CLINICAL REVIEW

Application Type	Efficacy Supplement
Application Number(s)	202834(S-014), 208277(S-002) for Partial Onset Seizures 202834(S-015), 208277(S-003) for Primary Generalized Tonic Clonic Seizures
Priority or Standard	Priority
Submit Date(s)	3/28/2018
Received Date(s)	3/28/2018
PDUFA Goal Date	9/28/2018
Division/Office	DNP/ODE-1
Reviewer Name(s)	Natalie Getzoff, MD
Review Completion Date	9/25/2018
Established/Proper Name	Perampanel
Trade Name	Fycompa
Applicant	Eisai, Inc
Dosage Form(s)	Tablets and oral suspension
Applicant Proposed Dosing Regimen(s)	8-12 mg QD
Applicant Proposed Indication(s)/Population(s)	• Treatment of partial onset seizures with or without secondarily generalized seizures in patients with epilepsy 2 years of age and older • Treatment of primary generalized tonic-clonic seizures in patients with epilepsy 2 years of age and older
Recommendation on Regulatory Action	• APPROVAL of treatment of seizures in patients 4 years and older with partial onset seizures • DISAPPROVAL of proposed expansion of treatment for primary generalized tonic-clonic seizures below age 12 years and for monotherapy use in patients with primary generalized tonic-clonic seizures
Recommended Indication(s)/Population(s) (if applicable)	• Treatment of partial onset seizures with or without secondarily generalized seizures in patients with epilepsy 4 years of age and older • Adjunctive therapy for treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older (unchanged from current indication)

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Glossary

AC	advisory committee
AE	adverse event
AED	antiepileptic drug
AR	adverse reaction
BPCA	Best Pharmaceuticals for Children Act
BMI	body mass index
BP	blood pressure
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
CNS	central nervous system
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
DMC	data monitoring committee
DNP	Division of Neurology Products
ECG	electrocardiogram
eCTD	electronic common technical document
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
MedDRA	Medical Dictionary for Regulatory Activities

mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OXC	oxcarbazepine
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PGTC	primary generalized tonic-clonic
PGTCS	primary generalized tonic-clonic seizure
PI	prescribing information or package insert
PK	pharmacokinetics
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
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SJS	Stevens Johnson Syndrome
SUDEP	sudden unexplained death in epilepsy
TEAE	treatment emergent adverse event
TEN	toxic epidermal necrolysis
VPA	valproic acid, valproate

1. Executive Summary

1.1. Product Introduction

The Applicant proposes to expand the indication for perampanel (proprietary name Fycompa) tablets and oral suspension to pediatric patients ages 2 to less than 12 for partial onset seizures (POS) and primary generalized tonic clonic seizures (PGTCS) in the United States (US). Perampanel, the active ingredient in Fycompa, is a noncompetitive and selective α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonist. AMPA receptors can mediate glutaminergic activity in the cortex, and an AMPA-antagonist may reduce excitatory activity. Reduction of excitatory activity may lead to an anticonvulsant effect, and, as noted by the Applicant, there are some animal data (reduction of seizures in rat models) to support this hypothesis.

Fycompa is currently marketed in the US as 2, 4, 6, 8, 10, and 12 mg tablets and an oral suspension of 0.5 mg/ml for the following indications:

- Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 12 years of age and older, and
- Adjunctive therapy for the treatment of primary generalized tonic-clonic seizures in patients with epilepsy 12 years of age and older.

The expanded indication proposed by the Applicant is as follows:

- Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 2 years of age and older, and
- Treatment of primary generalized tonic-clonic seizures in patients with epilepsy 2 years of age and older.

1.2. Conclusions on the Substantial Evidence of Effectiveness

Efficacy of a drug to treat partial onset seizures in children down to 2 years of age is extrapolated from adult efficacy based on adequate dose-exposure data in the proposed age range and sufficient safety data. In Studies 311 and 232, the Applicant provided sufficient dose-exposure pharmacokinetic data to support extrapolation of efficacy of perampanel in patients with partial onset seizures 4 to 12 years of age, but there were not enough dose-exposure data in patients 2 to < 4 years to allow for determination of safety in that population.

1.3. Benefit-Risk Assessment

Benefit-Risk Integrated Assessment

Perampanel is an AMPA antagonist that has anticonvulsant activity. It is already approved for adjunctive and monotherapy use in the treatment of partial onset seizures (POS) and adjunctive use in the treatment of primary generalized tonic-clonic seizures (PGTCS) in patients 12 years and older, based on four phase 3 randomized, placebo-controlled, efficacy trials in adults and adolescents. POS are commonly seen in patients with a multitude of epilepsy disorders and, when refractory to treatment, are associated with significant adverse consequences, such as severe trauma, depression, anxiety, and sudden death.

FDA has determined that extrapolation of efficacy from adults to pediatric patients age 2 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. Fycompa was approved for marketing in the US in 2012 for treatment of POS in adults and adolescents. The clinical trials supporting that approval, along with PK modeling and simulation studies of the pediatric population, support evidence of effectiveness in children 4 years of age and older. There were insufficient PK data in this submission to determine the dose-exposure and therefore safety in patients 2 to < 4 years of age.

The safety profile of perampanel is well-characterized in adults and adolescents. The open-label, long-term safety data in pediatric patients 2 to < 12 years included in this supplemental NDA submission did not raise any new clinical concerns, and the frequently seen adverse events in these studies were similar to those seen in the placebo-controlled trials. No new safety signal was identified.

I recommend approval of perampanel for monotherapy and adjunctive therapy use for treatment of POS in patients 4 years of age and older, as effectiveness (based on similar dose exposures) and safety in patients 4 to <12 years of age are demonstrably similar to that seen in adults and adolescents with POS. There is no current procedure for extrapolation of adult efficacy in PGTCS to the pediatric population or for extrapolation of adjunctive use to monotherapy use in PGTCS. Therefore, the Applicant's proposal to extrapolate these uses/populations is not supported, and I recommend that the PGTCS indication remain unchanged.

1.4. Patient Experience Data

The basis of efficacy for this submission is extrapolation of adult and adolescent efficacy to pediatric patients with partial onset seizures. No efficacy data were included; thus this section is not applicable.

2. Therapeutic Context

2.1. Analysis of Condition

The Applicant proposes expansion of two current indications for this application, based on extrapolation of efficacy from adult patients to pediatric patients:

- Treatment of partial-onset seizures with or without secondarily generalized seizures in patients with epilepsy 2 years of age and older (current indication for partial-onset seizures is adjunctive or monotherapy in patients ≥12 years of age and older)
- Treatment of primary generalized tonic-clonic seizures in patients with epilepsy 2 years of age and older (current indication for primary generalized tonic clonic seizures is adjunctive therapy in patients 12 years of age and older)

Epilepsies affect individuals of all ages and are some 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 1000, 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

[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.

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 or primary generalized seizures are associated with poorer quality of life due to 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]

Seizures are classified as partial or primary generalized, depending on the location of onset of the seizure.[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].

As opposed to POS, PGTCS have apparent clinical or EEG onset in both hemispheres of the brain, with no clear focus or foci. PGTCS are associated with idiopathic generalized epilepsy and several generalized epilepsy syndromes. Onset of PGTCS typically starts in older children, adolescents, and young adults, but does present in children as young as 2 years. One critical EEG hallmark of a susceptibility to generalized seizures, including PGTCS, are well-formed generalized spike-wave discharges. These are occasionally seen, but are not well developed,

[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
[9] Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for Revised Classification of Epilepsies and Epileptic Syndromes. Epilepsia. 30(4):38%399, 1989
[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

widely distributed and highly stereotyped until 2 to 3 years of age.

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 used to treat pediatric patients with POS include phenobarbital, primidone, phenytoin, carbamazepine, vigabatrin, and felbamate. These are not included in the table due to lack of clear pediatric indications, lack of NDA approval, or contraindication for use as first line treatment due to adverse drug effects.

Since there is no DNP extrapolation approach for the treatment of primary generalized tonic clonic seizures and the Applicant's rationale for expansion of the indication is based completely upon extrapolation of adult and adolescent efficacy to children, current treatment options for this indication will not be discussed.

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
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

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

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

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

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

Fycompa was originally approved for adjunctive treatment of partial onset seizures (POS) in patients ≥ 12 years of age on October 22, 2012. This approval was based on results of three controlled efficacy trials. Fycompa was subsequently approved for adjunctive treatment of primary generalized tonic clonic seizures (PGTCS) in patients ≥ 12 years of age on June 19, 2015, based on a single, controlled efficacy trial. An oral suspension was approved for use in these indications. Fycompa was also approved for use as monotherapy in patients 12 years of age and older with partial onset seizures on July 26, 2017. This approval was based on extrapolation of efficacy and safety using pharmacokinetic analyses of data previously included in the original NDA-202834 submission.

3.2. Summary of Presubmission/Submission Regulatory Activity

As noted above, Fycompa was approved on October 22, 2012 for adjunctive treatment of POS in patients 12 years of age or greater, on June 19, 2015 for adjunctive treatment of PGTCS in patients ≥ 12 years of age, and on July 26, 2017 for monotherapy treatment of patients ≥ 12 years of age with POS. Interactions with the Applicant on the indication for use of Fycompa in patients < 12 years of age include the following:

- General Advice letter (11/15/2015) sent to all companies with approval for adjunctive treatment of POS outlining the Division's decision to accept extrapolation of efficacy from adult to pediatric patients with POS and the data necessary to support such a submission (see Section 3.4 below);
- Type C Written Response Only (WRO, 5/16/2016) to (among other issues) discuss the acceptability of Study 311 to fulfill the Division of Neurology Products (DNP's) requirements for extrapolation of adult efficacy in POS to pediatric patients ≥ 4 years of age (on face the study was deemed acceptable) and potential for extrapolation of adult efficacy in patients with PGTCS to pediatric patients (No: *"Inclusion of primary generalized tonic-clonic (PGTC) patients in Study 311 will not support extrapolation of efficacy for PGTC seizures. However, safety and PK data collected in pediatric patients with PGTC seizures may be used as supportive data in patients with POS."*)
- General advice letter (9/13/2016) on the acceptability of extrapolation to POS monotherapy in AEDs approved for adjunctive therapy in POS (see Section 3.4 below);
- Type C meeting (12/18/2017) in which questions on a variety of topics were answered, including one regarding current thinking on extrapolation of adult PGTCS data to support use in pediatric patients (response: such data are not available);
- Type B meeting (1/29/2018) to discuss the data necessary to support a sNDA for

extrapolation of adult data to pediatric patients. The sponsor proposed extrapolation for POS and PGTCS down to 2 years of age. The sponsor was referred to the General Advice Letter (11/12/15) in which the policy of extrapolation of adult efficacy data to pediatric patients was specifically defined as applicable to POS only and down to 4 years of age. Other questions included acceptability of a Summary of Clinical Safety in lieu of an Integrated Summary of Safety, information needed to support extrapolation for monotherapy use in pediatric patients with POS (but not PGTCS), and priority review designation if submitted in response to a Written Request.

- Pediatric Written Request (WR) sent to the sponsor on 3/20/2018. This WR was issued based on the sponsor's submission on 11/3/2017 with requested revisions submitted on 12/4/2017. This WR was the product of multiple Proposed Pediatric Study Request (PPSR) submissions by the Applicant with multiple rounds of edits/"negotiations" from DNP:
    - PPSR #1 submitted to FDA on 4/30/2010, No Agreement response from DNP/DPMH on 4/4/2012
    - PPSR #2 submitted 12/13/2012, DNP responded 6/3/2013
        - PPSR #2 "v2" submitted on 6/14/2013, comments from DNP 2/4/2014
        - PPSR #2 "v3" submitted on 3/4/2014, comments from DNP 10/10/2014
        - PPSR #2 "v4" submitted on 9/30/2016, comments from DNP 6/1/2017
    - PPSR #3 submitted on 11/3/2017, revised by Applicant to comply with current PPSR template on 12/4/2017

Reviewer's Comments: DNP had a number of discussions regarding extrapolation of adult efficacy in POS to pediatric patients and extrapolation of monotherapy in patients with POS with the Applicant prior to the issuance of the general advice letters on pediatric and monotherapy extrapolation. As the substance of those interactions with the Applicant were uncertain pending finalization of the extrapolation policies, they are not summarized here.

