CLINICAL and STATISTICAL REVIEW

Application Type	Supplemental NDA
Application Number(s)	21446 (S-035) 22488 (S-013)
Priority or Standard	Priority
Submit Date(s)	November 3, 2017
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Division / Office	Division of Neurology Products Office of New Drugs
Reviewer Name(s)	Philip H. Sheridan, M.D. Xiangmin Zhang, Ph.D. Kun Jin, Ph.D. James Hung, Ph.D.
Review Completion Date	April 29, 2018
Established Name	Pregabalin
(Proposed) Trade Name	Lyrica
Therapeutic Class	Anticonvulsant
Applicant	Pfizer Inc.
Formulation(s)	Capsule, oral suspension
Dosing Regimen	2.5-14 mg/kg/day, max 600 mg daily
Indication(s)	Treatment of Partial Onset Sz.

Intended Population(s) Patients 4 years old and above

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1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

LYRICA (pregabalin) is recommended for approval as adjunctive therapy for the treatment of partial-onset seizures (POS) in patients who are 4 years of age and older. There is adequate support for the safety and efficacy of LYRICA tablets and oral suspension for the treatment of partial-onset seizures in patients 4 to < 17 years of age. Efficacy and dosing recommendations are based on both a randomized, double-blind, placebo-controlled clinical trial in children 4-16 years of age with POS (Study A0081041) and on an extrapolation of efficacy from adult data with supportive clinical pharmacology pediatric pharmacokinetic (PK) data. The safety analysis did not reveal any new safety concerns.

1.2 Risk Benefit Assessment

The overall risk benefit analysis of LYRICA in pediatric patients is acceptable. Pediatric patients with partial-onset seizures often suffer from debilitating epilepsy with a high risk of status epilepticus, as well as associated learning and behavior difficulties and developmental delay. Despite the use of currently approved therapies, often as polypharmacy, many children continue to experience frequent seizures and require additional medication options.

The FDA has recently determined that extrapolation of efficacy from adults to pediatric patients age 4 years and older is appropriate for partial-onset seizures based on similar pathophysiology of POS in both adults and children in this age range, as well as a review of several marketed antiepileptic drugs showing similar exposure-response relationships in both pediatric and adult subjects with POS[1,2]. LYRICA was approved for marketing in the US in 2005 for treatment of POS in adults. The adult clinical trials supporting that approval and the pediatric efficacy and safety trial (Study A0081041), along with PK modeling and simulation studies of the pediatric population, are used in this supplement to support evidence of effectiveness in children 4 years of age and older.

The safety profile of LYRICA is well-characterized in adults. The safety data on a total of 323 patients 4 to 16 years of age with POS included patients from the controlled clinical trial Study A0081041 (201 patients treated with pregabalin of the 295 enrolled) and the two open-label, long-term safety studies (297 patients including 175 patients who received pregabalin in both Study A0081041 and OLE Study 1106). This safety data did not reveal any new concerning safety signals, and common adverse events noted in pediatric subjects were similar to those noted in adults. No new safety signal was identified.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

None

1.4 Recommendations for Postmarket Requirements and Commitments

There are no new recommendations for additional postmarket requirements. Routine postmarket surveillance will continue.

2 Introduction and Regulatory Background

2.1 Product Information

Lyrica (pregabalin) was approved for adjunctive therapy in the treatment of partial-onset seizures 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 alpha2-delta site (an auxiliary subunit of voltage-gated calcium channels).

Pregabalin is approved in more than 130 countries. In the United States (US), pregabalin is indicated for the adjunctive therapy of adult patients with partial onset seizures; 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; pregabalin is indicated for the treatment of peripheral and central neuropathic pain in adults and generalized anxiety disorder in adults. In Japan, pregabalin is indicated for the treatment of neuropathic pain and fibromyalgia.

The approved dose range for the adjunctive treatment of partial onset seizures in adults is 150 to 600 mg/day, administered twice daily (BID) or 3 times daily (TID). The most common adverse effects reported with pregabalin in placebo-controlled adjunctive studies in adults with partial onset seizures were dizziness (32%) and somnolence (22%). Since initial market approval of pregabalin in 2004 through January 2016 it is estimated that approximately (b) (4) patient-years of exposure have accumulated worldwide.

These supplemental applications seek to extend the current indication for the adjunctive treatment of partial-onset seizures (POS) to include pediatric patients down to 4 years of age based both on a randomized, double-blind, placebo-controlled pediatric clinical trial (Study A0081042) and on pediatric extrapolation. These supplemental applications also partially fulfill a pediatric written request and Pediatric Research Equity Act (PREA) post-marketing requirements as discussed in section 2.5 of this review.

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. This determination was based on the similarity of POS in pediatric patients 4 years of age and older and in adults and also based on an analysis of multiple antiepileptic drugs, conducted by the FDA, that demonstrated a similar exposure-response relationship in pediatric and adult patients with POS. Extrapolation based on this analysis applies only to POS in pediatric patients 4 years of age and older, and not to POS in pediatric patients 1 month of age to less than 4 years of age or to other forms of epilepsy. The following is required to support an indication for the treatment of POS in patients 4 years and older that relies upon extrapolation:

- Approved indication for the treatment of POS in adults.
- A pharmacokinetic analysis to determine a dosing regimen that provides similar drug exposure (at levels demonstrated to be effective in adults) in pediatric patients 4 years of age and older and in adult patients with POS. This analysis requires pharmacokinetic data from both the adult and pediatric (4 years of age and older) populations.
- Long-term open-label safety study(ies) in pediatric patients 4 years of age and older.

2.2 Table of Currently Available Treatments for Proposed Indications

There are many anticonvulsants approved for POS in adults, but only a smaller number are approved in children. The majority of approved products for pediatrics are for adjunctive therapy only.

Table 1. Currently available AEDS approved for POS

AED	Adjunctive therapy in Pediatric POS	Monotherapy in Pediatric POS
Levetiracetam	Yes (≥ 1 month)	No
Valproic Acid	Yes (age not specified in dosing but label mentions age 3 months)	Yes (≥ 10 years)
Topiramate	Yes (≥ 2 years)	Yes (≥ 2 years)
Lamotrigine	Yes (≥ 2 years)	No (yes ≥ 16 years)
Gabapentin	Yes (≥ 3 years)	No
Oxcarbazepine	Yes (≥ 4 years)	Yes (≥ 4 years)
Vigabatrin	Yes (10-16 years), but not first line due to safety issues	No
Tiagabine	Yes (≥ 12 years)	No
Perampanel	Yes (≥ 12 years)	No
Primidone	Yes, generally	No
Phenytoin	Yes (age not specified)	No
Carbamazepine	Yes (age not specified)	No
Phenobarbital	seizure type not specified in label	No
Eslicarbazapine	Yes (≥ 4 years)	Yes(≥ 4 years)
Zonisamide	No	No
Lacosamide	Yes	Yes
Ezogabine	No	No
Felbamate	No*	No
Rufinamide	No*	No
Clobazam	No*	No

***Approved for pediatric patients with Lennox-Gastaut Syndrome (LGS)**

2.3 Availability of Proposed Active Ingredient in the United States

Pregabalin is approved and currently marketed as LYRICA in the United States for treatment of POS in patients 17 years and older, and it is thus readily available in both capsule and oral suspension formulations.

2.4 Important Safety Issues with Consideration to Related Drugs

There are no safety issues raised by related drugs. Lyrica itself has been approved since 2005.

2.5 Summary of Presubmission Regulatory Activity and Required Pediatric Assessments Related to Submission

LYRICA was originally approved for adjunctive treatment of partial-onset seizures in adults 17 years and older on June 10, 2005.

This supplemental application is to support extending the current indication for oral treatment of POS down to 4 years of age for use as adjunctive therapy.

Presubmission Regulatory Activity

This pediatric supplement is based both on the **efficacy and safety Study A0081041 and** on the extrapolation of efficacy from adults to children (**General Advice letter on pediatric extrapolation** sent from the Division of Neurology Products (DNP) to the sponsors of epilepsy-related products in November 2015).

Completed Study A0081041, entitled "A double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of pregabalin as adjunctive therapy in children 4-16 years of age with partial onset seizures" is the primary efficacy and safety study supporting the potential pediatric indication.

The protocol of Study A0081041 dated 18 March 2011 was submitted to the Investigational New Drug Application on 24 March 2011. Following feedback and agreements with the DNP on protocol topics including sample size, statistical considerations for the sample size, and further justification of dose levels proposed in the study, the study protocol was amended (Amendment 1) which increased the planned sample size from 153 (51 subjects per group) to 225 subjects (75 subjects per group). A blinded sample size re-estimation procedure was also introduced with a cap at a maximum of 270 subjects in total (90 pediatric subjects per group). The protocol with changes incorporated into Amendment 1 was resubmitted to the DNP on 23 November 2011. Amendment 2 of the study protocol was issued on 16 Mar 2015.

In the DNP General Advice letter dated November 12, 2015, the DNP outlined the basis for its acceptance of **pediatric extrapolation** in the treatment of partial-onset seizures and the requirements necessary to support such an indication. The DNP has determined that POS in pediatric patients 4 years of age and older are similar to POS in adults and that analysis of multiple antiepileptic drugs demonstrated a similar exposure-response relationship in both pediatric and adult patients with POS.[1]

The General Advice letter indicates that the requirements to support an indication for treatment of POS in pediatric patients age 4 and older that relies upon extrapolation include:

- An approved indication for the treatment of POS in adults.
- A pharmacokinetic analysis to determine the dosing regimen that provides drug exposures in pediatric patients age 4 and older similar to those in adult patients at levels demonstrated to be effective in adults.
- Long-term, open-label, safety studies in pediatric patients 4 years of age and older.

Required Pediatric Assessments and Written Request

The submission was discussed with the Pediatric Review Committee (PeRC) on February 14, 2018.

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which include new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Fulfilled

The January 4, 2010, approval letter for Lyrica Oral Solution (NDA 22488) includes the following deferred PREA postmarketing requirements:

1576-3 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 4 through 16 years, inclusive.

Upon review of these supplemental applications, the DNP concluded that the above requirement has been fulfilled by these supplemental applications.

Partially Addressed

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.

Upon review, the DNP has determined that these supplemental applications partially address these deferred PREA postmarketing requirements for studies conducted in the age group of 4 to 16 years.

Open

The sponsor is reminded in the approval letter that there are postmarketing requirements listed in the December 30, 2004 (NDA 21446), June 10, 2005 (NDA 21724), and January 4, 2010 (NDA 22488), approval letters that remain 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.

Pediatric Written Request

A pediatric written request was originally issued on June 8, 2005, and amended on October 17, 2006, July 30, 2010, September 26, 2013. and March 23, 2017. These supplemental applications partially fulfill its requirements.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The overall quality of the electronic submission was acceptable. The NDA supplement was submitted in eCTD format and conformed to CDISC SDTM standards. The information required for the review of the NDA was well organized, easy to navigate, and complete.

3.2 Compliance with Good Clinical Practices

The applicant states that the studies were conducted in accordance with good clinical practice, including archiving of essential documents.

3.3 Financial Disclosures

The applicant provided required information regarding financial disclosures and there was no evidence that significant bias was introduced into the results of these trials.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Lyrica is an already approved product.

4.2 Clinical Microbiology

No Clinical microbiology studies were included in this NDA supplement.

4.3 Preclinical Pharmacology/Toxicology

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

4.4 Clinical Pharmacology

Efficacy in pediatric patients with partial-onset seizures ≥ 4 years of age is based in part on extrapolation of dose-exposures in the adult population to that of the pediatric population.

4.4.1 Mechanism of Action

LYRICA (pregabalin) binds with high affinity to the alpha2-delta site (an auxiliary subunit of voltage -gated calcium channels) in central nervous system tissues. The precise mechanism by which LYRICA exerts its antiepileptic effects in humans remains to be fully elucidated. Results with genetically modified mice and with compounds structurally related to pregabalin (such as gabapentin) suggest that binding to the alpha2-delta subunit may be involved in pregabalin's antiseizure effects in animals.[3]

4.4.2 Pharmacodynamics

No specific studies evaluated the pregabalin pharmacodynamic effects in pediatric subjects.

There were no clinically significant effects of LYRICA on vital signs in the studies submitted in this application.

4.4.3 Pharmacokinetics and Pediatric Extrapolation

The Office of Clinical Pharmacology (OCP) review was performed by reviewers Dr. Michael Bewernitz and Dr. Dawei Li with Team Leaders Dr. Kevin Krudys and Dr. Angela Men.

In response to DNP's policy for extrapolation of efficacy for adjunctive therapy, the sponsor conducted pharmacokinetic modeling and simulation to determine a dosing regimen that would provide similar pregabalin exposure (at levels demonstrated to be effective in adults) in pediatric subjects 4 years of age and older to pregabalin exposure in adult subjects with POS. The adult PPK model was previously reviewed by OCP and had been found to be acceptable. The sponsor updated the adult PPK model by including the PK data from pediatric patients (pediatric pharmacokinetic study A0081074 and pediatric clinical trial A0081041).

The sponsor conducted PK simulations in virtual adult patients and virtual pediatric patients to derive pediatric dosing for initial dosing and maintenance dosing.

The proposed initiation doses derived from the sponsor's PK simulations turned out to be the same as the initiation regimen used in the controlled pediatric clinical trial A0081041. The Phase 1 escalating dose, multiple dose study A008174 (conducted in pediatric patients with POS to inform the dosing to be used in Study A0081041) demonstrated a higher weight-normalized clearance in patients with body weight less than 30 kg, Because of higher weight-normalized clearance in patients with body weight less than 30 kg, the Lyrica dose in Study A0081041 was increased by 40% to 3.5 mg/kg/day for patients weighing less than 30 kg randomized to the 2.5 mg/kg/day arm and to 14 mg/kg/day for patients randomized to the 10 mg/kg/day arm. Therefore, the following sentence has been added to section 12.3 Pharmacokinetics – Pediatric Pharmacokinetics – Pediatric Patients (4 to less than 17 years of age0 in the approved labeling: "A weight-based dosing regimen is necessary to achieve pregabalin exposures in pediatric patients aged 4 to less than 17 years similar to those observed in adults treated for partial onset seizures at effective doses [see Dosage and Administration (2.4)]."

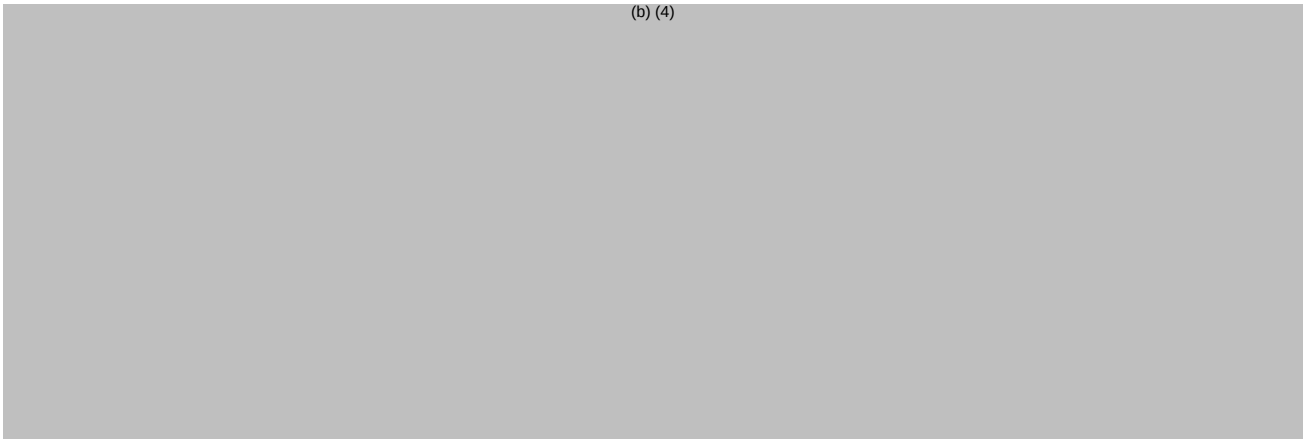
In the controlled pediatric clinical trial A0081041 (see Section 6.1 of this review for trial description), the high dose arm achieved a statistically-significant reduction in seizure rate compared to the placebo arm (-19.9%, p=0.0185). However, the low dose did not achieve statistically significant reduction in efficacy compared with the placebo arm (effect size -9.93%, p=0.2577). Therefore, as part of the Clinical Pharmacology review, Dr. Bewernitz conducted exploratory analyses to assess the dose-response relationship of the Phase 3 data from the current pediatric trial (A0081041) and the previous adult trials (1008-009, 1008-011, and 1008-034) to further assess the performance of the low-dose arm of A0081041. The change from baseline seizure rate was computed and plotted for each arm for each group of pediatric patients as well as each group of adult patients. This plot demonstrated that the low dose arms for pediatric patients (3.5 and 2.5 mg/kg/day) have a comparable change from baseline seizure rate compared to those of the low dose arms for adult patients (150-300 mg/day). In addition, the high dose arms for pediatric patients (14 and 10 mg/kg/day) demonstrated a change from baseline seizure rate that is consistent with that of the high dose arms in adult patients (e.g. 600 mg/day). Detailed plots and tables

of this analysis are available in the Clinical Pharmacology review by Dr. Bewernitz, Dr. Li, Dr. Krudys, and Dr. Men.

