

**Clinical trial results:****A Phase III Study of M071754 - A Single-Blind Study in Patients With Infantile Spasms****Summary**

EudraCT number	2017-000230-62
Trial protocol	Outside EU/EEA
Global end of trial date	27 March 2014

Results information

Result version number	v1 (current)
This version publication date	20 July 2017
First version publication date	20 July 2017

Trial information**Trial identification**

Sponsor protocol code	EFC12369
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-
Other trial identifiers	Japan Pharmaceutical Information Center: JapicCTI-142558

Notes:

Sponsors

Sponsor organisation name	Alfresa Pharma Corporation
Sponsor organisation address	2-2-9 Kokumachi, Chuo-ku, Osaka , Japan, 540-8575
Public contact	Executive Officer, Alfresa Pharma Corporation, contact-suishin-1@kaihatsu-alfresa-pharma.com
Scientific contact	Executive Officer, Alfresa Pharma Corporation, contact-suishin-1@kaihatsu-alfresa-pharma.com
Sponsor organisation name	Sanofi K.K.
Sponsor organisation address	3-20-2 Nishi-Shinjuku, Shinjuku-ku, Tokyo , Japan, 163-1488
Public contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.com
Scientific contact	Trial Transparency Team, Sanofi aventis recherche & développement, contact-US@sanofi.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 July 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	27 March 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To investigate the efficacy of orally-administered vigabatrin in subjects with infantile spasms, using changes in spasms frequency as an endpoint. Also to investigate the safety and pharmacokinetics.

Protection of trial subjects:

The study was conducted by investigators experienced in the treatment of pediatric subjects. The parent(s) or guardian(s) as well as the children were fully informed of all pertinent aspects of the clinical trial as well as the possibility to discontinue at any time. In addition to the consent form for the parent(s)/guardian(s), an assent form in child-appropriate language was provided and explained to the child. Repeated invasive procedures were minimized. The number of blood samples as well as the amount of blood drawn were adjusted according to age and weight. A topical anesthesia may have been used to minimize distress and discomfort.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 January 2013
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	Japan: 15
Worldwide total number of subjects	15
EEA total number of subjects	0

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)	15
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 9 centers in Japan from 31 January 2013 to 27 March 2014. A total of 15 subjects were screened, out of which 13 were treated with the investigational drug.

Pre-assignment

Screening details:

The study consisted of 5 periods: a screening period, a dose adjustment period, a maintenance administration period, a dose tapering period, and a follow-up period.

Period 1

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

Arms

Arm title	Vigabatrin
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Arm description:

Water as Placebo (for Vigabatrin) twice a day for first 3 days in dose adjustment period. From Day 4, subjects received Vigabatrin 50 mg/kg/day to 150 mg/kg/day up to a maximum of 3 g/day, administered during three periods: dose adjustment period (6 days - 8 weeks), followed by maintenance administration period (2 weeks) and then dose tapering period (3 weeks).

Arm type	Experimental
Investigational medicinal product name	Vigabatrin
Investigational medicinal product code	M071754
Other name	
Pharmaceutical forms	Granules for oral solution in sachet
Routes of administration	Oral use

Dosage and administration details:

Dose adjustment period: Vigabatrin started from Day 4 at a dose of 50 mg/kg/day (25 mg/kg/day twice a day) as initial dose; dose increased by 25-50 mg/kg/day on Day 4 after the start of Vigabatrin, if spasms had not disappeared and there was no safety concern. Thereafter, similar dose increments until spasms disappeared or up to a maximum dose of 150 mg/kg/day (75 mg/kg twice a day; up to a maximum of 3 g/day). Maintenance administration period (MAP): subjects receiving appropriate dose in dose adjustment period or who reached a dose of 150 mg/kg/day (75 mg/kg/day twice a day; up to a maximum of 3 g/day) continued in MAP at the same dose for 2 weeks. Dose tapering period: Unless immediate discontinuation of Vigabatrin was required, the dose was tapered by 25-50 mg/kg/day every 3-4 days over a 3 week period.

Investigational medicinal product name	Water as Placebo (for Vigabatrin)
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral solution
Routes of administration	Oral use

Dosage and administration details:

Water as Placebo orally twice a day for first 3 days in the dose adjustment period.

Number of subjects in period 1^[1]	Vigabatrin
Started	13
Completed maintenance period	8
Entered dose tapering period	1
Completed	1
Not completed	12
Changed medication at Dose adjustment period	3
Changed medication at Maintenance period	1
Entered LTS12745 study	7
Investigator discretion at Dose adjustment period	1

Notes:

[1] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.

Justification: A total of 15 subjects were screened, out of which 13 were treated with the investigational drug. Subject Disposition and Baseline Characteristics are presented for the 13 subjects who received investigational drug.

Baseline characteristics

Reporting groups

Reporting group title	Overall Study
Reporting group description:	
Vigabatrin 50 mg/kg/day (25 mg/kg/day twice a day) to 150 mg/kg/day (75 mg/kg/day twice a day) up to a maximum dose of 3 g/day, administered during three periods: Dose adjustment period (6-8 weeks), followed by a maintenance administration period (2 weeks), followed by Dose tapering period (3 weeks).	

Reporting group values	Overall Study	Total	
Number of subjects	13	13	
Age categorical Units: Subjects			
Age continuous Units: months arithmetic mean standard deviation	13.8 ± 6.9	-	
Gender categorical Units: Subjects			
Female	7	7	
Male	6	6	
Aetiology of infantile spasms Units: Subjects			
Brain malformation	2	2	
Neurocutaneous syndrome	5	5	
Chromosomal/genetic abnormality	3	3	
Unknown	3	3	
Basis for diagnosis of infantile spasms: Series formation Units: Subjects			
Spasms - Series formation: Yes	13	13	
Spasms - Series formation: No	0	0	
Basis for diagnosis of infantile spasms: Hypsarrhythmia Units: Subjects			
Hypsarrhythmia: Yes	13	13	
Hypsarrhythmia: No	0	0	
Basis for diagnosis of infantile spasms: Developmental regression Units: Subjects			
Developmental regression: Yes	12	12	
Developmental regression: No	1	1	

End points

End points reporting groups

Reporting group title	Vigabatrin
Reporting group description: Water as Placebo (for Vigabatrin) twice a day for first 3 days in dose adjustment period. From Day 4, subjects received Vigabatrin 50 mg/kg/day to 150 mg/kg/day up to a maximum of 3 g/day, administered during three periods: dose adjustment period (6 days - 8 weeks), followed by maintenance administration period (2 weeks) and then dose tapering period (3 weeks).	

Primary: Percentage of Subjects With Reduction of At Least 50% From Baseline in Frequency of Spasms on Date of Assessment of Primary Endpoint of Spasms

End point title	Percentage of Subjects With Reduction of At Least 50% From Baseline in Frequency of Spasms on Date of Assessment of Primary Endpoint of Spasms ^[1]
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End point description:

Subjects who achieved at least 50% reduction from baseline in frequency of infantile spasms on the date of assessment of primary end point of spasms (defined as two days prior to the maintenance administration start date [Day -2 and Day -1]) were reported in this endpoint. Analysis was performed on efficacy analysis set that included all subjects who were treated with the investigational drug.

End point type	Primary
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End point timeframe:

2 days before the start of maintenance period (6 days - 8 weeks)

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 endpoint is descriptive in nature, no statistical analysis is provided.

End point values	Vigabatrin			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: percentage of subjects				
number (confidence interval 95%)	61.5 (31.6 to 86.1)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Reduction of At Least 50% From Baseline in Frequency of Spasms on Date of Assessment of Frequency of Spasms During Maintenance Administration Period

End point title	Percentage of Subjects With Reduction of At Least 50% From Baseline in Frequency of Spasms on Date of Assessment of Frequency of Spasms During Maintenance Administration Period
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End point description:

Subjects who achieved at least 50% reduction from baseline in frequency of infantile spasms on the date of assessment of frequency of spasms during the maintenance administration period (defined as a two day period comprising the maintenance administration period end date and the previous day) were reported in this endpoint. Analysis was performed on efficacy analysis set. Number of subjects

analyzed=subjects evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
End of 2 days of Maintenance period (3-10 weeks)	

End point values	Vigabatrin			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percentage of subjects				
number (confidence interval 95%)	88.9 (51.8 to 99.7)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Disappearance of Spasms on Date of Assessment of Frequency of Spasms during Maintenance Administration Period

End point title	Percentage of Subjects with Disappearance of Spasms on Date of Assessment of Frequency of Spasms during Maintenance Administration Period
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End point description:

Subjects whose spasms were disappeared on the date of assessment during the maintenance administration period (defined as a two day period comprising the maintenance administration period end date and the previous day) were reported in this endpoint). Analysis was performed on efficacy analysis set. Number of subjects analyzed=subjects evaluable for this endpoint.

End point type	Secondary
End point timeframe:	
End of 2 days of Maintenance period (3-10 weeks)	

End point values	Vigabatrin			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percentage of subjects				
number (confidence interval 95%)	66.7 (29.9 to 92.5)			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects with Complete Disappearance of Infantile Spasms

End point title	Percentage of Subjects with Complete Disappearance of Infantile Spasms
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End point description:

Subjects whose spasms had disappeared on the date of assessment of spasms during the maintenance administration period and whose brainwaves during the maintenance administration period showed no signs of hypsarrhythmia, were reported as complete disappearance presented. Hypsarrhythmia was assessed by the Central Brain wave Assessment Committee. Analysis was performed on efficacy analysis set. Number of subjects analyzed=subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

End of 2 days of Maintenance period (3-10 weeks)

End point values	Vigabatrin			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percentage of subjects				
number (not applicable)	44.4			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Hypsarrhythmia findings on Maintenance Administration Period End Date Compared With During Screening Period

End point title	Percentage of Subjects With Hypsarrhythmia findings on Maintenance Administration Period End Date Compared With During Screening Period
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End point description:

A contingency table was prepared for evaluation of hypsarrhythmia on the end day of the maintenance administration period and compared with the hypsarrhythmia status at the screening period. Subjects who showed any change in hypsarrhythmia (disappeared, improved, no change, deteriorated) were reported. Analysis was performed on efficacy analysis set. Number of subjects analyzed=subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

End of day of Maintenance period (3-10 weeks)

End point values	Vigabatrin			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: percentage of subjects				
number (not applicable)				
Disappeared	44.4			
Improved	33.3			

No change	22.2			
Deterioration	0			

Statistical analyses

No statistical analyses for this end point

Secondary: Percentage of Subjects With Comprehensive Evaluation of Efficacy by Principal Investigator or Sub-Investigator Including Impression of Guardians

End point title	Percentage of Subjects With Comprehensive Evaluation of Efficacy by Principal Investigator or Sub-Investigator Including Impression of Guardians
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End point description:

The comprehensive evaluation of efficacy of Vigabatrin as "effective or ineffective" by the Principal investigator or sub-investigators including the guardians' opinion for the subjects was evaluated. Analysis was performed on efficacy analysis set. Number of subjects analyzed=subjects evaluable for this endpoint.

End point type	Secondary
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End point timeframe:

End of day of Maintenance period (3-10 weeks)

End point values	Vigabatrin			
Subject group type	Reporting group			
Number of subjects analysed	9			
Units: Percentage of Subjects				
number (not applicable)				
Effective	88.9			
Ineffective	11.1			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All Adverse Events (AEs) were collected from signature of the informed consent form up to the final visit (Week 19) regardless of seriousness or relationship to investigational product.

Adverse event reporting additional description:

Reported AEs are treatment-emergent adverse events that is AEs that developed/worsened during the 'on treatment period' (time from dose adjustment period until follow up period). Analysis was performed on safety analysis set that included all subjects who were treated with investigational drug.

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	Vigabatrin
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Reporting group description:

Water as Placebo (for Vigabatrin) twice a day for first 3 days in dose adjustment period. From Day 4, subjects received Vigabatrin 50 mg/kg/day to 150 mg/kg/day up to a maximum of 3 g/day, administered during three periods: dose adjustment period (6 days - 8 weeks), followed by maintenance administration period (2 weeks) and then dose tapering period (3 weeks).

Serious adverse events	Vigabatrin		
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 13 (7.69%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Respiratory, thoracic and mediastinal disorders			
Asthma			
subjects affected / exposed	1 / 13 (7.69%)		
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	Vigabatrin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	12 / 13 (92.31%)		
Vascular disorders			
Hypertension			

subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
General disorders and administration site conditions Pyrexia subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Respiratory, thoracic and mediastinal disorders Pneumonia Aspiration subjects affected / exposed occurrences (all) Upper Respiratory Tract Inflammation subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 3 1 / 13 (7.69%) 1		
Psychiatric disorders Agitation subjects affected / exposed occurrences (all) Insomnia subjects affected / exposed occurrences (all) Mood Altered subjects affected / exposed occurrences (all) Sleep Disorder subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 4 2 / 13 (15.38%) 2 2 / 13 (15.38%) 2 1 / 13 (7.69%) 1		
Investigations Alanine Aminotransferase Decreased subjects affected / exposed occurrences (all) Alanine Aminotransferase Increased subjects affected / exposed occurrences (all)	4 / 13 (30.77%) 4 1 / 13 (7.69%) 1		
Injury, poisoning and procedural complications			

Contusion subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Fall subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Cardiac disorders Bradycardia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Mitral Valve Incompetence subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Nervous system disorders Somnolence subjects affected / exposed occurrences (all)	6 / 13 (46.15%) 6		
Cerebral Atrophy subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Epilepsy subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Blood and lymphatic system disorders Neutropenia subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Gastrointestinal disorders Enterocolitis subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2		
Anal Fissure subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Constipation subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		

Vomiting subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
Skin and subcutaneous tissue disorders Dermatitis Diaper subjects affected / exposed occurrences (all) Erythema subjects affected / exposed occurrences (all) Miliaria subjects affected / exposed occurrences (all)	2 / 13 (15.38%) 2 2 / 13 (15.38%) 2 1 / 13 (7.69%) 2		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all) Conjunctivitis subjects affected / exposed occurrences (all) Nasopharyngitis subjects affected / exposed occurrences (all) Pharyngitis subjects affected / exposed occurrences (all) Pneumonia subjects affected / exposed occurrences (all) Respiratory Syncytial Virus Infection subjects affected / exposed occurrences (all) Respiratory Tract Infection subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1 1 / 13 (7.69%) 1		
Metabolism and nutrition disorders			

Decreased Appetite subjects affected / exposed occurrences (all)	1 / 13 (7.69%) 1		
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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? No

Limitations and caveats

None reported