3.3. Foreign Regulatory Actions and Marketing History

As of March 2018, marketing authorizations for Fycompa have been granted in more than 50 countries worldwide for a for the adjunctive treatment of POS with or without secondarily generalized seizures in patients with epilepsy aged 12 years and older (18 years and older in Canada). Commercial launch has taken place in over 30 countries. There are no reported safety concerns specific to markets outside the US. The International birthdate for perampanel is July 23, 2012, based on the initial approval by EMA.

3.4. Background Information Regarding Pediatric and Monotherapy Extrapolation

FDA conducted a lengthy review process and determined that it was acceptable to extrapolate to pediatric patients 4 years of age and older the effectiveness of drugs approved for the treatment of partial onset seizures (POS) in adults[13]. This determination was based on similarity of the underlying disease in the adult and pediatric populations, as well as a similar exposure-response relationship in pediatric and adult patients with POS[14]. This extrapolation does not apply to patients < 4 years of age or to other types of epilepsy. In order to support an indication for treatment of POS in pediatric patients ≥ 4 years of age based upon extrapolation, sponsors were instructed to provide the following in a General Advice Letter dated November 12, 2015:

- *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 will require 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.*

Since the initial implementation of the pediatric extrapolation approach in 2015, further clarification of partial onset seizures as a clinical entity supports the similarity of the clinical manifestation of POS in patients as young as 2 years of age to that of adults[15]. While the pharmacokinetic data are not as robust in patients under age 4, there are some PK data to support the extrapolation of adult efficacy in POS to patients 2-4 years of age. Therefore, the Applicant's proposal to extrapolate adult efficacy to patients 2 to <12 years of age would be acceptable depending on the adequacy of the PK and safety data submitted.

A second General Advice Letter was sent to sponsors dated September 13, 2016, which stated that the Division of Neurology Products (DNP) had *"determined that it is acceptable to extrapolate efficacy and safety of drugs approved as adjunctive therapy for the treatment of partial onset seizures (POS) to their use as monotherapy for the treatment of POS. This extrapolation applies to both adult and pediatric populations, provided that efficacy and safety as adjunctive therapy for the treatment of POS have been previously established in the respective age range."* This determination was based on FDA analysis of drugs approved for both adjunctive and monotherapy demonstrating that dosages and exposures of drugs when

[13] 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.
[14] Pellock JM, Carman WJ, Thyagarajan V, et al. Efficacy of antiepileptic drugs in adults predicts efficacy in children, A systematic review. Neurology 2012;79:1482–1489
[15] Pellock JM, Arzimanoglou A, D'Cruz O, et al. Extrapolating evidence of antiepileptic drug efficacy in adults to children ≥2 years of age with focal seizures: The case for disease similarity. Epilepsia, 58(10):1686–1696, 2017

used as monotherapy are within the ranges of dosages and exposures for those drugs when used as adjunctive therapy for POS.

There is no current procedure for extrapolation of adult efficacy in PGTCS to the pediatric population or for extrapolation of adjunctive use to monotherapy use in PGTCS. In this sNDA submission, the Applicant provided a meta-analysis of a number of published studies in drug treatment of patients with PGTCS. This analysis is insufficient to support extrapolation of adult efficacy data in PGTCS to pediatric patients for two significant reasons. Firstly, the PK data from these studies are not available for review, nor is there a large amount of PK data from a number of clinical efficacy studies of multiple seizure drugs in pediatric patients with PGTCS to allow for generalization of results. Secondly, the clinical and electrographic definition of PGTCS has changed over time, and it is unclear what percent of patients in the studies included in the meta-analysis would have PGTCS vs. other seizure types (such as POS) as ascertained by current clinical criteria. Therefore, the Applicant's proposal to extrapolate these uses/populations is not supported and the PGTCS indication will remain unchanged.

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

4.1. Office of Scientific Investigations (OSI)

An OSI audit was not requested.

4.2. Product Quality

See the review by the Chemistry, Manufacturing and Control reviewer.

4.3. Clinical Microbiology

Not applicable

4.4. Nonclinical Pharmacology/Toxicology

No new nonclinical information was included in this submission.

4.5. Clinical Pharmacology

Please see The Office of Clinical Pharmacology review for a full discussion of the

pharmacokinetics data.

Efficacy in pediatric patients with POS 4 to < 12 years of age is based on extrapolation of dose-exposures in the adult population to that of the pediatric population and is supported by the PK data included in this supplemental NDA submission. The proposed pediatric dosing is the same as that for adults.

Although the most current approach is to accept extrapolation of adult efficacy to pediatric patients with POS down to 2 years of age, there were insufficient PK data in patients <4 years of age in Studies 311 and 232 to characterize the dose-exposure in patients < 4 years of age, especially because the pharmacokinetics of perampanel are unique. Unlike the dosing of other AEDs, the dosing for Fycompa in pediatric patients down to age 4 years is the same as for adults although patients weighing less than 16 kg were not studied. A postmarketing requirement to study PK and safety in children age 2 years to < 4 years will be required.

4.6. Devices and Companion Diagnostic Issues

Not applicable

4.7. Consumer Study Reviews

Not applicable

5. Sources of Clinical Data and Review Strategy

Two open-label PK, safety, and tolerability studies of perampanel oral suspension in pediatric patients with epilepsy form the basis of this review (Table 2).

5.1. Table of Clinical Studies

Table 2: Clinical Studies in Patients Contributing Safety Data

Study ID	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled/ completed	Study Population	No. of Centers and Countries
E2007-G000-232 (Core and Extension)	Multiple ascending dose, open label study with long-term extension	Perampanel OS, 0.5 mg/mL Dose: 0.015 mg/kg up to 0.18 mg/kg, given PO QHS	Primary: PK of perampanel in pediatric subjects Secondary (Efficacy): • Percent change in 28-day seizure frequency in the Treatment Phase compared to Baseline. • Responder rate (proportion of patients with a 50% decrease in 28-day seizure frequency during the Maintenance Period compared to Baseline). • Seizure-free rate during the Maintenance Period. • Clinical Global Impression of Change at end of treatment. Safety endpoints: frequency of AEs, clinical laboratory parameters, vital signs, ECG, growth parameters (height, weight, thyroid and IGF-2), C-SSRS outcomes, and Photo-sensitivity Questionnaire results	Core: 11 weeks for pts entering the LTE phase, 15 for those not transitioning) Extension: 52 weeks	Core: 50/42 Extension: 41/27	Pediatric patients 2 to <12 years of age with epilepsy (POS or PGTCS)	Core: 15 sites enrolled in the US Extension: 14 sites in the US

Study ID	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled/ completed	Study Population	No. of Centers and Countries
E2007-G000-311 (Core and Extension)	Multicenter, open-label, single-arm study with an Extension Phase.	Perampanel OS, 0.5 mg/mL Dose: 12-16 mg/day PO, depending on concomitant AEDs	Primary: Safety and tolerability [which include incidence of treatment-emergent adverse events (TEAEs) and SAEs, laboratory parameters, vital signs, and ECG parameters] Secondary: • The relationship between plasma levels of perampanel and efficacy endpoints separately for each seizure type • The relationship between plasma levels of perampanel and cognition endpoints including change from baselines in ABNAS, CBCL, and LGPT. • Change from baseline at Week 23 and Week 52 in ABNAS, CBCL, and LGPT • Changes from baseline at Week 23 and Week 52 in growth and development parameters (height, weight, thyroid, and IGF-1) • Change from baseline in EEG and the frequency of EEG abnormalities during awake	Core: 23 weeks for pts entering the LTE phase, 27 for those not transitioning) Extension: 29 weeks (+4 weeks follow-up)	Core Study: POS: 144/67 PGTCS: 27/10 Extension: POS: 67/1 PGTCS: 9/1	Pediatric patients 4 to <12 years of age with epilepsy (POS or PGTCS)	80 study sites: Belgium (4), France (6), Hungary (4), Japan (23), Korea (5), Latvia (1), Poland (3), Spain (6), and the US (28)

Study ID	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled/ completed	Study Population	No. of Centers and Countries
			and sleep state • Proportion of patients with any treatment-emergent reports of suicidal ideation and behavior on the C-SSRS • The median percent change in seizure frequency per 28 days during Treatment Phase (Titration + Maintenance), and during Extension phase compared to the Pretreatment Phase. • Proportion of responders (25%, 50%; and 75% responders) during Maintenance Period and Extension phase • Proportion of subjects who are seizure-free during Maintenance Period and Extension phase • CGI-C				

ABNAS: Aldenkamp–Baker Neuropsychological Assessment Schedule; CBCL: Child Behavior Check List; LGPT: Lafayette Grooved Pegboard Test
Source: SCS, Table 2.7.4-1, supplemented with information from CSRs for Studies 232 and 311.

5.2.Review Strategy

A safety determination was made by evaluating data from two open-label PK and safety studies in pediatric patients with epilepsy. This review focuses solely on safety. No efficacy data were included in the submission, and efficacy will be determined based on extrapolation from adult and adolescent data to pediatric patients. A PK analysis for exposure and dosing was performed by the Office of Clinical Pharmacology and is summarized in their review.

6. Review of Relevant Individual Studies Used to Support Efficacy

Not applicable. See Section 8.2 for a description of the studies used to support safety in patients 2 to < 12 years of age with partial onset seizures.

7. Integrated Review of Effectiveness

Efficacy in pediatric patients with POS 4 to < 12 years of age is based on extrapolation of dose-exposures in the adult and adolescent population to that of the pediatric population. There were insufficient PK data in patients <4 years of age in Studies 311 and 232 to characterize the dose-exposure in patients < 4 years of age.

8. Review of Safety

8.1. Safety Review Approach

The primary safety data were generated from two uncontrolled, open-label, PK/safety studies in pediatric patients with epilepsy:

- Study 232: Multiple ascending dose, open label study (including a long-term extension [LTE] phase) of perampanel in pediatric patients (ages 2-12 yrs) with epilepsy and inadequately controlled seizures.
- Study 311: Multicenter, open-label, single-arm study (includes LTE phase) of perampanel in pediatric patients (ages 4-12 yrs) with inadequately controlled POS or PGTCS.

The Applicant did not provide a pooled safety dataset for FDA analysis with their initial sNDA submission, but in response to an Information Request on June 5, 2018, submitted a pooled dataset on July 13, 2018. Most of my independent analyses were performed on this integrated and pooled safety database.

A 120-day Safety Update was submitted on July 19, 2018 and was reviewed. Twenty-three more patients were enrolled in Study 311 after the original data cutoff and were included in the 120-day Safety Update. The safety analyses were performed primarily on the data included in the original sNDA submission. Review of the 120-day Safety Update did not materially change overall TEAE rates and did not raise any new clinical concerns.

The safety analysis focused on treatment-emergent adverse events (TEAEs), SAEs, severe TEAEs, most common TEAEs, and those TEAEs that led to discontinuation. The applicant also identified significant adverse events of interest using the known safety profile of perampanel, as well as other antiepileptic drugs (AEDs).

Some AEs were coded under slightly different terms, although the underlying events were very similar and/or related. Therefore, several AE terms were recoded to avoid underestimating prevalence of a specific adverse event. Some terms were also recoded for ease of review, although none rose to the level of a new safety concern. The following table shows the original AE code on the left, and revised codes on the right. Terms that only resulted in the addition of one or two cases after recoding are not included in the table.

Table 3: Recoded AE Codes to Group Similar Terms

Original Coded Preferred Term(s)	Recoded Term
Abdominal pain upper, Abdominal discomfort	Abdominal pain
Atonic seizures, Petit mal seizures, Generalized tonic clonic seizure, Epilepsy, Seizure Cluster	Seizures
Pharyngitis streptococcal, Viral pharyngitis, Oropharyngeal pain, Tonsillitis	Pharyngitis
Allergic Rhinitis	Rhinitis
Vision blurred	Visual impairment
Viral gastroenteritis, enteritis	Gastroenteritis
Otitis media acute, Otitis media, Otitis externa	Ear infection
Viral upper respiratory tract infection, Upper respiratory tract inflammation	Upper Respiratory Tract Infection
Eczema, Urticaria, Dermatitis contact, Erythema, Rash papular, Dermatitis, Dermatitis diaper, Drug eruption, Rash maculo-papular	Rash
Allergic rhinitis	Rhinitis
Acute sinusitis	Sinusitis
Salivary hypersecretion	Drooling
Middle insomnia	Insomnia
Atypical pneumonia	Pneumonia

Of note, there were no placebo-controlled data for review; therefore, any conclusions regarding clinical meaningfulness of the safety data must be regarded with care.

8.2. Description of Clinical Trials Used to Support Safety

8.2.1. Study E2007-G000-311 (Study 311):

An Open-Label, Multicenter Study with an Extension Phase to Evaluate the Safety, Tolerability, and Exposure-Efficacy Relationship of Perampanel Oral Suspension when Administered as an Adjunctive Therapy in Pediatric Subjects (Age 4 to less than 12 years) with Inadequately Controlled Partial-Onset Seizures or Primary Generalized Tonic-Clonic Seizures

Study 311 is an ongoing multi-center, open-label, single arm, Phase 3 study to investigate the safety and pharmacokinetics of perampanel in patients 4 to <12 years of age with epilepsy. The purpose of the study was to evaluate the safety and tolerability of perampanel oral suspension as adjunctive therapy in pediatric patients with inadequately controlled POS or PGTCS. The planned sample size was 160 patients, and enrollment was stratified by age (4 to <7 years, 7 to <12 years).

Patients in the core phase of this study had a maximum treatment duration of 23 weeks (>52 weeks, if enrolled in the extension phase). Doses were titrated up to 12 mg QD in patients not on enzyme-inducing antiepileptic drugs (EIAEDs) and to 16 mg QD in patients taking an EIAED.

Blood samples for PK assessments were collected using sparse sampling technique at weeks 15, 19, 23 and at early discontinuation (if needed). Safety was assessed via all AEs and SAEs, clinical laboratory monitoring, vital signs, ECGs, physical and neurological examinations. Growth and development (weight, height, thyroid, and insulin-like growth factor-1 [IGF-1]), cognition and behavior, and suicidality (C-SSRS) were also assessed.

8.2.2. Study E2007-G000-232

An Open-Label Pilot Study With an Extension Phase to Evaluate the Pharmacokinetics, and to Generate Preliminary Safety, Tolerability, and Efficacy of Perampanel (E2007) Oral Suspension When Given as an Adjunctive Therapy in Pediatric Subjects From 2 to Less Than 12 Years of Age With Epilepsy

Study 232 is a completed, open label, single arm, Phase 2 study to explore the safety and pharmacokinetics of perampanel in patients 2 to <12 years of age with epilepsy. The purpose of the study was to evaluate the PK and generate preliminary safety, efficacy, and tolerability of perampanel oral suspension as adjunctive therapy in pediatric patients with epilepsy. The

planned sample size was 60 patients, and enrollment was stratified by age (2 to <7 years, 7 to <12 years).

Patients in the core phase of this study had a maximum treatment duration of 11 weeks (up to 52 weeks total if enrolled in the extension phase). Doses were initiated at 0.015 mg/kg and up-titrated over 7 weeks to a maximum daily dose of 0.18 mg/kg (≈12 mg/70 kg) QD. Maintenance period was 4 weeks.

Blood samples for PK assessments were collected using sparse sampling technique at weeks 1, 5, 9, 11 and at early discontinuation (if needed). Safety assessments included all AEs and SAEs, clinical laboratory testing, vital signs, ECGs, physical and neurological examinations, growth and development information (weight, height, thyroid, and IGF-1), and assessment of suicidal ideation/behavior (C-SSRS).

8.3. Review of the Safety Database

8.3.1. Overall Exposure

All clinical safety data were generated in Studies 311 and 232. The data from these studies constitute the safety database and provide the primary basis for comparisons of frequencies of adverse events, abnormal laboratory values, electrocardiograms, and vital signs. The primary sNDA safety database includes a total of 211 patients who were exposed to at least one dose of perampanel (Table 4). There were four patients in whom no safety assessments were made and were excluded from the safety analysis dataset.

Table 4: Total Exposure, pooled Studies 232 and 311

	Number of patients exposed to the study drug:		
Study	**≥1 dose**	**>6 months**	**≥12 months**
Total	N=211	N=78	N=20
Study 311	N=161	N=45	N=1
Study 232	N=50	N=33	N=19

Source: ADEX, pooled dataset

Of the 171 patients enrolled in Study 311, 161 received at least one dose of perampanel, although 4 of these patients had no post-dose safety assessment and are not included in the safety database. Seventy-seven patients completed the core study, while 56 patients were still considered as ongoing in the core Study 311 as of January 31, 2018. Seventy-six patients enrolled in the extension phase of Study 311, 46 of whom opted for treatment. Of the 46 treated patients in Study 311 (ext), 2 (4.3%) have discontinued and 42 were still ongoing.

All of the patients enrolled in Study 232 (n=50) received at least one dose of perampanel. Forty-two patients completed the core study, and 41 enrolled in extension phase, 8 (19.5%) of whom

have discontinued. Disposition of patients from each study, stratified by age, are summarized below in Table 5 and Table 6.

Study 311 was ongoing at the time of submission of the sNDA, so more patients had been enrolled after the data cutoff. These patients were included in the 120-Day Safety Update. At the time of the data cutoff for the 120-Day Safety Update, a total of 230 patients had received at least one dose of perampanel, 114 had been exposed to the drug for >6 months, and 21 for ≥1 year.

Reviewer's comment: The pediatric patient exposure in the PI will not be the same as that above, as patients < 4 years of age will not be included. Exposure in the PI will be as follows: a total of 225 patients had received at least one dose of perampanel, 110 had been exposed to the drug for >6 months, and 20 for ≥1 year.

The most common reason for discontinuation in both studies was adverse event: 11 patients (6.8%) and 3 patients (6%) in Studies 311 and 232, respectively. Other causes of discontinuation in >3% of patients included lack of efficacy, patient and "other", as seen below. The rate of discontinuation was consistent with that seen in the trials in the adult/adolescent populations. In Study 232, Subj (b) (6) was coded as discontinuing due to lack of efficacy, but a generalized convulsion was the proximate cause for his discontinuation. Therefore, the disposition table has been revised accordingly. Please see Section 8.5.3 for discussion of the discrepancies in the disposition due to adverse events.

