GABA-1 Study Summary

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

Product	**GABAPENTIN**
Protocol No.	**GABA-1**
EudraCT No.	**2014-004851-30**
Phase	**phase III**
First Patient First Visit (FPFV)	**12/09/2018**
Last patient Last Visit (LPLV) *The date is referred to the last visit of the last patient enrolled in the study*	**01/02/2019**
Date of early study termination:	**18/06/2019**
Sponsor	**PHARmaceutical Research Management (PHARM) srl** Via Einstein – Loc. Cascina Codazza 26900 Lodi, Italy
Sponsor's Representative	**Dr. Donato Bonifazi** PHARM SRL Via Einstein – Loc. Cascina Codazza 26900 Lodi, Italy
Study Scientific Coordinator/Trial Coordinating Investigator	**Dr. Florentia Kaguelidou** Center of Clinical Investigations, INSERM CIC 1426, Hôpital Robert Debré, Assistance Publique-Hopitaux de Paris, 48 Boulevard Sérurier, 75019 Paris, France
Funder	**European Commission** (FP7 Framework Research Program "HEALTH2010.4.2-1: Off-patent medicines for children")
Version	**1.0**
Date of the report	**11/12/2019**

EudraCT No: 2014-004851-30	
Title: 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	
Rationale: there is an unsatisfied need for adequate pharmacological treatment of neuropathic chronic pain in children. Gabapentin has been successfully used to treat neuropathic pain in adults and has been used off-label to treat children with the same condition. The GABA-1 trial is designed to demonstrate the efficacy of gabapentin oral solution (syrup) relative to tramadol and to document the safety profile of gabapentin in this indication.	
Phase: III	
Study Period: 12th of September 2018 (FPFV)– 18th of June 2019	
Study Design: randomized, double-blind, double-dummy, active-controlled, parallel group, multicentre, non-inferiority study.	
Centres:	
Site 1 (coordinating centre)	Assistance Publique Hôpitaux de Paris - APHP Hôpital Robert Debré Centre of Clinical Investigations, INSERM CIC1426 Boulevard Sérurier 48, 75019, Paris, France Principal Investigator (Country Coordinator): Dr. Florentia Kaguelidou Hôpital d'Enfants Armand Trousseau - recruitment satellite centre depending on Country Coordinator Dr. Florentia Kaguelidou Centre de Référence de la migraine de l'enfant et de l'adolescent et du Centre de la douleur 26 avenue du Docteur Arnold-Netter, 75012 Paris Sub-Investigator: Dr. Barbara Tourniaire
Site 2	Assistance Publique Hôpitaux de Paris - APHP Hôpital Necker Centre d'évaluation et de traitement de la douleur Rue de Sèvres 149, 75015, Paris, France Principal Investigator: Dr. Céline Greco
Site 3	Assistance Publique Hôpitaux de Marseille - APHM Hôpital La Timone Service de Pédiatrie et d'hematologie-oncologie pédiatriques Rue Saint-Pierre 264, 13005, Marseille, France Principal Investigator: Dr. Cécile Mareau
Site 4	Centre Hospitalier Régional Universitaire de Lille - CHRU Lille Pôle Enfant Service de Neuropédiatrie - Consultation Douleur Enfant 2, Avenue Oscar Lambret, 59037, Lille, France Principal Investigator: Dr. Justine Avez-Couturier
Site 5	Qendra Spitalore Universitare Nene Tereza General Pediatric Clinic - Pediatric Department Rruga e Dibrës 372, 1000 Tiranë, Albania Principal Investigator: Prof. Ermira Kola
Site 6	Universitaetsklinikum Erlangen Department of Paediatrics and Adolescent Medicine Loschgestraße 15, D-91054 Erlangen, Germany Principal Investigator: Prof. Regina Trollmann
Site 7	Geniko Nosokomeio Paidon I Agia Sofia

