

**Clinical trial results:****Twelve-month study on the immunogenicity, safety, and efficacy of Zarzio®/Filgrastim HEXAL® in patients with severe chronic neutropenia****Summary**

EudraCT number	2011-001118-32
Trial protocol	DE SE
Global end of trial date	25 September 2015

**Results information**

Result version number	v1 (current)
This version publication date	06 April 2016
First version publication date	06 April 2016

**Trial information****Trial identification**

Sponsor protocol code	EP06-401
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**Additional study identifiers**

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01859637
WHO universal trial number (UTN)	-

Notes:

**Sponsors**

Sponsor organisation name	Sandoz GmbH
Sponsor organisation address	Biochemiestr. 10, Kundl, Austria, 6250
Public contact	Strategic Planning Biopharma Clinical Development, Sandoz , +49 8024 476 - 0, biopharma.clinicaltrials@sandoz.com
Scientific contact	Strategic Planning Biopharma Clinical Development, Sandoz , +49 8024 476 - 0, biopharma.clinicaltrials@sandoz.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 2015
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	25 September 2015
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

The primary objective of this study is to evaluate the immunogenicity of long-term treatment of SCN patients with Sandoz' filgrastim in terms of the incidence of anti-rhG-CSF antibodies.

Protection of trial subjects:

The patients were recommended to be treated in adherence with the SmPC of Zarzio®/Hexal filgrastim® regarding dosage and administration, contraindications, warnings, precautions and undesirable effects. The investigator was to promote compliance by instructing the patient to take the study drug exactly as prescribed and by stating that compliance was necessary for the patient's safety. The patient was instructed to contact the investigator, if he/she was unable to take the study drug as prescribed for any reason.

Background therapy:

NAP

Evidence for comparator:

NAP

Actual start date of recruitment	01 June 2011
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	Sweden: 4
Country: Number of subjects enrolled	Germany: 2
Worldwide total number of subjects	6
EEA total number of subjects	6

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)	5
From 65 to 84 years	1
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

First patient first visit: 05-Jul-2011

Last patient first visit: 12-Feb-2013

Last patient last visit: 13-Mar-2014

### Pre-assignment

Screening details:

The study enrolled adult patients with established congenital, cyclic or idiopathic severe chronic neutropenia. Eligible patients were either already on therapy with a rhG-CSF product or therapy-naïve patients who required rhG-CSF treatment.

### Period 1

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

Blinding implementation details:

NAP

### Arms

Arm title	Overall patients
Arm description: -	
Arm type	Experimental
Investigational medicinal product name	Zarzio®/Hexal filgrastim®
Investigational medicinal product code	EP2006
Other name	Sandoz filgrastim®, Hexal filgrastim®, Zarzio®
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Subcutaneous use

Dosage and administration details:

300 microg/0.5 ml (30 MU) in a syringe with a concentration of the compounded solution for filling of 600 microg/ml in a 0.5ml container

480 microg/0.5 ml (48 MU) in a syringe with a concentration of the compounded solution for filling of 960 microg/ml in a 0.5ml container

Number of subjects in period 1	Overall patients
Started	6
Completed	6

## Baseline characteristics

### Reporting groups

Reporting group title	Overall patients
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Reporting group description: -

Reporting group values	Overall patients	Total	
Number of subjects	6	6	
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)	5	5	
From 65-84 years	1	1	
85 years and over	0	0	
Age continuous			
Units: years			
median	45		
full range (min-max)	27 to 77	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	1	1	
Severe chronic neutropenia			
Units: Subjects			
Congenital neutropenia	1	1	
Cyclic neutropenia	1	1	
Idiopathic neutropenia	4	4	
G-CSF pre-treatment			
Units: Subjects			
Yes	6	6	
Height			
Units: cm			
arithmetic mean	165.7		
full range (min-max)	159 to 174	-	
Weight			
Units: kg			
arithmetic mean	74.3		
full range (min-max)	55 to 98	-	

## End points

### End points reporting groups

Reporting group title	Overall patients
Reporting group description: -	

### Primary: Absolute neutrophile count - values

End point title	Absolute neutrophile count - values <sup>[1]</sup>
End point description: This was done to ensure that patients were effectively treated to avoid neutropenic complications	
End point type	Primary
End point timeframe: At screening, baseline, week 6, month 3, month 6, month 9 and month 12 absolute neutrophile counts where measured	

#### 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: As the study was stopped after 6 patients based on a decision making process with the EMA, only descriptive analyses was performed

End point values	Overall patients			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: 10 <sup>9</sup> /L				
median (full range (min-max))				
Screening	2.3 (0.9 to 4.4)			
Baseline	3.3 (0.8 to 12.2)			
Week 6	10.2 (1 to 23.3)			
Month 3	2.3 (1.2 to 28.8)			
Month 6	2.9 (1.4 to 13.2)			
Month 9	4.2 (1.4 to 21.6)			
Month 12	4 (1.4 to 22.2)			

### Statistical analyses

No statistical analyses for this end point

### Secondary: Absolute neutrophile count - changes from baseline

End point title	Absolute neutrophile count - changes from baseline
End point description:	
End point type	Secondary

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End point timeframe:

Screening, week 6, month 3, month 6, month 9, month 12

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<b>End point values</b>	Overall patients			
Subject group type	Reporting group			
Number of subjects analysed	6			
Units: 10 <sup>9</sup> /L				
median (full range (min-max))				
Screening	-1.3 (-10.9 to 2.8)			
Week 6	6.9 (-11.2 to 16.4)			
Month 3	-0.2 (-11 to 25.5)			
Month 6	-0.7 (-10.8 to 12.4)			
Month 9	1.5 (-9.6 to 14.7)			
Month 12	1.6 (-10.8 to 18.9)			

### **Statistical analyses**

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No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

adverse events were recorded throughout the whole study duration

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	17.0
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### Reporting groups

Reporting group title	Overall patients
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Reporting group description: -

<b>Serious adverse events</b>	Overall patients		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 6 (16.67%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Renal and urinary disorders			
Nephrolithiasis	Additional description: patient 0101 experienced severe nephrolithiasis leading to hospitalization. No action was taken re IMP. Event resolved completely 17 days after onset. No suspected relationship to investigational medicinal product. Patient completed study as planned.		
subjects affected / exposed	1 / 6 (16.67%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Frequency threshold for reporting non-serious adverse events: 1 %

<b>Non-serious adverse events</b>	Overall patients		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 6 (100.00%)		
Investigations			
Neutrophil count decreased			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		
Surgical and medical procedures			
Tooth extraction			
subjects affected / exposed	1 / 6 (16.67%)		
occurrences (all)	1		

Nervous system disorders Headache subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 3		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)  Local swelling subjects affected / exposed occurrences (all)  Malaise subjects affected / exposed occurrences (all)	2 / 6 (33.33%) 2  1 / 6 (16.67%) 1  1 / 6 (16.67%) 1		
Gastrointestinal disorders Abdominal pain subjects affected / exposed occurrences (all)  Diarrhoea subjects affected / exposed occurrences (all)  Mouth ulceration subjects affected / exposed occurrences (all)  Vomiting subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1  1 / 6 (16.67%) 1  1 / 6 (16.67%) 2  1 / 6 (16.67%) 1		
Skin and subcutaneous tissue disorders Alopecia subjects affected / exposed occurrences (all)  Pruritus subjects affected / exposed occurrences (all)  Skin induration	1 / 6 (16.67%) 1  1 / 6 (16.67%) 1		

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 6 (50.00%) 5		
Genital infection fungal subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Gingivitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Groin abscess subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Herpes virus infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Mucosal infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 2		
Oral herpes subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Pneumonia subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Rash pustular subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 4		
Sinusitis			

subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Subcutaneous abscess subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Tonsillitis subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		
Upper respiratory tract infection subjects affected / exposed occurrences (all)	1 / 6 (16.67%) 1		

## **More information**

### **Substantial protocol amendments (globally)**

Were there any global substantial amendments to the protocol? No

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported