Clinical trial results:
Pharmacokinetics, efficacy, tolerability and safety evaluation of the therapy with subcutaneous immunoglobulin in the treatment of hypo or agammaglobulinaemic patients. Open label phase II/III study

Summary

EudraCT number	2010-020167-20
Trial protocol	IT
Global end of trial date	22 April 2013

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	KB047

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	Roberta Macchia, Kedrion SpA, +39 0583767326, r.macchia@kedrion.com
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Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-000454-PIP01-08
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	22 April 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2013
Global end of trial reached?	Yes
Global end of trial date	22 April 2013
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluation of pharmacokinetics, efficacy, and safety of Kedrion 16% subcutaneous immunoglobulin preparation (Kedrion SCIg)

Protection of trial subjects:

A Data Safety Monitoring Board (DSMB) was established and maintained active for the total study duration to have an independent scrutiny of the study and to guarantee of safety for those subjects who were recruited in the study.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 August 2011
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	Italy: 33
Worldwide total number of subjects	33
EEA total number of subjects	33

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)	5
Adolescents (12-17 years)	5
Adults (18-64 years)	23
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	33
Number of subjects completed	33

Period 1	
Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded
Arms	
Arm title	Single arm
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	SCIg 16%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Subcutaneous use

Dosage and administration details:

Following the enrolment in the study, each patient was treated with the IMP, at a dose of 100 mg/kg BW/week for 6 months (26 weeks).

Number of subjects in period 1	Single arm
Started	33
Completed	20
Not completed	13
Physician decision	5
Consent withdrawn by subject	1
Study interruption	6
Pregnancy	1

Baseline characteristics

Reporting groups	
Reporting group title	overall trial

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	33	33	
Age categorical			
Males or females aged between 2 and 60 years (≥ 2 and ≤ 60 years).			
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)	5	5	
Adolescents (12-17 years)	5	5	
Adults (18-64 years)	23	23	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Males and females			
Units: Subjects			
Female	13	13	
Male	20	20	

End points

End points reporting groups

Reporting group title	Single arm
Reporting group description: -	
Subject analysis set title	Intention to Treat Population
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Intention-to-treat (ITT) population defined as all patients who received the first infusion of IMP and who had at least one efficacy assessment, i.e. patients with availability of data on bacterial infections at any clinical visit	
Subject analysis set title	Per Protocol Population
Subject analysis set type	Per protocol
Subject analysis set description:	
Per-Protocol (PP) population, defined as all patients included in the ITT population who did not have any major protocol violation	
Subject analysis set title	Safety Population
Subject analysis set type	Safety analysis
Subject analysis set description:	
Safety population defined as all enrolled patients who received the first infusion of IMP	

Primary: Annualized rate of acute severe bacterial infections (SBIs)

End point title	Annualized rate of acute severe bacterial infections (SBIs)[1]
End point description:	
The number of severe acute bacterial infections and the number of patients with severe acute bacterial infection during the study were summarized using descriptive statistics and the severe acute bacterial infections annualized rate was presented. The limit of acceptability was 1 severe infection/patient/year.	
End point type	Primary
End point timeframe:	
For all the 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 for the Trial was descriptive only and for this reason we cannot fill in the fields related to this section

End point values	Single arm	Intention to Treat Population	Per Protocol Population	
Subject group type	Reporting group	Subject analysis set	Subject analysis set	
Number of subjects analysed	32	32	32	
Units: Acute SBIs				
number (not applicable)	0.223	0.223	0.223	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

For all the study period

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	14.0

Reporting groups

Reporting group title	safety population

Reporting group description: -

Serious adverse events	safety population		
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 33 (12.12%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Immune system disorders			
Anaphylactic shock			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Pneumonitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Bronchial pneumonia			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia bacterial			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	safety population		
Total subjects affected by non-serious adverse events subjects affected / exposed	30 / 33 (90.91%)		
Vascular disorders			
Cyanosis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Hypertension			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pallor			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Presyncope			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
General disorders and administration site conditions			
Application site erythema			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Chills			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	19		
Fatigue			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Induration			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Infusion site erythema			

subjects affected / exposed	15 / 33 (45.45%)		
occurrences (all)	139		
Infusion site induration			
subjects affected / exposed	10 / 33 (30.30%)		
occurrences (all)	117		
Infusion site pain			
subjects affected / exposed	14 / 33 (42.42%)		
occurrences (all)	54		
Infusion site pruritus			
subjects affected / exposed	11 / 33 (33.33%)		
occurrences (all)	74		
Infusion site swelling			
subjects affected / exposed	24 / 33 (72.73%)		
occurrences (all)	310		
Infusion site warmth			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	31		
Injection site urticaria			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	13		
Local swelling			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	2		
Malaise			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Pyrexia			
subjects affected / exposed	7 / 33 (21.21%)		
occurrences (all)	8		
Respiratory, thoracic and mediastinal disorders			
Bronchospasm			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Cough			

subjects affected / exposed occurrences (all) Dyspnoea subjects affected / exposed occurrences (all) Nasal obstruction subjects affected / exposed occurrences (all) Oropharyngeal pain subjects affected / exposed occurrences (all) Productive cough subjects affected / exposed occurrences (all) Rhinorrhoea subjects affected / exposed occurrences (all)	2 / 33 (6.06%) 4 1 / 33 (3.03%) 1 2 / 33 (6.06%) 2 2 / 33 (6.06%) 2 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Psychiatric disorders Panic attack subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Investigations Blood pressure decreased subjects affected / exposed occurrences (all) Body temperature increased subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	5 / 33 (15.15%) 22		
Ear and labyrinth disorders Ear pain subjects affected / exposed occurrences (all) Vertigo	1 / 33 (3.03%) 1		

subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Eye disorders Conjunctivitis subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Dyspepsia subjects affected / exposed occurrences (all) Gastrointestinal motility disorder subjects affected / exposed occurrences (all) Vomiting subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1 2 / 33 (6.06%) 2 3 / 33 (9.09%) 8 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1 1 / 33 (3.03%) 1		
Skin and subcutaneous tissue disorders Urticaria subjects affected / exposed occurrences (all)	 2 / 33 (6.06%) 2		
Renal and urinary disorders Dysuria subjects affected / exposed occurrences (all)	 1 / 33 (3.03%) 1		
Musculoskeletal and connective tissue disorders Arthralgia			

subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	3		
Back pain			
subjects affected / exposed	3 / 33 (9.09%)		
occurrences (all)	7		
Infections and infestations			
Bronchitis			
subjects affected / exposed	5 / 33 (15.15%)		
occurrences (all)	10		
Cystitis			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Gastroenteritis			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Influenza			
subjects affected / exposed	1 / 33 (3.03%)		
occurrences (all)	1		
Nasopharyngitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Oral herpes			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Pharyngitis			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		
Rhinitis			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	5		
Sinusitis			
subjects affected / exposed	4 / 33 (12.12%)		
occurrences (all)	4		
Upper respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)		
occurrences (all)	2		

Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		
Vulvovaginal candidiasis subjects affected / exposed occurrences (all)	1 / 33 (3.03%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
22 April 2013	Following the occurrence of the study discontinuation in 4 paediatric patients due to expected ADRs (3 of them possibly caused by allergic reactions, 1 of them was serious), the study sponsor examined, together with the DSMB and the study coordinator, the nature and the possible causes of the ADRs. Released tests were repeated on the IMP (anti-D antibodies, character, protein composition, molecular size distribution, IgA and IgM determination, Fc function of immunoglobulin, anti-A and anti-B haemagglutinins, pyrogens) and toxicity tests on the devices used for the SC administration were performed; they confirmed results in compliance with finished product specifications. In addition to the above tests, further non-routine tests (IgE determination, anticomplementary activity, prekallikrein activator, abnormal toxicity) have shown an IgE content of the batches used by patients with the above ADRs that was higher than that used in the other patients. Due to the impossibility of establishing a clear relationship between the batch used in the study and the occurrence of these ADRs (at that time the results of all analyses were not available) and that no other IMP batches for replacement of the only batch used in patients with ADRs would be rapidly available, the sponsor, in agreement with the DSMB and the study coordinator, decided to prematurely interrupt the study in order to maximise the patients protection and integrity. The decision on the interruption of the study was taken before all above analyses that led to the exclusion of causes linked with the used batch were completed. Additional comparative analyses have shown an even higher content of IgE in marketed SCIg products; for this reason Kedrion considers that this parameter was not responsible for the adverse reactions.	-

Notes:

Limitations and caveats

None reported