Table 5: Disposition of Subjects in the Safety Dataset, Study 311 (core)

	≥4 to <7 Years (N=41) n (%)	≥7 to <12 Years (N=120) n (%)	Total (N=161) n (%)
Not Treated, n (%)	2	8	10
Treated, n (%)	41	120	161
Completed Core Study, n (%)	19 (46.3)	58 (48.3)	77 (47.8)
Discontinued Core Study, n (%)	4 (9.8)	24 (20.0)	28 (17.4)
Ongoing, n (%)	18 (43.9)	38 (31.7)	56 (34.8)
Primary reason for discontinuation, n (%)			
Adverse event	3 (7.3)	8 (6.7)	11 (6.8)
Subject choice	0	7 (5.8)	7 (4.3)
Inadequate therapeutic effect	0	5 (4.2)	5 (3.1)
Lost to follow-up	0	0	0
Withdrawal of consent	1 (2.4)	1 (0.8)	2 (1.2)
Other	0	3 (2.5)	3 (1.9)

Source: Table 14.1.1.5.2, Study 311 CSR

Table 6: Disposition of Subjects in the Safety Dataset, Study 232 (core)

	≥2 to <7 Years (N=22) n (%)	≥7 to <12 Years (N=28) n (%)	Total (N=50) n (%)
Treated, n (%)	22 (100)	28 (100)	50 (100)
Completed Core Study, n (%)	20 (90.9)	22 (78.6)	42 (84.0)
Discontinued Core Study, n (%)	2 (9.1)	6 (21.4)	8 (16.0)
Primary reason for discontinuation, n (%)			
Adverse event	1 (4.5)	2 (7.1)	3 (6.0)
Lost to follow-up	0	1 (3.6)	1 (2.0)
Subject choice	1 (4.5)	0	1 (2.0)
Inadequate therapeutic effect	0	0	0
Withdrawal of consent/assent	0	1 (3.6)	1 (2.0)
Other	0	2 (7.1)	2 (4.0)

Source: Study 232 ADDS (JMP)

8.3.2. Relevant characteristics of the safety population:

In general, the demographic characteristics of the populations were similar between the two studies (Table 7). The most prominent difference in baseline demographics between the two studies was the number of Asian patients: 38.7% in Study 311 and none in Study 232. There was a greater percentage of patients in the younger age cohort in Study 232 (44%) compared to Study 311 (24.8%), although the mean and median ages in the two studies were similar. and more females in Study 311 (47.1%) as compared to Study 232 (32%). The baseline demographics in the extension study populations were generally similar, as well.

Table 7: Baseline Demographics, Studies 311 and 232

Category	Study 311 (N=157)	Study 232 (N=50)
Age (year), n	157	50
Mean (SD)	8.2 (2.13)	7.1 (2.74)
Median	8.0	7.5
Min, Max	4, 11	2, 11
Age group, n (%)		
2 or 4 to <7 years	39 (24.8)	22 (44.0)
7 to <12 years	118 (75.2)	28 (46.0)
Sex, n (%)		
Male	83 (52.9)	34 (68.0)
Female	74 (47.1)	16 (32.0)
Race, n (%)		
White	85 (56.7)	40 (80.0)

Category	Study 311 (N=157)	Study 232 (N=50)
Black or African American	4 (2.7)	6 (12.0)
Japanese	52 (34.7)	0
Other Asian	6 (4.0)	0
American Indian or Alaskan Native	1 (0.7)	0
Other	2 (1.3)	4 (8.0)
Missing	7	
Ethnicity, n (%)		
Hispanic or Latino	11 (7.4)	9 (18.0)
Not Hispanic or Latino	138 (92.6)	41 (82.0)
Missing	8	
Weight (kg), n	157	50
Mean (SD)	29.09 (10.966)	28.82 (14.038)
Median	25.50	24.90
Min, Max	16.1, 64.7	11.9, 85.7
Height (cm), n	156	46
Mean (SD)	127.68 (14.362)	123.47 (19.843)
Median	126.20	121.70
Min, Max	89.6, 157.8	53.5, 152.8
BMI (kg/m2), n	156	46
Mean (SD)	17.312 (3.4165)	18.88 (7.992)
Median	16.499	16.58
Min, Max	10.76, 27.87	14.0, 65.0

Source: Study 311 CSR, Table 14.1.4.1.1.1 and Study 232 CSR, Table 14.1.4.1.1.

With respect to baseline disease characteristics, all patients in both studies were diagnosed with epilepsy using ILAE criteria and EEG. Only patients with POS or PGTCS were enrolled in Study 311, while 16 patients (32%) in Study 232 were diagnosed with an epilepsy syndrome, such as idiopathic focal epilepsy or Lennox-Gastaut syndrome (LGS).

Reviewer's comment: The primary difference between the two studies with respect to underlying disease characteristics was the inclusion of patients with epilepsy syndromes in Study 232. The large majority of patients in both studies had focal or partial onset seizures prior to enrollment: 139 (88.5%) in Study 311 and 42 (84%) in Study 232. Although the PK data to be used to support the expansion of the indication to pediatric patients with POS 4 to <12 years of age included data from patients with primary generalized or other seizure types, these data are not sufficient to support extrapolation of efficacy in PGTCS, as has been conveyed to the Applicant on several occasions. Safety concerns are not expected to be significantly different in the patients with refractory epilepsies other than POS, as these patients are also often on multiple AEDs and have similar epilepsy-related risk factors such as SUDEP.

8.3.3. Adequacy of the safety database:

Based on the characteristics in Table 7, the development program is deemed to provide generally adequate information about the safety of perampanel use in patients with POS 4 to <12 years of age. The primary limitation of the safety data included in this sNDA is that there were no placebo controls for comparison; therefore, the primary assessment of safety remains dependent on data from the placebo-controlled trials in adolescents and adults with POS.

