Clinical trial results:
Tolerability and safety evaluation of the administration of Ig VENA at high infusion rates. Open label phase III study.

Summary

EudraCT number	2013-000961-36
Trial protocol	DE IT
Global end of trial date	31 March 2015

Results information

Result version number	v1 (current)
This version publication date	07 August 2016
First version publication date	07 August 2016

Trial information

Trial identification

Sponsor protocol code	KB057

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Kedrion S.p.A.
Sponsor organisation address	Località Ai Conti, Barga, Lucca, Italy, 55051
Public contact	Chiara Guarnieri, Kedrion SpA, 0039 0583767320, c.guarnieri@kedrion.com
Scientific contact	Chiara Guarnieri, Kedrion SpA, 0039 0583767320, c.guarnieri@kedrion.com

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	04 December 2014
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 December 2014
Global end of trial reached?	Yes
Global end of trial date	31 March 2015
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Evaluation of tolerability and safety of Ig VENA administered at high infusion rates

Protection of trial subjects:

According to the study protocol:
"Each infusion will be conducted at an increasing rate as follows:

- 20/30 minutes at 1 ml/kg/hr,
- 20/30 minutes at 2 ml/kg/hr,
- 20/30 minutes at 4 ml/kg/hr,
- 20/30 minutes at 6 ml/kg/hr,
- Until the end of the infusion at 8 ml/kg/hr

The rate of infusion will be increased only if the patients did not present side effects in the previous infusion speed.
For AEs that occur during infusion, the following data will be recorded:
- infusion rate in effect at the time of AE onset,
- time of onset of AEs and
- time of AEs change materially in intensity and/or resolve
If an infusional AE occurs during the infusion, the study staff will decrease the infusion rate every 15 minutes until a rate at which symptoms have subsided is reached. Should the reaction become intolerable, the infusion will be stopped. The subject will exit the study and go back to the treatment schemes adopted and tolerated before his entrance in the study.
In case of Adverse Event, patients will be managed according to the instructions given in the product SmPC and standard practice at the site".

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 January 2014
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	Germany: 6
Country: Number of subjects enrolled	Italy: 37
Worldwide total number of subjects	43
EEA total number of subjects	43

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)	43
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	43
Number of subjects completed	43

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Single arm

Arm description: -

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

Dosage and administration details:

Dosage
ID patients
0.2-0.8 g/kg (as reported in the SmPC). Subjects had to receive a total of 3 infusions of the IMP according to
their treatment scheme (every 3 or 4 weeks ± 4 days) as follows:
3-week scheme:
- Week 0/Infusion 1 (day 0);
- Week 3/Infusion 2 (day 21 ± 4)
- Week 6/Infusion 3 (day 42 ± 4)
4-week scheme:
- Week 0/Infusion 1 (day 0);
- Week 4/Infusion 2 (day 28 ± 4)
- Week 8/Infusion 3 (day 56 ± 4)

ITP patients
The two alternative treatment schedules reported in the SmPC were allowed:
0.8-1 g/kg given on day 1; this dose could be repeated once within 3 days, or
0.4 g/kg given daily for 2 to 5 days.

Method of administration
Infusions started at an initial rate of 1 ml/kg/hr for 20 minutes. If well tolerated, the rate of administration could
be increased to a maximum rate of 8 ml/kg/hr (2 ml/kg/hr; 4 ml/kg/hr; 6 ml/kg/hr; 8 ml/kg/hr) at 20/30 minutes
intervals (depending on dosage and/or body weight the patient could not reach the maximum infus

Number of subjects in period 1	Single arm
Started	43
Completed	42
Not completed	1
Physician decision	1

Baseline characteristics

Reporting groups

Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	43	43	
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)	43	43	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	44.7		
standard deviation	± 14.7	-	
Gender categorical Units: Subjects			
Female	20	20	
Male	23	23	

Subject analysis sets

Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis

Subject analysis set description:

Safety population included all enrolled patients who received the first infusion of IMP

Reporting group values	Safety Population		
Number of subjects	43		
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)	0		
Children (2-11 years)	0		
Adolescents (12-17 years)	0		
Adults (18-64 years)	43		

From 65-84 years	0		
85 years and over	0		

Age continuous			
Units: years			
arithmetic mean	44.7		
standard deviation	± 14.7		
Gender categorical			
Units: Subjects			
Female	20		
Male	23		

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description: -	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population included all enrolled patients who received the first infusion of IMP	

Primary: Verify that Ig VENA can be administered at higher infusion speed than for current SPC

End point title	Verify that Ig VENA can be administered at higher infusion speed than for current SPC[1]
End point description:	
End point type	Primary
End point timeframe:	
Evaluations during all study period	

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: Statistical Analysis conducted was descriptive only and for this reason we cannot fill in the fields related to this issue

End point values	Single arm			
Subject group type	Reporting group			
Number of subjects analysed	43			
Units: Local or systemic reaction				
number (not applicable)	55			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs reporting during all study period	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	All population (safety)

Reporting group description: -

Serious adverse events	All population (safety)		
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 43 (6.98%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Surgical and medical procedures			
Ileostomy			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Erysipelas			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Parvovirus infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 0.42 %

Non-serious adverse events	All population (safety)		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 43 (41.86%)		
Investigations			
Glucose urine present			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Platelet count decreased			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Injury, poisoning and procedural complications			
Lumbar vertebral fracture			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Headache			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Radiculopathy			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Somnolence			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Chest pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Fatigue			

subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Pyrexia			
subjects affected / exposed	4 / 43 (9.30%)		
occurrences (all)	5		
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Diarrhoea			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Frequent bowel movements			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Nausea			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Vomiting			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	4		
Dyspnoea			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Laryngeal discomfort			
subjects affected / exposed	3 / 43 (6.98%)		
occurrences (all)	3		
Productive cough			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Psychiatric disorders			

Insomnia			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Musculoskeletal and connective tissue disorders			
Back pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Musculoskeletal pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Myalgia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Neck pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Pain in extremity			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Infections and infestations			
Conjunctivitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Cystitis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Ear infection			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Influenza			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	2		
Rhinitis			

subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Sinusitis			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	3		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
12 November 2013	Protocol Amendment No. 1 was generated following requests of Ethic Committees from Germany (Hannover EC), and updated the study period, gave further specifications on exclusion of patients unable to provide the informed consent, and added the SF-36v2 Quality of Life Questionnaire both at Screening and Follow-up visits for ID and ITP patients. This Amendment was approved by German CA only (not by Italian CA)
19 December 2013	Protocol Amendment No. 2 was generated following requests of the Italian Health Authority (AIFA), and updated the study period, gave further specifications on the objectives of the study, on inclusion/exclusion criteria, on dosage and mode of administration of the IMP, added the SF-36 questionnaire, and corrected some other minor items on statistics, management of adverse events and references (some of changes above reported were the same requested from German EC and included in the Protocol Amendment 1
14 November 2014	Protocol Amendment No. 3 was generated following requests of Ethic Committe from Germany (Hannover EC) and from German CA (PEI), and updated the Statistical Analysis Plan (attached to the Study Protocol).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported