Clinical trial results:
Add-on therapy with low dose fenfluramine in Lennox Gastaut epilepsy

Summary

EudraCT number	2015-004008-46
Trial protocol	BE
Global end of trial date	19 July 2024

Results information

Result version number	v1 (current)
This version publication date	30 January 2025
First version publication date	30 January 2025

Trial information

Trial identification

Sponsor protocol code	FFA-LGS

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	UZ Leuven
Sponsor organisation address	Herestraat 49, Leuven, Belgium, 3000
Public contact	Lieven Lagae, UZ Leuven, lieven.lagae@uzleuven.be
Scientific contact	Lieven Lagae, UZ Leuven, lieven.lagae@uzleuven.be

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	01 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 January 2018
Global end of trial reached?	Yes
Global end of trial date	19 July 2024
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To study the potential effect of add-on fenfluramine in refractory Lennox Gastaut epilepsy. (exploratory dose finding add-on trial).
- Dose finding study add on low dose FFA (0,2 or 0,4 or 0,8 mg/kg/day, max 30 mg/day)
- Number of responders at each dosage (responder : min 50 % decrease of nr of seizures per 4 weeks compared to baseline period)
- Safety of low dose FFA

Protection of trial subjects:

To minimize stress and pain during blood collections in pediatric study subjects, a combination of psychological and physical strategies is employed. Distraction techniques such as cartoons, toys, or virtual reality headsets help divert the child’s attention, reducing anxiety and perceived discomfort. Topical anesthetics, like numbing creams or sprays, are applied to the skin to desensitize the area before needle insertion. For added comfort, vibrating cold pads or other pain-relief devices may be used near the site to confuse nerve signals and further reduce pain. Staff are trained to use gentle, child-centered communication to reassure and guide the child through the procedure, and allowing parents to be present provides an additional layer of emotional support. These methods collectively ensure that blood collection is as stress-free and painless as possible.

To avoid stress during other assessments such as ECG, echo and collection of vital signs, we made sure the communication was gentle and child-centered and that

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	22 March 2016
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	Belgium: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	7
Adolescents (12-17 years)	6
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The first patient was recruited on 22 MAR 2016 and the last patient on 20 JUL 2016.
A phase 3 study was initiated during this trial and therefore the recruitment officially ended on 6 OCT 2017.
The last follow-up visit of the remaining subjects took place in JUL 2024.

Pre-assignment

Screening details:

1. Electro-clinical epilepsy syndrome compatible with Lennox Gastaut syndrome
2. Drug resistant: at least 4 documented seizures in the last 4 weeks before inclusion
3. Age between 3 and 18 years
All the subjects that were screened were enrolled in the study.

Period 1

Period 1 title	Baseline period
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

Not blinded.

Arms

Arm title	Baseline

Arm description: -

Arm type	no intervention
Investigational medicinal product name	No product
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Anticoagulant and preservative solution for blood
Routes of administration	Auricular use

Dosage and administration details:

No product

Number of subjects in period 1	Baseline
Started	13
Completed	13

Period 2

Period 2 title	Overall trial
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	IMP dosing

Arm description:

Dosing IMP: starting dosage 0.2 mg/kg/day BID; second step: 0.4 mg/kg/day BID; max dosage 0.8 mg/kg/day BID or 30 mg/day BID.
Review of epileptic seizures is performed on each milestone and IMP dose increases if subject is non-responder (< 50% reduction of total number of clinically observable seizures with a motor component (GTC or/and TS or/and AS or/and M or/and FS) compared to baseline).

Arm type	Experimental
Investigational medicinal product name	Fenfluramine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

Oral solution of fenfluramine (2.5 mg/mL)
Dosage: starting dosage 0.2 mg/kg/day BID; second step: 0.4 mg/kg/day BID; max dosage 0.8 mg/kg/day BID or 30 mg/day BID

Number of subjects in period 2	IMP dosing
Started	13
Week 8	13
Week 12	13
Week 16	10
Completed	10
Not completed	3
Adverse event, non-fatal	1
Lack of efficacy	2

Period 3

Period 3 title	Extension period
Is this the baseline period?	No
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Dosing IMP

Arm description:

Dosing IMP: continuing at IMP dose of end of overall study period (0.2 mg/kg/day BID, 0.4 mg/kg/day BID or 0.8 mg/kg/day BID (max 30 mg/day BID)).
Review of epileptic seizures is performed every 3 month.
If subject is non-responder (< 50% reduction of total number of clinically observable seizures with a motor component (GTC or/and TS or/and AS or/and M or/and FS) compared to baseline), subjects are excluded from the study.