8.4. Adequacy of Applicant's Clinical Safety Assessments

8.4.1. Issues Regarding Data Integrity and Submission Quality

The Applicant did not provide a pooled safety dataset (combined Studies 311 and 232) for analysis. An Information Request (May 24, 2018) was sent requiring a combined safety dataset to the Applicant within 3 weeks. The Applicant responded on May 31, 2018, noting that DNP stated that an Integrated Summary of Safety (ISS) would not be necessary in the pre-sNDA meeting (January 25, 2018), and that based on that response, the Applicant had not prepared integrated datasets. The Applicant stated that completing a pooled dataset within that timeframe would be nearly impossible because the data structures for the studies were different and would require reprogramming to combine the datasets, complicated by the fact that the two studies used different versions of the MedDRA dictionary, requiring a full re-coding of Adverse Events and Concomitant Medications. DNP responded, noting that this information was necessary, and allowing for 6 weeks. The Applicant provided the pooled safety datasets on July 13, 2018.

8.4.2. Categorization of Adverse Events

Adverse events (AEs) were defined similarly in both protocols:

- *Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product*
- *Any new disease or exacerbation of an existing disease*
- *Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that resulted in symptoms, a change in treatment, or discontinuation of study drug*
- *Recurrence of an intermittent medical condition (eg, headache) not present at pretreatment (Baseline)*
- *An abnormal laboratory test result was considered an AE if the identified laboratory*
- *abnormality led to any type of intervention, whether prescribed in the protocol or not.*

All AEs were followed until resolution or for 30 days after the patient's last study visit, whichever came first. Serious adverse events (SAEs) were followed until the event resolved or

the issue stabilized.

For the purpose of the safety analysis, a treatment emergent adverse event (TEAE) was defined as an AE that occurred during treatment, having been absent at baseline, reemerged during treatment, or worsened in severity during treatment compared to baseline (when the AE was continuous).

An SAE was defined in both protocols as *any untoward medical occurrence that at any dose:*

- *Resulted in death*
- *Was life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this did not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)*
- *Required inpatient hospitalization or prolongation of existing hospitalization*
- *Resulted in persistent or significant disability/incapacity*
- *Was a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)*

Reviewer's comment: The adverse event definitions and characterizations are acceptable.

8.4.3. Routine Clinical Tests

In Studies 311 and 232, clinical lab data were collected at screening and throughout the study at various visits. During Study 311 (core), laboratory testing occurred at baseline and at weeks 11, 23, 27, and at early discontinuation. During the extension phase of Study 311, laboratory testing occurred at weeks 40 and 52, as well as at early discontinuation. In Study 232, laboratory tests were obtained at visits 7, 11, and 15 (if follow-up) and at early discontinuation. During the extension phase of Study 311, laboratory testing occurred at weeks 16, 28, 40, 52, and 56, as well as at early discontinuation. A serum pregnancy test was performed on females of child-bearing age at screening, and urine pregnancy tests were performed at all visits.

Clinical laboratory tests in both studies consisted of

- Hematology: RBC, hemoglobin, hematocrit, platelets, and WBC with differential (neutrophils, Bands lymphocytes, monocytes, eosinophils, basophils);
- Serum Chemistry/Hepatic Enzymes: sodium, potassium, HCO2, alkaline phosphatase, AST, ALT, total bilirubin, direct bilirubin, BUN, creatinine, glucose, calcium, albumin, cholesterol, triglycerides, phosphorus, LDH, total protein, globulin, uric acid, CPK, TSH, fT3, free fT4, IGF-1;
- Urinalysis

Vital signs, ECGs, and physical and neurological examinations were performed/collected during

both studies.

8.5. Safety Results

8.5.1. Deaths

One patient had a TEAE that resulted in death during Study 311 (core). Subj (b) (6) was a 4-year-old boy who was receiving 16 mg perampanel. He was found in bed in cardiorespiratory arrest on Study day 68. Resuscitation was unsuccessful. Brain CT revealed cerebral edema and *"A virology test was positive for Influenza A".* A whole-body CT was performed, which revealed *"multiple adenopathies, and thickening of the digestive walls."* An autopsy was performed, which was consistent with *"a subacute infectious process affecting the lungs and myocardium, confirming multiple organ infection with viral myocarditis."* Cause of death was viral myocarditis and was not considered to be related to the study drug.

There were no deaths reported during the entirety of Study 232 or during the extension phase of Study 311.

Reviewer's comment: The single death reported during Studies 311 and 232 does not appear to be related to perampanel and does not raise new clinical concerns.

8.5.2. Serious Adverse Events

A total of 59 serious adverse events (SAEs) were reported in 30 patients (14.5%) overall. A greater percentage of patients in Study 232 (15/50, 30%) experienced an SAE than in Study 311 (15/157, 9.6%). Twenty-three of the 59 SAEs occurred in 18 patients (8.7%) during the long-term extension. SAEs led to discontinuation of treatment in 5 patients (2.4%), one of which was fatal (see Section 8.5.1 above).

Seizures were the most common SAE, occurring in 9 patients (4.3%) overall. The only other SAEs that occurred in more than one patient were gastroenteritis, mental status changes, and status epilepticus, which occurred in 2 patients (1%) each. SAEs are summarized by PT in Table 8 below. Please see Table 9 for a listing of all SAEs by subject. Please see Section 8.5.4 for discussion of SAEs related to behavior (hostility- and aggression-related SAEs).

Reviewer's comment: The SAE rate in pooled Studies 311 and 232 was 14.5%, with the greater incidence occurring in Study 232 (30% vs. 9.6% in Study 311). This SAE rate is greater than that reported in the pooled phase 3 controlled adult/adolescent trials (perampanel 5.5%, placebo 5.0%). As noted by Dr. Mary Doi in her safety review of the original Fycompa NDA for POS, the

treatment emergent SAE rate in the entire epilepsy study pool was 17.3% in all phase 2/3 double blind and OLE epilepsy trials, which is similar to the incidence in pooled Studies 311 and 232. Most patients continued with treatment with only 5 patients (2.4%) withdrawing from the study due to SAE.

As noted above, the most common TESAEs were seizures (4.3%) and thus related to the patients' underlying reason for treatment with perampanel.

