Clinical trial results:
Randomized, double-blind, double-dummy, active controlled, multicentre, non-inferiority phase-III study to compare the pharmacokinetic, efficacy and safety of gabapentin liquid formulation to tramadol in children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic or mixed pain.

Summary

EudraCT number	2014-004851-30
Trial protocol	NL DE FR GR GB PL IT
Global end of trial date	18 June 2019

Results information

Result version number	v1 (current)
This version publication date	04 January 2020
First version publication date	04 January 2020
Summary attachment (see zip file)	GABA-1 Study Summary (GABA-1_Study Summary_11.12.19.pdf)

Trial information

Trial identification

Sponsor protocol code	GABA-1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02722603
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	PHARM – Pharmaceutical Research Management srl
Sponsor organisation address	Via Einstein Loc. Cascina Codazza, Lodi, Italy, 26900
Public contact	Trial Management, PHARM – Pharmaceutical Research Management srl, 0039 3287919866, trialmanagement@pharmsrl.com
Scientific contact	Trial Management, PHARM – Pharmaceutical Research Management srl, 0039 3287919866, trialmanagement@pharmsrl.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	Yes
EMA paediatric investigation plan number(s)	EMEA-001310-PIP01-12
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	11 September 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	02 February 2019
Global end of trial reached?	Yes
Global end of trial date	18 June 2019
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

To assess the efficacy of gabapentin relative to tramadol for the treatment of moderate to severe chronic neuropathic or mixed pain in children from 3 months to less than 18 years of age assessed by the difference in average pain scores between treatment arms at the end of the treatment period

Protection of trial subjects:

Study procedures were compliant with the Convention for the Protection of Individuals with regard to Automatic Processing of Personal Data (Strasbourg, 28.I.1981).
All laboratory specimens, evaluation forms, reports, video recordings, and other records that leave the site have been identified only by the patient sequential number to maintain subject confidentiality.
During the trial, at each visit, all the assessments have been conducted with a constant attention to the minimisation of pain and distress to the patient.
In accordance with applicable country-specific regulatory requirements, the sponsor obtained the authorisation of the regulatory authority and the favourable opinion/approval of the concerned ethics committee to conduct the study prior to a site initiating the study in any country.
Information Sheet was provided and written consent was obtained from the legal guardian for each subject before participation in the study. Children took part in the information process under the responsibility of parents and the investigator according to their age
and maturity level.

Background therapy:

None

Evidence for comparator:

Tramadol, a weak opioid approved for smaller children throughout Europe, was used as comparator in GABA-1 study.
Tramadol has demonstrated efficacy in adults with neuropathic pain and its effectiveness could be extrapolated in children. This approach was discussed within the Paediatric Committee of the EMA (PDCO) that validated the protocol and explicitly requested the inclusion of children from 3 months although recognizing that the diagnosis and treatment of neuropathic pain in this population is currently very empirical and tramadol is only authorized for patients from one year of age.

Actual start date of recruitment	31 May 2017
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	Germany: 2

Worldwide total number of subjects	2
EEA total number of subjects	2

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)	2
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 recruitment started on May 2017 and finished on June 2019.
12 clinical centres were involved in 8 EU and non-EU Countries: Albania (1), France (4), Germany (1), Greece (1), Italy (2), Poland (1), The Netherlands (1), the United Kingdom (1).

Pre-assignment

Screening details:

The screening period, starting at Day 1 and following consent, was of maximum 7 days to allow for all screening results to be obtained and validated.
A wash-out period (max 3 days) could be required if the patient was on an analgesic medication.

Period 1

Period 1 title	Treatment period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

The protocol has been designed to ensure double-blind conditions at randomisation and throughout the treatment period. Blinding was ensured by elaborating identical (matching) placebos for both the investigational (gabapentin) and the comparator (tramadol) drug.
Gabapentin and placebo were indistinguishable in appearance. Also, labelling did not allow recognizing actual treatment. The same for Tramadol and placebo.

Arms

Are arms mutually exclusive?	Yes
Arm title	Gabapentin

Arm description:

Experimental arm in which patients were administered gabapentin + placebo_tramadol

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

Dosage and administration details:

Route: oral, liquid formulation with unique concentration of 75mg/ml.
Mode of administration: administration of gabapentin oral solution (syrup) three times daily, directly via graduated syringes for oral use without any dilution.
Treatment was initiated at a starting dose in mg/kg/day and was titrated up until clinical response, according to a predefined matrix to a maximum dose in mg/kg/day.
Titration was flexibly optimised in order to maximise the potential benefits while minimising risk of adverse events. There were a maximum of 5 possible dose adjustments during the 3 weeks optimisation period.
Dosing for gabapentin were defined according to 2 weight groups. Dosing schedule for gabapentin is the following:
Day 1 - starting dose in mg/kg/day;
Day 3 - 2 times the starting dose in mg/kg/day;
Day 5 - 3 times the starting dose in mg/kg/day;
Day 14 - 2 times the dose of Day 5 in mg/kg/day;
Day 21 - 3 times the dose of Day 5 in mg/kg/day.

Arm title	Tramadol

Arm description:

Comparator arm in which patients were administered tramadol + placebo_gabapentin

Arm type	Active comparator
Investigational medicinal product name	Tramadol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Oral drops, solution
Routes of administration	Oral use

Dosage and administration details:

Route: oral drops, solution with unique concentration of 100 mg/mL.
Mode of administration: administration of tramadol oral drops three times daily. The drops should be administered orally and be diluted with water before administration.
Treatment was initiated at a starting dose in mg/kg/day and was titrated up until clinical response according to a predefined matrix to a maximum dose in mg/kg/day. Titration was flexibly optimised in order to maximise the potential benefits while minimising risk of adverse events. There were a maximum of 5 possible dose adjustments during the 3 weeks optimisation period. Dosing of tramadol was performed according to the following dosing schedule:
Day 1 - starting dose = 1 mg/kg/day;
Day 3 - 2 mg/kg/day;
Day 5 - 3 mg/kg/day;
Day 14 - 5 mg/kg/day;
Day 21 - 8 mg/kg/day
The maximum dose of 400mg/day for tramadol is maintained.

Number of subjects in period 1	Gabapentin	Tramadol
Started	1	1
Completed	1	1

Baseline characteristics

Reporting groups	
Reporting group title	Gabapentin
Reporting group description:	
Experimental arm in which patients were administered gabapentin + placebo_tramadol	
Reporting group title	Tramadol
Reporting group description:	
Comparator arm in which patients were administered tramadol + placebo_gabapentin	

Reporting group values	Gabapentin	Tramadol	Total
Number of subjects	1	1	2
Age categorical			
The 2 patients enrolled in the study belong to the 'Children' age category. They were both 11 years old at study enrollment.			
Units: Subjects			
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	1	1	2
Adolescents (12-17 years)	0	0	0
Gender categorical Units: Subjects			
Female	0	1	1
Male	1	0	1

End points

End points reporting groups

Reporting group title	Gabapentin
Reporting group description:	
Experimental arm in which patients were administered gabapentin + placebo_tramadol	
Reporting group title	Tramadol
Reporting group description:	
Comparator arm in which patients were administered tramadol + placebo_gabapentin	

Primary: Average pain score

End point title	Average pain score[1]
End point description:	
Average pain score at the end of the treatment period (average of two measures each day for 3 days before EOS visit, V10) as assessed by age-appropriate pain scales	
End point type	Primary
End point timeframe:	
12th of September 2018 - 1st of February 2019	

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: Due to the limited number of enrolled patients (2), only descriptive analyis have been performed

End point values	Gabapentin	Tramadol		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	1	1		
Units: scale score				
number (not applicable)	0	2		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 12th of September 2018 - 1st of February 2019	
Assessment type	Systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	22
Reporting groups	
Reporting group title	Gabapentin
Reporting group description: Experimental arm in which patients were administered gabapentin + placebo_tramadol	
Reporting group title	Tramadol
Reporting group description: Comparator arm in which patients were administered tramadol + placebo_gabapentin	

Serious adverse events	Gabapentin	Tramadol	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)	0 / 1 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Gabapentin	Tramadol	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	
Nervous system disorders			
Finger tremor			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences (all)	2	2	
Tremor			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	

Dizziness			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Sore throat			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	2	0	
Sternum pain			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Fever			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences (all)	2	5	
Obstipation			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Vomiting			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences (all)	1	1	
Decreased appetite			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Stomach pain			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Taste disorders			

subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Bloating			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Bronchitis			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Cold			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Cough			
subjects affected / exposed	1 / 1 (100.00%)	1 / 1 (100.00%)	
occurrences (all)	1	1	
Psychiatric disorders			
Lack of concentration			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Renal and urinary disorders			
Voiding disorder			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Neck pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Thorax pain			
subjects affected / exposed	0 / 1 (0.00%)	1 / 1 (100.00%)	
occurrences (all)	0	1	
Backache			
subjects affected / exposed	1 / 1 (100.00%)	0 / 1 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Gastroenteritis			

subjects affected / exposed occurrences (all)	0 / 1 (0.00%) 0	1 / 1 (100.00%) 1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 July 2017	Please find below a summary of the protocol substantial changes: • the recruitment will start with patients ≥ 3 years until results from the ongoing non-clinical toxicological study will confirm the safety of gabapentin in the age subset 3 months - <3 years. • One of the secondary endpoints has been modified in order to include, as responders, patients with an average pain score of 4/10 at baseline and an average pain score of 3/10 at the End Of Study; • Another secondary endpoint has been changed in order to report the daily pain intensity score instead of the average pain. • Three exclusion criteria have been added to avoid potential side effects due to the administration of the IMPs: a) subjects with history of severe respiratory impairment; b) subjects with history of substance abuse in particular opioids; c) subjects with fructose intolerance, diabetes, glucose – galactose malabsorption or lactase - isomaltase deficiency. • The exclusion criterion: subjects born prematurely, before 36th week of gestational age, if recruited during the first year of age, has been added to comply with the maximum level of blood volume to be collected in paediatric clinical study. • The endpoint: extent of pain valuated in visit 1, 2 and 10 using the pain chart, has been added to help physician to localize the painful area. • The suicide ideation/ behaviour assessment at the end of taper visit (v11) has been added for safety reason.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
18 June 2019	The GABA-1 study has been early terminated in all the Countries involved in the trial, due to insufficient recruitment. A total of two patients, both from the same clinical site (in Germany), were enrolled and randomised in the trial. No patient was receiving the treatment at time of early termination.	-

Notes:

Limitations and caveats

None reported