Arm type	Experimental
Investigational medicinal product name	Fenfluramine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Syrup
Routes of administration	Oral use

Dosage and administration details:

Oral solution of fenfluramine (2.5 mg/mL)
Continuation of dose of overall study period (0.2 mg/kg/day BID, 0.4 mg/kg/day BID or max dosage 0.8 mg/kg/day BID or 30 mg/day BID)

Number of subjects in period 3[1]	Dosing IMP
Started	9
Completed	2
Not completed	7
Consent withdrawn by subject	2
Adverse event, non-fatal	1
Lack of efficacy	4

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: 1 subject completed the overall study but chose to not enter the extension period.

Baseline characteristics

Reporting groups	
Reporting group title	Baseline period
Reporting group description:	
Collecting baseline seizure frequency for each subject for 4 weeks. This number will be used to compare the seizure frequency with in the next phase of the trial. Drug regimen will remain stable during baseline.	

Reporting group values	Baseline period	Total	
Number of subjects	13	13	
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)	7	7	
Adolescents (12-17 years)	6	6	
Adults (18-64 years)	0	0	
From 65-84 years	0	0	
85 years and over	0	0	
Age continuous Units: years			
arithmetic mean	11.7		
standard deviation	± 4.4	-	
Gender categorical Units: Subjects			
Female	4	4	
Male	9	9	
Lennox Gastaut epilepsy etiology Units: Subjects			
genetic	4	4	
structural	2	2	
unknown	7	7	
Presence of atonic seizures/drop attacks Units: Subjects			
present	9	9	
absent	4	4	
seizure frequency			
baseline median seizure frequency per month including multiple seizures types (ie, combinations of tonic, generalized tonic–clonic, myoclonic, absence, and atonic seizures/drop attacks)			
Units: unit(s)			
median	61		
full range (min-max)	21 to 1360	-	
Weight Units: kilogram(s)			
median	45.4		

standard deviation	± 20.2	-	
Amount of failed antiepileptic treatments			
Amount of failed antiepileptic treatments			
Units: unit(s)			
median	5		
full range (min-max)	3 to 7	-	
medication treatment duration			
Units: year			
median	8		
full range (min-max)	2 to 15	-	
Amount of current antiepileptic treatments			
Units: unit(s)			
median	4		
full range (min-max)	2 to 4	-	

End points

End points reporting groups

Reporting group title	Baseline
Reporting group description: -	
Reporting group title	IMP dosing
Reporting group description:	
Dosing IMP: starting dosage 0.2 mg/kg/day BID; second step: 0.4 mg/kg/day BID; max dosage 0.8 mg/kg/day BID or 30 mg/day BID. Review of epileptic seizures is performed on each milestone and IMP dose increases if subject is non-responder (< 50% reduction of total number of clinically observable seizures with a motor component (GTC or/and TS or/and AS or/and M or/and FS) compared to baseline).	
Reporting group title	Dosing IMP
Reporting group description:	
Dosing IMP: continuing at IMP dose of end of overall study period (0.2 mg/kg/day BID, 0.4 mg/kg/day BID or 0.8 mg/kg/day BID (max 30 mg/day BID)). Review of epileptic seizures is performed every 3 month. If subject is non-responder (< 50% reduction of total number of clinically observable seizures with a motor component (GTC or/and TS or/and AS or/and M or/and FS) compared to baseline), subjects are excluded from the study.	

Primary: ≥50% reduction in median CS frequency

End point title	≥50% reduction in median CS frequency[1]
End point description:	
End point type	Primary
End point timeframe:	
In the 20 weeks of IMP treatment.	

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: No specific statistical analyses are used, except for medians and percentages.

End point values	IMP dosing			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: %	62			

Statistical analyses

No statistical analyses for this end point

Secondary: Convulsive seizure frequency per month at the last visit

End point title	Convulsive seizure frequency per month at the last visit
End point description:	
Median seizure frequency at the last visit for the intenttotreat study population (N = 13)	
End point type	Secondary

End point timeframe:

Seizure frequency at the last visit

End point values	IMP dosing			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: unit(s)				
median (full range (min-max))	31 (2 to 890)			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction in convulsive seizure frequency

End point title	Reduction in convulsive seizure frequency

End point description:

End point type	Secondary

End point timeframe:

Median reduction seizure frequency at the last visit compared with baseline for the intenttotreat study population.

End point values	IMP dosing			
Subject group type	Reporting group			
Number of subjects analysed	13			
Units: %	53			

Statistical analyses

No statistical analyses for this end point

Secondary: Convulsive seizure frequency per month at the last visit in patients who completed 20 weeks of IMP treatment

End point title	Convulsive seizure frequency per month at the last visit in patients who completed 20 weeks of IMP treatment

End point description:

End point type	Secondary

End point timeframe:

Mean reduction in convulsive seizure frequency at the last visit compared to the baseline in the patients who completed 20 weeks of IMP treatment.

End point values	IMP dosing			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: unit(s)				
median (full range (min-max))	22 (2 to 136)			

Statistical analyses

No statistical analyses for this end point

Secondary: Reduction of convulsive seizures at the last visit in patients who completed 20 weeks of IMP treatment

End point title	Reduction of convulsive seizures at the last visit in patients who completed 20 weeks of IMP treatment

End point description:

End point type	Secondary

End point timeframe:

The value of the last visit in patients who completed 20 weeks of IMP treatment was compared with baseline.

End point values	IMP dosing			
Subject group type	Reporting group			
Number of subjects analysed	10			
Units: %	60			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Possibly related adverse event reported from baseline period, the overall study and extension period until 15 months.

Adverse event reporting additional description:

Adverse events were reported during every visit and self-reporting by participants

Assessment type	Systematic

Dictionary used

Dictionary name	UZ Leuven guidelines
Dictionary version	1

Reporting groups

Reporting group title	Fenfluramin

Reporting group description: -

Serious adverse events	Fenfluramin		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 13 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Fenfluramin		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 13 (46.15%)		
Nervous system disorders			
Decreased alertness			
subjects affected / exposed	2 / 13 (15.38%)		
occurrences (all)	2		
Sleepiness			
subjects affected / exposed	1 / 13 (7.69%)		
occurrences (all)	1		
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	4 / 13 (30.77%)		
occurrences (all)	4		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
19 January 2016	Adding template of epileptic seizure diary.
08 March 2016	- Adding recruitment letter to send to potential families. - Adding Sub-I. - Updated investigator brouchure. - Adjustments to the protocol: - Adding information on how to deal with subjects with reproductive potential (adding pregnancy tests, information on sperm and egg donation and contraception use,...) - Adding prohibited food consumptions (grapefruit and seville oranges) - Adding prohibited concomitant medication (felbamate, drugs that interact with central serotonin and drugs that potentially interact with fenfluramin via CYP2D6, CYP3A4 and/or CYP2B6 pathways)
25 August 2017	Changes to the protocol: - Adding information on not completing ICF's on subjects that become 18 years during the clinical study since they are mentally not capable to. - Adding information on changing the IMP dose in case of adverse events - Adding the possibility on continuing IMP dosing when the subject is a non-responder but has an effect on the severity and/or duration of the epileptic seizures. - Adding the possibility to change the IMP dose in the extension phase regardless of the fact that the subject is a responder or not. - Adding the possibility for non-responder subjects to enter the extension phase - Updating the flowchart for the extension phase so that safety blood samples, blood AED levels and cardiac evaluation are not necessary each visit.
24 April 2018	Clarifications in the study protocol: - On each on site visit the convulsive seizures are counted starting 28 days before the on site study visit. - Frequency of cardiologic assessments (ECG and echo) and blood collections in the extension period are performed at descretion of the PI but once a year at minimum. - AED levels are determined in the standard of care clinical follow-up. - Visit window of extension phase study visit is 3 months +/- 2 weeks. - Harmonizing seizure type abbreviations. - Dose adjustments during the extension phase are respons/effect dependant with a dose of minimum 0.1 mg/kg/day and a maximum of 30 mg/day. Reasons for dose adjustments need to be document in the source documents and CRF.
09 August 2019	As part of the European General Data Protection Regulation (GDPR), which has been in force since May 2018, an information letter will be prepared to inform (by phone and/or email) study patients, who are still participating in the study after May 2018, how their personal data will be managed, stored and used.
13 February 2020	New version of investigator brochure.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study is limited by the small sample size and lack of a placebo control group.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/30146701