Dr Bewernitz concluded that, overall, this dose-efficacy relationship provides additional support for the sponsor's proposed dose regimen which is shown in the table below (reproduced from the Clinical Pharmacology review).

Table 2 Lyrica Dosage Schedule for Pediatric Patients Aged 4 to 17 Years Old

(b) (4)



Dosing in pediatric patients with renal impairment:

The sponsor requested that dosing for pediatric patients with renal impairment be addressed outside of these current pediatric supplemental applications. This dosing will be based on further pharmacokinetic data analysis.

Therefore, in section 2.7 Dosing for Adult Patients with Renal Impairment and section 8.6 Renal Impairment in approved labeling, the following statement will appear: "The use of LYRICA in pediatric patients with compromised renal function has not been studied."

Please see the Office of Clinical Pharmacology review for a full discussion of methods and issues related to pharmacokinetics in the pediatric studies.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

Table 3 Summary of LYRICA Pediatric Epilepsy Clinical Development Program

Type of Study	Study Title and Description	Status (number of subjects enrolled)
Phase 1 PK/Safety/ Tolerability Study	**A0081074**: A placebo-controlled, escalating dose, multiple dose study to evaluate the safety, tolerability, and PK of pregabalin in pediatric patients with POS Age range: 1 month to 16 years of agea	Completed (N=65)
Phase 3 Controlled Efficacy and Safety Studies	**A0081041:** A double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and safety of pregabalin as adjunctive therapy in children 4-16 years of age with POS	Completed (N=295)
	A0081042: 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 POS	Ongoing (N=100 enrolled of 150 planned, as of 31 May 2017b)
	A0081105: A randomized, double-blind, placebo-controlled, parallel- group, multicenter trial of pregabalin as adjunctive therapy in pediatric and adult subjects with PGTC seizures Age range: 5 to 65 years	Ongoing (N=127 enrolled of 168 planned, as of 31 May 2017b)
Phase 3 Uncontrolled 1-Year Safety Studies	**A0081075**: A 12-month, open-label extension study evaluating the safety and tolerability of flexible doses of pregabalin in pediatric patients with POS Age range: 1 month to 16 years of agea Study population: Subjects who participated in Study A0081074	Completed (N=54)
	A0081106: A 12-month open-label study to evaluate the safety and tolerability of pregabalin as adjunctive therapy in pediatric subjects 1 month to 16 years of age with POS and pediatric and adult subjects 5 to 65 years of age with PGTC seizures Study population: Eligible subjects who participated in studies **A0081041, A0081042**, or **A0081105** and de novo POS subjects	Ongoing (N=420 enrolled as of 31 May 2017b)

Abbreviations: N = number of subjects; PK = pharmacokinetics; POS = partial onset seizures; PGTC = primary generalized tonic-clonic

a. The youngest subject enrolled was 3 months of age.
b. Enrollment data on file. Enrollment cut-off date as per Section 1.1.2.

5.2 Review Strategy

This review is a combined clinical and statistical review.

Dr Xiangmin Chang, Dr. Kin Jun, and Dr. James Hung provided the statistical review of efficacy from the controlled clinical trial A0081041.

Dr. Philip Sheridan provided the clinical evaluation of the trials and reviewed the safety data on a total of 323 subjects 4 to 16 years of age with POS that were treated with pregabalin in double-blind Study A0081041 (completed), open label extension (OLE)

Study A0081075 (completed), and OLE Study A0081106 (as of the 31 January 2017 data cut-off date for ongoing Study A0081106).

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Study A0081041

A double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and short-term safety of pregabalin as adjunctive therapy in children 4-16 years of age with POS. (completed)

5.3.2 Study A0081075

A 12-month, open-label extension study evaluating the safety and tolerability of flexible doses of pregabalin in pediatric patients with POS who had previously participated in pharmacokinetic study A0081074. (completed)

5.3.3 Study A0081106

A 12-month, open-label extension study evaluating the safety and tolerability of pregabalin as adjunctive therapy in pediatric subjects 1 month to 16 years of age with POS and pediatric and adult subjects 5 to 65 years of age with primarily generalized tonic clonic (PGTC) seizures. (ongoing)

6 Review of Efficacy from Controlled Trial A0081041

Note: Further evidence of efficacy is based on an extrapolation of efficacy from adult data with supportive clinical pharmacology pediatric pharmacokinetic (PK) data as described in section 4.4 (Clinical Pharmacology) of this review. The combined evidence from this extrapolation and from controlled trial A0081041 support approval of Lyrica as adjunctive therapy for the treatment of partial-onset seizures (POS) in patients who are 4 years of age and older.

6.1 Description of Controlled Trial A0081041

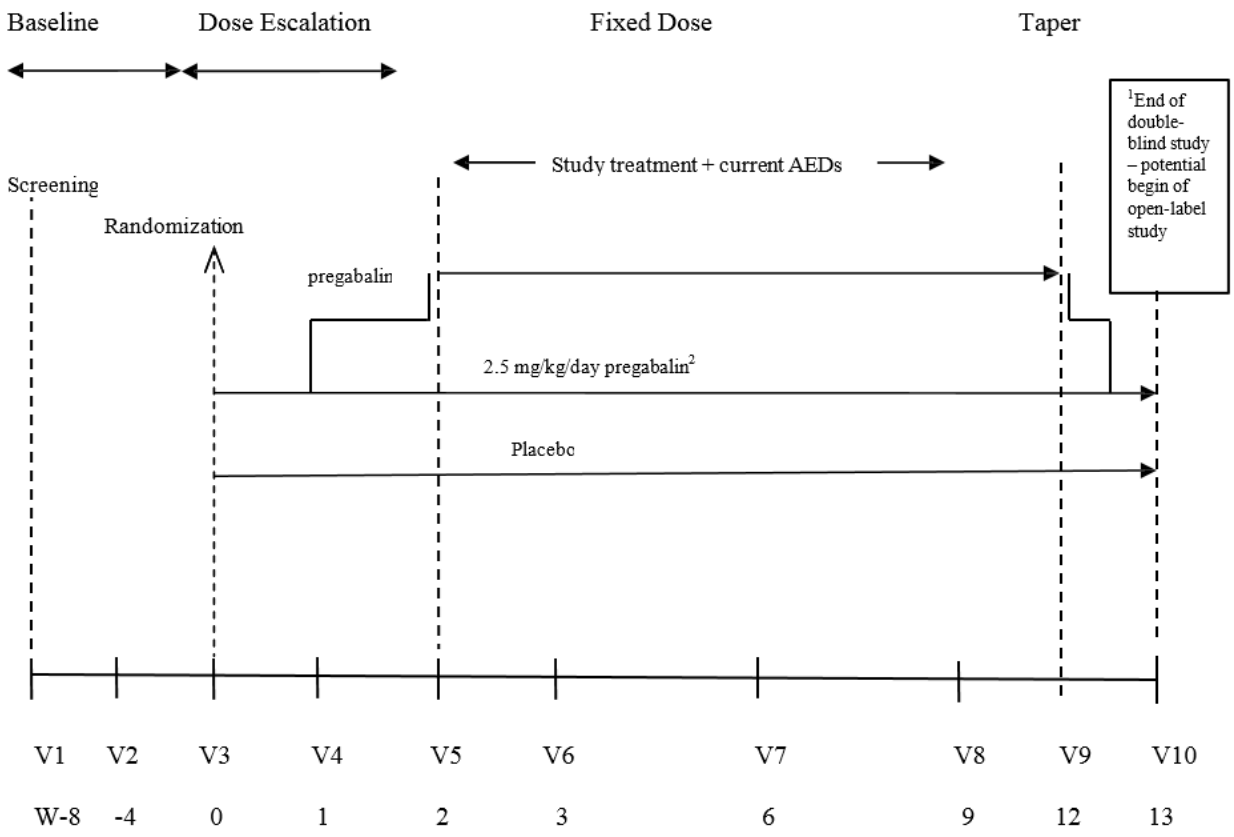
The efficacy of Lyrica as adjunctive therapy in partial onset seizures was established in a 12-week, randomized, double-blind, placebo-controlled, multicenter study

(n = 295) in pediatric patients 4 years to less than 17 years of age with partial onset seizures with or without secondary generalization.

During an 8-week baseline period, patients had to experience at least 6 partial onset seizures with no seizure-free period exceeding 4 weeks. The mean duration of epilepsy was 6 years and the mean and median baseline seizure frequencies were 57 and 18 seizures per month, respectively. Approximately 74% of the patients were taking 2 to 3 concurrent AEDs at baseline. Among the Lyrica-treated patients, 87% completed the double-blind phase of the study.

In this study, Lyrica 2.5 mg/kg/day (maximum 150 mg/day) and 10 mg/kg/day (maximum 600 mg/day) were compared to placebo. Administration of each daily dose was divided into two equal doses (twice a day dosing). Because of higher weight-normalized clearance in patients with body weight less than 30 kg, the Lyrica dose was increased by 40% to 3.5 mg/kg/day for patients weighing less than 30 kg randomized to the 2.5 mg/kg/day group or to 14 mg/kg/day for patients randomized to the 10 mg/kg/day group.

Figure 1 Overview of Study Design for A0081041



Abbreviations: AED=antiepileptic drug; V=visit; W=week
1 = Eligible subjects were potentially assessed for open-label study A0081106. If considered eligible, subjects completed the end of study activities for Study A0081041 at V10.
2 = Dose was 14 mg/kg/day (instead of 10 mg/kg/day) and 3.5 mg/kg/day (instead of 2.5 mg/kg/day) for subjects <30 kg.

6.2 Data and Analysis Quality

The electronic submissions of the study are located at
\\cdsesub1\evsprod\NDA021446\0408\m5\53-clin-stud-rep\535-rep-effic-safety-stud\partial-onset-seizures\5351-stud-rep-contr\a0081041
\\cdsesub1\evsprod\NDA021446\0408\m5\datasets\a0081041\

The data quality and analysis quality are adequate. The reviewer was able to perform independent review using the sponsor's submitted datasets and confirm the sponsor's analysis results.

6.3 Statistical Methodologies

The efficacy analysis population was all randomized patients who took at least one dose of study drug during the 12-week treatment period and who had baseline and at least one follow-up efficacy assessment visit.

The primary endpoint of 28-day seizure rate was transformed on a logarithmic scale after adding a value of 1 to account for any zero seizure incidence. log(28 day seizure rate + 1) was analyzed using a linear model with the logarithmic transformation of 28 day seizure rate + 1 at baseline as the covariate and treatment, weight group (< 30 kg, ≥ 30 kg), and geographic region (Asia-Pacific, Europe, United States, Rest of the World) as effects.

The key secondary endpoint of responder rate, defined as subjects who have a greater than or equal to 50% reduction in partial seizure rate from baseline during the double-blind treatment phase, was analyzed using a logistic regression, with treatment, weight group, and geographical region as effects.

In order to control the overall type I error, tests of multiple endpoints and doses were planned in the following order, each step at the two-sided significance level of 0.05:

Step 1. Test equal treatment of pregabalin 10 mg/kg/day vs placebo for the primary endpoint
Step 2. Test equal treatment of pregabalin 2.5 mg/kg/day vs placebo for the primary endpoint
Step 3. Test equal treatment of pregabalin 10 mg/kg/day vs placebo for the key secondary endpoint
Step 4. Test equal treatment of pregabalin 2.5 mg/kg/day vs placebo for the key secondary endpoint

The Applicant clarified in the statistical analysis plan that if only Step 1 is rejected then only Step 3 is performed. However, this inflates the overall type I error.

The initial planned sample size is 225 patients (i.e. 75 patients per group). A blinded sample size re-estimation using the method described in Keiser and Friede (2011) was planned when 180 patients completed the study. The maximal sample size after the sample size re-estimation was 270 (i.e. 90 patients per group).

6.4 Blinded Sample Size Re-Estimation Results

The blinded sample size was conducted on 182 patients who completed the study. The re-estimated sample size exceeded the sample size limit of 270 total patients. Therefore, the sample size was adjusted to 270 patients.

6.5 Patient Disposition and Demographics

A total of 372 patients were recruited and 295 (79.5%) patients randomized. Among the 295 patients, 94 patients (31.9%) were randomized to the placebo group, 104 (35.3%) to the 2.5 mg/kg/day group, and 97 (32.9%) to the 10 mg/kg/day group. A total of 36 patients discontinued the study: 10, 10, and 16 patients were from the placebo group, 2.5 mg/kg/day group, and 10 mg/kg/day group, respectively, which amount to 10.6%, 9.6%, and 16.5% of the intent-to-treat (ITT) populations of these groups. The patient disposition of the ITT population is provided in Table 4.

Table 4 Study A0081041 patient disposition

Number (%) of Subjects	Pregabalin		Placebo n (%)
	2.5 mg/kg/day n (%)	10 mg/kg/day n (%)	
Treated	104	97	94
Completed	94 (90.4)	81 (83.5)	84 (89.4)
Discontinued	10 (9.6)	16 (16.5)	10 (10.6)
Adverse Event	1 (1.0)	4 (4.1)	0
Insufficient clinical response	3 (2.9)	4 (4.1)	5 (5.3)
No longer willing to participate	1 (1.0)	2 (2.1)	2 (2.1)
Other	2 (1.9)	1 (1.0)	0
Protocol violation	3 (2.9)	4 (4.1)	3 (3.2)
Death	0	1 (1.0)	0

[Source: Table 3 on page 15 of the sponsor's integrated summary of effectiveness]

The demographic characteristics of the randomized population are presented in Table 5. The three treatment groups appeared similar in age, race, and sex distributions. There were more males than females in the randomized population (54.9% vs. 45.1%). The average age of this population was 10.2 years old (standard deviation = 3.7). Most patients (69.2%) were white.

Table 5 Study A0081041 patient demographic characteristics, randomized patients

	Pregabalin 10 mg/kg/day	Pregabalin 2.5 mg/kg/day	Placebo	Total
Number (%) of subjects	**N=97**	**N=104**	**N=94**	**N=295**
Sex				
Male	56 (57.7)	52 (50.0)	54 (57.4)	162 (54.9)
Female	41 (42.3)	52 (50.0)	40 (42.6)	133 (45.1)
Age (years)				
Mean	10.1	10.2	10.3	10.2
SD	3.5	3.9	3.7	3.7
Range	4-16	4-16	4-16	4-16
Race (%)				
White	64 (66.0)	75 (72.1)	65 (69.1)	204 (69.2)
Black	2 (2.1)	1 (1.0)	1 (1.1)	4 (1.4)
Asian	27 (27.8)	28 (26.9)	28 (29.8)	83 (28.1)
Other	4 (4.1)	0 (0.0)	0 (0.0)	4 (1.4)
Weight (kg)[a]				
Mean	37.2	36.7	36.8	36.9
SD	18.9	17.1	16.8	17.6
Range	13.0-106.0	10.5-83.1	13.0-87.5	10.5-106.0

Abbreviation: N = number of subjects in group; SD = standard deviation.
a. Weight at Visit 1.

[Source: Table 20 on page 132 of the sponsor's clinical study report]

6.6 Efficacy Results

The primary analysis results are presented in Table 6. Pregabalin 10 mg/kg/day was significantly (p-value = 0.0185) better than placebo in reducing logarithmic transformed 28-day seizure rate. The comparison between the pregabalin 2.5 mg/kg/day and placebo in the primary endpoint was not significant (p-value = 0.2577), although the pregabalin-placebo treatment difference was in the direction favoring the treatment effect of pregabalin 2.5 mg/kg/day.

Statistical reviewer's comment:
The efficacy appeared to be driven by two foreign sites. After removing data from either Site 1013 or Site 1047, the pregabalin-placebo treatment differences in terms of log seizure rate were still in the directions favoring pregabalin but the pregabalin-placebo comparison turned out not significant for either dose.

One sensitivity analysis using the multiple imputation method provided similar results to the primary analysis results. Under the ranked analysis of covariance and Wilcoxon-Mann Whitney test (performed on the logarithmic transformed 28-day seizure rate), the numerical results of these analyses favored the effect of pregabalin over placebo, but none of the pregabalin-placebo comparison showed statistical significance. The nominal p-values under the ranked analysis of covariance were 0.0529 and 0.3594 for the

pregabalin 10mg/kg/day group and pregabalin 2.5 mg/kg/day group, respectively, compared to placebo; the nominal p-values under the Wilcoxon-Mann Whitney test were 0.3616 and 0.9738 for the pregabalin 10mg/kg/day group and pregabalin 2.5 mg/kg/day group, respectively, compared to placebo.

Table 6 Study A0081041 primary analysis

		Pregabalin 10 mg/kg/day N=97	Pregabalin 2.5 mg/kg/day N=104	Placebo N=93
Baseline	n	97	104	93
	Mean	3.19	3.27	3.18
	95% CI of Mean	(2.93, 3.44)	(3.03, 3.50)	(2.91, 3.44)
	Standard Deviation	1.269	1.215	1.302
Overall	n	96	103	93
	LS Mean	2.74	2.86	2.96
	95% CI of LS Mean	(2.60, 2.88)	(2.72, 2.99)	(2.82, 3.10)
	Standard Error	0.072	0.070	0.073
	Versus Placebo (log)			
	LS Mean Difference	-0.22	-0.10	
	95% CI of LS Mean Difference	(-0.41, -0.04)	(-0.29, 0.08)	
	Standard Error	0.094	0.092	
	P-value	0.0185	0.2577	

Abbreviations: ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent to treat; LS = least square; N = number of subjects from ITT population for the given group; n = the number of subjects in the ITT population under each treatment group at each visit.

