EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Keppra

(Levetiracetam)

Procedure No. EMEA/H/C/000277/P46/072 & 075

CHMP assessment report for paediatric use studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse event
AED	Anti-epileptic drug
CI	Confidence Interval
CNS	Central nervous system
CRO	Clinical research organisation
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
EMEA	European Medicine Agency
EP	Evaluation Period
EU	European Union
GTC	Generalized Tonic Clonic (seizures)
ICH	International Conference on Harmonisation
IEC	Independent ethics committee
IRB	Institutional review board
LEV	Levetiracetam
MedDRA	Medical Dictionary for Regulatory Activities
PCS	Possibly Clinically Significant
PGTC	Primary generalized tonic-clonic seizures
PPS	Per Protocol Set
Q1	25^{th} Percentile
Q3	75^{th} Percentile
SAE	Serious adverse event
SD	Standard deviation
SOC	System Organ Class
SOP	Standard operating procedure
SPC	Summary of Product Characteristics
SS	Safety Set
TP	Treatment Period
TEAE	Treatment-emergent adverse event
WHO	World Health Organization

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I. RECOMMENDATION

The CHMP noted the submission of two paediatric studies in accordance with Article 46 of Regulation (EC) No 1901/2006, hereafter referred to as Paediatric Regulation, and confirmeds that there was no impact on either the Product Information or on the benefit-risk balance of the EU authorised formulations of Keppra.

II. INTRODUCTION

This assessment report concerns two study reports submitted under Article 46 of the Paediatric Regulation. Both studies are open-label, single-arm, multi-centre studies which investigated the efficacy and safety of adjunctive treatment with levetiracetam in Japanese paediatric patients ≥4 to <16 years) with uncontrolled generalized tonic-clonic (GTC) seizures despite treatment with 1 or 2 antiepileptic drug(s).

Levetiracetam (LEV) dry syrup, a formulation (approved for use in Japan in June 2013) developed for use in Japan for children and in patients who have difficulty swallowing tablets, is not a registered formulation in the EU, so no changes to the approved EU Product Information for Keppra are proposed following the completion of this study. At this time, the MAH considers that the standard immediate release formulations of Keppra allow for appropriate use of LEV in paediatric patients in the EU.

III. STUDIES

III.1 Study N01223

III.1.1 Introduction

Study N01223 was an open label multicentre trial, using but a single arm, with the goal of investigating the efficacy, safety, and pharmacokinetics of levetiracetam used as adjunctive therapy in Japanese paediatric patients equal to or older than 4 and younger than 16 years of age whom have uncontrolled partial seizures despite treatment with 1 or 2 anti-epileptic drug(s).

A total 30 investigators in 30 centres participated, all located in Japan.

The study consisted of two periods, the first one taking 28 weeks to complete, including an 8 week baseline period, and 4 week up-titration period, a 10 week evaluation period and a 6 week withdrawal period. Patients whom had finished the first period were eligible to participate in the second in order to continue receiving Keppra until market approval.

III.1.2 Objectives

First Period

Primary: To evaluate the efficacy of Levetiracetam (LEV) dry syrup at doses up to a maximum of 60mg/kg/day (or 3000mg/day if ≥ 50 kilograms) if used as an adjunctive therapy in Japanese paediatric subjects ≥4 to <16

years old with uncontrolled partial seizures despitetreatment with 1 or 2 antiepileptic drugs (AEDs).

Secondary: To evaluate the safety and pharmacokinetics of LEV dry syrup (up to 60mg/kg/day or 3000mg/day if ≥ 50 kgs).

Second Period

Primary: Provide LEV to willing subjects deemed to benefit from long-term treatment.

Continuous evaluation of the safety of long-term LEV administration at doses from 20mg/kg/day (1000mg/day if ≥ 50 kgs) to 60mg/kg/day (3000mg/day if ≥ 50 kgs).

Secondary: Continuous evaluation of the efficacy and pharmacokinetics of long-term administration of LEV at doses ranging from 20mg/kg/day to 60mg/kg/day or 1000mg/day to 3000mg/day if ≥ 50 kgs.

III.1.3 Study Methodology

The study was an open-label, single-arm, multi-center study consisting of 2 periods in Japanese children ≥4 to <16 years old with uncontrolled partial seizures despite treatment with 1 or 2 concomitant AED(s). The study consisted of two periods, the first one of which took 28 weeks and had 4 sub-periods: Baseline, Up-Titration, Evaluation and Withdrawal. This was then followed by a second period in which participants of the first period could enter in order to continue receiving Keppra until market approval in Japan.

The first period consisted of obtaining the patient's informed consent, checking her/his eligibility, starting the patient on a dose of 20 mg LEV/KG/day (1000mg/day), followed by a four week up-titration (20mg/kg/day or 1000mg/day for 2 weeks and 40mg/kg/day or 2000mg/day for 2 weeks). They then entered the Evaluation Period, during which the subjects received LEV 60mg/kg/day or 3000mg/day for 10 weeks, and the investigators were permitted to decrease the dose to 40mg/kg/day or 2000mg/day once if any issues in tolerability were confirmed When the subject or investigator decided to stop treatment, the dose was gradually decreased at rate of 20mg/kg/day (1000mg/day if over 50kg) every two weeks. Two weeks after the last dose a final visit was to take place, where it would also be decided if continuing treatment in period 2 would be beneficial of not.

After patients were admitted to the second period they began individualized LEV treatment based on the dose they had received at the end of the evaluation sub-period of the first treatment period. Those subjects with a body weight over 20 kilograms were allowed to change their received formulation to tablets or back again at any time during this period. As long as concomitant AED had been stable for at least 4 weeks, the investigators were allowed to change dose and mode of administration of LEV and AED administered to patients. Introduction of

AEDs other than those taken already during the first period was forbidden. Discontinuation during this period was done at a rate of 10mg/kg/day to 20mg/kg/day or 500mg/day to 1000mg/day (if bodyweight ≥ 50kg) every 2 weeks.

In the protocol a total of 70 subjects was planned to be randomized (As this study was aimed to confirm the clinical efficacy of LEV in Japanese paediatric patients and seeing that study N159 demonstrated the superiority of LEV against placebo treatment, the latter's estimate methodology was used to establish the needed sample size for this study), with a total of 73 patients being entered into the first period and receiving at least one dose of LEV in practice. Of these 73 subjects 62 completed the first period and eventually 55 of these entered the second period.

III.1.4 Exclusion and Inclusion Criteria

Only subjects between 4 and 16 years of age, with a bodyweight of 11 kilograms or above, but below 82 kilograms, with uncontrolled partial seizures, whether or not secondarily generalized which had been diagnosed and confirmed at least 6 months before the first visit could participate. In addition, subjects had to have been experiencing at least 4 partial seizures during the 4 weeks prior to visit 1, and have at least 4 partial seizures during the first and last 4 weeks of the baseline period. The subject had to be on a stable AED treatment consisting of no more than 2 AEDs during the 4 weeks prior to visit 1 and AED treatments could not be changed during baseline, up-titration and evaluation sub-periods, while outright deletion or addition of AEDs were forbidden during the entire study.

In order to be eligible for the second study period, the subject in question had to have completed the first period and deemed needing to be continuously treated with LEV by the investigators.

A history of status epilepticus in the 3 months preceding visit 1, having treatable seizure etiology, having epilepsy secondary to a progressive cerebral disease or any other progressively neurodegenerative disease, uncountable seizures due to clustering, pseudo seizures, having Lennox-Gastaut syndrome, progressive CNS or psychiatric disorders, clinically significant acute/chronic/terminal illnesses, conditions that might interfere with study protocol adherence or medicine metabolisation, being on a ketogenic diet and having a known allergy to pyrrolidone derivatives or a history of multiple drug allergies were all reasons to be denied entry into the study population.

III.1.5 Endpoints

First period

The primary efficacy endpoint was the percentage reduction from baseline in partial seizure frequencies per week during the treatment period (up-titration and evaluation).

The most important secondary efficacy variables were:

- The percentage reduction in partial seizure frequency per week from Baseline over the Evaluation Period

- Partial seizure frequency per week over the Treatment Period
- Partial seizure frequency per week over the Evaluation Period
- Partial seizures 50% responder rate (the proportion of subjects with 50% or more reduction from Baseline in the frequency of partial epileptic seizures) over the Treatment Period
- Partial seizures 50% responder rate (the proportion of subjects with 50% or more reduction from Baseline in the frequency of partial epileptic seizures) over the Evaluation Period
- Seizure freedom over the Treatment Period
- Seizure freedom over the Evaluation Period
- Levetiracetam plasma concentrations throughout the study
- Adverse events (AEs)
- Laboratory assessments, including blood chemistry, hematology, and urinalysis
- Electrocardiograms (ECGs)
- Vital signs (blood pressure, pulse rate, and body temperature)
- Body weight and height

Second period

The primary variable was the incidence of AEs over the Second Period.

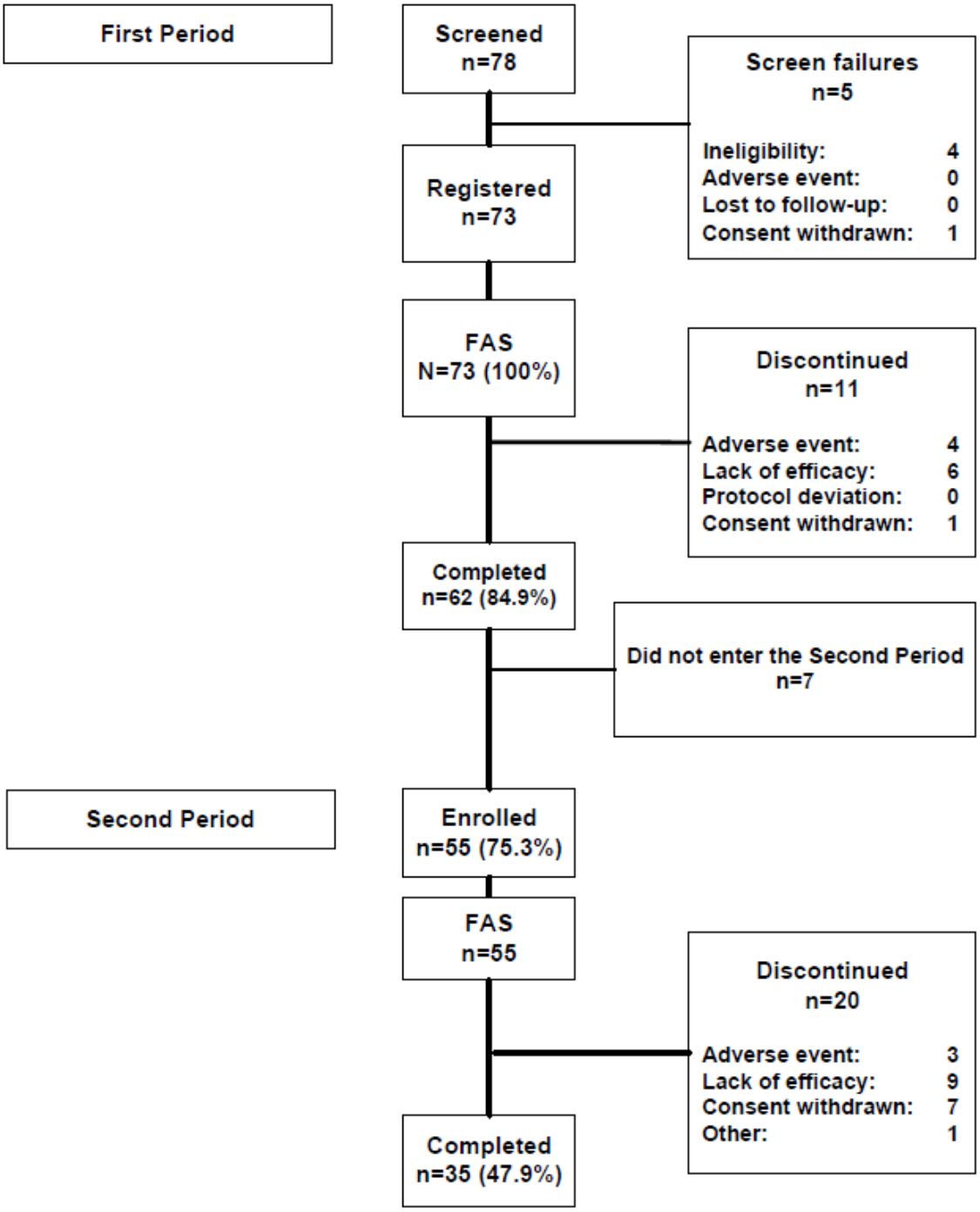
The most important secondary variables collected were:

- The incidence of adverse drug reactions (ADRs) over the Second Period
- The percentage reduction from Baseline in partial seizure frequency per week by 3-month windows over the evaluation period in the second period (excluding the withdrawal period)

III.1.6 Subject Disposition

The subject disposition for this study is summarized in flowchart 1.

Flowchart 1 : Subject disposition



Efficacy deviations which had an impact on the efficacy, were reported by 3 subjects (4.1%) in period 1. Of these 3 subjects, 1 subject was partially excluded from the PPS and 2 subjects were totally excluded.

Demographic profiles concerning a number of important characteristics during both periods are detailed below:

Table 1: **Demographic characteristics**

Characteristic		Statistic	First Period N=73	Second Period N=55
Age (years)		Mean (SD)	10.1 (3.4)	10.4 (3.4)
		Median	11.0	11.0
		Min - max	4-15	4-15
Age class (years)	≥4 to <8	n (%)	22 (30.1)	15 (27.3)
	≥8 to <12	n (%)	22 (30.1)	17 (30.9)
	≥12 to <16	n (%)	29 (39.7)	23 (41.8)
Gender	Male	n (%)	41 (56.2)	30 (54.5)
	Female	n (%)	32 (43.8)	25 (45.5)
Race	Japanese	n (%)	73 (100.0)	55 (100.0)
	Non-Japanese	n (%)	0	0
Body weight (kg)		Mean (SD)	32.43 (13.20)	34.46 (13.92)
		Min - max	14.6 - 68.5	13.4 - 68.7
Height (cm)		Mean (SD)	134.55 (20.69)	137.53 (20.17)
		Min - max	98.0 - 173.5	100.0 - 175.4
BMI (kg/m^2)		Mean (SD)	17.15 (2.99)	17.42 (3.24)
		Min - max	10.9 - 26.0	11.7 - 26.2
Hospitalization status				
	Inpatient	n (%)	0	0
	Outpatient	n (%)	73 (100.0)	55 (100.0)

BMI=body mass index; FAS=Full Analysis Set; Max=maximum, Min=minimum; SD=standard deviation

Table 2: **History of epilepsy**

History characteristic	Statistics	First Period N=73	Second Period N=55
Epilepsy duration (years)	Mean (SD)	6.46 (3.80)	6.54 (3.71)
	Median	6.10	6.20
	Min-max	0.60 - 15.60	0.80 - 15.60
Age at onset (years)	Mean (SD)	4.06 (3.37)	4.26 (3.30)
	Median	3.50	3.90
	Min-max	0.00 -12.40	0.00 - 12.40
Seizure type			
Partial onset seizures	n (%)	73 (100.0)	55 (100.0)
Generalized seizures	n (%)	9 (12.3)	7 (12.7)
Unclassified epileptic seizures	n (%)	8 (11.0)	6 (10.9)
Clusters	n (%)	20 (27.4)	16 (29.1)
Focus localization			
Frontal	n (%)	47 (64.4)	34 (61.8)
Temporal	n (%)	16 (21.9)	14 (25.5)
Occipital	n (%)	10 (13.7)	6 (10.9)
Parietal	n (%)	9 (12.3)	7 (12.7)
Unknown	n (%)	14 (19.2)	11 (20.0)

FAS=Full Analysis Set; Max=maximum, Min=minimum; SD=standard deviation

Table 3: Epilepsy etiology

Seizure subtype	First Period N=73 n (%)	Second Period N=55 n (%)
Unknown	38 (52.1)	30 (54.5)
Congenital	18 (24.7)	13 (23.6)
Perinatal events	6 (8.2)	4 (7.3)
Cranial trauma	2 (2.7)	1 (1.8)
Brain surgery	1 (1.4)	0
Cerebral infection	6 (8.2)	5 (9.1)
Metabolic cause	1 (1.4)	0
Other	3 (4.1)	2 (3.6)

FAS=Full Analysis Set

Table 4: Partial seizure frequency

Statistics	First Period N=73
n	73
Mean (SD)	19.49 (30.99)
Median	7.67
Q1 - Q3	2.50 - 18.71
Min-max	1.0 - 170.9

FAS=Full Analysis Set; Max=maximum, Min=minimum; Q1=25th percentile; Q3=75th percentile; SD=standard deviation

Table 5: Concomitant AEDs

Therapeutic subgroup (ATC3) WHO drug generic name	First Period N=73 n (%)	Second Period N=55 n (%)
Antiepileptics	**73 (100)**	**55 (100)**
Valproate sodium	37 (50.7)	25 (45.5)
Carbamazepine	22 (30.1)	17 (30.9)
Lamotrigine	18 (24.7)	12 (21.8)
Clobazam	15 (20.5)	10 (18.2)
Phenytoin	10 (13.7)	6 (10.9)
Topiramate	10 (13.7)	8 (14.5)
Zonisamide	10 (13.7)	9 (16.4)
Clonazepam	9 (12.3)	9 (16.4)
Sultiame	4 (5.5)	3 (5.5)
Acetazolamide	2 (2.7)	2 (3.6)
Gabapentin	2 (2.7)	2 (3.6)
Phenobarbital	1 (1.4)	1 (1.8)
Hypnotics and sedatives	**1 (1.4)**	**1 (1.8)**
Nitrazepam	1 (1.4)	1 (1.8)

AED=antiepileptic drug; ATC=anatomical therapeutic chemical; FAS=Full Analysis Set; WHO=World Health Organization

Important deviations, which led to exclusion from the efficacy analysis, were reported by 3 subjects (4.1%). Of the 3 subjects, 1 subject was partially excluded from the PPS and 2 subjects were totally excluded. The former reported a deviation for the use for restricted concomitant medication and rescue medications at Visit 7, which led to the data for this subject after Visit 7 to be excluded from the efficacy analysis in the PPS. One subject used restricted concomitant medications Prior to the first dose of LEV treatment at Visit 3, and another used the rescue medications at Visit 3. Therefore, the data for these 2 subjects were totally excluded from the PPS. No subjects reported protocol deviations for subject eligibility in efficacy.

III.1.7 Efficacy Results

The primary efficacy endpoint, the median percentage reduction from baseline in partial seizures per week during the 14-week treatment period attained 43.21% (26.19 < 95%CI < 52.14%), which meant that the predefined criterion for a positive efficacy result (the lower limit of the 95% CI at greater than 16.3%, the median percentage reduction of the seizure frequency per week of the subjects in the placebo group of a double-blind, placebo-controlled, multicenter study (N159)) was met.

Table 6: Percentage reduction over the Treatment Period for the First Period (FAS)

	Seizure frequency per week		Percentage reduction overall
	Baseline Period	Treatment Period	
Statistics	All subjects N=73		
n	73	73	73
Mean (SD)	19.49 (30.99)	14.61 (25.29)	29.11 (56.29)
Median	7.67	3.92	43.21
95% CI	NAV	NAV	26.19 - 52.14
Q1-Q3	2.50 - 18.71	0.93 - 17.08	2.08 - 63.26
Min-Max	1.0 - 170.9	0.0 - 149.9	−204.8 - 100

CI=confidence interval; max=maximum; min=minimum; NAV=not available; Q1=25th percentile; Q3=75th percentile; SD=standard deviation

Subgroup analysis on age, gender, body weight, epileptic syndrome, baseline seizure frequency per week and number and types of concomitant AEDs did not reveal any demographic characteristic that may influence the above result, with subgroup median percentage reductions lying between 20.35% and 63.26%.

Table 7: Percentage reduction in seizure frequency over the Treatment Period by age (FAS)

Age category	Seizure frequency per week		Percentage reduction by age
	Baseline Period	Treatment Period	
Statistics	N=73		
4 to 7 years			
n	22	22	22
Median	10.43	3.89	45.88
Q1-Q3	2.92 - 21.13	0.86 - 20.07	8.93 - 88.74
8 to 11 years			
n	22	22	22
Median	9.72	11.07	26.62
Q1-Q3	2.75 - 27.44	1.79 - 30.88	−36.71 - 56.02
12 to 15 years			
n	29	29	29
Median	4.57	2.77	46.94
Q1-Q3	2.43 - 11.71	0.87 - 5.33	20.35 - 63.26

FAS=Full Analysis Set; Q1=25th percentile; Q3=75th percentile

Table 8: Percentage reduction in seizure frequency over the Treatment Period by gender (FAS)

Gender	Seizure frequency per week		Percentage reduction by gender
	Baseline Period	Treatment Period	
Statistics	N=73		
Male			
n	41	41	41
Median	8.29	3.92	45.71
Q1-Q3	3.76 - 21.13	1.43 - 13.81	8.93 - 64.31
Female			
n	32	32	32
Median	6.13	4.19	36.27
Q1-Q3	1.95 - 16.67	0.85 - 18.39	−1.34 - 61.29

FAS=Full Analysis Set; Q1=25th percentile; Q3=75th percentile

Table 9: Percentage reduction in seizure frequency over the Treatment Period by body weight (FAS)

Body weight	Seizure frequency per week		Percentage reduction by body weight
	Baseline Period	Treatment Period	
Statistics	N=73		
<Q1			
n	18	18	18
Median	9.64	3.96	45.88
Q1-Q3	1.96 - 36.00	0.44 - 31.50	2.97 - 88.74
≥Q1 to <Q2			
n	18	18	18
Median	14.60	15.44	26.66
Q1-Q3	7.38 - 48.53	3.75 - 33.88	−4.68 - 56.02
≥Q2 to <Q3			
n	19	19	19
Median	3.88	3.92	37.89
Q1-Q3	1.69 - 14.25	1.05 - 5.33	−9.64 - 59.32
≥Q3			
n	18	18	18
Median	4.61	2.31	49.75
Q1-Q3	2.00 - 9.88	0.87 - 4.93	24.57 - 63.26

FAS=Full Analysis Set; <Q1=0kg to 20.5kg; ≥Q1 to <Q2=20.5kg to 30.5kg; ≥Q2 to <Q3=30.5kg to 42.5kg; Q1=25th percentile; Q3=75th percentile

Table 10: Percentage reduction in seizure frequency over the Treatment Period by epileptic syndrome (FAS)

Epileptic syndrome	Seizure frequency per week		Percentage reduction by epileptic syndrome
	Baseline Period	Treatment Period	
Statistics	N=73		
Symptomatic			
n	41	41	41
Median	9.57	3.75	38.57
Q1-Q3	4.13 - 24.63	1.05 - 27.79	8.93 - 66.97
Cryptogenic			
n	28	28	28
Median	4.20	4.21	39.88
Q1-Q3	1.86 - 10.79	0.90 - 9.51	−12.19 - 57.67
Idiopathic			
n	3	3	3
Median	2.43	1.25	63.26
Q1-Q3	1.98 - 61.06	0.89 - 4.44	37.03 - 92.73
Unknown			
n	1	1	1
Median	17.08	9.70	43.21
Q1-Q3	17.08 - 17.08	9.70 - 9.70	43.21 - 43.21

FAS=Full Analysis Set; Q1=25th percentile; Q3=75th percentile

Table 11: Percentage reduction in seizure frequency over the Treatment Period by baseline seizure frequency (FAS)

BSFW	Seizure frequency per week		Percentage reduction by BSFW
	Baseline Period	Treatment Period	
Statistics	N=73		
<25%			
n	18	18	18
Median	1.58	0.83	57.99
Q1-Q3	1.33 - 1.94	0.22 - 0.89	37.89 - 81.88
≥25% <50%			
n	19	19	19
Median	4.34	3.29	20.35
Q1-Q3	3.64 - 5.77	1.79 - 4.71	−19.70 - 52.14
≥50% <75%			
n	17	17	17
Median	11.71	5.52	43.21
Q1-Q3	9.57 - 16.57	2.77 - 13.50	−36.71 - 69.07
≥75%			
n	19	19	19
Median	48.53	33.88	27.04
Q1-Q3	24.63 - 65.38	13.81 - 60.40	9.64 - 47.42

BSFW=Baseline seizure frequency per week; FAS=Full Analysis Set; Q1=25th percentile; Q3=75th percentile

Table 12: Percentage reduction in seizure frequency over the Treatment Period by the number of concomitant AEDs (FAS)

Concomitant AEDs	Seizure frequency per week		Percentage reduction by concomitant AEDs
	Baseline Period	Treatment Period	
Statistics	N=73		
1 AED			
n	5	5	5
Median	3.64	0.82	47.52
Q1-Q3	1.33 - 6.13	0.43 - 3.21	38.57- 81.88
2 AEDs			
n	68	68	68
Median	8.07	4.47	40.55
Q1-Q3	2.63 - 20.00	1.13 - 18.39	1.59 - 61.29

AED=anti-epileptic drug; FAS=Full Analysis Set; Q1=25th percentile; Q3=75th percentile

Table 13: Percentage reduction in seizure frequency over the Treatment Period by the type of concomitant AEDs (FAS)

Concomitant AEDs Statistics	Seizure frequency per week		Percentage reduction by con-AEDs used by ≥10 subjects
	Baseline Period	Treatment Period	
	N=73		
Valproate sodium			
n	37	37	37
Median	11.71	5.33	37.03
Q1-Q3	4.88 - 24.70	2.29 - 27.79	12.27 - 56.02
Carbamazepine			
n	22	22	22
Median	4.66	2.00	52.37
Q1-Q3	2.43 - 9.88	0.82 - 5.33	2.08 - 86.39
Lamotrigine			
n	18	18	18
Median	3.97	4.68	12.09
Q1-Q3	1.96 - 17.25	1.21 - 27.79	−25.35 - 52.86
Clobazam			
n	15	15	15
Median	16.78	12.50	27.13
Q1-Q3	4.98 - 27.44	4.93 - 35.37	−9.11 - 48.37
Phenytoin			
n	10	10	10
Median	3.14	1.86	58.22
Q1-Q3	1.43 - 12.13	0.15 - 8.64	2.08 - 86.15
Topiramate			
n	10	10	10
Median	6.18	5.22	23.76
Q1-Q3	2.00 - 11.71	1.05 - 19.36	−23.35 - 52.90
Zonisamide			
n	10	10	10
Median	4.32	2.99	45.36
Q1-Q3	1.35 - 8.40	0.87 - 4.71	27.04 - 64.31

AED=anti-epileptic drug; FAS=Full Analysis Set; Q1=25th percentile; Q3=75th percentile

During the Up-Titration Period, the subjects received LEV 20mg/kg/day (1000mg/day if over 50 kgs) for 2 weeks, 40mg/kg/day (2000mg/day if over 50 kgs) for 2 weeks, and then started 60mg/kg/day (3000mg/day) if tolerability was confirmed. The median percentage reduction in seizure frequency during this sub-period was 32.87%. The median percentage reduction at each visit from visit 4 until visit 8 ranged between 37.05 and 44.39%, with the reduction in seizure frequency appearing to be sustained over time.

The seizure frequency per week was 3.50 at Visit 4 when LEV treatment had started, compared to 6.25 at Visit 3 prior to LEV treatment. The reduction in seizure frequency was seen at the time of the initial LEV dose of 20mg/kg/day and the percentage reduction appeared to be sustained over time.

The median percentage reduction in seizure frequency during the second period was 41.32%, closely mirroring the percentage seen in the first period. The efficacy of LEV treatment was shown to be sustained over time as an adjunctive therapy in a long term use.

The percentage reduction in seizure frequency per week and actual seizure frequency seen in period 2 is summarized in table 14. There were no subjects who were seizure free during the Second Period

Table 14: Percentage reduction in seizure frequency by 3-month window over the Evaluation Period during the Second Period (FAS)

Period/Window	Statistics	Seizure frequency per week	Percentage reduction
		N=55	
Overall Evaluation	n	55	
	Mean (SD)	10.10 (27.43)	34.71 (58.88)
	Median	1.81	41.32
	Q1-Q3	0.66 – 8.22	15.37 - 82.40
	Min-max	0.0 - 190.1	−197.5 - 99.0
>6 months to ≤9 months	n	53	
	Mean (SD)	10.12 (23.06)	30.91 (67.68)
	Median	1.90	37.29
	Q1-Q3	0.53 - 6.01	10.18 - 88.65
	Min-max	0.0 - 139.6	−250.0 - 100.0
>12 months to ≤15 months	n	47	
	Mean (SD)	6.92 (12.98)	39.62 (65.92)
	Median	1.37	50.00
	Q1-Q3	0.53 – 6.09	15.23 - 92.50
	Min-max	0.0 – 55.7	−195.6 - 100.0
>18 months to ≤21 months	n	43	
	Mean (SD)	6.34 (14.03)	51.16 (58.51)
	Median	1.18	64.17
	Q1-Q3	0.15 - 3.20	29.61 - 95.50
	Min-max	0.0 - 70.8	−206.9 - 100.0
>24 months to ≤27 months	n	39	
	Mean (SD)	6.27 (13.12)	52.76 (65.73)
	Median	0.84	76.52
	Q1-Q3	0.23 - 3.58	36.09 - 95.37
	Min-max	0.0 - 50.9	−192.9 - 100.0
>30 months to ≤33 months	n	32	
	Mean (SD)	6.43 (12.60)	65.75 (47.38)
	Median	0.65	86.88
	Q1-Q3	0.04 - 5.75	53.08 - 99.88
	Min-max	0.0 - 47.8	−99.1 - 100.0
>36 months to ≤39 months	n	5	
	Mean (SD)	9.29 (14.40)	77.42 (24.71)
	Median	2.44	79.12
	Q1-Q3	0.00 - 10.02	66.65 - 100.0
	Min-max	0.0 - 34.0	41.3 - 100.0

FAS=Full Analysis Set; Max=maximum; Min=minimum; Q1=25th percentile; Q3=75th percentile; SD=standard deviation

III.1.8 Pharmacokinetics/-dynamics - Results

The fact that all subjects received the protocol-defined LEV dosage during the first period and second period was reflected in the observed LEV plasma concentrations. During the second period, the doses administered to the subjects were higher than those during the first period, leading to very limited number of concentrations for the 10 mg/kg/bid target dose group. Although 23 subjects (41.8%) switched from the dry syrup to the tablets and the number of concentrations is lower during the second period, the concentrations vs time points profile observed during the second period was overall similar to that observed during the first period.

Overall, the concentrations for both the first period and second period were below 30µg/mL for the target dose of 10mg/kg/bid, below 50µg/mL for the target dose of 20mg/kg/bid, and below 80µg/mL for the target dose of 30mg/kg/bid. The increase of concentrations seemed to be in proportion to the dose with maximal concentrations reached between 1 and 4 hours post dose. The concentrations subsequently decreased and remained quantifiable for at least 16 hours for each dose. The resulting concentrations were within the levels seen in previous studies.

III.1.9 Safety Results

Safety evaluations for periods of +3 years in this study indicated that LEV at the doses provided throughout (20 to 60 mg/kg/day or 1000 to 3000 mg/day if over 50 kilos) was well-tolerated in the subject group studied.

During the whole of the study the mean duration of exposure to LEV was 714.25 (SD = 448.93) days with a mean dose of 47.37mg/kg (SD = 11.42) in 73 subjects. The total exposure to LEV throughout the study (expressed in days) and the mean LEV daily doses are summarised in tables 6 and 7.

Table 15: Days of exposure to LEV (FAS) during All Periods

Statistics	First Period[a] N=73	Second Period[b] N=55	All Periods N=73
Mean (SD)	96.16 (21.96)	820.36 (304.63)	714.25 (448.93)
Median	98.00	928.00	952.00
Q1 – Q3	97.00 – 105.00	619.00 - 1027.00	196.00 - 1103.00
Min-max	14.0 – 133.0	98.0 - 1179.0	14.0 - 1277.0

FAS=Full analysis set; LEV=levetiracetam; Min=minimum, Max=maximum; Q1=25th percentile, Q3=75th percentile; SD=standard deviation

[a] Data from the Treatment + Down-Titration Period are presented.

[b] Data from the Evaluation + Down-Titration Period are presented.

Table 16: **Mean LEV daily dose (mg/kg) (FAS) during All Periods**

Statistics	First Period[a] N=73	Second Period[b] N=55	All Periods N=73
Mean (SD)	45.92 (7.87)	50.74 (10.84)	47.37 (11.42)
Median	48.87	54.63	51.11
Q1 – Q3	42.24 – 51.43	44.70 - 59.79	41.33 - 57.54
Min-max	20.0 – 54.3	26.1 - 63.8	20.0 - 62.9

FAS=Full Analysis Set; LEV=levetiracetam; Min=minimum, Max=maximum; Q1=25th percentile, Q3=75th percentile; SD=standard deviation

[a] Data from the Treatment + Down-Titration Period are presented.

[b] Data from the Evaluation + Down-Titration Period are presented.

There were 802 treatment-emergent adverse events (TEAEs) reported in 70 subjects (95.9% of study population), 91 adverse drug reactions (ADRs) in 43 subjects (58.9%) and 14 SAEs in 8 subjects (11%). Discontinuations and dosage adaptions due to TEAEs were reported in 7 and 16 subjects respectively. Of all the reported TEAEs 3 were severe, with a case of status epilepticus, somnolence and a near-drowning with fatal consequences.

Table 17: **Overall summary of TEAEs during each period (FAS)**

Category	First Period[c] N=73 n[b] (%)	Second Period[c] N=55 n[b] (%)	All Periods[c] N=73 n[b] (%)
Any TEAEs	60 (82.2)	54 (98.2)	70 (95.9)
Serious TEAEs	0	8 (14.5)	8 (11.0)
Discontinuation due to TEAEs	4 (5.5)	3 (5.5)	7 (9.6)
Any ADRs[a]	41 (56.2)	15 (27.3)	43 (58.9)
Severe TEAEs	1 (1.4)	2 (3.6)	3 (4.1)
Deaths	0	1 (1.8)	1 (1.4)
TEAEs requiring dose change	12 (16.4)	6 (10.9)	16 (21.9)

ADR=adverse drug reaction; FAS=Full Analysis Set; TEAE=treatment-emergent adverse event

[a] ADRs are defined as TEAEs except the AEs judged as not related.

[b] n=number of subjects reporting at least 1 TEAE in that category.

[c] This Table covers Treatment Period + Down-Titration Period + Follow-Up Period.

Before treatment start (visit 3), 72 pretreatment adverse events (AEs) were noted in 40 subjects (54,8% of participants) with the most frequently reported ones being nasopharyngitis and upper respiratory tract infection (respectively 23.3 and 6.8 percent of subjects), while all other pretreatment AEs had an incidence lower than 2.7%. Three pretreatment serious adverse events (SAEs) were noted, pneumonia, tibia fracture, and convulsion, all which resolved without sequelae.

The most frequently reported ADR was somnolence in 31 subjects (42.5%), that is to say 30 subjects (41.1%) in the first and 2 subjects (3.6%) during the second period. The majority of the ADRs were mild or moderate in intensity. There was only 1 severe ADR of somnolence during the first period. The event did not resolve; however, it did not lead to study discontinuation. There was 1 serious ADR of acetonaemic vomiting during the second period. The event was judged

by the investigator as unlikely related to LEV and resolved 3 days after the event onset.

The most frequently reported TEAEs were nasopharyngitis in 54 subjects (74.0%), followed by somnolence in 34 subjects (46.6%). The former showed a consistent occurrence pattern across periods with 39.7% and 76.4% of subjects developing this AE during the first and second periods respectively. Somnolence showed a marked drop off going from the first to second period, with the incidence dropping from 43.8% to 12.7%.

As stated earlier, 3 severe TEAEs occurred during the study, a case of somnolence during the first period (considered related to LEV, unresolved but the subject continued study participation), and one case of status epilepticus (considered not related to LEV treatment and resolved) and another of (fatal) near drowning in the second (considered not related to study treatment).

In regards to the fatal near drowning, the cause was considered to be the onset of a seizure while taking a bath, which led to a cardiopulmonary arrest. On the day following the event onset the subject's symptom did not improve despite the treatment and he died.

Over both periods there were 14 SEAs in 8 subjects (11.0%). Of these 1, the near drowning, was fatal, as expounded upon earlier, but all other resolved during the study.

Overall, age and body weight did not appear to influence the incidence of AEs and no trends were noted. All SAEs, other than the status epilepticus and near drowning (TE)AEs, were mild to moderate in intensity. Only one event, namely conversion disorder, led to study discontinuation while all other SAEs did not require changes in LEV doses.

A total of 7 subjects (9.6%) discontinued LEV treatment due to 8 TEAEs, with 4 subjects (5.5%) leaving the study during the first period and 3 subjects (5.5%) doing so during the second.

The clinical laboratory evaluations did not indicate any clinically significant changes, though there were parameters in hematology, blood chemistry, and vital signs that indicated possibly clinically significant (PCS) values. Nevertheless, the incidence of each parameter was relatively low and no trends to increase or decrease from the baseline values were noted.

The high incidences of treatment-emergent PCS values in body weight (too low) were reported as 24.7% in the first and 34.5% in the second period. Nevertheless, the mean change from the baseline in the actual value at Visit 8 and Last Visit was an increase of 0.7kg and 6.0kg respectively, with there being no clinically meaningful decreases in mean body weight. Weight decrease is recognized as an ADR for LEV in the approved product labeling, and the observed changes from the Baseline weight in this study did not constitute an additional safety concern.

III.1.10 Conclusions by the MAH

The efficacy results showed a reduction in the median percentage of partial seizures from Baseline across all time intervals and subsequent maintenance of efficacy throughout the study periods. The results on the PPS were positive and very similar to the results of the FAS analyses. This confirmed the robustness of the FAS analyses.

The efficacy of LEV treatment was verified and deemed clinically relevant because the median percentage reduction from baseline in partial seizure frequency per week over the 14-week Treatment Period in the FAS was 43.21% and the 95% CI was between 26.19% and 52.14%. The lower limit of the 95% CI, 26.19%, was greater than the predefined value of 16.3%, which was the median percentage reduction of the seizure frequency per week of the subjects in the placebo group of a 28-week, double-blind, placebo-controlled, multicenter study (N159).

Similar to the First Period, there was a reduction in the median percentage of seizures during the Second Period. The median percentage reduction in seizure frequency over the Evaluation Period during the Second Period was 41.32% compared to the First Period; 43.21% over the 14-week Treatment Period during the First Period. The efficacy of LEV treatment was sustained over time as an adjunctive therapy in a long term use.

The safety profile showed that long-term treatment with LEV was generally well tolerated in the subjects in this study. Levetiracetam was safe and well tolerated, as evaluated by the safety data, which covered longer than 3 years for the subjects with exposure to LEV.

Nasopharyngitis and somnolence were reported as distinctive TEAEs throughout the study. Nasopharyngitis was the most frequently reported TEAEs with the incidence of 74.0% during the All Periods, and consistently occurred across the study periods. An increase in the incidence of nasopharyngitis was observed during the Second Period. This was considered due to the influence of the study duration that was longer in the second period.

Somnolence appeared to be related to LEV treatment. After the first dose of LEV 20mg/kg/day, 32.9% of the subjects reported somnolence during the Up-Titration Period. The onset of this event was increased to 43.8% during the First Period and was markedly decreased to 1.9% at the first 6 months of the Second Period. The subjects who experienced somnolence appeared to adapt the LEV dose, which led to the decrease in the number of the subjects who reported the event later in the course of study. Somnolence assessed as an ADR was reported by 42.5% of subjects during the All Periods with an exception of 1 event that was severe, while all events were mild in intensity. The severe somnolence was a result of aggravation of a mild somnolence that occurred 2 days after the initiation of LEV treatment. Worsening of the intensity was associated with an increase of LEV dose during the Evaluation Period. Although the somnolence did not resolve, the subject who experienced the severe somnolence continued the study participation with a decreased LEV dose, which was also indicative that the subject could adapt the LEV dose and continue LEV treatment.

The only ADR assessed as serious was an event of acetonaemic vomiting, which was judged by the investigator as unlikely related to LEV and resolved 3 days after the event onset. With an exception of a fatal SAE of near drowning (considered not related to the treatment), all other SAEs resolved during the study.

There were parameters in hematology, blood chemistry, and vital signs that indicated PCS values; however, the incidence of each parameter was relatively low and no trends in shifts from Baseline were noted.

The high incidences of treatment-emergent PCS values (too low) in body weight were reported as 24.7% in the First Period and 34.5% in the Second Period. In spite of this, the incidences of treatment-emergent PCS values in body weight did not suggest that the body weight became notably low after LEV treatment. The mean change in weight at Visit 8 from the Baseline was an increase of 0.7kg and there were no clinically meaningful decreases in mean body weight.

In conclusion, long-term adjunctive treatment with LEV at the doses of 20mg/kg/day or 1000mg/day to 60mg/kg/day or 3000mg/day was effective in Japanese children aged ≥4 to <16 years with partial onset seizures. Levetiracetam plasma concentrations were within the ranges seen in previous studies. The results of efficacy measures demonstrated a reduction in seizures from Baseline and maintenance of efficacy. Levetiracetam was safe and well tolerated, as evaluated by the safety data which covered longer than 3 years for the subjects with exposure to LEV.

III.2 Study N01363

III.2.1 Introduction

Study N01363 was an n open-label, single-arm, multicenter study to evaluate the efficacy and safety of adjunctive treatment with levetiracetam in Japanese paediatric patients (≥4 to <16 years) with uncontrolled generalized tonic-clonic (GTC) seizures despite treatment with 1 or 2 antiepileptic drug(s).

III.2.2 Objectives

To evaluate the efficacy and safety of LEV dry syrup at doses up to 60mg/kg/day or 3000mg/day used as adjunctive therapy in Japanese paediatric subjects aged ≥4 to <16 years with uncontrolled GTC seizures, despite treatment with 1 or 2 antiepileptic drugs (AED[s]).

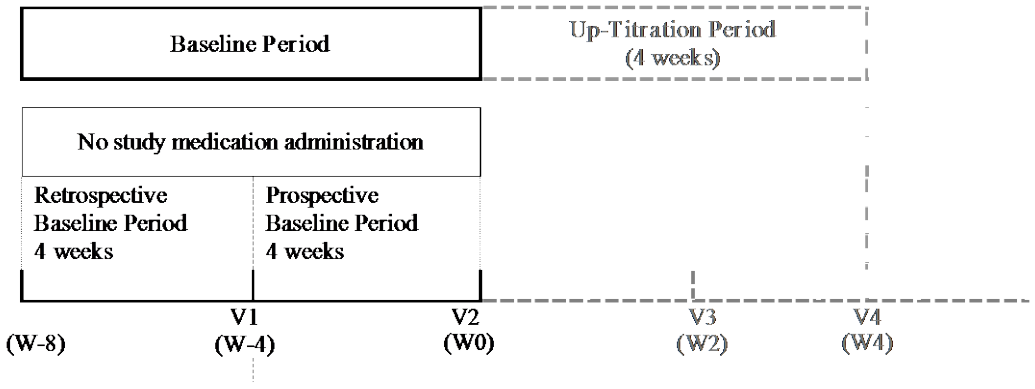
No other objectives, secondary or primary were planned.

III.2.3 Study Methodology

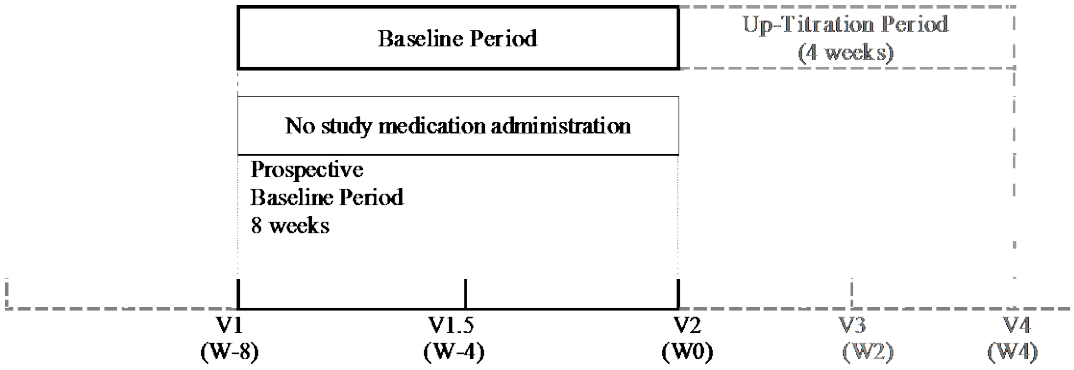
This study was designed as an open-label, single-arm, multicenter study taking 34 weeks, excluding a 4-week Retrospective Baseline, divided in 4 periods:

- Combined Baseline Period (8 weeks: 4-week Retrospective Baseline + 4-week Prospective Baseline): During this period, informed consent was obtained and eligibility assessed. A daily record card was dispensed and samples for laboratory assessments were collected for the blood chemistry, hematology, urinalysis, and pregnancy test (if applicable). For subjects without Retrospective Baseline documentation, an 8-week Prospective Baseline Period was scheduled.

Retrospective 4 weeks + Prospective 4 weeks:



Prospective 8 weeks:
(No Retrospective Baseline documentation)



V=visit; W=week

- Up-Titration Period (4 weeks): During this period, subjects started the LEV treatment at 20mg/kg/day (subject weighing ≥50kg started at 1000mg/day) that was up-titrated to 60mg/kg/day (subject weighing ≥50kg was up-titrated to 3000mg/day). The LEV dose was increased by 20mg/kg/day every 2 weeks (subject weighing ≥50kg was increased by 1000mg/day).
- Evaluation Period (20 weeks): During this period, subjects were administered LEV at 60mg/kg/day or 3000mg/day.
- Withdrawal Period (6 weeks including the 2-week follow up after the last LEV intake): During this period, the LEV dose was reduced as gradually as possible to protect subjects from aggravation of seizures, considering the subject's safety. All of the subjects in this period were required to attend a Follow-Up Visit 2 weeks after the last dosing of the treatment with LEV.

At the end of the evaluation period, if the Investigator decided to continue LEV treatment and the subject agreed, the latter continued the treatment with open-label LEV in the long-term follow-up study, N01361. If the Investigator decided to discontinue LEV treatment, the subject entered the Withdrawal Period.

It was planned for least 15 subjects to enroll in this study, but even if this number was reached, further subject recruitment was to be continued until the time when the last subject first visit was completed in N01159, a different study to evaluate the efficacy and safety of adjunctive treatment with LEV in subjects aged ≥16 years with GTC seizures. In reality, enrollment ended after 13 subjects were enrolled in the study due to difficulties in enrolling eligible subjects (with permission of the Japanese Pharmaceutical and Medical Devices Agency).

III.2.4 Exclusion and Inclusion Criteria

Inclusion criteria (*selected, for full list see study report*)

- Japanese paediatric subjects aged ≥4 to <16 years with uncontrolled GTC seizures, with a body weight ≥11kg and <82kg at the time of the first visit.
- The subject had to have had at least 3 GTC seizures during the 8-week Combined Baseline Period (at least 1 GTC seizure during the Retrospective

Baseline Period and at least 1 GTC seizure during the Prospective Baseline Period), and historical seizure must have been prospectively recorded on a DRC in order to be acceptable.

- The subject had been on a stable dose of 1 or 2 AEDs for the last 4 weeks (potassium bromide and sodium bromide for the last 12 weeks) prior to the Combined Baseline Period and during the Combined Baseline Period.
- A female subject with childbearing potential (without a history of hysterectomy or bilateral oophorectomy) was eligible if she used a medically accepted contraceptive method for the duration of the study participation

Exclusion criteria (*selected, for full list see study report*)

- Lactation or pregnancy.
- Previous exposure to LEV.
- Diagnosis of Lennox-Gastaut Syndrome.
- Presence of any sign (clinical or imaging procedures) suggesting a progressive brain lesion/disease; in particular, progressive disorder with epileptic seizures subject who had psychogenic nonepileptic seizures, a history of brain surgeries for the purpose of epilepsy treatment, confirmed focal epilepsy based on clinical signs (seizure types), with consistent EEG and MRI features.
- A history of convulsive or non-convulsive status epilepticus while taking concomitant AEDs for the last 3 months prior to Visit 1.
- A known clinically significant acute or chronic illness
- Clinically significant electrocardiogram abnormalities.
- A subject who had clinically significant deviations from the reference range or values for laboratory parameters such as for example creatinine clearance, platelet count, etcetera
- Following a ketogenic diet during the 4 weeks prior to the Combined Baseline Period.
- Having a disorder or condition that might have interfered with the absorption, distribution, metabolism, or excretion of drugs.
- Having received other investigational drugs, unapproved medication, or medical devices for the last 4 weeks prior to the Combined Baseline Period.

III.2.5 Endpoints

Efficacy: primary

The percent reduction from the Combined Baseline Period (4-week Retrospective Baseline and 4-week Prospective Baseline) in the GTC seizure frequency per week over the 24-week Treatment Period (Up-Titration and Evaluation Periods).

Efficacy: secondary

- The percentage reduction in GTC seizure frequency per week from the Combined Baseline Period over the Evaluation Period
- The GTC seizures 50% responder rate (the proportion of subjects with 50% or more reduction from the Combined Baseline Period in the frequency of GTC seizures) during the Treatment Period
- The GTC seizures 50% responder rate (the proportion of subjects with 50% or more reduction from the Combined Baseline Period in the frequency of GTC seizures) during the Evaluation Period
- The GTC seizure freedom over the Evaluation Period
- The GTC seizure freedom over the Treatment Period

Efficacy: other

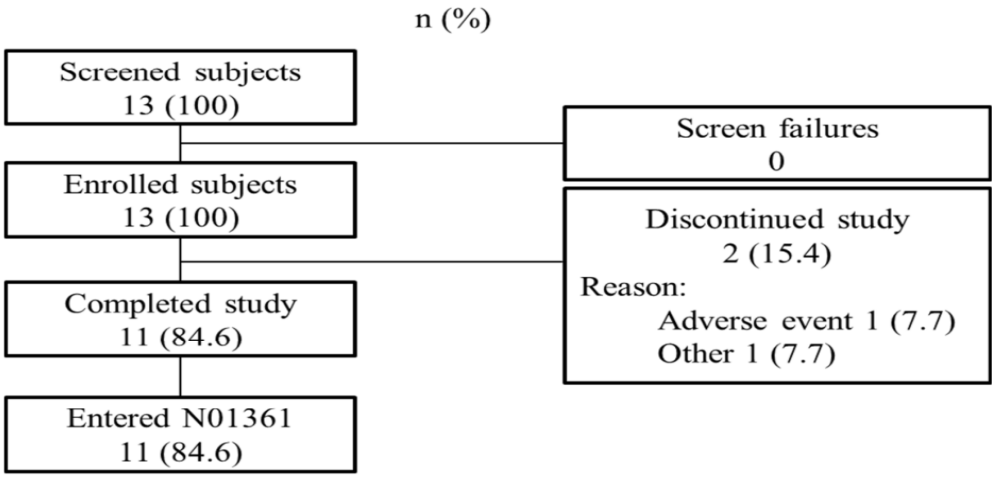
See study report.

Safety

Safety information collected during the study

III.2.6 Subject Disposition

In total 13 subjects were screened and enrolled; there were no screen failures. Eleven subjects (84.6%) completed the study and entered the follow-up study, N01361. Two subjects (15.4%) discontinued the study.



Note: N01361 was an open-label, long-term, follow-up study for subjects ≥4 years of age.
Note: Subject 306-01807 discontinued the study for reason of other; the subject was administered an additional antiepileptic drug.

One subject (7.7%) discontinued the study due to adverse drug reactions (ADRs) of headache and somnolence. The ADRs were moderate in intensity, not serious, and were resolved upon follow up.

The other discontinuation was due to reasons classified as 'other'.

One subject (7.7%) had 1 important protocol deviation whereby the Up-Titration Period was not started with administration of LEV 20mg/kg/day as described in the Protocol, but instead with LEV 40mg/kg/day. No action was taken in regards to this deviation.

III.2.7 Efficacy Results

The primary efficacy variable, the median percentage reduction in GTC seizure frequency per week from the Combined Baseline Period over the Treatment Period, was 56.52% with a CI as shown in table 1.

Table 1: Descriptive statistics of GTC seizure frequency during the Combined Baseline Period and over the Treatment Period

Statistic	LEV Total N=13			
	Combined Baseline Period	Treatment Period	Reduction	Percentage reduction
n	13	13	13	13
Mean (SD)	5.52 (10.09)	5.33 (12.10)	0.18 (2.37)	45.47 (50.34)
Median (Min, Max)	1.63 (0.5, 36.9)	0.83 (0.0, 42.7)	0.60 (-5.8, 3.3)	56.52 (-45.4, 100.0)
Q1, Q3	0.75, 3.69	0.08, 2.50	0.03, 0.79	1.01, 89.08
95% CI for median	-	-	-0.39, 2.24	-15.74, 98.18

CI=confidence interval; LEV=levetiracetam; Max=maximum; Min=minimum; Q1=25th percentile; Q3=75th percentile; SD=standard deviation

The percentage of GTC seizures per week was reduced from the Combined Baseline Period over the Treatment Period across all subgroups by age, gender, epileptic syndrome, Baseline seizure frequency, and concomitant AEDs at Baseline. Although some differences in percentage reduction of GTC seizures were observed between subgroups, there were too few subjects to permit meaningful comparisons.

Table 2: **Percentage reduction of GTC seizure frequency per week from the Combined Baseline Period over the Treatment Period by subgroup (FAS)**

Treatment group Subgroup	n	Percentage reduction of GTC seizures per week		
		Mean (SD)	Median (Min, Max)	Q1, Q3
Age (years)				
Child (<12)	6	28.90 (63.56)	26.89 (-45.4, 98.2)	-22.20, 89.08
Adolescent (≥12)	7	59.67 (34.53)	56.52 (1.0, 100.0)	43.46, 100.00
Gender				
Male	9	33.45 (49.10)	48.72 (-45.4, 98.2)	-15.74, 68.00
Female	4	72.52 (47.95)	94.54 (1.0, 100.0)	45.05, 100.00
Epileptic syndrome: Idiopathic				
No	9	28.73 (50.05)	48.72 (-45.4, 98.2)	-15.74, 68.00
Yes	4	83.14 (26.95)	94.54 (43.5, 100.0)	66.27, 100.00
Epileptic syndrome: Cryptogenic or symptomatic				
No	13	45.47 (50.34)	56.52 (-45.4, 100.0)	1.01, 89.08
Yes	0	-	-	-
Epileptic syndrome: Symptomatic				
No	6	72.96 (26.27)	72.80 (43.5, 100.0)	48.72, 100.00
Yes	7	21.91 (55.59)	1.01 (-45.4, 98.2)	-22.20, 69.52
Baseline seizure frequency/week				
<1	6	59.19 (55.66)	78.54 (-45.4, 100.0)	43.46, 100.00
≥1	7	33.71 (46.23)	48.72 (-22.2, 98.2)	-15.74, 69.52
Concomitant AEDs at Baseline				
1	5	74.01 (21.75)	69.52 (43.5, 100.0)	68.00, 89.08
2	8	27.63 (55.94)	24.86 (-45.4, 100.0)	-18.97, 77.35

AED=antiepileptic drug; FAS=Full Analysis Set; GTC=generalized tonic-clonic; Max=maximum; Min=minimum; Q1=25th percentile; Q3=75th percentile; SD=standard deviation

Generalized tonic-clonic seizure frequency also showed improvement from the Combined Baseline Period over the Evaluation Period; the median percent reduction in GTC seizure frequency per week was 64.70% as seen in table 3.

Table 3: **Generalized tonic-clonic seizure frequency per week and reduction from the Combined Baseline Period over the Evaluation Period (FAS)**

Statistic	LEV Total N=13			
	Combined Baseline Period	Evaluation Period	Reduction	Percentage reduction
n	12	12	12	12
Mean (SD)	5.50 (10.54)	5.77 (12.86)	-0.27 (2.60)	44.93 (51.86)
Median (Min, Max)	1.25 (0.5, 36.9)	0.64 (0.0, 43.0)	0.54 (-6.2, 2.3)	64.70 (-36.0, 100.0)
Q1, Q3	0.75, 3.56	0.07, 2.39	-0.12, 0.70	-8.29, 92.38
95% CI for median	-	-	-0.24, 0.75	-16.74, 97.81

CI=confidence interval; FAS=Full Analysis Set; LEV=levetiracetam; Max=maximum; Min=minimum; Q1=25th percentile; Q3=75th percentile; SD=standard deviation

The GTC 50% responder rates for the Treatment Period and Evaluation Period were 53.8% (7 of 13 subjects) and 58.3% (7 of 12 subjects), respectively. Four

subjects were 75% responders for the Treatment Period (30.8%) and Evaluation Period (33.3%).

Generalized tonic-clonic seizure freedom in subjects was also similar between the Treatment Period and Evaluation Period. Two subjects were seizure free during the former and 2 were likewise during the latter.

The time to the first GTC seizure during the Treatment Period ranged from Day 1 (the first day of LEV treatment) for 1 subject, to Day 169 and Day 173 of the Treatment Period for the 2 subjects who remained seizure free.

There was no worsening of GTC seizure frequency during the Up-Titration Period and overall improvement in GTC seizure frequency was seen at each visit after starting treatment with LEV.

III.2.8 Safety Results

In total 41 treatment-emergent AEs (TEAEs) that were mild or moderate in severity were reported and no treatment-emergent serious AEs (SAEs) or deaths occurred.

As mentioned earlier, one subject discontinued the study due to adverse drug reactions (ADRs).

The most frequently reported TEAEs were nasopharyngitis, convulsion, and somnolence, each reported by 3 subjects (23.1%) overall. Adverse drug reactions were reported by 5 subjects (38.5%) overall. The most frequently reported ADR was somnolence, reported by 3 subjects (23.1%) overall.

In general, ≤2 subjects reported post-baseline values that were considered possibly clinically significant (PCS) for any hematology or blood chemistry variable; no urinalysis results were PCS. Shifts from not PCS at Baseline to PCS post Baseline were reported for hematocrit (too high), leukocytes (too high), neutrophils (too low), triglycerides (too high), and urate (too high).

The most frequently reported vital sign measurement with a PCS shift from Baseline was diastolic blood pressure (DBP). Six subjects (46.2%) reported DBP measurement shifts from not PCS at Baseline to too low or too high post Baseline. Systolic blood pressure measurements also showed PCS shifts from Baseline for 2 subjects and pulse rate measurements shifted for 1 subject (7.7%). These changes were not considered clinically significant by the Investigator.

One subject (9.1%) reported an abnormal ECG finding of prolonged QT interval at Visit 9. The event was considered a clinically significant ADR that was not serious, mild in intensity, and was resolved after entering the long-term follow-up study.

None of the observed laboratory values or physical examination presented findings that were of concern.

Table 4: Incidence of TEAEs overall and by period of onset (SS)

Category	LEV Total N=13		
	Overall n (%) [#]	Up-Titration Period n (%) [#]	Evaluation Period n (%) [#]
Number of subjects "at risk"	-	13	12
Any TEAEs	13 (100) [41]	8 (61.5) [13]	11 (91.7) [28]
Serious TEAEs	0	0	0
Discontinuations due to TEAEs	1 (7.7) [2]	1 (7.7) [2]	0
ADRs (drug-related TEAEs)	5 (38.5) [7]	4 (30.8) [5]	2 (16.7) [2]
Severe TEAEs	0	0	0
Deaths	0	0	0

ADR=adverse drug reaction; LEV=levetiracetam; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE in that category.
Note: Percentages were based on the number of "at risk" subjects in that period.
Note: [#] was the number of individual occurrences of the TEAE in that category.
Note: Subjects who entered a period were regarded as "at risk" for this period.

Table 5: Treatment-emergent adverse events overall and by period reported by at least 2 subjects overall (SS)

MedDRA System Organ Class Preferred term	LEV Total N=13		
	Overall n (%) [#]	Up-Titration Period n (%) [#]	Evaluation Period n (%) [#]
Number of subjects "at risk"	-	13	12
Any TEAE	13 (100) [41]	8 (61.5) [13]	11 (91.7) [28]
Gastrointestinal disorders	3 (23.1) [7]	1 (7.7) [3]	3 (25.0) [4]
Diarrhoea	2 (15.4) [5]	1 (7.7) [2]	2 (16.7) [3]
Infections and infestations	5 (38.5) [8]	2 (15.4) [2]	4 (33.3) [6]
Nasopharyngitis	3 (23.1) [5]	1 (7.7) [1]	2 (16.7) [4]
Nervous system disorders	7 (53.8) [10]	6 (46.2) [7]	2 (16.7) [3]
Convulsion	3 (23.1) [5]	2 (15.4) [2]	2 (16.7) [3]
Somnolence	3 (23.1) [3]	3 (23.1) [3]	0

LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE within the SOC/PT.
Note: Percentages were based on the number of "at risk" subjects in that period.
Note: [#] was the number of individual occurrences of the TEAE.
Note: Subjects who entered a period were regarded as "at risk" for this period.

Table 6: Incidence of ADRs (drug-related TEAEs) overall and by period of onset (SS)

MedDRA System Organ Class Preferred term	LEV Total N=13		
	Overall n (%) [#]	Up-Titration Period n (%) [#]	Evaluation Period n (%) [#]
Number of subjects "at risk"	-	13	12
Any ADR	5 (38.5) [7]	4 (30.8) [5]	2 (16.7) [2]
Gastrointestinal disorders	1 (7.7) [1]	0	1 (8.3) [1]
Diarrhoea	1 (7.7) [1]	0	1 (8.3) [1]
Investigations	1 (7.7) [1]	0	1 (8.3) [1]
Electrocardiogram QT prolonged	1 (7.7) [1]	0	1 (8.3) [1]
Nervous system disorders	4 (30.8) [5]	4 (30.8) [5]	0
Somnolence	3 (23.1) [3]	3 (23.1) [3]	0
Bradykinesia	1 (7.7) [1]	1 (7.7) [1]	0
Headache	1 (7.7) [1]	1 (7.7) [1]	0

ADR=adverse drug reaction; LEV=levetiracetam; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 ADR within the SOC/PT.
Note: [#] was the number of individual occurrences of the ADR.
Note: Subjects who entered a period were regarded as "at risk" for this period.

III.2.9 Conclusions by the MAH

Overall, the efficacy results demonstrated improvement in GTC seizure frequency with adjunctive LEV treatment across all population subgroups and over all study periods and visits. The primary efficacy variable was the reduction in GTC seizure frequency from the Combined Baseline Period over the Treatment Period. There were some differences in the median reduction when analyzed by subgroup, but given the small sample size, any interpretation of these results is difficult. Nonetheless, improvement in GTC seizure frequency was observed in all subgroups.

The secondary efficacy variables were the reduction in GTC seizure frequency from the Combined Baseline Period over the Evaluation Period and the GTC seizure 50% responder rates and seizure freedom over the Treatment Period and Evaluation Period, whereby the median percentage reduction over the Evaluation Period was 64.70%. The majority of subjects were 50% responders for the Treatment Period (53.8%) and the Evaluation Period (58.3%) and 2 subjects remained seizure free during these study periods.

From the Combined Baseline Period over the Treatment Period, there was also a 25% reduction in the number of any type of seizure per week. Levetiracetam is a treatment for other seizure types; thus, these results, while limited, are not unexpected.

The safety profile suggests LEV was generally well tolerated at this exposure in the paediatric subjects in this study and the AEs reported were consistent with the known safety profile for LEV.

Overall, there were no clinically relevant trends in TEAE incidence across study periods, gender, or age categories.

The evaluation of clinical laboratories and vital signs did not indicate any clinically significant trends in changes from Baseline across study periods.

The following overall conclusions for N01363 were drawn:

Levetiracetam at doses up to 60mg/kg/day or 3000mg/day was effective in reducing GTC seizure frequency when used as adjunctive therapy with 1 or 2 other AEDs in Japanese paediatric subjects aged ≥4 to <16 years. Furthermore, Levetiracetam was safe and well tolerated as evaluated by the safety data and there were no new safety concerns for LEV identified in this study.

However, due to the small size of N01363, drawing conclusions based on the limited results presented should obviously be cautioned.

IV. CHMP OVERALL CONCLUSIONS

In these studies, the efficacy and safety of adjunctive treatment with levetiracetam in Japanese paediatric patients (≥4 to <16 years) with uncontrolled generalized tonic-clonic (GTC) seizures despite treatment with 1 or 2 antiepileptic drug(s) was confirmed. Keppra was shown to be effective and safe in long-term treatment of these subjects.

As Keppra dry syrup, the formulation mainly used throughout these studies, is not a registered formulation in the EU, no changes to the approved Product Information for Keppra in the EU were proposed following completion of these studies. The MAH considered that the standard immediate release formulations of Keppra allow for appropriate use of levetiracetam in paediatric patients in the EU. This was considered acceptable by the CHMP.

These studies were solely submitted to comply with Article 46 of the Paediatric Regulations.