	Anaesthetic department & Pain Clinic Thivon & Papadiamantopoulou 1, 11527 Athens, Greece Principal Investigator: Dr. Eleana Garini
Site 8	Azienda Ospedaliero - Universitaria Consorziale Policlinico di Bari U.O.C. di Neuropsichiatria Infantile Piazza Giulio Cesare 11, 70124, Bari, Italy Principal Investigator (Country Coordinator): Prof. Lucia Margari
Site 9	Istituto Giannina Gaslini – Genova Unità Operativa Semplice Dipartimentale di Assistenza domiciliare e Continuità delle Cure Dipartimento Testa - Collo e Neuroscienze Via Gerolamo Gaslini 5, 16148, Genova, Italy Principal Investigator: Dr. Luca Manfredini
Site 10	Erasmus Universitair Medisch Centrum Rotterdam - Sophia Kinderziekenhuis Intensive Care and Department of Paediatric Surgery Department of Anesthesiology Wijtemaweg 80, 3015 CN, Rotterdam, The Netherlands Principal Investigator (Country Coordinator): Dr. Saskia N. De Wildt
Site 11	University Medical Center Utrecht, Wilhelmina Kinderziekenhuis Department of Anesthesiology Heidelberglaan 100, 3584 CX, Utrecht, The Netherlands Principal Investigator: Dr. Nico Wulffraat
Site 12	Alder Hey Children's Hospital NHS Foundation Trust Eaton Road, Liverpool, L12 2AP, UK Principal Investigator: Dr. Daniel Hawcutt
Site 13	Children's Memorial Health Institute 04-730 Warsaw, Poland Principal Investigator: Dr Anna Szumowska

Treatment: patients were randomised to receive one of the two investigational products (test or comparator) and the equivalent dose of the double dummy placebo formulation, i.e., (gabapentin + placebo_tramadol) or (placebo_gabapentin + tramadol). All treatments were administered by oral route.
Treatments initiated at a starting dose in mg/kg/day and were 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. A maximum of 5 possible dose adjustments were possible during the 3 weeks optimisation period.

IMP test: gabapentin

Route: oral, liquid formulation with unique concentration of 75mg/ml.
Mode of administration: administration of gabapentin oral solution (syrup) three times daily.

IMP comparator: tramadol

Route: oral drops, solution with unique concentration of 100 mg/ml.
Mode of administration: Administration of tramadol oral drops three times daily.

Objectives:

Primary objective:

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 by comparing the difference in average pain scores between intervention arms at the end of the treatment period.

Secondary objectives:

- to assess effect of gabapentin relative to tramadol on quality of life (physical, emotional, social and school functioning) and global satisfaction with treatment.
- to assess safety of gabapentin relative to tramadol for treatment of chronic neuropathic or mixed pain in children (3 months - 17 years of age).

- to characterise the population pharmacokinetic-pharmacodynamic (PKPD) relationship of gabapentin liquid formulation and provide confirmation of the recommended paediatric dose.

Additional exploratory objectives of the study:

- to describe the metabolomic profile following drug treatments.
- to explore genetic polymorphisms and their impact on pharmacokinetics (PK) and pharmacodynamics (PD).
- to assess the population pharmacokinetics of tramadol and, if feasible, its PKPD relationship in the paediatric population.

Efficacy analysis:

Primary endpoint

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:

- FLACC Scale (observational assessment scale) in children aged less than 3 years.
- FPS-R (self-assessment scale) for children aged 3 years to less than 8 years.
- Pain NRS-11 (self-assessment scale) for children aged 8 years to less than 18 years.

Secondary efficacy endpoints

a. Percentage of responders to treatment defined as subjects with a reduction of 30% from baseline or equal to 3/10 of pain intensity assessed by appropriate scale (FLACC, FPS-R and NRS-11) at the end of the study.

b. Daily pain intensity assessed by age appropriate scale (FLACC, FPS-R or NRS-11) during dose optimization (V3–V6).

c. Observational assessment using the NRS-11 completed by parents and investigator (or caregiver) at each visit.

d. Self-assessment of pain for children ≥8 years of age using the FPS-R pain scale at each visit.

e. Extent of pain evaluated as the number of painful areas using the pain charts at screening visit (V1), randomisation (V2) and EOS visit (V10).

f. Number of episodes of breakthrough pain (>4/10 pain score and use of rescue medications) during treatment period.

g. Number of rescue interventions required during treatment period.

Secondary safety endpoints

s. Incidence of adverse events at all visits (V1–V12).

t. Percentage of subjects discontinuing the trial due to treatment-emergent adverse events.

u. Aggressive behaviour in children aged >6 years using the Retrospective-Modified Overt Aggression Scale
at V2, V6 and EOS visit (V10).

v. Suicidal ideation/behaviour in subjects aged 6 years and older using the Columbia – Suicide Severity Rating Scale scores before IMP (screening V1), V6 and at the EOS visit (V10) and end of taper visit (V11).

Safety analysis

Safety aspects of the study were closely monitored by site investigators, by the sponsor's medical expert and by the independent Data Safety Monitoring Committee (DSMC). In addition, specific adverse events related to the use of gabapentin or tramadol were closely monitoring during the entire study period.

Assessment of Adverse Events severity and seriousness

The Investigator had to make an assessment of intensity for each Adverse Event (AE) and Serious Adverse Event (SAE) reported during the study.

Assessment of causality

The Investigator had to assess the causal relationship between adverse events and study medication, comparator, concomitant medication and research. All adverse events for which a causality link may be reasonably assessed by the Investigator or the sponsor are considered as suspicions of adverse reactions.

Severity of AEs

The Investigator had to grade the severity (mild-moderate-severe) of any AE.

Statistical methods: since only two patients were enrolled and randomized in the study, it was not possible to perform any statistical analysis as planned, except for the descriptive ones.	
Study Population: children from 3 months to less than 18 years of age experiencing moderate to severe chronic neuropathic or mixed pain	
Number of subjects	
Planned N	94
Enrolled, N	2
Randomised, N	2
Completed, N	2
Number of screening failures, N	0
Number of premature discontinuations, N	0
Demographics	
N (All subjects dosed)	2
Males/Females	1/1 Pt1: male Pt2: female
Age (Years)	Pt 1: 11 Pt 2: 11
Weight (Kg)	Pt 1: 43 Pt 2: 34
Height (Cm)	Pt 1: 150 Pt 2: 144
Pain characteristics	
Type of pain	Pt 1: Neuropathic Pt 2: Neuropathic
Frequency	Pt 1: Continuous Pt 2: Continuous
Duration (n. of weeks)	Pt 1: 14 Pt 2: 13
Treatment allocation	Pt 1: gabapentin/tramadol placebo Pt 2: tramadol/gabapentin placebo
Efficacy results (Efficacy population N=2)	
Average pain score before treatment (average of two measures each day for 3 days before IMP administration) - NRS-11 scale (10 points scale → 0= no pain; 10=worst possible pain)	Pt 1: 6 Pt 2: 5
Average pain score at the end of the treatment period (average of two measures each day for 3 days before the end of study visit) – NRS-11 scale (10 points scale → 0= no pain; 10=worst possible pain)	Pt 1: 0 Pt 2: 2
Percentage of responders to treatment at the end of the study	100%

Extent of pain evaluated as the number of painful areas using the pain charts at screening visit (V1), randomisation (V2) and EOS visit (V10)	Pt 1: 4(V1) - 4(V2) - 2(V10) Pt 2: 4(V1) - 4(V2) - 5(V10)
Number of episodes of breakthrough pain (>4/10 pain score and use of rescue medications) during treatment period	Pt 1: 1(V5) - 0(V6) - 6(V8) - 0(V9) - 0(V10) - 0(V11) Pt 2: 9(V5) - 1(V6) - 0(V8) - 0(V9) - 0(V10) - 0(V11)
Number of rescue interventions required during treatment period	Pt 1: 11 Pt 2: 49
Safety results (Safety population N=2): All adverse events (AEs) occurring before or after dosing were recorded	
Adverse Events:	
N	Pt 1: 16 Pt 2: 21
N. subjects with AEs	2
Serious Adverse Events (SAEs):	
N. subjects with any SAEs	0
• All the AEs were classified as Mild, with the exception of 1 event (Fever) classified as Moderate • 7 AEs (Cough, Nausea, Bronchitis, Common cold, Obstipation, Gastroenteritis) required a prescription drug therapy, while 3 AEs (Backache, Neck pain, Headache) required rescue medications or physiotherapy • No AE required the changing of the IMPs dose	
Percentage of subjects discontinuing the trial due to treatment-emergent adverse events	0
Aggressive behaviour in children aged >6 years using the Retrospective-Modified Overt Aggression Scale at V2, V6 and EOS visit (V10)	Pt 1: 9 (V2) – 0 (V6) – 3 (V10) Pt 2: 8 (V2) - 0 (V6) – 10 (V10)
Suicidal ideation/behaviour in subjects aged 6 years and older using the Columbia – Suicide Severity Rating Scale scores before IMP (screening V1), V6 and at the EOS visit (V10) and end of taper visit (V11).	No suicidal ideation/behaviour was detected before and during the treatment period
Conclusion: the GABA-1 study has been early terminated due to insufficient recruitment. A total of two patients, both from the same clinical site (in Germany), were enrolled and randomised in the trial. They completed all the visits, including the follow-up and did not show any Serious Adverse Event. No patient was receiving the treatment at time of early termination. Since only two patients completed the study, the minimum patient sample size expected for this trial could not be reached. Consequently, it is only possible to say that, for the patient treated with gabapentin, the investigational medicinal product showed a good efficacy-safety profile.	