[Source: Table 23 on page 137 of the sponsor's clinical trial report]

Based on the least squares means from the primary analysis results, percentage reduction relative to placebo can be derived from the following formula:

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

Therefore, the percentages of reduction relative to placebo are 21.0% and 10.5% for the pregabalin 10 mg/kg/day group and pregabalin 2.5 mg/kg/day group, respectively.

The secondary analysis results are presented in Table 7. Both pregabalin groups had numerically higher responder percentages (40.6% and 29.1%, respectively) compared to the placebo group (22.6%).

Statistical reviewer's comment:
The testing of hierarchy should stop when the pregabalin 2.5 mg/kg/day vs placebo was not significant for the primary endpoint.

Table 7 Study A0081041 secondary analysis

		Pregabalin 10 mg/kg/day N=97	Pregabalin 2.5 mg/kg/day N=104	Placebo N=93
Timepoint	n (%[b])	n (%)	n (%)	n (%)
Overall[a]	Number assessed	96	103	93
	Responder	39 (40.6)	30 (29.1)	21 (22.6)
	Non Responder	57 (59.4)	73 (70.9)	72 (77.4)
	Versus placebo pairwise p-value[c]	0.0068	0.2600	

[Source: Table 25 on page 142 of the sponsor's clinical trial report]

6.7 Subgroup Findings

Mean and median percent changes of the 28-day seizure rates (without logarithmic transformation) were presented by sex (Table 8), race (Table 9) and geographic region (Table 10), respectively. Overall, there is no compelling evidence from the subgroup analyses that a specific sex, race, or region subgroup benefits differently from Lyrica®.

Sex

Table 8 Study A0081041 mean and median percent changes by sex

	Pregabalin		Placebo
	2.5 mg/kg/day N = 104	10 mg/kg/day N = 97	N = 93
Male			
Number assessed	51[a]	55[a]	53
Median	-32.17	-32.80	-18.64
Mean (SD)	-34.49 (34.072)	-25.99 (61.325)	-14.44 (58.065)
Female			
Number assessed	52	41	40
Median	-24.72	-45.52	-11.07
Mean (SD)	-18.05 (41.553)	-34.67 (49.926)	-5.03 (75.970)

Source: ISE Appendix Table 2.3
Abbreviations: ITT= intent-to-treat; kg = kilograms; mg = milligrams; N = total number of subjects; SD = standard deviation
a. Two subjects (1 male in each pregabalin treatment group) had baseline seizure data and so were not excluded from the ITT population; however, they did not have seizure diary data during the treatment perioc and so were excluded from this analysis.

[Source: Table 12 on page 29 of the sponsor's integrated summary of effectiveness]

Race

Table 9 Study A0081041 mean and median percent changes by race

	Pregabalin		Placebo
	2.5 mg/kg/day N = 104	10 mg/kg/day N = 97	N = 93
White			
Number assessed	74[a]	63[a]	64
Median	-32.80	-48.04	-24.41
Mean (SD)	-30.18 (39.311)	-34.12 (61.116)	-14.55 (72.875)
Asian			
Number assessed	28	27	28
Median	-15.85	-35.65	-4.15
Mean (SD)	-16.26 (36.520)	-34.30 (35.940)	0.94 (47.350)
Black/Other			
Number assessed	1	6	1
Median	-8.97	28.30	-61.57
Mean (SD)	-8.97	37.47 (45.871)	-61.57

Source: ISE Appendix Table 2.4
Abbreviations: ITT= intent-to-treat; kg = kilograms; mg = milligrams; N = total number of subjects; SD = standard deviation
a. Two subjects (1 white subject in each pregabalin treatment group) had baseline seizure data and so were not excluded from the ITT population; however, they did not have seizure diary data during the treatment period and so were excluded from this analysis.

[Source: Table 13 on page 30 of the Applicant's integrated summary of effectiveness, with errors corrected by the statistical reviewer]

Geographic Region

Table 10 Study A0081041 mean and median percent changes by geographic region

Percent change from baseline in 28-day seizure rate	Pregabalin 2.5 mg/kg/day	Pregabalin 10 mg/kg/day	Placebo
Non-US			
N	95	90	87
Median	-30.27	-39.93	-19.44
Mean (SD)	-27.02 (38.828)	-33.54 (54.639)	-11.06 (67.922)
US			
N	8	6	6
Median	-17.60	6.91	7.21
Mean (SD)	-16.30 (38.722)	28.00 (59.247)	-0.70 (31.854)

[Source: the statistical reviewer]

6.7 Statistical Review Conclusions and Recommendations

Based on the statistical evidence from Study A0081041, pregabalin 10 mg/kg/day appears effective as adjunctive therapy in treating pediatric patients aged 4 to 16 years with partial onset seizures.

7 Review of Safety

7.1 Safety Data Sources

The primary sources of safety data were the following:

- Study A0081041 A double-blind, placebo-controlled, parallel-group, multicenter study of the efficacy and short-term safety of pregabalin as adjunctive therapy in children 4-16 years of age with POS. (completed)

- Study A0081075 A 12-month, open-label extension study evaluating the safety and tolerability of flexible doses of pregabalin in pediatric patients with POS who had previously participated in pharmacokinetic study A0081074. (completed)

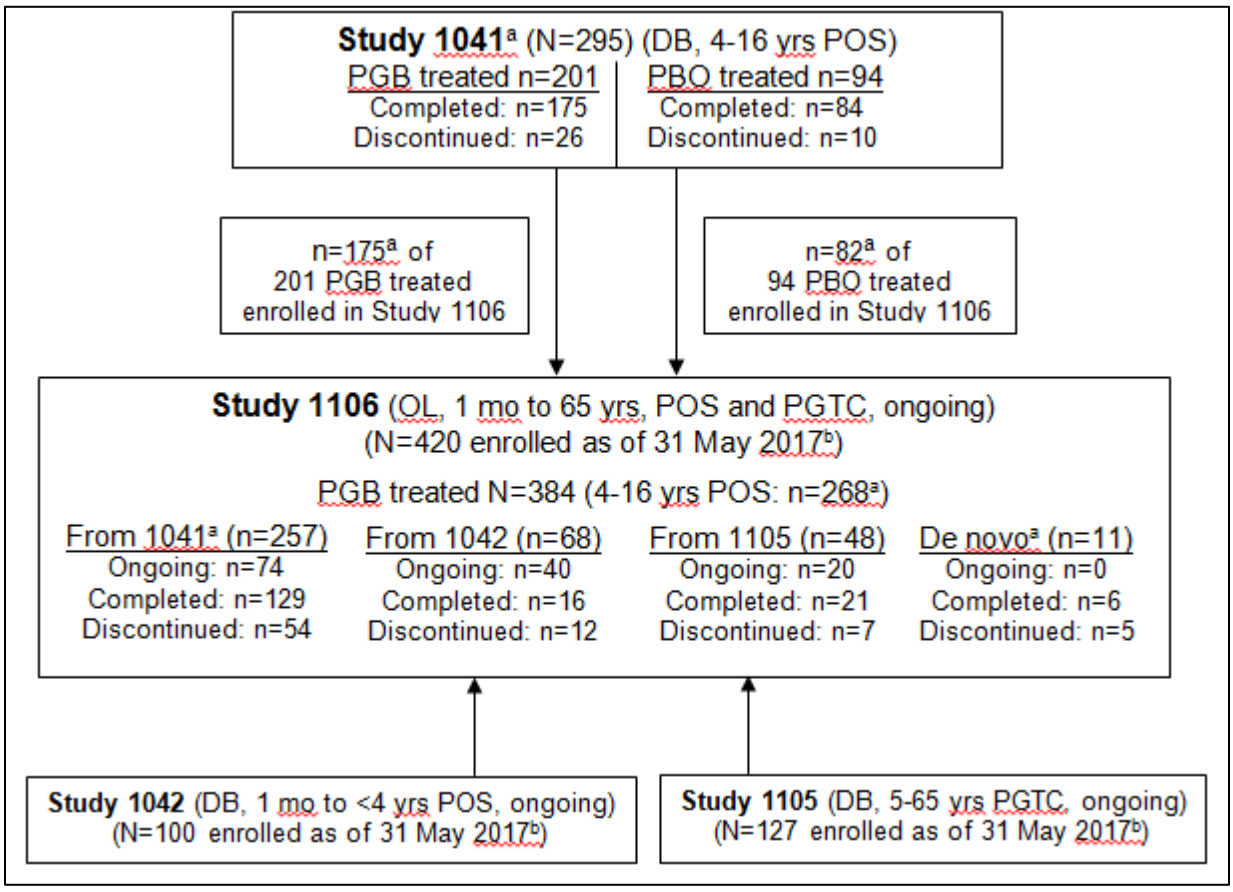
- Study A0081106 A 12-month, open-label extension study evaluating the safety and tolerability of pregabalin as adjunctive therapy in pediatric subjects 1 month to 16 years of age with POS and pediatric and adult subjects 5 to 65 years of age with primarily generalized tonic clonic (PGTC) seizures. (ongoing)

The safety analysis is based on a total of 323 subjects 4 to 16 years of age with POS that were treated with pregabalin in double-blind Study A0081041 (completed), open label extension (OLE) Study A0081075 (completed), and OLE Study A0081106 (as of the 31 January 2017 data cut-off date for ongoing Study A0081106). Of these 323 subjects, 26 subjects were only treated with pregabalin in double-blind Study A0081041 and did not participate in OLE Study A0081106, 175 subjects were treated both with pregabalin in double-blind Study A0081041 and with pregabalin in OLE Study A0081106 (re-exposures), 82 subjects were treated with placebo in double-blind Study A0081041 but were switched to pregabalin in OLE Study A0081106 (new exposures), 29 subjects were treated with pregabalin in OLE Study A0081075 (all were re-exposures since they received at least 1 dose of pregabalin during prior double-blind PK Study A0081074), and 11 subjects entered OLE Study A0081106 de novo (new exposures).

A total of 144 patients age 4 to 16 years from the OLE studies had > 1 year exposure at or above the recommended efficacious doses (by weight categories). Of these 65 were age 4 years to <10 years (3 from Study A0081075 and 62 from Study A0081106) and 79 were age 10 to 16 years ((3 from Study A0081075 and 76 from Study A0081106).

Overall, the safety profile of Lyrica in POS patients age 4 to 17 years was found to be similar to the safety profile in adults and no new safety signals were identified.

Figure 2 Source and Disposition of Safety Population Subjects: Studies 1041, 1042, 1105, 1106



Source: CSR 1041 Table 14.1.1.1 and Appendix Table 1.2.1.
4-16 POS refers to subjects 4 to 16 years of age with POS. Includes data through 31 January 2017 for ongoing Study 1106.
Age is based on age at screening of the first study the subject entered. The 4-16 year age group includes all subjects ≥4 years to <17 years of age.
Abbreviations: DB = double blind; OL = open label; PBO = placebo; PGB = pregabalin; PGTC = primary generalized tonic-clonic; POS = partial onset seizures
a. Subjects 4 to 16 years of age with POS.
b. Enrollment data on file. Enrollment cut-off date as per Section 1.1.2.

7.2 Major Safety Results

7.2.1 Deaths

Five subjects 4 to 16 years of age with POS with complex medical histories died, due to events considered unrelated to study medication, 1 subject during controlled Study 1041 and 4 subjects during open-label Study 1106.

Study 1041 Subject [redacted] (female, white, 10 years of age, in Greece) died due to pulmonary edema on Day 72. The subject had been receiving pregabalin 10 mg/kg/day (duration of treatment: 71 days). On Day 72, the subject was found dead in bed by her mother. Emergency response services were called and took the subject to the hospital where she was declared dead on arrival. The cause of death was subsequently determined at autopsy to be a result of pulmonary edema, which was considered by the investigator to be unrelated to pregabalin. The subject had a history of seizures attributed to perinatal injury, prematurity, intracerebral hemorrhage, and hydrocephalus, for which a ventriculoperitoneal shunt had been previously inserted. Additional medical history included quadriplegia, cerebral palsy, hypoplasia of the brainstem and cerebellum, microcephaly, and severe mental retardation. The investigator reported that there were no recent referrals to an emergency room, hospital, or other doctor, and that there were no new or recent AEs and no symptoms of disease or infection, including any related to her ventriculoperitoneal shunt.

Study 1106 Subject [redacted] (male, white, 15 years of age, in the United States) died on Day 298 due to intractable epilepsy and respiratory arrest. The subject had received pregabalin 600 mg/day (duration of treatment in Study 1106: 298 days) and had previously received pregabalin 10 mg/kg/day in Study 1041 for 48 days before being discontinued due to insufficient clinical response. The subject reportedly experienced a seizure, fell off a chair forward onto the floor, and was unable to breathe. The subject's mother called the paramedics who were not able to resuscitate the subject. The subject had a history of epilepsy, complex partial seizures, partial seizures that secondarily generalized, moderate mental retardation, and autism. The subject had been seen in the clinic about 3 weeks prior to the event and was stable with his usual number of seizures and unremarkable clinical laboratory results. Vital sign data, laboratory test, ECG and neurological and physical examinations results during the study were unremarkable. The investigator considered the events severe and not related to pregabalin.

Study 1106 Subject [redacted] (female, white, 11 years of age, in Hungary) died due to pneumonia on Day 109. The subject had received pregabalin 300 mg/day (duration of treatment in Study 1106: 108 days) and previously received placebo in Study 1041 for 91 days. The subject's medical history included being status post perinatal hypoxia and ischemia, neonatal seizures, multifocal cerebral bleeding as a newborn, spastic tetraparesis/cerebral palsy with severe psychomotor retardation, periventricular leukomalacia and ex-vacuo hydrocephalus, thalamic damage and pontocerebellar hypoplasia, and fasciotomy and tenotomy. On Day 108 the subject's mother reported that the subject had symptoms of cough and fever but was in otherwise good condition, and no medical treatment was sought. The subject's mother contacted the study site on Day 110 and informed the staff of the subject's death the previous day (Day 109) when the subject's mother found the subject dead in her bed. Seizure activity and anti-epilepsy drugs had remained stable throughout the study. The cause of death was determined at autopsy to be a result of
pneumonia which was considered by the investigator to be unrelated to pregabalin.

Study 1106 Subject [redacted] (female, white, 15 years of age, in the Ukraine) died due to brain edema on Day 249. The subject had received pregabalin 600 mg/day (duration of treatment in Study 1106: 249 days) and had previously received pregabalin 10 mg/kg/day in Study 1041 for 90 days. The subject had not reported any illness, symptoms, or complaints the evening prior to death; everything was "as usual". The autopsy report identified 2 diagnoses: brain edema and epilepsy; the investigator reported the cause of death as cerebral edema, considered severe and unrelated to pregabalin. The subject had a history of acute herpetic meningoencephalitis, cluster seizures, cognitive deficit, and speech underdevelopment. Study 1041 screening neurological exam showed the following abnormal findings: resting tremor, left and right side of body, positive Romberg, complex myopic astigmatism, slight deficit in right facial expression, and slightly increased reflexes in left ankle, brachioradialis, and knee. The last study visit was approximately 2 months prior on Day 183 and there were no unusual signs or symptoms.

Study 1106 Subject [redacted] (male, white, 9 years of age, in Serbia) died due to cardiopulmonary failure considered unrelated to pregabalin. The subject was hospitalized the day prior to his death, and had cough, respiratory dyspnea, and fever. The subject developed severe dyspnea despite treatment, including antibiotics, and died on 11 March 2017. The subject was ongoing in Study 1106 and was receiving pregabalin and valproic acid, and had previously received placebo in Study 1041. Relevant medical history included severe neonatal asphyxia (vacuum extraction, Apgar score 3/5), intracranial hemorrhage (secondary to the severe asphyxia), neonatal convulsions, and resultant cerebral palsy, psychomotor retardation, paraparesis, microcephaly, obstructive bronchitis, and pneumonia. He was hospitalized for 3 respiratory tract infection SAEs during Studies 1041 and 1106.

7.2.2 Nonfatal Serious Adverse Events

Controlled Study 1041

A total of 14 subjects experienced SAEs while receiving pregabalin treatment during Study 1041, 4 (3.8%) subjects in the pregabalin 2.5 mg/kg/day group and 10 (10.3%) subjects in the pregabalin 10 mg/kg/day group, compared to 7 subjects (7.4%) in the placebo group. The most common SAE was seizure, reported in 1 subject in the pregabalin 2.5 mg/kg/day group and 3 subjects each in the 10 mg/kg/day and placebo groups. Other SAE terms occurred in at most 1 subject in each treatment group. Three SAEs were considered to be treatment related: hallucination in the pregabalin 2.5 mg/kg/day group (Subject [redacted]), epilepsy (investigator term: worsening of epilepsy) in the pregabalin 10 mg/kg/day group (Subject [redacted]), and seizure (investigator term: increased seizures) in the placebo group (Subject [redacted] of

these, the hallucination and epilepsy were associated with permanent discontinuation of study medication

Two other treatment-emergent SAEs (hematemesis and aspiration pneumonia) and a non-treatment-emergent SAE (partial seizures) were associated with temporary discontinuation of study medication. Subject , who was assigned to the pregabalin 2.5 mg/kg/day group, experienced a non-treatment-emergent SAE of partial seizures on Day 1 prior to receiving the first dose of study medication.

Controlled and Uncontrolled Studies

A total of 45 of 323 (13.9%) pregabalin-treated subjects 4 to 16 years of age with POS experienced SAEs during Studies 1041, 1075, or 1106 prior to the 31 January 2017 cut-off date for clinical study data). SAEs reported in more than 1 subject in this population are summarized by PT in Table 16 and the most common (≥1% of subjects) were seizure (13 subjects, 4.0%) and pneumonia (7 subjects, 2.2%). Treatment-emergent SAEs reported for 1 subject each included: anxiety, brain edema, cellulitis, constipation, ear infection, electrolyte imbalance, emotional disorder, epiphyseal injury, gastritis, gastrooesophageal reflux disease, gingival hypertrophy, haematemesis, hallucination, Henoch-Schonlein purpura, hyponatraemia, lymphadenitis, periostitis, peritonitis, physical abuse, aspiration pneumonia, bacterial pneumonia, pulmonary edema, pyrexia, respiratory arrest, respiratory distress, respiratory tract infection, skin graft, status epilepticus, systemic viral infection, thermal burn, unresponsive to stimuli, and vomiting. Two subjects experienced SAEs considered to be related to pregabalin treatment, hallucination and epilepsy, both of which occurred in Study 1041 The 2 subjects with SAEs of suicide attempt are described in section 7.2.5 (Submission Specific Primary Safety Concerns) of this review.

7.2.3 Dropouts and/or Discontinuations

Controlled Study 1041

A total of 5/295 subjects permanently discontinued the study due to AEs, all 5 being pregabalin-treated patients.

Permanent treatment discontinuations due to AEs occurred for 1 (1.0%) subject in the pregabalin 2.5 mg/kg/day group, 4 (4.1%) subjects in the pregabalin 10 mg/kg/day group, and none in placebo-treated subjects. All AEs were related to treatment with study medication, and all resolved. The subject in the pregabalin 2.5 mg/kg/day group (Subject) discontinued due to an SAE of hallucination. In the pregabalin 10 mg/kg/day group, 3 subjects discontinued due to AEs of somnolence (mild in Subject and moderate in Subjects and) and an SAE of epilepsy (investigator term: “worsening of epilepsy” (Subject).

Controlled/Uncontrolled Studies

A total of 21 of 323 (6.5%) pregabalin-treated subjects 4 to 16 years of age with POS permanently discontinued from Studies 1041, 1075, and 1106 due to AEs. Eighteen (5.6%) subjects in this population discontinued due to treatment-related AEs. Five pregabalin-treated subjects 4 to 16 years of age with POS permanently discontinued from Study 1041 due to AEs. Seven additional subjects in this population discontinued due to AEs during Study 1075 and 9 subjects during Study 1106 (9 subjects).

7.2.4 Significant Adverse Events

Table 11 (from the approved labeling) lists all dose-related adverse reactions occurring in at least 2% of all Lyrica-treated patients in Study A0081041. Dose-relatedness was defined as an incidence of the adverse event in the 10 mg/kg/day group that was at least 2% greater than the rate in both the placebo and 2.5 mg/kg/day groups. In this study, 201 patients received Lyrica, and 94 patients received placebo for up to 12 weeks. A majority of pregabalin-treated patients in the clinical study had adverse reactions with a maximum intensity of "mild" or "moderate".

Table 11 Dose-related Adverse Reaction Incidence in a Controlled Trial in Adjunctive Therapy for Partial Onset Seizures in Patients 4 to Less Than 17 Years of Age

Body System Preferred Term	2.5 mg/kg/day[a] [N=104] %	10 mg/kg/day[b] [N=97] %	All PGB [N=201] %	Placebo [N=94] %
Gastrointestinal disorders				
Salivary hypersecretion	1	4	2	0
Investigations				
Weight increased	4	13	8	4
Metabolism and nutrition disorders				
Increased appetite	7	10	8	4
Nervous system disorders				
Somnolence	17	26	21	14

Abbreviations: N=number of patients; PGB = pregabalin.
[a] 2.5 mg/kg/day: Maximum dose 150 mg/day. Includes patients less than 30 kg for whom dose was adjusted to 3.5 mg/kg/day.
[b] 10 mg/kg/day: Maximum dose 600 mg/day. Includes patients less than 30 kg for whom dose was adjusted to 14 mg/kg/day.

The types of treatment-related adverse effects were similar to those reported in adult clinical trials. Although incidence rates cannot be directly compared between the short-term controlled adult studies and the long-term open-label pediatric studies, there did not appear to be a substantial difference in rates of reported events to raise a concern for a new or unique safety signal in the pediatric population. Overall, no new safety signals were identified.

7.2.5 Submission Specific Primary Safety Concerns

The following adverse events were identified to be of interest for this drug from experience in the adult patient population.

Dizziness

In controlled trial A0081041, dizziness was not observed to have a statistically significant increase over placebo for either pregabalin treatment arm, with a risk difference of 2.782% (95% CI: -2.325 to 8.575) for pregabalin 2.5 mg/kg/day and 2.029% (95% CI: -3.012 to 7.793) for pregabalin 10 mg/kg/day.

In the combined controlled/uncontrolled safety study population, no subjects discontinued from the studies permanently due to AEs of dizziness). Four (1.2%) subjects had a temporary discontinuation or dose reduction due to dizziness. All of these AEs were considered treatment related and resolved.

Somnolence

Somnolence (PT) was the most common AE in Study 1041, reported in 18 (17.3%) subjects receiving pregabalin 2.5 mg/kg/day (13 mild and 5 moderate), 25 (25.8%) subjects treated with pregabalin 10 mg/kg/day (19 mild and 6 moderate), and 13 (13.8%) subjects who received placebo treatment (12 mild and 1 moderate). The somnolence was considered treatment related for 17 (16.3%) subjects in the 2.5 mg/kg/day group, all 25 (25.8%) subjects in the 10 mg/kg/day group, and 12 (12.8%) subjects in the placebo group.

In the combined controlled/uncontrolled safety study population, sixty-five (20.1%) pregabalin-treated subjects 4 to 16 years of age with POS reported somnolence (PT) in Studies 1041, 1075, or 1106 (43 mild, 20 moderate, and 2 severe).

Peripheral Edema

There were no cases of peripheral edema in Study 1041 or 1075. Two subjects reported peripheral edema during Study 1106. Both events were mild and resolved.

Weight gain

See section 7.4.3 of this review.

Vision-related events

In controlled trial A0081041, none of the vision-related AEs in either pregabalin treatment group showed a statistically significant increase over placebo. Only vision blurred and visual brightness were considered treatment related. No subjects discontinued from the study due to vision-related AEs. For most subjects the vision-related events resolved before the last day of study medication.

In the combined controlled/uncontrolled safety study population, no subjects discontinued from their OLE study permanently due to vision-related AEs. Two subjects had temporary discontinuations or dose reductions due to vision-related AEs of diplopia and vision blurred.

Ataxia and Tremor

In controlled trial A0081041, there were no cases of ataxia or tremor. In pregabalin-treated subjects 4 to 16 years of age with POS in OLE Study 1106, there were 4 cases of ataxia (3 mild and 1 moderate in severity) and 1 case of resting tremor (mild).

Cognitive/neuropsychiatric events including behavioral effects (behavior/aggression, concentration/personality changes, or hyperkinesia)

In controlled trial A0081041, 6 (5.8%) subjects in the pregabalin 2.5 mg/kg/day group, 8 (8.2%) subjects in the pregabalin 10 mg/kg/day group, and 4 (4.3%) placebo subjects had AEs in the psychiatric disorders SOC. Irritability was the most frequently occurring AE in the psychiatric disorders SOC, with 1 subject each in the 2.5 mg/kg/day and placebo groups, and 3 subjects in the 10 mg/kg/day group. Other events in this SOC occurred in 1 subject at most per treatment group. One subject with a history of psychotic disorder reported an SAE of hallucination (Subject [redacted], pregabalin 2.5 mg/kg/day), considered severe and treatment related, which led to permanent discontinuation. Other events in this SOC occurred in 1 subject at most per treatment group and included abnormal behavior, aggression, agitation, and mood altered, among others for pregabalin-treated subjects.

In the combined controlled/uncontrolled safety study population, a total of 45 (13.9%) of subjects had AEs in the psychiatric disorders SOC. Three of the events were reported as severe: hallucination (the same patient described above in Study 1041) and 2 patients with suicide attempt (see Suicidal Ideation and Behavior immediately below in this section of this review). The most common events in the psychiatric disorders SOC (5 or more subjects) were aggression (9 subjects), abnormal behavior (7 subjects), and irritability (5 subjects). Other events included agitation (4 subjects), mood altered (3 subjects), anger (2 subjects), attention deficit/hyperactivity disorder, depression, emotional distress, mood swings and personality change (1 subject each) among others.

Euphoric effects

No cases of euphoria (Pt terms: elevated mood, euphoric mood, feeling drunk) in controlled trial A0081041 or in the combined controlled/uncontrolled safety study population.

Suicidal Ideation and Behavior

Two subjects in OLE Study A0081106 had the SAE of suicide attempt not clearly related to pregabalin. The first was a 12 year old girl with a previous history of suicidal ideation who was physically abused by a school classmate on Day 79 of Study A0081106; on Day 163 she attempted suicide by ingesting 10 sleeping pills and was subsequently discontinued on Day 196 (her past history of suicidal ideation being considered a protocol violation). The second was a 15 year old girl who had completed Study A0081041 but who took 5 Lorazepam 2.5 mg tablets on Day 26 of Study A0081106. The investigator did not feel this was attributable to ongoing psychological and behavioral issues rather than pregabalin-related but she was discontinued from Study A0081106 in Day 57 as a precaution.

Overall, these adverse events in pediatric patients were consistent with those adverse events seen in adult patients. There were no new safety signals.

7.3 Supportive Safety Results

7.4.1 Common Adverse Events

Pregabalin 2.5 mg/kg/day and 10 mg/kg/day dose levels administered BID were generally safe and well tolerated compared to placebo in subjects 4 to 16 years of age with POS. There were no unexpected safety findings detected in subjects 4 to 16 years of age with POS in the controlled and uncontrolled studies. The safety profile observed for pregabalin in pediatric subjects 4 to 16 years of age with POS was generally consistent with the known profile of pregabalin in prior epilepsy studies in adults, with the exception of childhood-related complaints such as upper respiratory tract infection and pyrexia, which were reported more often in pediatric subjects than in adults.

In the controlled pediatric epilepsy Study 1041, the most commonly reported all-causality AEs (>10% incidence) were somnolence for pregabalin 2.5 mg/kg/day (17.3%) and placebo (13.8%), and somnolence (25.8%), increased weight (13.4%), and increased appetite (10.3%) for pregabalin 10 mg/kg/day. These events are consistent with most common dose-related AEs in adults with POS described in the LYRICA USPI2 (AEs occurring at a rate at least 2% greater for the highest dose pregabalin

group compared with both the placebo and low dose groups). In pregabalin-treated subjects 4 to 16 years of age with POS from controlled and uncontrolled studies, the most common AEs (>10% incidence) were somnolence (20.1%), pyrexia (15.2%), upper respiratory tract infection (14.2%), weight increased (12.4%), and seizure (11.5%). Somnolence and weight increased were also common AEs (>10% incidence) in the adult population with POS from controlled studies (20.8% and 10.4%, respectively). A majority of pregabalin-treated subjects 4 to 16 years of age with POS in the controlled and uncontrolled studies had AEs with a maximum intensity of "mild" or "moderate" (10.2% were considered severe).

The PWR requirement for a minimum of 100 subjects 1 month to 16 years of age to be exposed to pregabalin treatment for 1 year in specified age categories was met for the 4 to <10 year old cohort and the 10 to 16 year old cohort; these subjects completed a year of treatment in Study 1075 or Study 1106 as of the cut-off date of 31 January 2017. A total of 170 subjects age 1 month to 16 years of age completed 1 year of exposure to pregabalin.

7.4.2 Laboratory Findings

The laboratory findings were reviewed from each study independently, and there was no evidence of any new safety concerns in the laboratory findings.

No other clinically significant lab shifts or patterns were identified.

7.4.3 Vital Signs, Height and Weight

Vital signs (Mean SBP, DBP and pulse rate) were analyzed by mean change from baseline for each study, and vital signs were also reviewed for markedly abnormal values. The majority of the vital sign mean changes from baseline noted throughout the studies were small and not clinically relevant. Weight and height were also analyzed as mean change from baseline and raised no clinical concerns.

Subjects in the pregabalin 2.5 mg/kg/day group gained an average of 1.6 kg from baseline to end of study, compared with 2.8 kg and 0.7 kg in the pregabalin 10 mg/kg/day and placebo groups, respectively. Pregabalin-treated subjects 4 to 16 years of age with POS from Studies 1041, 1075, and 1106 had a mean weight increase from baseline to final visit of 5.4 kg. Weight gain in some subjects may be partially attributable to normal growth and development; however, contribution from pregabalin and the pregabalin 10 mg/kg/day dose in particular cannot be excluded. The incidence of increased weight AEs was 3.8% for the pregabalin 2.5 mg/kg/day group, 13.4% for the pregabalin 10 mg/kg/day group, and 4.3% for the placebo group, which were similar to results for adults with epilepsy. There were no discontinuations due to weight gain in Study 1041; 1 subject permanently discontinued due to increased weight in Study 1106.

7.4.4 Electrocardiograms (ECGs)

There were no clinically relevant changes in PR interval or other ECG variables as a result of pregabalin treatment in the pediatric population age 4 to 16 years.

7.4.5 Special Safety Studies/Clinical Trials

There were no special studies performed in renal or hepatic impairment in pediatric subjects.

The sponsor requested that dosing for pediatric patients with renal impairment be addressed outside of these current pediatric supplemental applications. This dosing will be based on further pharmacokinetic data analysis. Therefore, in approved labeling, in section 2.7 Dosing for Adult Patients with Renal Impairment and section 8.6 Renal Impairment in approved labeling, the following statement will appear: “The use of LYRICA in pediatric patients with compromised renal function has not been studied.”

7.6 Additional Safety Evaluations

Not applicable.

7.7 Additional Submissions / Safety Issues

8 Postmarket Experience

The Pfizer Safety Database was queried for medically-confirmed postmarketing cases received through 31 May 2017 for pediatric patients (aged 4 to 16 years; or classified with an age group of child or adolescent). The query identified 332 relevant postmarketing cases in pediatric patients 4 to 16 years of age; of these, 20 cases reported epilepsy indications.

The most frequently reported AE (MedDRA v20.0 PT) in both subgroups was “product use issue”. In the pediatric population with an epilepsy indication, “product use issue” was reported 3 times; other similar PTs reported in this population were: drug administered to patient of inappropriate age (1), drug prescribing error (1), drug administration error (1), and off-label use (1). Constipation, drug ineffective, fall, gynecomastia, seizure, and somnolence were each reported in 2 patients. All other AEs were reported only once.

In the subgroup of 312 pediatric patients with a non-epilepsy indication, the most frequently reported AEs included product use issue, as described previously (94), drug administered to patient of inappropriate age (i.e., drug administered to pediatric patients since pregabalin not approved for use in this age group; 32), and off-label use (23). The other 2 AEs most frequently reported were dizziness (21) and somnolence (14), which are known to be associated with pregabalin administration.

In the subgroup of 20 pediatric patients who had a definite epilepsy indication, the most frequently reported AEs included product use issue (3), constipation (2), drug ineffective (2), fall (2), gynecomastia (2), seizure (2), and somnolence (2).

Reviewer's note: No new safety signals were identified from the postmarket data. Overall, adverse events reported from the off-label use of commercially available pregabalin were consistent with both those seen in the clinical study safety population, and those adverse events seen in adults.

9 Appendices

9.1 Literature Review/References

1. Men A, Mehrotra S, Bhattaram A et al. Full extrapolation of efficacy from adults to children of antiepileptic drugs indicated for the treatment of partial onset seizures: a scientific and regulatory perspective. Annual Meeting of American Epilepsy Society 2016: Abstract 1.075.
2. Pellock JM, Arzimanoglou A, D'Cruz O et al. Extrapolation evidence of antiepileptic drug efficacy in adults to children > 2 years of age with focal seizures: the case for disease similarity. Epilepsia 2017. doi: 10.1111/epi.13859
3. LYRICA® (pregabalin). Prescribing Information, Pfizer Inc:

9.2 Labeling Recommendations

Based upon the findings of this review, appropriate revisions to the label are suggested for Sections 1 Indications and Usage, 2 Dosage and Administration, Section 5 Warnings and Precautions, Section 6 Adverse Reactions, Section 8.4 Pediatric Use, Section 12 Clinical Pharmacology, and Section 14 Clinical Studies. Please see final approved labeling.

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/s/

XIANGMIN ZHANG
04/30/2018

KUN JIN
04/30/2018
I concur with the statistical review.

HSIEN MING J HUNG
05/01/2018

PHILIP H SHERIDAN
05/04/2018