Clinical trial results:
Efficacy of IntraVenous ImmunoGlobulins in Toxic Shock Syndromes: a Paediatric Pilot Study (IVIG)

Summary

EudraCT number	2013-005509-29
Trial protocol	FR
Global end of trial date	19 April 2019

Results information

Result version number	v1 (current)
This version publication date	02 July 2022
First version publication date	02 July 2022

Trial information

Trial identification

Sponsor protocol code	2013-841

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02219165
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Hospices Civils de Lyon
Sponsor organisation address	3 Quai des Célestins, Lyon, France, 69002
Public contact	Valerie Plattner, Hospices Civils de Lyon, 33 0472406840, valerie.plattner@chu-lyon.fr
Scientific contact	Etienne Javouhey, Hospices Civils de Lyon, 33 472 129 735, etienne.javouhey@chu-lyon.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	06 May 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 March 2019
Global end of trial reached?	Yes
Global end of trial date	19 April 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluer la faisabilité d’une étude contrôlée randomisée portant sur l’efficacité des immunoglobulines humaines normales en phase aiguë d’un choc toxique (staphylococcique ou streptococcique) en pédiatrie.

Protection of trial subjects:

- Implementation of a DSMB
- Anesthetic patches were proposed to patients when an extra venous puncture was performed specifically for the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 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: 30
Worldwide total number of subjects	30
EEA total number of subjects	30

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)	3
Children (2-11 years)	13
Adolescents (12-17 years)	14
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Patients were assessed for eligibility upon arrival in the intensive care unit. Once the investigator has confirmed the diagnosis of toxic shock syndrome, he informed the parents (and the patient when possible) orally and in writing. Randomization was performed after their consent.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	IVIG 2 g/kg-Albumin

Arm description:

The treatment was given in a single administration. The IvIG were in vials at a concentration of 10g / 100 mL. As the dose assigned was 2 g / kg, patients had to be dispensed with 1 vial for every 5 kg of body weight. Dose charts and administration rates were made available to investigators. The initial infusion rate was 0.3 ml / kg bw / h. If well tolerated, the administration rate could be gradually increased to 4.8 ml / kg bw / h.

Arm type	Experimental
Investigational medicinal product name	Privigen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

The treatment was given in a single administration. The IvIG were in vials at a concentration of 10g / 100 mL. As the dose assigned was 2 g / kg, patients had to be dispensed with 1 vial for every 5 kg of body weight. Dose charts and administration rates were made available to investigators. The initial infusion rate was 0.3 ml / kg bw / h. If well tolerated, the administration rate could be gradually increased to 4.8 ml / kg bw / h.

Arm title	Vialebex® 4%

Arm description:

In order to maintain the blind, administration details were the same as those of IvIG. The treatment was given in a single administration. Patients were dispensed with 1 vial for every 5 kg of body weight. The albumin was in vials at a concentration of 4 g / 100 mL, thus the dose in this arm was 0,8 g / kg. The same dose charts and administration rates were made available to investigators. The initial infusion rate was 0.3 ml / kg bw / h. If well tolerated, the administration rate could be gradually increased to 4.8 ml / kg bw / h.

Arm type	Placebo
Investigational medicinal product name	Vialebex
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Dosage and administration details (frequency of dosing, formulation details, etc) : In order to maintain the blind, administration details were the same as those of IvIG. The treatment was given in a single

administration. Patients were dispensed with 1 vial for every 5 kg of body weight. The albumin was in vials at a concentration of 4 g / 100 mL, thus the dose in this arm was 0,8 g / kg. The same dose charts and administration rates were made available to investigators. The initial infusion rate was 0.3 ml / kg bw / h. If well tolerated, the administration rate could be gradually increased to 4.8 ml / kg bw / h.

Number of subjects in period 1	IVIG 2 g/kg-Albumin	Vialebex® 4%
Started	15	15
Completed	14	13
Not completed	1	2
Consent withdrawn by subject	1	-
Lost to follow-up	-	2

Baseline characteristics

Reporting groups

Reporting group title	Overall trial

Reporting group description: -

Reporting group values	Overall trial	Total	
Number of subjects	30	30	
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)	3	3	
Children (2-11 years)	13	13	
Adolescents (12-17 years)	14	14	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
median	10.6		
inter-quartile range (Q1-Q3)	4 to 14.1	-	
Gender categorical Units: Subjects			
Female	15	15	
Male	15	15	

Subject analysis sets

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All the patients who signed the informed consent.

Reporting group values	Full Analysis Set		
Number of subjects	30		
Age categorical Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	0		
Newborns (0-27 days)	0		
Infants and toddlers (28 days-23 months)	3		
Children (2-11 years)	13		
Adolescents (12-17 years)	14		
Adults (18-64 years)	0		

From 65-84 years	0		
85 years and over	0		

Age continuous			
Units: years			
median	10.6		
inter-quartile range (Q1-Q3)	4 to 14.1		
Gender categorical			
Units: Subjects			
Female	15		
Male	15		

End points

End points reporting groups

Reporting group title	IVIG 2 g/kg-Albumin

Reporting group description:

The treatment was given in a single administration. The IvIG were in vials at a concentration of 10g / 100 mL. As the dose assigned was 2 g / kg, patients had to be dispensed with 1 vial for every 5 kg of body weight. Dose charts and administration rates were made available to investigators. The initial infusion rate was 0.3 ml / kg bw / h. If well tolerated, the administration rate could be gradually increased to 4.8 ml / kg bw / h.

Reporting group title	Vialebex® 4%

Reporting group description:

In order to maintain the blind, administration details were the same as those of IvIG. The treatment was given in a single administration. Patients were dispensed with 1 vial for every 5 kg of body weight. The albumin was in vials at a concentration of 4 g / 100 mL, thus the dose in this arm was 0,8 g / kg. The same dose charts and administration rates were made available to investigators. The initial infusion rate was 0.3 ml / kg bw / h. If well tolerated, the administration rate could be gradually increased to 4.8 ml / kg bw / h.

Subject analysis set title	Full Analysis Set
Subject analysis set type	Full analysis

Subject analysis set description:

All the patients who signed the informed consent.

Primary: Feasibility

End point title	Feasibility[1]

End point description:

End point type	Primary

End point timeframe:

Day 1

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical test in this study as it's only a descriptive analysis

End point values	IVIG 2 g/kg-Albumin	Vialebex® 4%	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	15	30	
Units: Recruitment rate	61	61	61	

Statistical analyses

No statistical analyses for this end point

Primary: Protocol deviations rate

End point title	Protocol deviations rate[2]

End point description:

End point type	Primary

End point timeframe:

PICU discharge

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical test in this study as it's only a descriptive analysis

End point values	IVIG 2 g/kg-Albumin	Vialebex® 4%	Full Analysis Set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	15	15	30	
Units: rate	3	5	8	

Statistical analyses

No statistical analyses for this end point

Primary: Missing data rate

End point title	Missing data rate[3]

End point description:

End point type	Primary

End point timeframe:

month 12

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: There is no statistical test in this study as it's only a descriptive analysis

End point values	IVIG 2 g/kg-Albumin	Vialebex® 4%		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	15	15		
Units: rate	1	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

At day 1, day 2, day 3, day 4, day 5, PICU discharge, day 60, month 12

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	NA

Reporting groups

Reporting group title	Total

Reporting group description: -

Serious adverse events	Total		
Total subjects affected by serious adverse events			
subjects affected / exposed	9 / 30 (30.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Cardiac disorders			
Left ventricular dysfunction			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pericarditis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Pain			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Appendicitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Respiratory, thoracic and mediastinal disorders			
Pleural effusion			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Compartment syndrome			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Fasciitis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arthritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hypoxic-ischaemic encephalopathy			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Total		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	21 / 30 (70.00%)		
Injury, poisoning and procedural complications			
Limb injury			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Vascular disorders			

Hypertension			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Surgical and medical procedures			
Continuous haemodiafiltration			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Hyperthermia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Gastroenteritis			
subjects affected / exposed	3 / 30 (10.00%)		
occurrences (all)	3		
Vomiting			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Skin and subcutaneous tissue disorders			
Skin exfoliation			
subjects affected / exposed	8 / 30 (26.67%)		
occurrences (all)	8		
Diffuse alopecia			
subjects affected / exposed	2 / 30 (6.67%)		
occurrences (all)	2		
Pruritus			

subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Rash erythematous			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Rash maculo-papular			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Infections and infestations			
Ear infection			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Escherichia pyelonephritis			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Hypernatraemia			
subjects affected / exposed	1 / 30 (3.33%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
18 December 2015	- 12-month increase in the length of recruitment - Details provided in the protocol (dose of treatment administered to patients whose BMI for age is <3 ° percentile or> 97 ° percentile; nature of the data collected between Day 2 and Day 5 ; nature of the deviations from the protocol that will be used in the decision-making process concerning the implementation of the efficacy study; statistical analyses to be performed at the end of the trial)
25 April 2016	- Kawasaki disease added as a non-inclusion criterion - Adaptation of fluid bolus volume required for inclusion to the age of patients - Precision regarding the definition of patients mistakenly included (for staphylococcal shocks) - The sentences on how and when to administer study treatment have been reworded - Addition of a visit at Month 12

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported