally, a maintenance dose -per os- of 6g per day for 7 days and a relay dose of 1.8g per day up to 37 weeks' gestation.

Investigational medicinal product name	n-acetylcystéine 7.5g/500mL
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Injection

Dosage and administration details:

Severe MAP patients will receive N-acetylcysteine in the form of an IV test bolus (1.5 g) over 1 hour, followed by an IV loading dose (7.5 g) over 4 hours and, finally, a maintenance dose -per os- of 6g per day for 7 days and a relay dose of 1.8g per day up to 37 weeks' gestation.

Investigational medicinal product name	N acetylcystéine 600mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Severe MAP patients will receive N-acetylcysteine in the form of an IV test bolus (1.5 g) over 1 hour, followed by an IV loading dose (7.5 g) over 4 hours and, finally, a maintenance dose -per os- of 6g per day for 7 days and a relay dose of 1.8g per day up to 37 weeks' gestation.

Arm title	Placebo

Arm description:	
Injectable placebo was administered only for severe MAP.	
Arm type	Placebo
Investigational medicinal product name	GLUCIDION G5
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Injection
Dosage and administration details:	
Injectable placebo will only be administered in cases of severe MAP.	
Investigational medicinal product name	Placebo comprimé blanc dragéifié (COOPER)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details:	
Moderate MAP patients will receive an oral placebo The per os switch will be made with the first meal following interruption of the IV route, with a minimum delay of 4 hours.	

Number of subjects in period 1	N-Acetylcystéine	Placebo
Started	20	19
Completed	20	19

Baseline characteristics

Reporting groups	
Reporting group title	N-Acetylcystéine
Reporting group description:	
Injectable NAC was administered only for severe MAP.	
Reporting group title	Placebo
Reporting group description:	
Injectable placebo was administered only for severe MAP.	

Reporting group values	N-Acetylcystéine	Placebo	Total
Number of subjects	20	19	39
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)	20	19	39
From 65-84 years	0	0	0
85 years and over	0	0	0
Age continuous Units: years			
median	31	29	
full range (min-max)	25.25 to 36	24.5 to 35.5	-
Gender categorical Units: Subjects			
Female	20	19	39
Male	0	0	0

Subject analysis sets	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
all patients randomized without violation of inclusion criteria.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
- meeting all inclusion/non-inclusion criteria - with at least 7 days of treatment (exclusion of 8 patients, ident. 3, 6 ,13, 17, 28, 31, 34, 37) - with venous cord blood sampling at delivery (4 exclusions, ident. 7, 11, 33, 39) - having taken the requested dose within the first 7 days (2 exclusions, ident. 2 and 10)	

Reporting group values	FAS	Per protocol	
Number of subjects	39	25	
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)	39	25	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	NK	NK	
full range (min-max)	NK to NK	NK to NK	
Gender categorical Units: Subjects			
Female	39	25	
Male	0	0	

End points

End points reporting groups

Reporting group title	N-Acetylcystéine
Reporting group description:	
Injectable NAC was administered only for severe MAP.	
Reporting group title	Placebo
Reporting group description:	
Injectable placebo was administered only for severe MAP.	
Subject analysis set title	FAS
Subject analysis set type	Full analysis
Subject analysis set description:	
all patients randomized without violation of inclusion criteria.	
Subject analysis set title	Per protocol
Subject analysis set type	Per protocol
Subject analysis set description:	
- meeting all inclusion/non-inclusion criteria - with at least 7 days of treatment (exclusion of 8 patients, ident. 3, 6 ,13, 17, 28, 31, 34, 37) - with venous cord blood sampling at delivery (4 exclusions, ident. 7, 11, 33, 39) - having taken the requested dose within the first 7 days (2 exclusions, ident. 2 and 10)	

Primary: glutathione concentration (GSH reduced form) in red blood cells from venous cord blood collected at birth

End point title	glutathione concentration (GSH reduced form) in red blood cells from venous cord blood collected at birth
End point description:	
End point type	Primary
End point timeframe:	
at birth	

End point values	N-Acetylcystéine	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	19		
Units: Micromolaire				
median (full range (min-max))	402 (355 to 501)	458.5 (326.25 to 640.75)		

Statistical analyses

Statistical analysis title	efficacité
Comparison groups	N-Acetylcystéine v Placebo

Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	superiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Mean difference (net)

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 7th day post partum or hospital discharge	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	24.1

Reporting groups	
Reporting group title	All patient randomized

Reporting group description: -

Serious adverse events	All patient randomized		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 14 (28.57%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Congenital, familial and genetic disorders			
Anal atresia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pre-eclampsia			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Retroplacental haematoma			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Third stage postpartum haemorrhage			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	All patient randomized		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	13 / 14 (92.86%)		
Congenital, familial and genetic disorders			
Glucose-6-phosphate dehydrogenase deficiency			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Pregnancy, puerperium and perinatal conditions			
Retained placenta or membranes			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Abdominal pain upper			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Diarrhoea			

subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Haemorrhoids			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Oesophageal pain			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	3 / 14 (21.43%)		
occurrences (all)	3		
Infections and infestations			
Amniotic cavity infection			
subjects affected / exposed	1 / 14 (7.14%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 14 (14.29%)		
occurrences (all)	2		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
15 March 2019	Modification of inclusion criteria
01 April 2020	Changes to RCP Extension Change number of subjects

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported