CLINICAL REVIEW

Application Type	Efficacy Supplemental NDA
Application Number(s)	021446 (S-036), 022488 (S-014)
Priority or Standard	Priority
Submit Date(s)	8/27/2018
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Division/Office	DNP/ODE-1
Reviewer Name(s)	Emily R. Freilich, MD
Review Completion Date	April 22, 2019
Established/Proper Name	Pregabalin
(Proposed) Trade Name	Lyrica
Applicant	Pfizer Inc
Dosage Form(s)	Capsule and oral solution
Applicant Proposed Dosing Regimen(s)	3.5-14 mg/kg/day divided TID
Applicant Proposed Indication(s)/Population(s)	Treatment of partial-onset seizures in patients age 1 month and older
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Treatment of partial-onset seizures in patients age 1 month and older

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Glossary

AC	advisory committee
AE	adverse event
AED	anti-epileptic drug
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
CT	computed tomography
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
E-DMC	External Data Monitoring Committee
EEG	electroencephalogram
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat

IVRC	interactive voice response system
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MRI	magnetic resonance imaging
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMAR	population modeling and analysis report
PMC	postmarketing commitment
PMR	postmarketing requirement
POS	partial-onset seizures
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
PWR	Pediatric Written Request
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event
TME	targeted medical event
US	United States

1. Executive Summary

1.1. Product Introduction

Lyrica (Pregabalin) was approved for adjunctive therapy in the treatment of partial-onset seizures (POS) in adult patients with epilepsy aged 17 years and older in June 2005. The anticonvulsant mechanism of action for pregabalin is believed to be related to its high affinity binding to the alpha-2-delta site (α2-δ), an auxiliary subunit of voltage-gated calcium channels. In 2018, the indication was extended down to 4 years of age and older.

Pregabalin is approved in over 130 countries. In the United States (US), pregabalin is indicated for the treatment of POS in patients age 4 years and older; pregabalin is also indicated for the management of neuropathic pain associated with diabetic peripheral neuropathy, post-herpetic neuralgia, neuropathic pain associated with spinal cord injury, and fibromyalgia. In the European Union (EU), pregabalin is indicated as adjunctive therapy in adults with partial seizures with or without secondary generalization, the treatment of peripheral and central neuropathic pain in adults, and for generalized anxiety disorder in adults.

The approved dose range for the adjunctive treatment of POS in adults is 150 to 600 mg/day, administered twice daily (BID) or 3 times daily (TID). The approved dose ranges in pediatric patients are 2.5 mg/kg/day -10 mg/kg/day for pediatric patients ≥ 30 kg, and 3.5 – 14 mg/kg/day for pediatric patients weighing 11 to 30 kg. The most common adverse events reported with pregabalin in placebo-controlled adjunctive studies in adults with POS were dizziness (32%) and somnolence (22%). Since initial market approval of Pregabalin in 2004 through January 2016 it is estimated that approximately 34,065,954 patient-years of exposure have accumulated world-wide.

This supplemental application seeks to extend the current indication for the adjunctive treatment of partial-onset seizures (POS) to include pediatric patients down to 1 month of age based on a randomized, double-blind, placebo-controlled pediatric clinical trial (Study A0081042). This supplemental application, along with the supplement approved in May 2018, also fulfill the pediatric written request and Pediatric Research Equity Act (PREA) post-marketing requirements as discussed in Section 3.2 of this review.

Of note, the Division of Neurology Products (DNP) issued a General Advice letter on November 12, 2015, indicating that it is acceptable to extrapolate to pediatric patients 4 years of age and older, the effectiveness of drugs approved for the treatment of POS in adults. The indication for pregabalin in pediatric patients 4 years to 16 years of age was approved in May 2018 based on the results of a single, double-blind, placebo-controlled pediatric clinical trial, as well as extrapolation of efficacy.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Evidence of effectiveness for Lyrica for the treatment of partial-onset seizures in patients 1 month to < 4 years of age is based on the positive results from a single, multicenter, double-blind, placebo-controlled pivotal trial.

The level of evidence provided is adequate to support the conclusion that pregabalin is effective for treatment of POS in this age range.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

The overall benefit-risk analysis of LYRICA in pediatric patients with partial-onset seizures (POS) age 1 month to < 4 years is acceptable. Patients with POS often have refractory epilepsy with difficult-to-treat seizures which not only increases the risk for status epilepticus and sudden death in epilepsy patients (SUDEP), but also, especially in this age group, increases the risk of neurocognitive and neurobehavioral co-morbidities and developmental delays. There is only a single-approved therapy (levetiracetam) for treatment of POS in patients 1 month to < 2 years of age, and a few more treatments that are approved for treatment in patients 2 to < 4 years of age. Despite the use of these therapies and off-label use of other treatments available for POS, many children continue to suffer from frequent seizures and require new treatment options. Off-label use of treatments in this population may also lead to the use of ineffective or unsafe doses.

LYRICA was previously approved for the treatment of POS in adults in 2005, and then was approved down to pediatric patients 4 years of age and older in May 2018. The current submission includes a single pediatric efficacy and safety study (A0081042) which demonstrates effectiveness of LYRICA in reduction in seizures in patients 1 month to < 4 years of age, based on a primary efficacy endpoint of change from baseline in log-transformed 24-hour seizure frequency as determined by 48-72 hours of video-EEG read by a central reader. The study demonstrates effectiveness at the highest dose of 14 mg/kg/day divided into three daily doses. LYRICA also has a unique advantage of not having any significant drug-drug interactions, which makes it beneficial in patients who are already on polypharmacy for their AEDs or in medically complex patients who have multiple comorbid conditions and concomitant medications.

The safety profile of LYRICA is well-characterized in adults, and was found to be similar in older pediatric patients age 4 to 16 years. Safety data was evaluated on a total of 182 patients 1 month to < 4 years of age from the pivotal study (A0081042) as well as the long-term open-label extension studies (A0081106 and A0081075). The safety data did not reveal any new safety signals, and the common adverse events were similar to those noted in adults, as well as respiratory tract infections and pneumonia which are common in this young pediatric population with chronic medical conditions. Somnolence is the most common adverse drug reaction, and it can be monitored for during dose titration. Although no patients younger than 4 months of age received LYRICA in the controlled portion of the study, there is sufficient clinical experience and PK simulation/modeling to assure the safety in patients as young as 1 month of age, especially given the proposed titration recommended in dosing.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Partial-onset seizures are often refractory and difficult to treat. • Partial-onset seizures may be diagnosed in children as young as 1 month of age, and may be more severe and more difficult to treat in the youngest patients. • Partial-onset seizures, when not adequately treated, may lead to worse developmental and neurocognitive outcomes. • Partial-onset seizures increase the risk of life-threatening conditions such as status epilepticus, as well as risk for sudden death. • The increasing availability of treatments for POS in older patient populations makes enrollment into placebo-controlled studies challenging.	There is a considerable unmet need for treatments of POS in the youngest patients between 1 month and < 4 years of age, despite difficulties with recruitment and reluctance of patients/families and investigators to enroll young infants in placebo-controlled studies.
Current Treatment Options	• The FDA-approved treatments for POS approved for patients younger than 4 years of age are levetiracetam (1 month and older) and topiramate, lamotrigine, and oxcarbazepine (2 years and older), gabapentin (3 years and older), and valproate (age not specified). • Significant off-label use of AEDs approved in adult and older pediatric patients for treatment of POS.	The only currently approved treatment for POS down to 1 month of age is levetiracetam. Many other drugs are being used off-label in these young patients, without adequate knowledge of the appropriate effective and tolerated doses.
Benefit	• In a single adequate and well-controlled pivotal Study 1042, pregabalin demonstrated effectiveness at 14 mg/kg/day compared to placebo in change from baseline in the log-transformed 24-hour seizure rate, as documented on pre- and post-treatment video-EEG recordings. • The 50% responder rate was numerically, but not statistically, significant at the higher 14 mg/kg/day dose. • Pregabalin has a unique benefit among many AEDs, because of its	Pregabalin 14 mg/kg/day was effective in reducing the 24-hour seizure rate, which is both clinically and statistically significant, in patients younger than 4 years of age. The treatment benefit was also significant in patients under 2 years of age when analyzed by age. Despite challenges in trial design and

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	renal clearance and lack of drug-drug interactions.	execution, a clinically meaningful reduction in seizures of 44% relative to placebo was noted in the high dose treatment arm. Pregabalin may have a unique benefit in medically complex patients who are on multiple medications, or refractory epilepsy patients on multiple AEDs, because of its lack of drug-drug interactions.
Risk and Risk Management	• Pregabalin appears well tolerated in patients 1 month of age and older. • The adverse events seen were quite similar to those described in adults and in older pediatric patients. • The most common dose-related adverse event seen is somnolence which can be monitored during dose titration. • Other common adverse events seen were pneumonia and respiratory tract infections and fever, which are commonly seen in pediatric patients and especially common in patients with complex medical conditions. • There were no new safety signals identified in these young patients and no age-related increase in adverse events.	Pregabalin was generally safe and well-tolerated in this age group, with no new safety signals identified. The safety profile was consistent to that which is seen in older pediatric patients and adults, other than childhood-related complaints of upper respiratory tract infection, pneumonia, and pyrexia, which are more common in pediatric patients.

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1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

□	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	□ Clinical outcome assessment (COA) data, such as	[e.g., Sec 6.1 Study endpoints]
	□ Patient reported outcome (PRO)	
	□ Observer reported outcome (ObsRO)	
	□ Clinician reported outcome (ClinRO)	
	□ Performance outcome (PerfO)	
	□ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Sec 2.1 Analysis of Condition]
	□ Observational survey studies designed to capture patient experience data	
	□ Natural history studies	
	□ Patient preference studies (e.g., submitted studies or scientific publications)	
	□ Other: (Please specify)	
□	Patient experience data that were not submitted in the application, but were considered in this review:	
	□ Input informed from participation in meetings with patient stakeholders	
	□ Patient-focused drug development or other stakeholder meeting summary reports	[e.g., Current Treatment Options]
	□ Observational survey studies designed to capture patient experience data	
	□ Other: (Please specify)	
x	Patient experience data was not submitted as part of this application.	

2. Therapeutic Context

2.1. Analysis of Condition

The applicant proposes expansion of the current indication for treatment of partial-onset seizures in patients with epilepsy 4 years of age and older down to 1 month of age, based on a safety and efficacy study in pediatric patients age 1 month to < 4 years. Epilepsy affects individuals of all ages and is one of the most common neurologic disorders in all age groups. A large meta-analysis of population-based epilepsy studies found the point prevalence of epilepsy to be 6.38 per 10000, the lifetime prevalence 7.6 per 1000, annual cumulative incidence of 67.77 per 100,000 persons, and an incidence rate of 61.44 per 100,000 person-years.[1] In an analysis based on health insurance claims, the incidence and prevalence estimate of epilepsy in the US pediatric population in 2012 were 6.8 per 1000 and 104 per 100,000 children, respectively[2]. Although 8 to 10% of the population will experience a seizure during their lifetime, only 2 to 3% will go on to develop epilepsy[3]. Partial-onset seizures occurred in ~57% of patients with epilepsy assessed over a 50-year period in Rochester, MN[4], and ranges from 12% to 71% in a variety of published epidemiological studies, depending on diagnostic criteria and country being assessed[5]. In an analysis of a pediatric database in Norway, 19% of children with epilepsy were found to have primary generalized tonic-clonic seizures[6].

Uncontrolled partial-onset seizures are associated with poorer quality of life because of a variety of limitations (e.g., inability to drive, social isolation, difficulty maintaining employment), and also can cause significant adverse consequences, including severe trauma, depression, anxiety, and sudden death.[7,8]. Uncontrolled epilepsy in the pediatric patients, especially in those patients with earlier age of seizure onset, is also associated with developmental delays

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[1] Fiest KM, Sauro KM, Wiebe S, et al. Prevalence and incidence of epilepsy A systematic review and meta-analysis of international studies. Neurology 2017:88; 296-303

[2] Kim H, Thurman DJ, Durgin T, et al. Estimating Epilepsy Incidence and Prevalence in the US Pediatric Population Using Nationwide Health Insurance Claims Data. J Child Neurology 2016, Vol. 31(6) 743-749

[3] Gavvala JR and Schuele SU. New-Onset Seizure in Adults and Adolescents A Review. JAMA. 2016;316(24):2657-2668

[4] Hauser WA, Annegers JF, Rocca WA. descriptive epidemiology of epilepsy: contributions of population-based studies from Rochester, Minnesota. Mayo Clin Proc. 1996 Jun;71(6):576-86.

[5] Banerjee PN, Filippi D, Hauser WA. The descriptive epidemiology of epilepsy—a review. Epilepsy Res. 2009 Jul;85(1):31-45.

[6] Aaberg KM, Surén P, Søraas CL, et al. Seizures, syndromes, and etiologies in childhood epilepsy: The International League Against Epilepsy 1981, 1989, and 2017 classifications used in a population-based cohort. Epilepsia. 2017 Nov;58(11):1880-1891.

[7] Baranowski CJ. The quality of life of older adults with epilepsy: A systematic review. Seizure. 2018 Aug;60:190-197.

[8] Sadr SS, Javanbakht J, Javidan AN, et al. Descriptive epidemiology: prevalence, incidence, sociodemographic factors, socioeconomic domains, and quality of life of epilepsy: an update and systematic review. Arch Med Sci. 2018 Jun;14(4):717-724

and worse neurocognitive outcomes.[9] Focal or partial-onset seizures involve only a portion of the brain at the onset, originating in one or more localized foci. Seizures that originate focally and spread to involve the majority or entirety of the brain are a subset of focal seizures, called secondarily generalized seizures[10]. Recently proposed terminology by the International League Against Epilepsy (ILAE) has redefined POS as "focal seizures" with a variety of seizure subtypes: focal aware seizures, focal impaired awareness seizures, focal motor seizures, focal non-motor seizures, and focal to bilateral tonic–clonic seizures[11]. The term POS will be used throughout this review. Partial or focal seizures may begin with motor, sensory, autonomic, or psychic symptoms, depending on the location of the electrical discharge[12].

2.2. Analysis of Current Treatment Options

A total of 16 drugs are approved for use in the treatment of partial-onset seizures in pediatric patients with varying degrees of supporting efficacy data. Table 1 below summarizes the currently approved drugs that have clearly-defined indications for use in pediatric patients with POS and efficacy data to support the claims. Other drugs not listed here that are used to treat pediatric patients with POS include phenobarbital, primidone, phenytoin, carbamazepine, vigabatrin, and felbamate. These are not included in the table because of lack of clear pediatric indications, lack of NDA approval, or contraindication for use as first-line treatment due to adverse drug effects.

Of the below drugs listed in Table 1, the only drugs approved for patients younger than 4 years of age:

- levetiracetam (1 month of age and older)
- lamotrigine, topiramate, and oxcarbazepine (2 years of age and older)
- gabapentin (3 years of age and older)
- valproic Acid (age not specified)

Table 1 Summary of Drugs Currently Approved for Treatment of Partial-Onset seizures

Product (s) Name	Relevant Pediatric Indication	Year of Pediatric Approval	Route and Frequency of Admin.	Efficacy Information	Important Safety and Tolerability Issues

[9] Nickels KC, Zaccariello MJ, Hamiwka LD, Wirrell EC. Cognitive and Neurodevelopmental Comorbidities in Paediatric Epilepsy. Nat Rev Neurol. 2016 Aug; 12(8):465-476.
[10] Scheffer IE, Berkovic S, et al. ILAE classification of the epilepsies: Position paper of the ILAE Commission for Classification and Terminology. Epilepsia. 2017 Apr; 58(4):512-521
[11] Fisher RS. The New Classification of Seizures by the International League Against Epilepsy 2017. Curr Neurol Neurosci Rep (2017) 17: 48
[12] Chang BS and Lowenstein DH. Mechanisms of Disease: Epilepsy. NEJM (2003) 349;13

Brivaracetam (BRV)	Treatment of partial-onset seizures in patients 4 years of age and older	2018	PO/IV, BID Weight-based dosing pediatric pts	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Adverse reaction in pediatric patients similar to those seen in adults. Warnings: Neurological Adverse Reactions (somnolence and fatigue, dizziness and disturbance in gait and coordination), Psychiatric Adverse Reactions (including aggression, anger, agitation, depression, hallucination, paranoia, acute psychosis, and psychotic behavior), bronchospasm and angioedema.
Eslicarbazepine (ESL)	Treatment of partial-onset seizures in patients 4 years of age and older	2017	PO, QD Weight-based dosing ages 4-17 yrs	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Pediatric safety data not significantly different from adult data. Warnings: Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN), DRESS, anaphylaxis and angioedema, hyponatremia, dizziness, gait/coordination disturbance, somnolence/fatigue, cognitive dysfunction, impaired vision, DILI
Lacosamide (LCM)	Treatment of partial-onset seizures in patients 4 years of age and older	2017	PO only (safety of IV formulation unknown in pediatric patients), BID Weight-based dosing pediatric pts <50 kg	Adjunctive and monotherapy use approved in pediatric population based on extrapolation of efficacy from adult studies using pediatric PK data, as well as adequate pediatric safety data.	Adverse reaction in pediatric patients similar to those seen in adults. Warnings: dizziness and ataxia, cardiac rhythm and conduction abnormalities (prolonged PR, Atrial fibrillation and Atrial flutter), syncope, Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS),

Lamotrigine (LTG)	Adjunctive therapy in patients aged 2 years and older: • partial-onset seizures. • primary generalized tonic-clonic seizures. • generalized seizures of Lennox-Gastaut syndrome. Monotherapy in patients ≥16 years of age only.	2003 (pediatric adjunctive POS)	PO, BID Weight-based dosing for patients 2-12 years of age	Placebo-controlled efficacy trial in 199 patients aged 2 to 16 years. Primary efficacy endpoint: percentage change from baseline in all partial-onset seizures. The median reduction of all POS was 36% in patients treated with LAMICTAL and 7% on placebo (P<0.01).	Serious skin rash, including in pediatric patients (one death in controlled pediatric trials), TEN. Significant rash with concurrent valproate. Hemophagocytic Lymphohistiocytosis, DRESS, hematologic abnormalities (neutropenia, leukopenia, anemia, thrombocytopenia, pancytopenia), Aseptic Meningitis,
Levetiracetam (LEV)	Adjunctive therapy in the treatment of: • POS in patients one month of age and older with epilepsy • PGTCS in patients 6 years of age and older with idiopathic generalized epilepsy	2000 (4-17 years) 2012 (1 mo to 4 years) 2014 (IV)	PO/IV, BID Weight-based dosing in ped patients	1 mo to 4 yrs: RPCT evaluating the efficacy and tolerability in patients with refractory POS. Primary endpoint was responder rate, with statistically significantly greater number of responders on Keppra than on placebo	Warnings: Behavioral abnormalities and psychotic symptoms, somnolence and fatigue, anaphylaxis and angioedema, SJS and TEN, coordination difficulties, reduction in WBC and neutrophil counts (statistically sig worse in Keppra-treated pediatric patients than those on placebo), hypertension (particularly in the 1 mo to 4 yr study)

Topiramate (TPM)	• Initial monotherapy in patients ≥2 years of age with POS or PGTCS • Adjunctive therapy for adults and pediatric patients (2 to 16 years of age) with POS or PGTCS	2009 (pediatric adjunctive POS)	PO, BID Weight-based dosing ages 2-9 yrs	Monotherapy: RCT (high dose [400 mg] vs low dose [50 mg] TPM) in pts ≥10 yrs with POS or PGTCS. Primary endpoint was between-group comparison of time to first seizure during the double-blind phase, which statistically favored the high dose. Monotherapy in pts 2-9 yrs was demonstrated via PK bridging. Adjunctive: 1 RPCT in POS patients 2-16 yrs and 1 RCPT in patients ≥2 yrs with PGTCS. Primary efficacy endpoint was median percent reductions in seizure rates compared to baseline, vs placebo. Both studies had statistically significant reduction in MSF.	Warnings for adult and pediatric patients: Acute Myopia and Secondary Angle Closure Glaucoma, Visual Field Defects, Oligohidrosis and Hyperthermia, Metabolic Acidosis, Cognitive/ Neuropsychiatric Adverse Reactions (lower in peds than adults), Hyperammonemia and Encephalopathy, Kidney Stones,

Oxcarbazepine (OXC)	• Monotherapy in the treatment of partial seizures in children 4-16 years • Adjunctive therapy in the treatment of partial seizures in children 2-16 years	2000 (adjunctive use in pediatric POS)	PO, BID Weight-based dosing ages 2-16	Monotherapy – 4 RPCTs demonstrated efficacy in patients ages 8 and older primarily using study exit due to seizure as the efficacy measure. A 5th study in patients 1 mo to 16 years did not demonstrate efficacy, but this failure was felt to be due to design flaws, not lack of efficacy Adjunctive POS: 3 efficacy trials incl. pediatric patients (15 to 66 yrs, 3-17 yrs, and 1 mo to 4 yrs). Primary efficacy endpoint was between-group comparison of the percentage change in partial seizure frequency in the double-blind treatment phase relative to baseline phase for the 2 RCPTs, both of which favored OXC over placebo. For the 3rd pediatric trial (1 mo to 4 yrs) the 1° endpoint was change in seizure frequency per 24 hours compared to the seizure frequency at baseline, which also statistically favored OXC, but no evidence of effectiveness below age 2 yrs.	Hyponatremia, Anaphylactic Reactions and Angioedema, SJS and TEN (both seen in children and adults), DRESS, hematologic abnormalities, risk of seizure aggravation (especially PGTC) Cognitive/Neuropsychiatric Adverse Reactions (cognitive slowing, somnolence, coordination abnormalities) seen in pediatric patients,

Valproate, Valproic Acid (VPA)	Monotherapy and adjunctive therapy in the treatment of patients with complex partial seizures that occur either in isolation or in association with other types of seizures, ages 10 yrs and older		PO/IV, TID or BID depending on formulation	2 RPCTs in patients (patient ages not identified), primary endpoint was reduction in seizures compared to baseline vs placebo, with statistically significant difference.	Hepatotoxicity (including fatalities) particularly in patients < 2 yrs and in first 6 mos of treatment. Other warnings: Birth defects, Pancreatitis, thrombocytopenia, hyperammonemia, hypothermia, somnolence
Gabapentin (GBP)	Adjunctive therapy in the treatment of partial onset seizures, with and without secondary generalization, in adults and pediatric patients 3 years and older with epilepsy	2000 (adjunctive use in pediatric POS)	PO, TID Weight-based dosing for patients 3-11 years of age	Placebo-controlled efficacy trial in 247 pediatric patients with POS. Comparison of response ratio to placebo statistically significant (-0.146 vs -0.079) but responder rate not significantly different frequency)	Somnolence and sedation, dizziness, DRESS In pediatric patients: Neuropsychiatric Adverse Reactions (emotional lability, hostility and aggression, concentration issues, and hyperkinesia
Tiagabine (TGB)	Adjunctive therapy in adults and children 12 years and older in the treatment of partial seizures		PO, BID	3 RPCTs with primary endpoint of median reduction in seizure frequency in patients with POS (statistically favored TGB over placebo)	Cognitive/Neuropsychiatric Adverse Events (impaired concentration and somnolence), Generalized Weakness, serious rash

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

As noted above, Lyrica was originally approved for adjunctive treatment of partial-onset seizures in adults 17 years and older on June 10, 2005. The indication was extended to include treatment of POS in patients age 4 years and older on May 3, 2018.

3.2. Summary of Presubmission/Submission Regulatory Activity

This pediatric supplement is based on an efficacy and safety study A0081042 (Study 1042), as well as two long-term extension studies Study A0081106 (ongoing) and Study A0081075. The completed Study 1042, entitled "A double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of pregabalin as adjunctive therapy in children 1 month through < 4 years of age with partial onset seizures" is the primary efficacy and safety study supporting the potential expanded pediatric indication. The protocol was submitted in December 2013 and agreed to as a Special Protocol Assessment (SPA). The study was planned, in part, to fulfill requirements of a PREA PMR as well as a Pediatric Written Request (PWR). The PWR was originally issued June 8, 2005, and amended on October 17, 2006, July 30, 2010, September 26, 2014, and March 23, 2017. It was partially fulfilled with the supplement approved on May 3, 2018.

In a Type C Meeting in October 2017, the applicant asked to split this supplement into two parts, 2a and 2b. They requested the ability to submit sufficient information to fulfill their Pediatric Written Request (PWR) and PREA requirements prior to the PWR deadline of September 28, 2018, and prior to patent expiration in December 2018 as Supplement 2(a). Then they would plan to submit the remainder of the application necessary to allow for a new pediatric indication in patients 1 month to < 4 years of age, pending final data analysis from the conclusion of the study, as Supplement 2(b).

The applicant proposed that Supplement 2(a) would include draft labeling, request for exclusivity determination, clinical overview to support labeling changes, clinical study report for Study 1042, a meta-analysis of long-term studies 1075/1106, and a population model and analysis (PMAR) report for pharmacokinetics (PK). Supplement 2(b), which was proposed to be submitted as a Major Amendment, would include the remainder of the draft labeling, a summary of clinical pharmacology, a PMAR for dosage and exposure-efficacy response, an Integrated Summary of Efficacy, and Integrated Summary of Safety, and administrative items such as Financial Disclosures and Bioresearch Monitoring Request Items.

The Agency agreed to this proposed plan and Part 2(a) was submitted on August 27, 2018. At the time the Part 2(a) application was filed, it was determined that the applicant did fulfill their PWR. On December 3, 2018, the applicant submitted Part 2(b) as a Major Amendment, as planned, to extend the pediatric treatment indication down to 1 month of age, thus extending the PDUFA deadline by 3 months.

The Division met with the Pediatric Exclusivity Board, and Pediatric Exclusivity was granted on November 21, 2018. As part of fulfillment of the PWR, the submission was granted priority review status.

Of note, the applicant still has the following PREA postmarketing requirements, which were partially fulfilled with the approval in May 2018 in pediatric patients down to 4 years of age.

The June 10, 2005, approval letter for Lyrica capsules (NDA 21724) and the January 4, 2010, approval letter for Lyrica Oral Solution (NDA 22488) include the following deferred PREA postmarketing requirements:

> 1359-4: Deferred pediatric study under PREA for the treatment of partial onset seizures in pediatric patients ages 1 month [44 weeks gestational age] to 16 years.
>
> 1576-4: Deferred pediatric study under PREA, a 12-month open label extension study to evaluate the safety of pregabalin in pediatric patients with partial onset seizures ages 1 month through 16 years, inclusive.

The following PREA requirements are still open:

> 1118-1 & 1359-1: Complete an adequate and well-controlled clinical study or studies to better assess the ophthalmologic effects of pregabalin.
>
> 1576-2: Deferred pediatric study under PREA, a randomized, double-blind, placebo-controlled study to evaluate the efficacy, pharmacokinetics, and safety of pregabalin in pediatric patients with partial onset seizures ages 1 month through 3 years, inclusive.

3.3. Foreign Regulatory Actions and Marketing History

Pregabalin is approved in more than 130 countries. In the EU, it is indicated only in adults with partial seizures with or without secondary generalization, treatment of peripheral and central neuropathic pain, and generalized anxiety disorder in adults. In Japan, pregabalin is indicated for peripheral neuropathic pain and fibromyalgia.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

Please see OSI review for full details of the clinical site inspection done for clinical Site 1209, of Dr. Karakulova of the Russia Federation. The study records from Site 1209 were reviewed in support of this efficacy supplement, and the study appeared to have been conducted adequately with data supportive of the indication.

As part of the inspection, a Note to File was discovered that included a recommendation to destroy and replace all packing slips for investigation product orders sent to the clinical site

between 1/2017 and 10/2017, because of potential information which might cause an unblinding event if combined with information not included on the packing slips. Although not included in the NDA submission, in response to an Information Request, the applicant provided further information which is summarized in the OSI review. There was not sufficient information provided to assure us that unblinding had not occurred in regards to six individual patients. At the request of OSI, the statistical team performed a sensitivity analysis without these six patients, and there was no resulting change to the primary efficacy endpoint. The remainder of the site inspection was adequate, and the final compliance classification of the inspection of Site 1209 was No Action Indicated (NAI).

4.2. Product Quality

Lyrica is an already approved product.

4.3. Clinical Microbiology

No clinical microbiology studies were included in this NDA supplement.

4.4. Nonclinical Pharmacology/Toxicology

A nonclinical program to support the pediatric clinical development was previously conducted.

4.5. Clinical Pharmacology

See finalized Office of Clinical Pharmacology review for full discussion of pharmacokinetics in pediatric patients.

4.6. Devices and Companion Diagnostic Issues

Not applicable.

4.7. Consumer Study Reviews

Not applicable.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

Reference ID: 4432875

Table 2 Table of Individual Clinical Studies

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4432875

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
A0081042		Phase 3, double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of pregabalin as adjunctive therapy in children 1 month to < 4 years of age with POS.	PGB 7 mg/kg/day TID PGB 14 mg/kg/day TID Placebo TID	Primary Endpoint: The log-transformed double-blind 24-hour seizure rate for all POS collected at Visit 6 as determined by the central reader. Secondary endpoint: Responder rate, defined as subjects who had ≥50% reduction from baseline in partial seizure rate during double-blind V-EEG assessment. Safety	21 days of treatment	175	Patients with POS age 3 months to < 4 years Mean age 28.2 months	Multisite international 64 centers in 23 countries (screened) Highest enrolling countries Ukraine and Philippines

Reference ID: 4432875

				endpoints: adverse events, laboratory, physical examinations, vitals, neurological e examinations and ECG data.				
		Studies to Support Safety						
A0081075		A 12-month, open-label extension study evaluating safety and tolerability of flexible doses of pregabalin in pediatric patients with POS.	PGB 2.5, 5, 7.5, 10, or 15 mg/kg/day BID	Safety Endpoints: Adverse events, clinical laboratory assessments, vital signs, and physical and neurologic examinations, ECGs.	12 months	54 (25 patients < 4 years of age)	Patients 1 month to 16 years of age with POS, who participated in Study A0081074. 16 1 -23 months 15 2-6 years 12 7-11 years 11 12-16 years	US (11) Korea (1) Mexico (1)
A0081106		A 12-month open-label study to evaluate the safety and tolerability of pregabalin as adjunctive therapy in pediatric patients age 1 month to 16 years with POS, and pediatric and adult patients age 5 to 65 years with PGTC seizures	Pediatric patients ≥ 30 kg: 2.5 mg/kg/day – 10 mg/kg/day Pediatric patients < 30 kg: 3.5 mg/kg/day –	Safety Endpoints: Adverse events, clinical laboratory assessments, vital signs, and physical and neurologic examinations, ECGs.	12 months	576 (ongoing) 163 patients < 4 years of age	Patients 1 month to 16 years of age with POS and patients 5 – 65 years of age with PGTC seizures. Patients could enroll de novo (POS), or from study A0081041, A0081042, or A0081105.	Multisite international

			14 mg/kg/day Adult patients: 150 mg- 600 mg/day					
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
A0081074		Phase 1, placebo-controlled, escalating dose, multiple dose study to evaluate the safety, tolerability, and PK of Pregabalin in pediatric patients with POS.	2.5, 5, 10, 15 mg/kg/day (maximum 900 mg/day)	PK Evaluations and Safety Evaluations		65	Pediatric patients age 1 month to 16 years of age	28 centers in 4 countries; France (1), Korea (1), Mexico (3) USA (23)

Reference ID: 4432875

5.2. Review Strategy

This clinical review will examine Study 1042, the single double-blind, placebo-controlled pivotal trial in this age group, which is considered sufficient to demonstrate evidence of effectiveness in this patient population given prior approvals and demonstration of effectiveness in adults and older pediatric patients age 4 years to 16 years.

A separate Biometrics review will provide Dr. Xiangmin Zhang's statistical analyses. I will also discuss the clinical relevance of the applicant-provided analyses for efficacy from Study 1042. Section 7 is not relevant to this applicant because there is reliance on a single pivotal study for efficacy.

I will perform my own safety analyses based on data provided by the applicant from pivotal Study 1042, as well as the open-label, long-term extension studies Study 1075 and Study 1106 in Section 8 of this review.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. A Double-blind, Placebo-Controlled, Parallel-Group, Multicenter Study of the Efficacy and Safety of Pregabalin as Adjunctive Therapy in Children 1 Month Through < 4 Years of Age with Partial Onset Seizures

6.1.1. Study Design

Overview and Objective

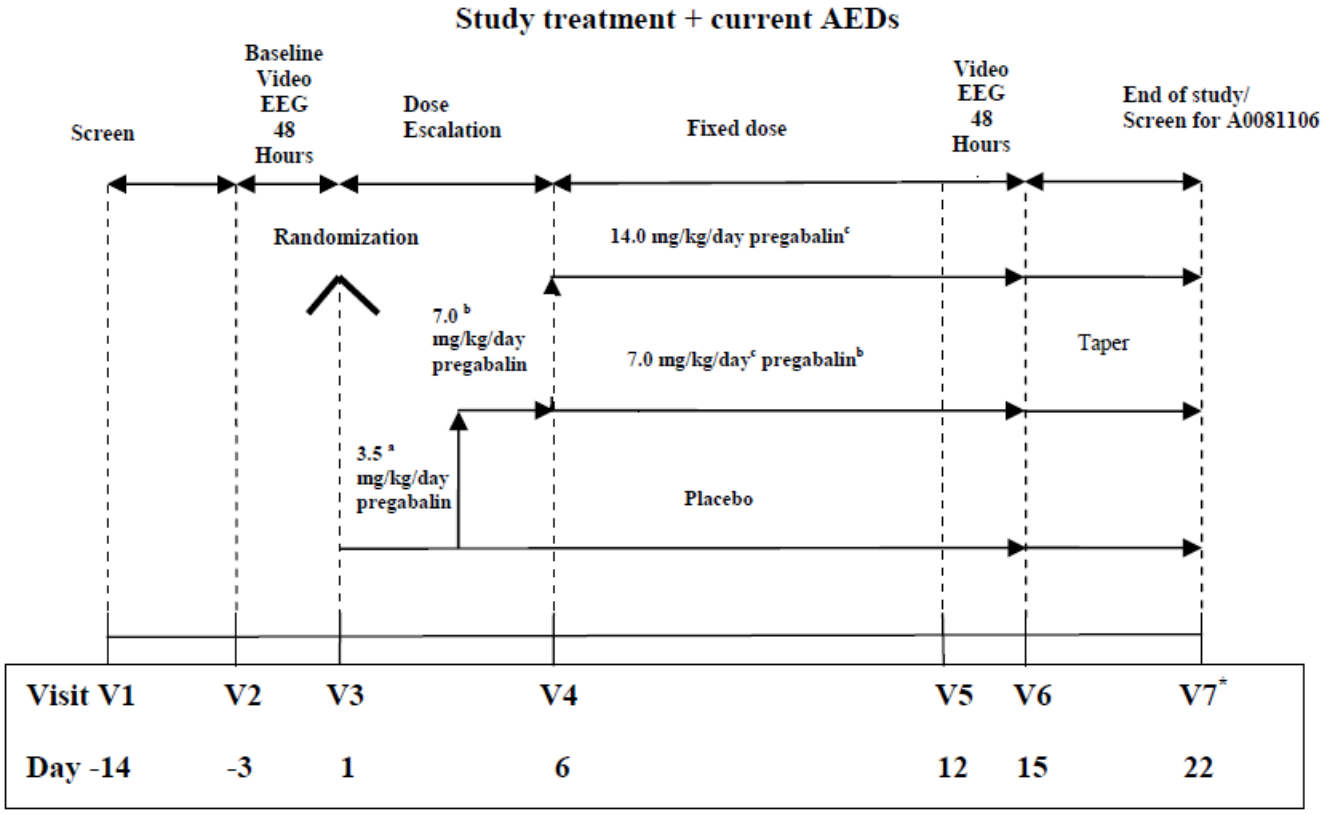
Study 1042 is a Phase 3 double-blind, placebo-controlled, parallel-group, multicenter study of pregabalin in pediatric patients age 1 month to < 4 years of age, with a primary objective to evaluate the efficacy of two dose levels of pregabalin compared to placebo as an adjunctive treatment in reducing the frequency of partial-onset seizures in pediatric patients age 1 month through < 4 years of age, as well as to evaluate safety and tolerability of pregabalin in this age group.

Trial Design

- Basic study design
  The study was a Phase 3, double-blind, placebo-controlled, randomized, parallel-group design, composed of 4 phases (see Error! Reference source not found.), with a total double-blind treatment phase of 21 days:

1. Video-EEG baseline phase with a target minimum of 48 hours of video EEG recording.
2. Five-day double-blind dose escalation phase
3. Nine-day double-blind fixed dose treatment phase, including a video-EEG evaluation over final 3 days at the end of the 9-day period, with a target minimum of 48 hours and a total recording duration of up to 72 hours.
4. Seven-day double-blind taper phase.

Figure 1 Study Design Diagram



* Eligible subjects may be assessed for screening into study A0081106 and complete end of study activities for A0081042 at Visit 7 (V7)
a [3 mg/kg/day for subjects 1 to 3 months of age];
b [6 mg/kg/day for subjects 1 to 3 months of age];
c [12 mg/kg/day for subjects 1 to 3 months of age]

Reviewer's comment: See choice of control arm later for full discussion of strengths and limitations of such a study design.

- Trial Location

The study was conducted and managed by a contract research organization (CRO), (b) (4). There were a total of 114 sites planned for enrollment in 29 countries, including Argentina, Belarus, Belgium, Bosnia and Herzegovina, Bulgaria, China, France, Germany, Greece, Hungary, Israel, Lebanon, Malaysia, Netherlands, Philippines, Poland, Republic of Korea, Romania, Russian Federation, Serbia, Singapore, Slovakia, South Africa, Spain, Taiwan, Thailand, Turkey, Ukraine, and the United States.

Reviewer's comment: Given the proposed patient population targeted by this indication, although there were limited patients from the United States enrolled in the study, the international population of pediatric patients with POS is not felt to differ significantly from the United States population.

- Choice of Control Group
  The use of placebo was the appropriate choice for a control group in this patient population and for this indication. Comparison to a placebo arm was felt to be necessary to fulfill the scientific objectives and regulatory requirements to demonstrate both efficacy and safety in this population, as a comparator is needed to reliably assess change in seizure frequency, given the variability among patients in baseline seizure frequency, type, and variable time between seizures.

  Reviewer's comment: Placebo-controlled studies are considered essential for determination of effectiveness in studies for the treatment of POS, especially given the high interpatient variability in the severity, frequency, and duration of seizures. However, there has been evolving discussions on the difficulty with recruitment in this age range and study design, as well as parent and investigator resistance to enrolling patients in this vulnerable age range into placebo-controlled studies, which has contributed to challenges in the execution of such studies. The patients available for the studies has changed, given both earlier evaluations for epilepsy surgery, with newer abilities to detect structural lesions earlier in patients with focal epilepsy, and newer AEDs available for off-label use. Combined with the availability of genetic testing to determine epilepsy etiology, these advances have led to a smaller "pool" of refractory epilepsy patients younger than 2-4 years of age that would be both eligible and willing to participate in such studies.

  At the time of study design, it was also felt that video-EEG was the most accurate measure of seizure frequency in these young patients, given the equally high likelihood of finding either electrographic seizures without clinical correlate, or non-epileptic movements that may be mistaken as seizures. Therefore, the 48-72 hour requirement for video-EEG assessment at baseline and during the treatment phase for seizure frequency, to be read by a blinded central reader, was considered the most reliable

and accurate method of determining the primary endpoint. The Video-EEG requirement, however, is also labor- and resource-intensive, plays a large role in the challenges with enrollment of both sites and patients into the study, and resulted in prolonged study duration.

The duration of placebo exposure in these young infants who are at risk for developmental delays, likely correlated with severity and duration of seizure activity, has also always been a matter of particular concern in designing such trials. This study was fortunate to be able to shorten the double-blind period to only 14 days of double-blind treatment, which made the study more palatable to providers and parents to enroll in the study; nevertheless, the investigators still struggled with enrollment and study completion.

Overall, the choice of placebo in this study was necessary; because this study was able to limit the double-blind treatment period to 21 days, it was possible, although extremely challenging, for the study to reach completion. Further discussions will be required concerning whether future studies should rely on V-EEG for seizure counting, given the discrepancies in the local site investigator's interpretation of the baseline EEGs (allowing enrollment) compared to the central reader's subsequent interpretation of the EEG which did not find POSs on the baseline EEGs for a number of enrolled patients, resulting in missing data (See 6.1.2).

- Diagnostic Criteria
  Patients 1 month to < 4 years of age with partial-onset seizures. See inclusion criteria below for more detailed criteria required for enrollment.

- Key Inclusion/Exclusion criteria

  Inclusion Criteria
  - Age 1 month (44 weeks gestational age) to < 4 years of age, inclusive, with a diagnosis of epilepsy with seizures classified as simple partial, complex partial, or partial becoming secondarily generalized according to ILAE diagnostic criteria[13] and diagnosis confirmed by:
    - Patient's seizure history, family history, and neurological exam
    - Previous contrast-enhanced CT or MRI scan of brain and prior EEG testing that were consistent with a diagnosis of focal-onset epilepsy and no

[13] Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizure and epilepsies: report of the ILAE Commission on the Classification and Terminology, 2005-2009. Epilepsia 2010; 51(4):676-85.

demonstrated progressive abnormality
    - If CT or MRI scan was needed, it would be performed as soon as possible after Visit 1 or on day of visit, and completed and reviewed prior to randomization
- On a stable dose of 1 to 3 AEDs (for 7 days prior to screening). A benzodiazepine used on a regular basis at a stable dosage was considered one of the concurrent antiepileptic treatments. Vagus Nerve Stimulation (VNS) was also considered 1 of the concurrent treatments, when present.
- At least 3 observed seizures in the month prior to screening
- At least 2 partial-onset seizures, as determined by the investigator, during the 48-hour baseline Video-EEG phase.

Exclusion Criteria
- Presence of any primary generalized seizures which may have included
    - Clonic, tonic, and clonic-tonic seizures (except secondarily generalized seizures)
    - Absence seizures
    - Infantile spasms
    - Myoclonic, myoclonic atonic, myoclonic tonic seizures
- Lennox-Gastaut syndrome, Benign Epilepsy with Centrotemporal Spikes (BECTS) and Dravet syndrome
- Current diagnosis of febrile seizures or seizure related to an ongoing acute medical illness
- Exacerbation of POS due to fever within 60 days of screening
- Status epilepticus within 1 year prior to screening
- Any change in AED regimen within 7 days of screening visit or during Baseline Phase
- Progressive CNS lesion or progressive encephalopathy
- Progressive inborn errors of metabolism
- Known or suspected chronic hematologic, hepatic, or renal disease
- Estimated CLcr < 80 ml/min/1.73 m^2
- Concomitant use of gabapentin, felbamate, and vigabatrin was prohibited
- Previous treatment with pregabalin
- Weight > 30.0 kg

Reviewer's comment: The inclusion/exclusion criteria appear appropriate for the study as designed. However, this reviewer notes that the minimum requirement of having 3 seizures in the month before screening is likely low to subsequently then note at least 2 seizures during a 48-hour EEG, and then be able to see a significant treatment effect two weeks later. For a study design such as this, with reliance on EEG and short treatment period, it would seem that patients with more frequent baseline seizure rate (multiple seizures daily) would be ideal, and that lower baseline seizure rates would make it more

difficult to discern a treatment effect, if present.

- Dose Selection
  The recommended dose range for adult patients with POS is 150 to 600 mg/day, which approximates 2.5-10 mg/kg/day for an average 60 kg adult patient. The recommended dose range for pediatric patients with POS age 4 to 16 years of age and weighing ≥ 30 kg is 2.5-10 mg/kg/day (maximum 600 mg/day) and the recommended dose range for patients weighing 11 kg to < 30 kg is 3.5-14 mg/kg/day, all given in 2 or 3 divided doses.

  Pediatric pharmacokinetics in Study 1074 predicted that the doses chosen for this study would provide exposures comparable to those achieved by 300 mg/day and 600 mg/day in adults. Given renal clearance (normalized for body weight) is approximately 40% higher in pediatric patients < 30 kg, a daily dose that is 40% higher relative to that for adults was needed. Furthermore, TID dosing was selected because the ½ life was expected to be approximately 3-4 hours, shorter than the ½ life in older patients. The dose was also adjusted slightly downward for those patients 1 month to 3 months of age because of the difference in renal drug clearance in the very young infants.

- Study Treatments
  Patients who completed the baseline phase and met eligibility criteria were randomized in a double-blind manner to a fixed dose of either of the following, administered orally, TID, in equally divided doses:
  - Placebo
  - Pregabalin 7 mg/kg/day (6 mg/kg/day for patients 1 to 3 months of age)
  - Pregabalin 14 mg/kg/day (12 mg/kg/day for patients 1 to 3 months of age)

  Drug dose levels will be adjusted by age to account for potential differences in renal drug clearance, with the anticipation that resultant total daily exposures are comparable throughout the age range of 1 month to < 4 years of age.

  The following table summarizes the doses during the dose escalation, fixed-dose, and taper phase of the study.

Table 3 Double-Blind Dosing by Study Treatment and Phase

DOUBLE-BLIND PHASES						
	Dose Escalation Phase		**Fixed-Dose Phase**		**Taper Phase***	
	Age >3 months	**Age ≤3 months**	**Age >3 months**	**Age ≤3 months**	**Age >3 months**	**Age ≤3 months**
Treatment[a]						
Placebo	Placebo	Placebo	Placebo	Placebo	Placebo	Placebo
Level 1:-	3.5 mg/kg/day x 5 days	3.0 mg/kg/day x 5 days	7.0 mg/kg/day x 9 days	6.0 mg/kg/day x 9 days	3.5 mg/kg/day x 7 days	3.0 mg/kg/day x 7 days
Level 2:	**Step 1:** 3.5 mg/kg/day x 2 days **Step 2:** 7.0 mg/kg/day x 3 days	**Step 1:** 3.0 mg/kg/day x 2 days **Step 2:** 6.0 mg/kg/day x 3 days	14 mg/kg/day X 9 days	12 mg/kg/day X 9 days	**Step 1:** 7.0 mg/kg/day x 4 days **Step 2:** 3.5 mg/kg/day x 3 days	**Step 1:** 6.0 mg/kg/day x 4 days **Step 2:** 3.0 mg/kg/day x 3 days

* Subjects who will not participate in Study A0081106 will discontinue study medication following the completion of the taper phase. For subjects who will enter Study A0081106, all subjects will initiate that study at a dose of 3.5 mg/kg/day [3 mg/kg/day for subjects 1 to 3 months of age] and may then escalate according to protocol requirements.

a Study drug will be administered TID in equally divided doses.

- Assignment to Treatment

After completion of baseline phase, patients who met eligibility criteria were randomized to treatment at Visit 3. Patients were randomized in a 2:1:2 ratio to 1 of the 3 treatments described above (placebo, pregabalin 7 mg/kg/day, and pregabalin 14 mg/kg/day). Randomization was assigned by an interactive voice response system (IVRC) according to the randomization code provided by the Clinical Statistics Department.

- Blinding

The study was double-blind, and patient, parent/caregiver and investigator, sponsor and/or designees did not know what study medication was being given. Pregabalin or identically-appearing placebo was administered orally TID. Each individual had a unique blinding code and the blind was broken only in an emergency situation, at which point, the applicant would have been contacted prior to breaking the blind and reason would be fully documented on CRF.

Study medication was dispensed in two bottles, Bottle A and Bottle B. For the pregabalin 7 mg/kg/day group, Bottle A contained pregabalin 20 mg/mL solution, and Bottle B contained placebo. For the pregabalin 14 mg/kg/day group, both bottles contained pregabalin 20 mg/mL solution, and for the placebo group, both medication bottles contained placebo.

To maintain blinding, patients received equivalent volumes of liquid relative to age and weight regardless of treatment arm. There were two interim safety analyses conducted by an External Data Monitoring Committee (E-DMC). The blinding of the study was preserved according to the procedure in the E-DMC charter, and no study team member had access to the unblinded data.

- Administrative Structure

There was an External Data Monitoring Committee (E-DMC) responsible for ongoing monitoring of the efficacy and safety of the patients in the study. Any recommendations made by the DMC to alter conduct of the study would be forwarded to Pfizer for final decision.

- Procedures and Schedule

Table 4 Schedule of Procedures

Study Periods	**Screening**	**48 Hour Video-EEG Baseline Recording**	**Double Blind Dose Escalation Phase**		**Double-Blind Fixed Dose Treatment Phase**		**48 Hour Video-EEG Treatment Recording**	**Taper/Termination Phase**	
								Completion of Double Blind Fixed Dose Phase and Begin Taper Phase[b]	**End of Study or Early Termination**
Clinic Visit Number	**Visit 1**	**Visit 2**	**Visit 3**	***PV**	**Visit 4**	***PV**	**Visit 5[l]**	**Visit 6**	**Visit 7**
Study Day	**-14 ± 3**	**-3 to -1**	**1 ± 1**	**4 ± 1**	**6 ± 1**	**9 ± 1**	**12 to 14 ± 1**	**15 ± 2**	**22 ± 3**
Informed consent	X								
Record demographic information	X								
Record medical history	X								
Record seizure history	X								
Perform physical and neurological examination	X[a]		X[e]						X[a]
Review inclusion/exclusion criteria	X		X						
Record antiepileptic medication history	X								
Record all prior and/or concomitant medications and non-drug treatments and procedures	X	X	X	X	X	X	X	X	X
Dispense seizure event log		X[i]					X		
Collect and review seizure event log			X					X	
Initiate Video electroencephalogram (EEG)		X					X		
Download Video-EEG data and send to reader			X					X	
Perform head CT or MRI[c]	X								

Study Periods	Screening	48 Hour Video-EEG Baseline Recording	Double Blind Dose Escalation Phase		Double-Blind Fixed Dose Treatment Phase		48 Hour Video-EEG Treatment Recording	Taper/Termination Phase	
								Completion of Double Blind Fixed Dose Phase and Begin Taper Phase[b]	End of Study or Early Termination
Clinic Visit Number	Visit 1	Visit 2	Visit 3	*PV	Visit 4	*PV	Visit 5[l]	Visit 6	Visit 7
Study Day	-14 ± 3	-3 to -1	1 ± 1	4 ± 1	6 ± 1	9 ± 1	12 to 14 ± 1	15 ± 2	22 ± 3
Perform 12-lead electrocardiogram (ECG)	X								X
Collect and record vital signs	X		X		X		X	X	X
Record height/length	X		X						
Record weight	X		X						
Collect blood and urine samples for clinical laboratory assessments[m]	X		X					X	X
Randomization[d]			X[j]						
Collect blood sample for pregabalin pharmacokinetics[h]					X[f]			X[g]	X[h]
Evaluate and record study medication compliance					X		X	X	X
Dosing compliance training/review and demonstration			X		X		X		
*Telephone visit to assess dosing compliance and AE's				X		X			
Dispense dosing diary			X		X		X	X	
Collect and review dosing diary					X		X	X	X
Dispense study medication			X[k]		X			X	
Assess and record adverse events		X	X	X	X	X	X	X	X

a. Full physical and neurological exams at this visit.

b. Subjects who require early discontinuation should begin the taper period at the time the decision is made to discontinue. All Visit 6 and 7 procedures should be performed as possible.

c. If not performed previously. In the event that a CT or MRI scan is needed, it should be performed as soon as possible after Visit 1 if it cannot be performed the day of this visit and must be completed and reviewed prior to randomization.

d. Subjects who meet all inclusion and none of the exclusion criteria will be randomized on Day 1 of Visit 3 and study drug will be dispensed at this visit.

e. Neuro and physical exams at this visit will be brief.

f. Two pharmacokinetic (PK) samples will be collected at Visit 4 (Section Pharmacokinetic Analyses).

g. One PK sample will be collected at Visit 6 (Section Pharmacokinetic Analyses).

h. A PK sample should be collected as close as possible to the occurrence of a serious adverse event when feasible and clinically indicated. Additionally, a PK sample should be collected at Visit 7 if subject withdraws early from the study (eg, prior to initiation of the taper phase and if less than 48 hours has elapsed since last dose).

i. Dispense seizure event log to track seizure events duringVideo-EEG and train parent(s)/guardian(s)/caregiver(s) on its use and completion.

j. Verify the criteria for total number of qualifying seizures has been met by review of the Video-EEG by the investigator prior to randomization.

k. Administer first dose of study medication in clinic.

l. Subjects who complete or terminate Video-EEG recording before Day 15 will continue fixed dosing until beginning the taper phase at Visit V6 on Day 15.

m. If it is not possible to collect a urine sample, despite appropriate efforts, the urine sample can be omitted for that visit. The reason for lack of sample must be recorded and documented in source documentation.

- Concurrent Medications

Patients were required to continue on their current AED therapy of 1 to 3 AED treatments at stable doses throughout the baseline and double-blind phase of treatment. Benzodiazepine medications used on a regular basis at a stable dosage was considered one of the concurrent AED treatments. VNS, if present and activated, was also considered one of the concurrent AED treatments. If patients required AED dose or regimen change during the study, they were required to be withdrawn.

Any medication taken by a patient other than the study medication (as specified by protocol) was considered a concomitant medication, including all AEDs. Non-prescription

Reference ID: 4432875

medications and herbal remedies were also considered concomitant medications.

A list of prohibited and permitted medications was provided in the study protocol.

- Treatment Compliance

Compliance was defined as the percentage of required doses that were ingested. If patients were consistently non-compliant with dosing regimen, as determined by the investigator, they were evaluated and discussed with the study clinician for possible study discontinuation.

Parent/caregiver completed a dosing diary and brought the diary and medication bottles to each clinic visit. Medication bottles were weighed by site staff when dispensed and returned to determine approximate volume of study medication used.

- Subject Completion, Discontinuation, or Withdrawal

Patients could withdraw from the study for any reason, including parent/caregiver request, adverse events, intercurrent illness, loss to follow-up, lack of efficacy, exacerbation of seizures relative to baseline, non-compliance, serious protocol violations, or concern for safety. The patients would undergo the withdrawal procedures similar to procedures required at the final visit. All efforts would be made to contact the patient's parent/caregiver and documented in the event they do not return for a scheduled visit.

Study Endpoints

- Primary Efficacy Endpoint

The primary endpoint is the log-transformed double-blind 24-hour seizure rate for all partial-onset seizures collected at Visit 6 (48-hour video EEG assessment phase) during the double-blind phase as determined by the central reader. The 24-hour seizure rate will be calculated as follows:

$$\text{Double Blind 24-hr EEG seizure rate} = \frac{\#\text{ of seizure in double} - \text{blind 48} - \text{hour assessment phase}}{\#\text{ hours of actual V} - \text{EEG monitoring}} \times 24$$

When the log-transformation is used, the quantity 1 is added to the double-blind 24-hour EEG seizure rate for all subjects to account for any possible "0" seizure incidence. Results will be reported as "percent change in seizures" relative to placebo. A minimum of 24 hours of evaluable Video EEG was required to utilize the EEG, otherwise the seizure rate would be set to missing.

Reviewer's comment: The study endpoint is appropriate, and is one that has been previously recommended and utilized for studies of POS in this very young age group. It has historically been the opinion of the Division that seizures in this age group may be

difficult to distinguish clinically from other non-epileptic abnormal movements and thus the primary endpoint should rely on video-EEG data rather than parent/caregiver report.

- Secondary Efficacy Endpoint

The secondary efficacy endpoint was the responder rate, defined as patients who have a ≥50% reduction from baseline in partial seizure rate during the double-blind 48-hour EEG period.

- Safety Endpoints

The evaluation of safety will include adverse event data, assessment of clinical laboratory data, and the results of physical examinations, vital signs, neurological examinations and electrocardiograms (ECGs).

Statistical Analysis Plan

All efficacy analyses will be performed on the modified-intent-to-treat (mITT) population, which consists of all patients who were randomized, and took at least one dose of study drug during the double-blind treatment phase, have a baseline with at least one partial-onset-seizure identified by Video-EEG and a follow-up Video-EEG. Video EEG assessments must include at least 24 hours of evaluable monitoring to be eligible for mITT population.

The primary analysis will be performed on the $\log_e$ (double-blind 24-hour EEG seizure rate +1) using a linear model with a treatment, age stratum, and geographical region as fixed factor effects and loge (baseline 24-hour EEG seizure rate + 1) as a continuous covariate. The linear model will include both dose groups, and the primary analysis will assess each dose of pregabalin versus placebo using ordinary estimation, in a step-wise fashion.

The secondary analysis will include the responder rate, defined as patients who have a ≥ 50% reduction from baseline in partial seizure rate during the double-blind 48-hour EEG phase.

Sample Size Justification

The study originally planned for a total of 123 patients to be randomized 2:2:1 ratio of placebo, dose level 1, and dose level 2, which was meant to allow a sufficient number of patients to be studied at each dose level for safety, while providing adequate power to detect a significant effect for dose levels 1 and 2, accounting for a potential 10% discontinuation rate, with a resulting sample size of the necessary 110 patients (44 placebo, 44 level 1, and 22 level 2).

The sample size rationale was based on the observed difference in $\log_e$(double-blind 24-hour seizure rate + 1/28) between pregabalin and placebo. With the above proposed 110 patients, the sample size was anticipated to provide at least 90% power to detect a true difference

between placebo and Level 2 dose, and at least 80% power to detect a true difference between placebo and Level 1 dose.

In the later version of the protocol (see below) the constant utilized in the log transformation of the 24-hour seizure rate for primary analysis was changed from "1/28" to "1" due to differences in the seizure rate distribution assumed during study design and that which was observed in the blinded data distribution. The constant ""1/28" added variability and decreased the normality of the data.

The blinded sample-size re-estimation was conducted after approximately 2/3 of the patients that make up the initial sample size have opportunity to complete the study, and the sample size was increased to approximately 150 patients based on plans detailed below.

Protocol Amendments

The protocol was amended in Asia, Europe, Middle East and South America on December 15, 2017 for clarifications regarding the change in the constant term in the transformation of seizure rate and the sample size decision rules. The Agency agreed to these changes without requiring a formal protocol amendment. The changes are summarized below:

- The transformation for the primary endpoint analysis is superseded in the protocol by the following: $\log_e$ (24-hour seizure rate +1) where the revision is to the constant term, to address any circumstances of zero seizure rates which is changed from "+1/28" to "+1". The revised term provided better approximation of normal distribution of the seizure data based on blinded data distribution. The constant "1/28" added variability to the data and decreased its normality. Therefore, the constant has been revised to "1"$\log_e$(24-hour seizure rate + 1).
- The decision rules for the blinded sample size re-estimation were clarified:
    - If the recalculated sample size is less than or equal to the original sample size of 123 subjects total, then the sample size will not be adjusted.
    - If the recalculated sample size is greater than the original sample size, then the following information will be considered:
        - If re-estimated sample size is between 123 and 150, then the sample size will be adjusted to the re-estimated sample size.
        - If re-estimated sample size exceeds 150, then it will be increased to a sample size of 150.

  The blinded sample size re-estimation was conducted, and sample size was increased to approximately 150 subjects.

6.1.2. Study Results

The applicant provided attestation that all studies were conducted in accordance with the CFR governing the protection of human subjects, Institutional Review Boards, and the obligations of clinical investigators in accordance with good clinical practice.

Financial Disclosure
Per the submitted Form 3454, there were no financial disclosures to report for the applicant or any of the clinical investigators for any of the covered clinical studies. The applicant reported due diligence utilizing reasonable efforts to obtain financial disclosure from one clinical investigator who left the institution where the study was conducted (Site 1025, Ericka Ross).

Patient Disposition
A total of 175 patients were randomized in Study 1042, and 169 patients completed the study. Of these, 163 patients continued into the long-term study extension in Study 1106. There were 2 discontinuations in the low dose group, 1 discontinuation in the high-dose group, and 3 discontinuations in the placebo group (See Table 5).

Table 5 Patient Disposition

Screened	231		
Randomized	175		
	Pregabalin 7 mg/kg/day	Pregabalin 14 mg/kg/day	Placebo
	71	34	70
Discontinued	2	1	3
Reasons for d/c:			
Medication error w/o AE	0	1	0
AE	0	0	1
No longer willing	1	0	1
Insufficient clinical response	1	0	1
Completed	69	33	67
Efficacy analysis population			
mITT[a]	59	28	53
ITT[b]	61	28	55
Safety analysis population	71	34	70

Source: Adapted from Study 1042 CSR Figure 2, reviewer verified
[a] mITT = primary efficacy population, randomized subjects who took at least 1 dose of study drug during double-blind treatment phase and had a baseline V-EEG with at least 1 POS seizure and had a treatment phase V-EEG
[b] ITT = randomized subjects who took at least 1 dose of study drug during the double-blind treatment phase and had a baseline with at least 1 POS identified by V-EEG

A total of 35 patients (20%) were excluded from the mITT population, including 12 from the 7 mg/kg/day group, 6 from the 14 mg/kg/day group, and 17 from the placebo group. The reasons are outlined below in Table 6.

Table 6 Reasons for Exclusion from mITT

Reason for Exclusion	Pregabalin 7 mg/kg/day N = 71	Pregabalin 14 mg/kg/day N = 34	Placebo N = 70
n = # excluded	12	6	17
No POS identified on baseline V-EEG by central reader	10	6	15
Non-evaluable treatment phase V-EEG	0	0	1
Discontinued prior to the treatment phase V-EEG	2	0	1

Source: Reviewer adapted from Study 1042 CSR Table 9, reviewer verified

Protocol Violations/Deviations

Protocol violations were deemed to be major if they were considered likely to have impact on the rights of the patients, safety of the patients, or validity of the data. There were 57 patients found to have major protocol violations (32.6%), and these patients were distributed throughout the treatment arms, with 20 patients in the pregabalin 7 mg/kg/day group, 10 patients in the 14 mg/kg/day group, and 27 patients in the placebo group.

The most common deviations were related to unavailability of laboratory test results due to laboratory issues, such as hemolysis, followed by investigational product deviations related to incorrect timing of use or missed doses, and informed consent deviations, related to timing/dating or use of incorrect version of the informed consent form.

The most notable protocol deviations are described below:

- Patient (b) (6) had an overdose where the patient received 9 mL of blinded oral solution (180 mg, 12 mg/kg) rather than intended 0.9 mL (17.5 mg, 1.17 mg/kg) for the initial dose on Day 1 of the study. Error was on the part of the investigator, and study medication was temporarily discontinued for 24 hours, with remaining Day 1 doses and the morning dose on Day 2 not given. The patient was hospitalized for observation, but had only mild somnolence and no additional AEs reported. Within 24 hours, it was determined that the pregabalin concentration would be similar to the trough concentration he would have had if he had received the correct dose, and dosing resumed at the appropriate dose on Day 2.
- Two patients ((b) (6), both in 14 mg/kg/day group) were administered the double-blind fixed dose for 16 and 18 study days, respectively, rather than protocol-specified 14 days, due to 'out-of-window" study visits, resulting in treatment duration that was longer than the protocol-specified 22 ± 3 days.
- Patient (b) (6) (7 mg/kg/day group) received a prohibited concomitant medication (chloral hydrate) as a sedating medicine for both baseline and double-blind video EEG recordings.
- Patient (b) (6) (placebo) stopped their routine AED, clonazepam, after

randomization, starting on Study Day 1.

Furthermore, the treatment group for 1 patient was accidentally revealed to the project programmer after the last patient's last visit, but prior to study unblinding.

Reviewer's comment: Overall, the protocol deviations were notable, but did not seem likely to have any significant impact on the ability to interpret the overall safety or effectiveness of the treatment in this age range.

Demographic Characteristics

Overall, the treatment groups among the mITT population were quite comparable regarding the demographic characteristics (Table 7). There were more male patients in all arms. The most patients (63.6% overall) were ≥ 24 months of age. There were 10% of patients under 12 months of age, but only 2 patients were in the pregabalin 14 mg/kg/day treatment arm. The youngest enrolled patient in the mITT population was 4 months of age. Overall the demographic characteristics of the mITT population were quite similar to the characteristics of the safety population (Table 14).

Table 7 Demographic Characteristics of the mITT Population

Demographic Parameters	Pregabalin 7mg/kg/day N = 59 n (%)	Pregabalin 14 mg/kg/day N = 28 n (%)	Placebo N = 53 n (%)	Total N =140 n (%)
Sex				
Male	40 (67.8)	15 (53.6)	28 (52.8)	83 (59.3)
Female	19 (32.2)	13 (46.4)	25 (47.2)	57 (40.7)
Age				
< 12 months	9 (15.3)	2 (7.1)	3 (5.7)	14 (10.0)
12 to < 24 months	16 (27.1)	7 (25.0)	14 (26.4)	37 (26.4)
≥ 24 months	34 (57.6)	19 (67.9)	36 (67.9)	89 (63.6)
Mean months (SD)	26.6 (13.0)	28.4 (12.4)	29.8 (11.6)	28.2 (12.4)
Min, max (months)	4, 48	4, 47	5, 47	4, 48
Race				
White	38 (64.4)	18 (64.3)	34 (64.1)	90 (64.3)
Asian	20 (33.9)	10 (35.7)	18 (34.0)	48 (34.3)
Other	1 (1.7)	0 (0.0)	1 (1.9)	2 (1.4)
Ethnicity				
Not Hispanic/Latino	58 (98.3)	27 (96.4)	51 (96.2)	136 (97.1)
Hispanic/Latino	1 (1.7)	1 (3.6)	1 (1.9)	3 (2.1)
No response	0 (0.0)	0 (0.0)	1 (1.9)	1 (0.7)
Weight (kg)				
Mean (SD)	11.5 (3.7)	11.2 (3.5)	11.4 (2.9)	11.4 (3.4)
Height (cm)				
Mean (SD)	85.0 (11.7)	83.2 (9.5)	86.7 (10.1)	85.3 (10.7)

Source: Reviewer analysis from demog dataset for Study 1042

Reviewer's comments: There are no significant trends or demographic differences between treatment arms in the mITT population. The mITT population will be used for the remainder of the efficacy analyses. Patients excluded from mITT had a mean age of 28.4 months (SD 13.5 months) with a minimum of 3 months and a maximum of 47 months. Of note, 15 of them (42.9%) were from 4 sites in the Ukraine, including 8 patients excluded from one site, and 3 patients each (8.6%) from Hungary, Russia, Serbia, and the United States.

Also, I noted that the youngest patient in the mITT population was 4 months of age.

Other Baseline Characteristics (e.g., disease characteristics, important concomitant drugs)

All patients in the mITT population had partial-onset seizures, with a mean duration since onset of seizures of 1.6 months. The baseline 24-hour seizure frequency rates are described below in Table 8.

Table 8 Summary of Baseline 24-hour Seizure Frequency Rates in mITT population

	Pregabalin 7 mg/kg/day N = 59	Pregabalin 14 mg/kg/day N = 28	Placebo N = 53	Total N = 140
Mean (SD)	18.0 (43.2)	8.8 (9.8)	7.4 (10.2)	12.2 (29.3)
Median	4.7	5.4	2.9	4.4
Min, Max	0.7, 255.0	0.3, 42.7	0.3, 56.2	0.3, 255.0

Source: Adapted from Study 1042 CSR Table 11, reviewer verified

Reviewer's comment: There was a lower mean and median baseline seizure frequency rate in the placebo group, and a much higher mean seizure frequency in the pregabalin 7 mg/kg/day group, likely because of a single outlier patient who had 255 seizures in a 24-hour period. Because there were differences in both the mean and median baseline seizure frequencies across treatment arms, the applicant did a post-hoc sensitivity analysis to adjust for baseline seizure frequency (see Efficacy Results, below).

The most frequent concurrent medical conditions were similar across the arms, and were cerebral palsy, developmental delay, microcephaly, and intellectual disability.

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

Treatment compliance was mainly comparable across treatment groups. Compliance was between 90-100% for 87.3% of patients in the pregabalin 7 mg/kg group, 88.2% of the patients in the pregabalin 14 mg/kg group, and 92.9% in the placebo group. Only one patient missed a dose in the pregabalin 7 mg/kg treatment arm, zero patients missed doses in the 14 mg/kg group, and 3 patients in the placebo arm missed a dose. A total of 12 patients took extra doses, and had between 1-3 extra doses. Mean compliance was 99.9% for pregabalin 7 mg/kg, 98.7% for 14 mg/kg and 99.0% for placebo group.

Most common concomitant AEDs during treatment were valproic acid, levetiracetam, and topiramate. (See Table 9)

Table 9 Most Common Concomitant Anti-Epileptic Drug Treatments

	Pregabalin 7 mg/kg/day (N=71)	Pregabalin 14 mg/kg/day (N=34)	Placebo (N=70)
Number (%) of Subjects with Any Concomitant AED Treatment	**71 (100.0%)**	**34 (100.0%)**	**70 (100.0%)**
Number of Subjects			
Valproic acid	28	17	38
Levetiracetam	27	10	20
Topiramate	16	7	15

Source: Section 14.4, Table 14.4.2.4.2
WHO-Drug (v201703) coding dictionary applied.
N is the number of subjects from the safety population for a given group.
Abbreviations: AED = anti-epileptic drug; WHO = World Health Organization.

Use of rescue medication was infrequent across all treatment groups; 3 patients (4.2%) in the pregabalin 7 mg/kg/day group, 2 patients (5.9%) in the pregabalin 14 mg/kg/day group, and 1 patient (1.4%) in the placebo group, took rescue medication in addition to the stable AEDs being administered during the study.

Efficacy Results – Primary Endpoint

The primary efficacy endpoint was the log-transformed double-blind 24-hour seizure rate, calculated and obtained from the 48-72-hour double-blind Video EEG (V-EEG) as described above. Treatment with pregabalin 14 mg/kg/day resulted in statistically significant reduction in the log-transformed 24-hour seizure rate compared to placebo, with p = 0.0223. The comparison between the pregabalin 7 mg/kg/day and placebo in the primary endpoint was not significant (p = 0.4606) (See Table 10, Figure 2).

Using back-transformation and least square means from the primary analysis results, the percentage reduction relative to placebo demonstrated a treatment differences relative to placebo of -44% for the pregabalin 14 mg/kg/day treatment arm, and 15% (increase) for the pregabalin 7 mg/kg/day treatment arm. Although the treatment difference between pregabalin 7 mg/kg/day group and placebo was not in the direction favoring pregabalin, the 95% confidence interval of this treatment difference does contain zero, meaning it does not indicate that the difference favors placebo.

Table 10 Primary Analysis *from Table 13 in CSR, reviewer verified*

Visit		Pregabalin 7 mg/kg/day (N=59)	Pregabalin 14 mg/kg/day (N=28)	Placebo (N=53)
Baseline	n	59	28	53
	Min	0.5	0.3	0.3
	Median	1.73	1.86	1.37
	Max	5.5	3.8	4.0
	Mean	2.03	1.86	1.66
	95% CI of Mean	(1.73, 2.33)	(1.49, 2.23)	(1.40, 1.91)
	SD	1.157	0.945	0.920
DB Phase	n	59	28	53
	Min	0.0	0.0	0.0
	Median	1.57	0.87	1.19
	Max	5.7	3.5	4.5
	Mean	1.81	1.10	1.36
	95% CI of Mean	(1.49, 2.12)	(0.69, 1.51)	(1.03, 1.69)
	SD	1.219	1.065	1.193
	LS Mean	1.69	1.15	1.58
	95% CI of LS Mean	(1.46, 1.92)	(0.83, 1.47)	(1.32, 1.83)
	Standard error	0.115	0.163	0.129
	Versus Placebo (log)			
	LS Mean Difference[a,b]	0.11	-0.43	
	95% CI of LS Mean Difference[a]	(-0.19, 0.42)	(-0.80, -0.06)	
	Standard error[a]	0.153	0.185	
	p-value[a,b]	0.4606	0.0223	
	Versus Placebo (%)			
	LS Mean Difference[a]	12.00	-34.87	
	95% CI of LS Mean Difference[a]	(-17.28, 51.65)	(-54.87, -6.00)	
	Standard error[a]	16.556	20.379	
	LS Mean Difference[b]	15.12	-43.94	

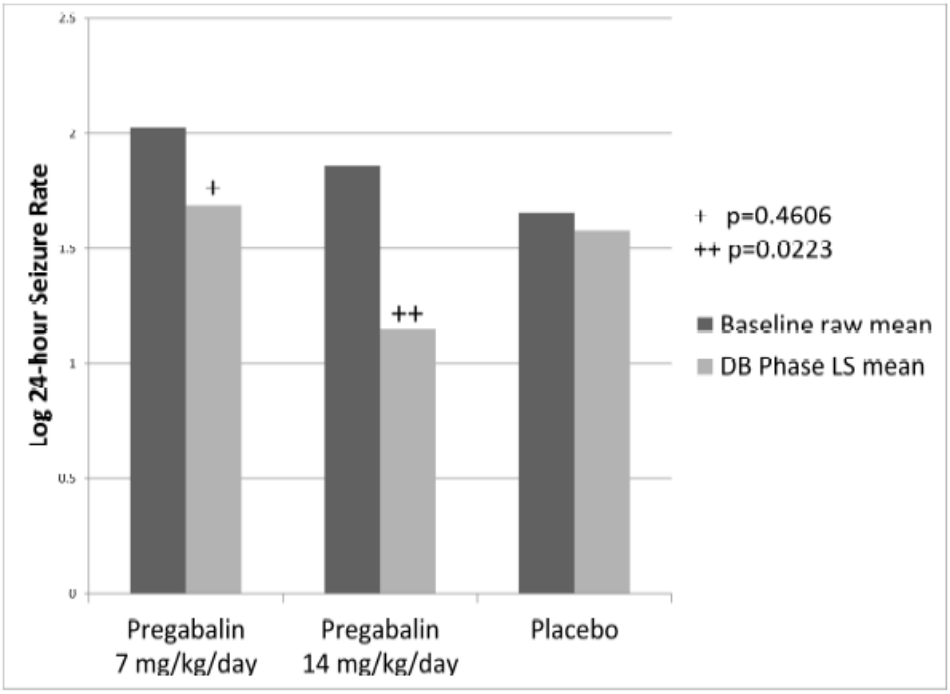
Source: Section 14.2, Table 14.2.1.1 and Section 16.1, Table 16.1.9.2.1
Baseline is the V-EEG seizure observed up to 72 hours. Double-blind phase indicates the V-EEG assessment performed at the end of the double-blind treatment phase.
N is the number of mITT subjects in each treatment group. For baseline, n is the number of subjects with a baseline value. For the double-blind phase, n is the number of subjects with values at both baseline and for the double-blind treatment phase.
The mITT population was the primary efficacy population and consisted of subjects who took at least 1 dose of study drug during the double-blind treatment phase, had a baseline with at least 1 POS identified by V-EEG, and had a treatment phase V-EEG.
Estimates and p-values are from an ANCOVA model including fixed effects for log baseline value, region, age strata, and treatment.
Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; DB = double-blind; LS = least squares; mITT = modified intent-to-treat; SD = standard deviation; V-EEG = video-electroencephalogram.

a. Back-transformation (a): Percent reduction in seizures was calculated as follows: 100%*[exp(X)-1], where X is the estimate of the difference of the log values between the 2 comparison groups based on the ANCOVA model (Section 9.7.3.1.1).
b. Back-transformation (b); Percent reduction in seizures was calculated as follows (Section 9.7.3.1.1):

$$100\% \times \frac{\left[\exp(\text{LSMean(pregabalin)}) - 1\right] - \left[\exp(\text{LSMean(placebo)}) - 1\right]}{\exp(\text{LSMean(placebo)}) - 1}$$

Reference ID: 4432875

Figure 2 Summary of Log-Transformed 24-Hour Seizure Rate During Double-Blind Treatment Phase - mITT Population – *from CSR Figure 3, reviewer verified*



Source: Section 14.2, Figure 14.2.1
Baseline is the V-EEG seizure observed up to 72 hours.
Double-blind phase indicates up to 72-hour V-EEG performed at the end of the double-blind treatment phase.
Comparisons are relative to placebo.
Abbreviations: DB = double-blind; mITT = modified intent-to-treat

As noted in Dr. Zhang's Biometrics review, the efficacy appeared to be driven by three foreign sites, and removal of any of the three sites resulted in no statistical significance for the pregabalin-placebo comparison (Site 1069, 1084, and 1209). Although two of these sites (1069 and 1084) were high-enrolling, Site 1209 only had three enrolled patients.

Reviewer's comments: As mentioned, a few foreign sites had large impact on efficacy results. Given the small sample size (n = 3) and high impact on efficacy analysis, site 1209 was inspected by OSI. Furthermore, I looked into the data from site 1209. There was a single patient who was an outlier that drove the efficacy results from site 1209, as this patient was randomized to the 14 mg/kg/day treatment group and had 85 seizures on the baseline V-EEG and 0 seizures on the double-blind treatment phase V-EEG. There were no noted irregularities with the EEG recording, with 47.8 hours of evaluable EEG time for the baseline EEG and 68.3 hours of evaluable EEG time for the treatment phase EEG. It was noted that all of the recorded seizures had identical "start" and "stop" times, but this was not unique to this patient or site, and was felt to represent not the actual duration of the seizure but the

timestamp for the central reader marking the seizure on the EEG. All of the seizures recorded in the raw-data listings either had the same start/stop time or were recorded as being exactly 3 seconds long, which is also not the duration of the observed electroclinical seizure activity but the time at which the seizures were marked.

Planned sensitivity analyses of the primary efficacy endpoint conducted by the applicant were the rank ANCOVA and the Wilcoxon-Mann-Whitney test for the log-transformed 24-hour seizure rate (POS) during the double-blind treatment phase and the mITT population. Neither of these analyses adjusts for the baseline differences between treatment groups. To adjust for differences in baseline seizure rates between the treatment groups, post-hoc sensitivity analyses were performed, changing the dependent variable from the log-transformed 24-hour seizure rate to the change from baseline in log-transformed 24-hour seizure rate. These are presented below and support the findings of the primary efficacy analysis (Table 11).

Table 11 Log-transformed 24-hour Seizure rate (Non-parametric planned and post-hoc sensitivity analyses; mITT population) *from ISS Table 7, reviewer-verified*

Log-transformed 24-hour seizure rate	Pregabalin 7 mg/kg/day N = 59	Pregabalin 14 mg/kg/day N = 28	Placebo N = 53
Planned sensitivity analyses			
Baseline phase			
Mean (SD)	2.03 (1.157)	1.86 (0.945)	1.66 (0.920)
Median (Min, Max)	1.73 (0.5, 5.5)	1.86 (0.3, 3.8)	1.37 (0.3, 4.0)
Double-blind phase			
Mean (SD)	1.81 (1.219)	1.10 (1.065)	1.36 (1.193)
Median (Min, Max)	1.57 (0.0, 5.7)	0.87 (0.0, 3.5)	1.19 (0.0, 4.5)
Ranked ANCOVA P-value	0.0924	0.1748	
Wilcoxon-Mann P-value	0.0384	0.3883	
Post-hoc sensitivity analyses			
Change from baseline			
Mean (SD)	-0.23 (0.743)	-0.76 (1.073)	-0.30 (0.678)
Median (Min, Max)	-0.14 (-2.2, 1.7)	-0.55 (-3.8, 1.8)	-0.18 (-2.1, 1.3)
Ranked ANCOVA P-value	0.5150	0.0534	
Wilcoxon-Mann P-value	0.5561	0.0258	

Source: CSR 1042 Tables 14.2.1.2 and 14.2.1.1.1 and CSR 1042 Section 16.1 Post-hoc Table 1 and Post-hoc Table 2
Abbreviations: ANCOVA = analysis of covariance; CSR = clinical study report; kg = kilogram; mg = milligram; max = maximum; min = minimum; mITT = modified intent-to-treat population; N = number of subjects; SD = standard deviation.

Demographic Subpopulations

Subpopulation analyses included an analysis of the 24-hour seizure rates at baseline and median change from baseline by sex, age, and race. The small sample size in some of the subgroups precludes meaningful subgroup analysis to demonstrate any differences between the subgroups; however, the subpopulation analyses were supportive of the primary efficacy results (Table 12). As noted in Dr. Zhang's biometric review, there were no compelling evidence from the subgroup analysis that a specific age subgroup, sex, or race benefits differently from pregabalin. Only 3 patients (one from each treatment arm) were from the United States, so subgroup analysis by region was not conducted.

Table 12 Median Percent Change by Age, Sex, and Race From Baseline to End of Double-Blind Treatment in 24-Hour Seizure Rate - mITT Population – *from ISS Table 9, Reviewer verified*

	Pregabalin		Placebo
	7 mg/kg/day	14 mg/kg/day	
AGE (<12 months, 12-24 months, and >24 months)			
<12 months (n)	9	2	3
Baseline	12.19 (1.4, 37.5)	6.47 (2.0, 11.0)	3.03 (2.0, 7.9)
% Change from Baseline	-28.68 (-76.1, 163.1)	-44.90 (-63.6, -26.2)	-44.13 (-58.0, 35.7)
12 to 24 months (n)	16	7	14
Baseline	4.83 (0.7, 206.2)	5.28 (0.3, 19.5)	6.07 (0.3, 56.2)
% Change from Baseline	-39.62 (-100.0, 371.4)	-37.49 (-100.0, 2099.7)	26.62 (-100.0, 291.7)
>24 months (n)	34	19	36
Baseline	3.94 (0.7, 254.9)	8.66 (0.7, 42.7)	2.75 (0.4, 34.9)
% Change from Baseline	-0.49 (-100.0, 1111.6)	-91.68 (-100.0, 94.1)	-33.90 (-100.0, 186.0)
AGE (<24 months and ≥24 months)			
<24 months (n)	25	9	17
Baseline	5.33 0.7, 206.2)	5.28 (0.3-19.5)	5.29 (0.3-56.2)
% Change from Baseline	-33.69 (-100.0, 371.4)	-37.49 (-100.0, 2099.7)	15.40 (-100.0, 291.7)
≥24 months (n)	34	19	36
Baseline	3.94 (0.7, 254.9)	8.66 (0.7, 42.7)	2.75 (0.4, 34.9)
% Change from Baseline	-0.49 (-100.0, 1111.6)	-91.68 (-100.0, 94.1)	-33.90 (-100.0, 186.0)
SEX			
Male (n)	40	15	28
Baseline	4.81 (0.7, 254.9)	8.98 (0.3, 27.4)	3.79 (0.3, 56.2)
% Change from Baseline	-23.15 (-100.0, 1111.6)	-85.98 (-100.0, 2099.7)	-33.15 (-100.0, 291.7)
Female (n)	19	13	25
Baseline	4.34 (0.7, 39.6)	4.40 (1.0, 42.7)	2.75 (0.7, 28.3)
% Change from Baseline	13.47 (-100.0, 371.4)	-42.41 (-100.0, 94.1)	-13.53 (-100.0, 186.0)
RACE			
White (n)	38	18	34
Baseline	4.09 (0.7, 86.6)	5.10 (0.7, 42.7)	2.55 (0.4, 56.2)
% Change from Baseline	-18.47 (-100.0, 371.4)	-54.75 (-100.0, 84.8)	-32.76 (-100.0, 291.7)
Asian (n)	20	10	18
Baseline	7.54 (0.7, 254.9)	7.16 (0.3, 19.5)	5.47 (0.3, 34.9)
% Change from Baseline	-6.36 (-100.0, 1111.6)	-82.66 (-100.0, 2099.7)	-17.36 (-100.0, 186.0)

Reviewer's comment: Because there were small numbers of patients in the < 12 months of age, a subgroup analysis using fewer subgroups of patients < 24 months and ≥ 24 months was also done, for which the median percent change indicated reductions in seizure rates with pregabalin 14 mg/kg/day group compared to placebo for both age groups. The treatment with pregabalin 7 mg/kg/day showed improvement in seizure rate compared to placebo in the age groups 12-24 months and in all patients < 24 months, but not those ≥ 24 months of age.

Data Quality and Integrity

Overall the data quality and analysis quality are adequate. I was able to perform independent review using the applicant's submitted datasets and confirm the results.

Efficacy Results – Secondary and other relevant endpoints

Secondary efficacy endpoint was the responder rate, defined as patients who had a ≥ 50% reduction from baseline in partial-seizure rate during the double-blind V-EEG period. The responder rate analysis demonstrated that the responder rate improved numerically compared to placebo in the pregabalin 14 mg/kg/day group (53.6% compared to 41.5%, p = 0.305), and that the responder rate for pregabalin 7 mg/kg/day was numerically less than placebo (30.5% compared to 41.5%, p = 0.2418).

As a safety parameter, long-term efficacy data was collected from the open-label, long-term extension Study 1106. There were 130 patients who continued from Study 1042 into Study 1006, all of whom began at 3.5 mg/kg/day and then had dosage adjusted based on efficacy and tolerance. Reduction in a median-28-day seizure rate was apparent from Month 1 and generally continued to decrease over time, indicating continued persistence of effect over time.

Dose/Dose Response
Data from both pediatric and adult populations had indicated an exposure-response relationship in POS in pediatric patients age 1 month to < 4 years. Therefore, it follows that a dose range which leads to exposures in this population equivalent to those provided within the approved dose ranges in patients 4 years and older is recommended.

A population pharmacokinetic analysis of adult and pediatric patients demonstrated that the pregabalin dosages of 3.5-14 mg/kg/day administered TID in pediatric patients 1 month to < 4 years of age achieve comparable pregabalin exposure to those patients 4 years and older at approved dose ranges.

Reference ID: 4432875

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

There is only a single efficacy study included in this review and therefore this section is not applicable.

7.1.1. Primary Endpoints

There is only a single efficacy study included in this review.

7.1.2. Secondary and Other Endpoints

There is only a single efficacy study included in this review.

7.1.3. Subpopulations

There is only a single efficacy study included in this review.

7.1.4. Dose and Dose-Response

There is only a single efficacy study included in this review.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

There is only a single efficacy study included in this review.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

The use of this drug in this patient population was studied in a way that is similar to how it will be used (and probably is currently used off-label) in this age group. As noted above, the youngest enrolled patient was 3.5 months of age, and the youngest patient in the mITT population was 4 months of age. However, there are no clinical reasons to think that efficacy would not be similar in those patients younger than 4 months of age. See Section 8.2 for a discussion of safety in this age group.

The TID dosing schedule may be problematic for compliance/adherence to dosing regimens; however, given the lack of approved therapies in this age group, the difficulty in treating POS in very young patients, and the reliance on a parent and/or caregiver for drug administration,

these pediatric patients will likely be able to receive treatment in compliance with the prescribed dosing regimen.

7.2.2. Other Relevant Benefits

As compared to many antiepileptic drugs that are currently available, pregabalin has the benefit of being predominantly excreted unchanged in the urine and undergoing negligible metabolism in humans. Therefore, the lack of drug-drug interactions with pregabalin will be a significant benefit for those patients who may be on multiple other seizure medications or other medically complex patients who are on many concomitant medications.

7.3. Integrated Assessment of Effectiveness

Overall, the data in this submission supports evidence of effectiveness of pregabalin 14 mg/kg/day for the treatment of POS in pediatric patients 1 month and older. The dosing regimen is similar to that proposed in older pediatric patients and will be titrated based on effectiveness and tolerability to the maximum recommended dosage of 14 mg/kg/day.

8. Review of Safety

8.1. Safety Review Approach

Safety was reviewed for the double-blind treatment period in Study 1042, as well as the open label extension studies Study 1106 and Study 1075 which both enrolled patients in the proposed 1 month to < 4 years of age target population.

Because there was a single placebo-controlled study and two open-label extension studies which lacked comparators, the data from all 3 studies were not pooled for the majority of the analyses. The three safety populations analyzed were Controlled Data from Study 1042 (n = 175), Controlled/Uncontrolled Data from the safety pool of all three studies 1042, 1075, and 1106 (n = 182), and Safety Data from Phase 1 PK study 1074 (n = 26).

8.2. Review of the Safety Database

8.2.1. Overall Exposure

For Study 1042, the protocol was designed to have a duration of treatment of 21 days. The median duration of treatment was 21 days for all treatment groups. In the pregabalin group, 69/71 patients completed ≥ 15 days of treatment, in the pregabalin 14 mg/kg group, 33/34 patients completed ≥ 15 days, and in the placebo group, 67/70 patients completed ≥ 15 days of treatment. Of note, the youngest pregabalin-treated patient was 4 months of age.

A total of 182 patients were treated with pregabalin in Studies 1042, 1075, and 1106 combined (Table 13). As of the initial December 29, 2017 cut-off date, of these 182 patients, 91 completed the study, 33 discontinued, and 58 are still ongoing. Of the 33 patients who discontinued treatment, reasons for discontinuation were: AEs (3), insufficient clinical response (12), medication error without AE (1), no longer willing to participate (9), death (2), and "other"(6).

Table 13 Duration of Exposure

	Number of patients 3 months to < 4 years exposed to the study drug[a]:				
Dosage	>= 1 dose	>=28 days	>=150 days	>=300 days	360 days or longer
2.5-14 mg/kg/day	N=182	N=151	N=104	N= 71	N=58

[a] As of initial cut-off date of December 29 2017

After review of the 90-day safety update, using a new cutoff date of October 15, 2018, a total of 195 patients age 1 month to < 4 years of age have been treated with pregabalin, and a total of 99 patients had completed > 360 days of treatment. Median treatment duration was 361 days, with 108 (55.4%) patients completing the studies, 47 (24.1%) patients ongoing, and 40 (20.5%) patients had discontinued.

8.2.2. Relevant characteristics of the safety population:

The key safety analyses were performed on the safety population from pivotal Study 1042, as well as the long-term extension studies. See Table 14 below for a summary of demographic characteristics. There were no significant demographic or baseline medical history characteristic differences among the treatment groups.

Table 14 Demographic characteristics of the safety analysis population

Demographic Parameters	Pregabalin 7mg/kg/day N = 71 n (%)	Pregabalin 14 mg/kg/day N = 34 n (%)	Placebo N = 70 n (%)	Total N =175 n (%)
Sex				
Male	45 (63.4)	20 (58.8)	38 (54.3)	103 (58.9)
Female	26 (36.6)	14 (41.2)	32 (45.7)	72 (41.1)
Age				
< 12 months	9 (12.7)	2 (5.9)	7 (10.0)	18 (10.3)
12 to < 24 months	18 (25.3)	10 (29.4)	19 (27.1)	47 (26.9)
≥ 24 months	44 (62.0)	22 (64.7)	44 (62.9)	110 (62.9)
Mean months (SD)	27.5 (12.7)	28.5 (12.5)	28.8 (12.6)	28.2 (12.6)
Min, max (months)	4, 48	4, 47	3, 47	3, 48
Race				
White	47 (66.2)	24 (70.6)	49 (70.0)	120 (68.6)
Asian	23 (32.4)	10 (29.4)	19 (27.1)	52 (29.7)
Other	1 (1.4)	0 (0.0)	2 (2.9)	3 (1.7)
Ethnicity				
Not Hispanic/Latino	69 (97.2)	33 (97.1)	68 (97.1)	170 (97.1)
Hispanic/Latino	2 (2.8)	1 (2.9)	1 (1.4)	4 (2.9)
No response	0 (0.0)	0 (0.0)	1 (1.4)	1 (0.6)
Weight (kg)				
Mean (SD)	11.7 (3.5)	11.4 (3.4)	11.4 (3.1)	11.5 (3.3)
Height (cm)				
Mean (SD)	86.1 (11.6)	84.1 (10.0)	85.6 (11.3)	85.6 (11.2)

Source: Adapted from Study 1042 CSR Table 10, reviewer verified

For the pooled data from the uncontrolled studies, the mean age was 27.2 months of age, with 13.7% younger than 12 months of age. The majority of patients were male and white. All patients in this population had POS with a mean duration since diagnosis of 1.6 years.

8.2.3. Adequacy of the safety database:

The safety database appears appropriate based on extent of exposure and range of ages in the safety population.

Reviewer's Comment: As noted above, there are no patients under 4 months of age who received pregabalin during the double-blind treatment phase. There were few patients under 1 year of age in all treatment arms of the study. The applicant is proposing an indication

down to 1 month of age. Although there is decreased renal clearance in patients 1 to 3 months of age, clinical pharmacology has addressed the safety of the starting dose based on the PK simulations provided by the applicant in this age group. Furthermore, from a clinical perspective, there are no safety concerns that would preclude using the drug in patients age 1 month to 3 months of age, given the conservative approach to dosing of starting at a low dose and titrating up to a maximum dose based on tolerability and clinical response. The most common adverse event (see below) is somnolence which would be able to be monitored for, and given the dose titration schedule, even the youngest patients at 1 month of age would be closer to 3 months of age by the time they reached the maximum dose. Given interpatient variability, there are no safety concerns to expanding the indication down to the youngest age that POS can be diagnosed, which is 1 month.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There were no concerns regarding the integrity of the data submitted for the safety review. The datasets provided by the applicant were complete and not misleading, and I was sufficiently able to reproduce the safety analyses of the applicant, and perform my own analyses when necessary.

8.3.2. Categorization of Adverse Events

Treatment Emergent Adverse Events (TEAE)
An adverse event (AE) was defined as any untoward medical occurrence in a clinical investigation where patient administered a product or medical device: the event need not necessarily have a causal relationship with the treatment or usage. All AEs reported during the course of the study from the first day of study treatment through and including 999 calendar days after last administration were considered Treatment-Emergent AEs (TEAEs).

A serious adverse event (SAE) is any untoward medical occurrence at any dose that:

- Results in death
- Is life-threatening (immediate risk of death)
- Requires in subject hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in congenital anomaly/birth defect.

Severity of AEs were graded as mild, moderate, or severe, to describe the maximum intensity of the adverse events as per following chart:

- MILD: does not interfere with subject's usual function
- MODERATE: interferes to some extent with subject's usual function
- SEVERE: interferes significantly with subject's usual function

All AES were coded using MedDRA v 20.1 coding dictionary. TEAEs were summarized by system organ class (SOC), preferred term (PATIENT), severity, and relationship to study drug.

TEAEs of Special Interest (Targeted Medical Events (TMEs))
The targeted medical events (TMEs) were identified in the Lyrica Safety Review Plan and are AEs of special interest based on the known adult safety profile for pregabalin.

The 3-tier approach for summarizing AEs will be implemented, and events will be classified into the following tier definitions:

- Tier 1: None
- Tier 2: Targeted Medical events (TMEs)
    - Point estimates and confidence intervals for the risk difference, computed as dose level 1 vs placebo and dose level 2 vs placebo
    - AEs will be arranged and sorted in descending point estimate of the risk measure
- Tier 3: Standard safety output (no new outputs)

Overall, the applicant's coding of AE terms was sufficient. A few similar terms were grouped together during my review to avoid underestimating any potential safety signals/risks. Thus the following terms were recoded as noted in Table 15 below.

Table 15 Recoded AE codes to Group Similar Terms

Original Coded Terms	Recoded Term
Upper respiratory tract Infection, respiratory tract infection viral	Upper Respiratory Tract Infection
Rhinitis, rhinitis allergic	Rhinitis
Anemia, hemoglobin decreased	Anemia
Seizure, epilepsy	Seizure
Ear infection, otitis media	Otitis media
Thrombocytopenia, platelet count decreased	Thrombocytopenia
Regurgitation, vomiting	Vomiting
Rash, skin erythema, skin irritation, viral rash	Rash
Somnolence, sluggishness, lethargy, hypersomnia	Somnolence

Reviewer's comment: Overall, the categorization and coding of TEAEs was appropriate and sufficient, especially given the well characterized safety profile in adult patients, as well as the approval in 2018 in pediatric patients age 4 to 16 years of age.

8.3.3. Routine Clinical Tests

Refer to Table 4, Schedule of Key Study Procedures for a summary of the performed clinical examinations. Routine clinical tests were performed including chemistries, hematology tests,

urinalysis, vital signs, ECG monitoring, physical exams and neurologic exams.

8.4. Safety Results

8.4.1. Deaths

There were no deaths in Study 1042.

Four patients died during the long-term extension study, although none were felt to be related to treatment by the investigator. These case narratives are summarized below.

- Patient (b) (6), 33-month-old boy with a history of POS secondary to traumatic brain injury from a motor vehicle accident, with developmental delay, neurogenic bladder, recurrent urinary tract infections and ventilator-associated acquired pneumonia. He had multiple episodes of community-acquired pneumonia, and he was hospitalized on Day 190 for pneumonia and respiratory distress. He subsequently died secondary to the pneumonia on Day 211.
- Patient (b) (6), a 3-year-old girl with a history of preterm birth with intraventricular hemorrhage, hydrocephalus s/p placement of ventriculoperitoneal shunt placement, cerebral palsy, malnutrition, cerebellar atrophy, and cerebral dysgenesis concerning for Dandy-Walker syndrome, who died on Day 15 of the long-term extension study, after completing Study 1042 for 21 days receiving placebo therapy. She was on concomitant carbamazepine, as well as baclofen for spasticity, and oxymetazoline hydrochloride and butamirate citrate for acute rhinopharyngitis/cough. She had worsening nasopharyngitis with concern for bacterial infection on Day 12, and was started on antibiotic therapy. She experienced dehydration and refused drinking and feeding resulting in hospitalization. She was then found to have occlusion of the VP shunt with worsening obstructive hydrocephalus and underwent shunt decompression, but developed cardiac failure and died on Day 15 due to brainstem herniation.
- Patient (b) (6), 6-month-old boy had multiple SAEs of pneumonia and status epilepticus during the study, and died 2 months after the last dose of pregabalin therapy. He received pregabalin in Study 1075 after receiving pregabalin treatment for 8 days in Study 1074. He started treatment in June 2011 at 6 months of age, and received 67.5 mg pregabalin through Study Day 55. He had no significant medical history and was on concomitant valproic acid at start of study. He was hospitalized on Day 21 for pneumonia and increased seizures requiring intubation. He also had bacterial sepsis at that time. He was extubated on Day 30, discharged home on Day 39. On Day 44 of the study, he had another episode of status epilepticus in the setting of fever, also requiring intubation and inotropic support due to prolonged status epilepticus and metabolic acidosis, again diagnosed with pneumonia (hospital-acquired) requiring IV antibiotics, as well as concomitant respiratory syncytial virus (RSV). He was extubated on Day 50, and study drug was discontinued on Day 55. He had recurrent status epilepticus on Day 56, ultimately requiring thiopental for seizure control. He had another episode of status

epilepticus on Day 61, and was diagnosed with malignant migrating partial seizures of infancy. He was extubated on Day 64. He was hospital-acquired bacterial infections of his central venous catheter, with continued frequent seizures. On Day 81, he went into status epilepticus that did not respond to any medications resulting in hypovolemic shock, bradycardia and metabolic acidosis, resulting in death on the same day.

- Patient (b) (6), 3-year-old girl died secondary to pneumonia 9 months after completing the study. She remained on pregabalin, and had been treated for 657 days. She had a history of post-meningitis hydrocephalus with ventriculoperitoneal shunt, microcephaly, developmental delay, cerebral palsy, and several past episodes of pneumonias. She developed fever, bradycardia, and respiratory distress, and presented to hospital with cyanosis and no vital signs, and died secondary to respiratory arrest despite CPR measures.

8.4.2. Serious Adverse Events

There were 5 serious adverse events (SAEs) during Study 1042 as noted in Table 16 below.

Table 16 Treatment-Emergent Adverse Events - Safety Analysis Set

	Pregabalin 7 mg/kg N = 71 n (%)	Pregabalin 14 mg/kg N = 34 n (%)	Placebo N = 70 n (%)	Total N = 175 n (%)
TEAEs	32 (45.1)	17 (50.0)	38 (54.3)	87 (49.7)
SAEs	0	1 (2.9)	4 (5.7)	5 (2.9)
Severe AEs	0	0	0	0
Discontinued due to AEs	0	0	1 (1.4)	1 (0.6)

Source: Adapted from Study 1042 CSR Table 17, reviewer- verified

None of the SAEs led to discontinuation from the study. The SAEs are briefly described below, including one patient who was randomized to pregabalin 14 mg/kg/day and 4 patients who were randomized to placebo.

- Patient (b) (6) (14 mg/kg/day), a 3-year-old girl with spastic quadriparetic cerebral palsy secondary to hypoxic ischemic encephalopathy at birth, with associated microcephaly, developmental delay, asthma, and POS, who experienced an SAE of pneumonia on Day 8, requiring hospitalization on Day 10, with complete resolution. She had a history of hospitalization for pneumonia in the past. Pneumonia resolved, no action taken.
- Patient (b) (6) (placebo), 10-month-old boy with history of hypoxic ischemic injury at birth, hydrocephalus, and cow's milk allergy, as well as POS since 1 month of age, was hospitalized with an episode of acute rhinitis requiring IV ceftriaxone on Day 26 and also had associated thrombocytosis and lymphocytosis with decreased neutrophil counts, related to underlying infection, which was mild in severity. No action taken and

symptoms resolved.

- Patient (b) (6) (placebo), 3-year-old boy with history of hypoxic ischemic brain injury and attention-deficit/hyperactivity disorder and POS, who had an SAE of increased frequency of seizures on Day 9, considered moderate in intensity and thought to be due to withdrawn background AEDs. On Day 8, patient had significant vomiting and sluggishness resulting in permanent discontinuation of study drug (last dose Day 7, see Section 8.4.3) and some of the patients' background AEDs. No further action taken.
- Patient (b) (6) (placebo), 18-month-old girl with a history of hypotonia, intellectual disability, and muscle spasticity, who experienced an episode of dehydration on Day 3, mild in severity, and treated with IV hydration and nutritional support. Resolved on Day 7, no action taken.
- Patient (b) (6) (placebo), 19-month-old boy with hypotonia and lack of speech, as well as history of pneumonia and asthma in the past, who experienced an SAE of choking with oral secretions on Day 15, which was moderate in severity. He had reported several days of salivary hypersecretion, and then was admitted for the required 72-hour video EEG. While in the hospital for Video EEG, he was noted to have difficulty in breathing which responded to nebulizer, and then had an event of circumoral cyanosis, pallor and was limp with possible near aspiration, which resolved with suctioning of thick secretions. He temporarily discontinued treatment on the day of the event, missing one morning dose. Resolved on the same day.

In the long-term extension studies, there were 33 patients who had SAEs. The only SAEs that occurred in more than one patient were pneumonia, seizure, asthma, and status epilepticus. Three of these patients with SAEs of status epilepticus, seizures, and thrombocytopenia led to permanent discontinuation from the studies. The thrombocytopenia was subsequently determined to be a laboratory error.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

No patients in either pregabalin group discontinued treatment due to TEAEs. There was one patient in the placebo group who discontinued treatment after a TEAE of vomiting (Patient (b) (6), described in Section 8.4.2)

In the long-term open-label extensions, three patients discontinued due to SAEs noted above in Section 8.4.2.

Reviewer's comment: Of note, due to the short duration of the double-blind treatment period (14 days), discontinuations would not have been expected in many patients.

8.4.4. Significant Adverse Events

There were no TEAEs of severe intensity reported in Study 1042. There were no Tier 2 AEs that were statistically significantly increased over placebo for either pregabalin treatment group.

See Section 8.5 for a discussion of product specific safety concerns.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

Table 17 includes all TEAEs that were reported in ≥ 2% in any pregabalin treatment arm, and in more than 2 patients. For example, if an AE was reported only in one patient in the pregabalin 14 mg/kg/day group, that AE is not included in the table, although it would have been 2.8% of that treatment arm. I have combined similar terms as per Table 15.

Table 17 AEs that are **≥** 2% of pregabalin population and greater than placebo

Adverse Event	Placebo N = 70 (%)	Pregabalin 7 mg/kg/day N = 71 (%)	Pregabalin 14 mg/kg/day N = 34 (%)	All Pregabalin N = 105 (%)
Nervous System Disorders				
Somnolence[a]	8.6	12.7	20.6	15.2
Falls	1.4	2.8	0	1.9
Change in Sleep Pattern	0	2.8	0	1.9
Infections and Infestations				
Viral Infection	2.9	4.2	5.9	5.7
Pneumonia	0	1.4	8.8	3.8
Bronchitis	1.4	0	5.9	1.9
Otitis Media	1.4	1.4	2.9	1.9
Nasopharyngitis	1.4	1.4	2.9	1.9
Gastrointestinal Disorders				
Diarrhea	0	5.6	0	3.8
Constipation	0	0	5.9	1.9
Hematologic Disorders				
Anemia	0	2.8	0	1.9
Other				
Application Site Irritation*	0	0	5.9	1.9

Source: Reviewer's analysis of Study 1042 Adverse dataset
[a] *includes somnolence, lethargy, sluggishness, hypersomnia*
**EEG electrode irritation*

The current Lyrica Prescribing Information defines dose-related AEs for patients 4 years of age and older as those AEs that occur in at least 2% of all pregabalin-treated patients, in which the incidence of the AE in the highest pregabalin dose group was at least 2% greater than the rate in both the lowest pregabalin dose group and placebo. Similar tables of such dose-related AEs are provided in the Lyrica USPI Section 6.1, in the 4 to 16 years of age population, as well as for the adult populations. The following table summarizes the "dose-related" AEs in the patients 1 month to < 4 years of age from Study 1042 and can potentially be included in the labeling.

Table 18 Dose-Related Adverse Events in at Least 2% of Pregabalin-Treated Patients - Study 1042

Adverse Event	Placebo N = 70 (%)	Pregabalin 7 mg/kg/day N = 71 (%)	Pregabalin 14 mg/kg/day N = 34 (%)	All Pregabalin N = 105 (%)
Somnolence *	8.6	12.7	20.6	15.2
Pneumonia	0	1.4	8.8	3.8
Viral Infection	2.9	2.9	5.9	3.8

Source: Reviewer's analysis of Study 1042 Adverse dataset
**includes related terms including lethargy, sluggishness, hypersomnia, and somnolence*

Including the data from the uncontrolled studies, the most common AEs reported in at least 10% of patients were respiratory tract infection, pyrexia, pneumonia, nasopharyngitis, somnolence and diarrhea.

Data from the 90-day safety update (with a data cut-off of October 15, 2018), included the most common adverse events, or those occurring in ≥ 5% of the pediatric patients, were (in decreasing order of frequency): upper respiratory tract infection, pyrexia, pneumonia, seizure, nasopharyngitis, viral infection, somnolence, cough, diarrhea, vomiting, increased appetite, gastroesophageal reflux disease, otitis media, and constipation.

8.4.6. Laboratory Findings

There were no clinically relevant changes for any laboratory parameters observed in median change from baseline to last observation, and no reports of potential Hy's Law cases.
No laboratory test abnormalities resulted in SAEs or resulted in discontinuation from the study.
There were laboratory-result associated AEs reported in all treatment groups with no single abnormal laboratory result being reported in more than one patient in each arm, except for 2 patients in the placebo arm who reported thrombocytopenia.

8.4.7. Vital Signs

No clinically relevant changes in blood pressure or heart rate were observed, and changes from baseline were similar across all treatment groups during Study 1042.

One patient in the placebo group ((b) (6)) did experience an AE of tachycardia, that was mild and felt to be related to the SAE of dehydration (See Section 8.4.2). Of note, there were also no clinically relevant changes in neurologic or physical examination noted in Study 1042.

8.4.8. Electrocardiograms (ECGs)

No clinically relevant changes in ECG variables were noted, and no patients met the criteria for

maximum increase from baseline in PR interval during the study. There was one patient in the placebo group who met the criteria for maximum increase from baseline in their QRS complex.

One patient in the placebo group [redacted] (b) (6)) had a reported AE of bradyarrhythmia and early repolarization that were felt to be mild in severity and resolved without discontinuation from the study.

8.5. Analysis of Submission-Specific Safety Issues

The following adverse events were identified to be of interest based on experience with the adult patient population and older pediatric population. However, the young age of the population may result in lower reporting of some of these adverse reactions that were reported in adults.

8.5.1. Dizziness

In Study 1042 there were no reports of dizziness. There was 1 patient with a report of imbalance. One patient in the long-term extension study population reported dizziness, which was moderate in severity, was not an SAE, and did not lead to treatment discontinuation.

Reviewer's comment: Dizziness may be hard to detect in patients younger than 4 years of age, other than if parents were to report difficulties with walking or balance.

8.5.2. Somnolence

Somnolence was defined per the applicant as any of the following reported AEs: somnolence, hypersomnia, and sedation. Lethargy, sluggishness and asthenia were also considered.

Overall in Study 1042, there were reports of somnolence in 8 patients in pregabalin 7 mg/kg arm, 6 patients in pregabalin 14 mg/kg arm, and 4 patients in the placebo group. Hypersomnia was additionally reported in 1 placebo patient and 1 patient in the pregabalin 14 mg/kg group. Sedation was not reported. One of the cases of mild somnolence was reported due to medication error. Lethargy was reported in 1 patient who received pregabalin 7 mg/kg. Sluggishness and asthenia were also reported in 1 patient in the placebo group. None led to discontinuation or dose reduction.

In the long-term extension studies, somnolence was overall reported in 19 (10.4%) of all patients in studies 1042, 1075, and 1106. One patient led to dose reduction. Hypersomnia was reported in one patient. There were no reports of sedation, lethargy, sluggishness or asthenia. No patients had discontinuation due to somnolence.

In the 90-day safety update, there were 2 additional cases of somnolence.

Reviewer's comment: For completeness, somnolence was combined with hypersomnia, lethargy, and sluggishness for the calculation of common TEAEs above.

8.5.3. Peripheral Edema

There were no cases of peripheral edema or edema-related events were reported in Study 1042. In the uncontrolled studies, there were no reports of peripheral edema. There was 1 patient who reported face swelling (allergic reaction), and 1 report of periorbital eye swelling (mosquito bite).

No further cases reported in the 90-day safety update.

8.5.4. Weight Gain

Weight gain events included either reports of weight increased, obesity, or overweight. There were none reported for Study 1042. In Study 1106, there were 3 patients who reported weight increased, with one report of overweight. No cases of obesity reported. None led to discontinuation or dose reduction.

There was an additional report of weight increased as an adverse event in the 90-day safety update.

8.5.5. Vision- related events

No vision-related AEs were reported in Study 1042. However, in the Eye Disorders SOC, there were reports of chalazion and mydriasis in Study 1042 in one patient each, both on 7 mg/kg/day group, which did not lead to dose reduction or discontinuation.
In the long-term extension studies, there were 6 patients reporting eye disorders including astigmatism, blepharitis, allergic conjunctivitis, eye swelling and hypermetropia, all of which were mild.

No new cases were reported in the 90-day safety update.

Reviewer's comment: Vision-related AEs may also be difficult to identify in patients younger than 4 years of age.

8.5.6. Ataxia/Tremor

None reported in Study 1042 or in the long-term extension studies.

8.5.7. Cognitive/neuropsychiatric events including behavioral effects and euphoria

In Study 1042, 1 patient had psychomotor hyperactivity (placebo), 1 agitation (placebo) and 4 patients reported irritability (3 patients in the pregabalin 7 mg/kg/day arm and 1 patient in the placebo arm). No cases of euphoria or suicidal ideation or behavior reported in Study 1042.

In the uncontrolled studies, there were reports of aggression(1), agitation(1), attention-deficit/hyperactivity disorder(2), irritability(6), restlessness (1) and psychomotor hyperactivity (5). No euphoria and no suicidal ideations were reported.

During the 90-day safety update, there was an additional report of agitation, and 3 more patients with reports of irritability identified.

Reviewer's comment: Although some of the neurologic and psychiatric adverse events could be detected by the parents/caregivers of these young patients, it would be hard to determine certain neurocognitive changes in this age group, especially complaints of euphoria, suicidal ideation, or even cognitive changes.

8.6. Safety Analyses by Demographic Subgroups

AGE
AEs were also analyzed by age into the following strata, patients < 12 months of age, patients 12 to < 24 months of age, and patients ≥ 24 months of age.

There were 5 patients < 12 months who had 10 AES, one of which was an SAE and is already described above. None resulted in discontinuation from the study, and none occurred in the pregabalin 14 mg/kg/day arm. AEs were reported in 4/9 (44.4%) patients in the pregabalin 7 mg/kg arm, and 1/8 (12.5%) in the placebo arm.

Among patients 12 to < 24 months of age, there were AEs in 8/20 pregabalin 7 patients, 6/11 (54.5%) pregabalin 14, and 10/21 (47.6%) in the placebo arm. In patients receiving pregabalin, none of the AEs were SAEs.

Reviewer's comment: Although the small numbers in the < 12 months age group make it hard to draw significant conclusions, there was no trend towards increasing or more severe AEs in the younger patients. Overall, the younger patients had similar rates of AEs as older pediatric patients, with no AEs in the youngest patients on the 14 mg/kg/day dose, and there were no newly identified safety signals were noted in the youngest patients receiving pregabalin.

SEX
There were overall similar proportions of male and female patients who reported AES in the pooled data, with 67.5% of male patients and 63.6% of female patients reporting AEs. SAEs were more commonly reported in male patients, although there were a higher number of male patients enrolled in the studies.

RACE
The incidence rates of AEs among races were analyzed for all studies, but no clinically meaningful differences were noted.

Extrinsic Factors
There were clinical pharmacology and biopharmaceutics studies which have provided evidence for lack of effect of any extrinsic factors on administration of pregabalin in adult subjects, as well as PK studies demonstrating no drug-drug interactions between pregabalin and commonly used AEDs. Pregabalin can be administered with or without food.

8.7. Additional Safety Explorations

8.7.1. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Prior to marketing, abuse potential of pregabalin was reviewed and pregabalin was placed into Schedule V of the Controlled Substance Act by the Drug Enforcement Agency with initial approval under NDA 021446. No abuse or dependence-related events were identified in Study 1042, and no changes are expected to the current Schedule placement of pregabalin.

A MedDRA SMQ on drug withdrawal was used by the applicant, and no cases of drug withdrawal convulsions were retrieved. There were convulsion-related events in the controlled and uncontrolled events, but these may be related to the underlying diagnosis of the patients and not due to withdrawal or rebound effects of the drug.

8.8. Safety in the Postmarket Setting

8.8.1. Safety Concerns Identified Through Postmarket Experience

The applicant reviewed postmarketing data with pregabalin use in pediatric patients < 4 years of age. Although there is a cumulative worldwide exposure to pregabalin estimated to be 46,275,317 patient-years, there are no reliable estimates of pediatric exposure data.

The applicant conducted a query of the Pfizer Safety Database for pediatric patients < 4 years of age, which included spontaneously-reported cases, published literature, non-interventional

studies, and Pfizer-sponsored marketing programs. There were 12 medically confirmed cases in the database for patients < 4 years of age. Of those 12 cases, 4 were reported in epilepsy indications.

- Two of these cases reported off-label use of pregabalin without accompanying AEs in pediatric patients.
- One case was a literature report of an 8-month-old boy with migratory focal epilepsy of infancy on multiple medications including pregabalin, clonazepam, levetiracetam, valproic acid, vigabatrin, and potassium bromide, who presented with status epilepticus, put into a barbiturate-induced coma, and later died due to status epilepticus and ventilator-associated pneumonia and metabolic acidosis.
- One case was a Pfizer-marketing case involving an 8.5-month-old girl with generalized tonic-clonic seizures and Rett syndrome, who received pregabalin 25 mg at bedtime x 1 week, followed by 25 mg twice daily. Seizure frequency did not improve, but she experienced lethargy, peripheral swelling and lip and oropharyngeal swelling which resolved with drug discontinuation.
- The other 8 cases were spontaneously reported and had an unknown indication or were for treatment of myalgia. Six of the 8 cases described off-label use without accompanying AEs. One case involved an infant who received 50 mg twice daily for juvenile idiopathic arthritis for 4 days and developed confusional state after stopping treatment with pregabalin. The final case was a 16-month-old boy who had muscle twitching 1 hour after taking pregabalin for myalgias.

Based on the available postmarketing reports from limited use in pediatric patients < 4 years of age, there were no new safety signals identified. During the 90-day safety update, no new adverse events secondary to pregabalin exposure were reported in the postmarketing database.

8.8.2. Expectations on Safety in the Postmarket Setting

Postmarket safety is expected to be in alignment with the established use of pregabalin in the treatment of partial-onset seizures in other patient populations. Routine pharmacovigilance is recommended.

8.8.3. Additional Safety Issues From Other Disciplines

None.

8.9. Integrated Assessment of Safety

Somnolence was the most frequently reported AE in both pregabalin groups and increased with increasing dose. Somnolence is a known adverse drug reaction with pregabalin. Overall the frequently reported adverse events in Study 1042 were similar to those seen in Study 1041 in

older pediatric patients age 4 to 16 years.

Pregabalin 7 mg/kg/day and 14 mg/kg/day were generally safe and well tolerated in pediatric patients age 1 month to < 4 years of age with POS (4 months to < 4 years of age).

9. Labeling Recommendations

9.1. Prescription Drug Labeling

The label has not been finalized at the time of this review. See final approved labeling.

9.2. Nonprescription Drug Labeling

Not applicable.

10. Risk Evaluation and Mitigation Strategies (REMS)

None required.

11. Postmarketing Requirements and Commitments

No additional requirements recommended. Routine postmarket surveillance will continue.

12. Appendices

12.1. References

See footnotes throughout.

12.2. Financial Disclosure

Covered Clinical Study (Name and/or Number): Study 1042

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 193		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 1		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

APPEARS THIS WAY ON ORIGINAL

Reference ID: 4432875

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/s/

EMILY R FREILICH
05/13/2019 09:47:19 PM

PHILIP H SHERIDAN
05/14/2019 07:18:02 AM