In general, the SAEs reported in Studies 311 and 232 are not dissimilar from those reported in the controlled clinical trials of perampanel. Due to the lack of a placebo comparator, and the low numbers of patients experiencing each SAE, no further conclusions on SAEs can be drawn.

Table 8: Incidence of treatment emergent SAEs, Studies 311 and 232

	Overall N=207		Study 311 N=157		Study 232 N=50	
SAE – preferred term	**n**	**%**	**n**	**%**	**n**	**%**
Any SAE	**30**	**14.5%**	**15**	**9.6%**	**15**	**30%**
All seizure (excl. status epilepticus)	9	4.3%	6	3.8%	3	6%
Gastroenteritis	2	1%	1	0.6%	1	2%
Mental status changes	2	1%	0		2	4%
Status epilepticus	2	1%	0		2	4%
Abnormal behavior	1	0.5%	0		1	2%
Acute respiratory failure	1	0.5%	1	0.6%	0	
Aggression	1	0.5%	1	0.6%	0	
Anticonvulsant drug level increased	1	0.5%	0		1	2%
Constipation	1	0.5%	0		1	2%
Cyanosis	1	0.5%	0		1	2%
Cyclic vomiting syndrome	1	0.5%	0		1	2%
Dehydration	1	0.5%	0		1	2%
Dental caries	1	0.5%	1	0.6%	0	
Developmental hip dysplasia	1	0.5%	0		1	2%
Disruptive mood dysregulation disorder	1	0.5%	1	0.6%	0	
Dysarthria	1	0.5%	1	0.6%	0	
Epiphysiolysis	1	0.5%	1	0.6%	0	
Foot deformity	1	0.5%	0		1	2%
Gait disturbance	1	0.5%	1	0.6%	0	
Hyperthermia	1	0.5%	1	0.6%	0	
Hypoglycemia	1	0.5%	0		1	2%
Hypotension	1	0.5%	0		1	2%
Influenza	1	0.5%	1	0.6%	0	
Mastoiditis	1	0.5%	0		1	2%

SAE – preferred term	Overall N=207		Study 311 N=157		Study 232 N=50	
	n	%	n	%	n	%
Muscle contracture	1	0.5%	0		1	2%
Otitis externa	1	0.5%	0		1	2%
Otitis media	1	0.5%	0		1	2%
Otitis media acute	1	0.5%	0		1	2%
Pleural effusion	1	0.5%	0		1	2%
Pneumonia	1	0.5%	0		1	2%
Rasmussen encephalitis	1	0.5%	1	0.6%	0	
Respiratory failure	1	0.5%	0		1	2%
Respiratory syncytial virus bronchiolitis	1	0.5%	0		1	2%
Septic shock	1	0.5%	0		1	2%
Somnolence	1	0.5%	1	0.6%	0	
Upper respiratory tract inflammation	1	0.5%	1	0.6%	0	
Viral myocarditis	1	0.5%	1	0.6%	0	
Vomiting	1	0.5%	1	0.6%	0	

Source: ADAE (AESER, AEDECOD, USUBJID, STUDYID) in JMP

Table 9: Summary of SAEs, Studies 311 and 232

Subj ID Age (y), Sex	Study Phase/ Period of AE Onset	Dose at SAE Onset	Duration of Treatment (Days)	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
Study 311								
(b) (6) 4, M	Core Study/ Maintenance	16 mg	67	Viral Myocarditis	68	Severe/ No	Withdrawn From Study	Fatal
(b) (6) 5, M	Core Study/ Titration	8 mg	56	Hyperthermia	39/41	Mild/ No	Dose Not Changed/ Treatment Given	Resolved
(b) (6) 8, F	Core Study/ Titration	2 mg	108	Petit mal epilepsy	4/7	Severe/ Yes	Dose Reduced/ Treatment Given	Resolved
		2 mg	108	Somnolence	7/20	Moderate/ No	Dose Not Changed/ None	Resolved
		6 mg	108	Petit mal epilepsy	71/75	Severe/ No	Dose Not Changed/ Treatment Given	Resolved
(b) (6) 6, M	Core Study/ Titration	2 mg	22	Epilepsy	2/5	Moderate/ Yes	Dose Not Changed/ None	Resolved
(b) (6) 11, M	Core Study/ Titration	10 mg	158	Aggression	46/50	Moderate/ No	Dose Not Changed/ None	Resolved
(b) (6) 5, M	Core Study/ Maintenance	16 mg	155	Seizure	14345	Moderate/ No	Dose Not Changed/ Treatment Given	Resolved
(b) (6) 8, F	Core Study/ Titration	4 mg	53	Epiphysiolysis	20/--	Severe/ No	Dose Not Changed/ None	Resolving
(b) (6) 4, M	Core Study/ Maintenance	7 mg/5	98	Gait disturbance	102/--	Moderate/ Yes	Drug Withdrawn/ Withdrawn From Study	Resolving
		7 mg/5	98	Dysarthria	102/--	Moderate/ Yes	Drug Withdrawn/ Withdrawn From Study	Resolving
		7 mg/5	98	Seizure	10209	Moderate/ Yes	Drug Withdrawn/ Withdrawn From Study	Resolved
(b) (6) 8, M	Core Study/ Titration	12 mg	48	Disruptive mood dysregulation disorder	38/--	Severe/ Yes	Drug Withdrawn/ Withdrawn From Study	Not Resolved

Subj ID Age (y), Sex	Study Phase/ Period of AE Onset	Dose at SAE Onset	Duration of Treatment (Days)	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
(b) (6) 11, M	Core Study/ Titration	2 mg	34	Rasmussen encephalitis	31/--	Moderate/ No	Drug Withdrawn/ Multiple	Not Resolved
(b) (6) 9, F	Core Study/ Maintenance	12 mg	154	Epilepsy	15152	Moderate/ No	Dose Not Changed/ Treatment Given	Resolved
	Pre- Treatment		154	Epilepsy	–19/–18	Moderate/ No	Not Applicable/ None	Resolved
	Extension/ Maintenance	12 mg	154	Epileptic seizure	168/169	Moderate/ No	Dose Not Changed/ Treatment Given	Resolved
		12 mg	154	Epileptic seizure	192/193	Moderate/ No	Dose Not Changed/ Treatment Given	Resolved
(b) (6) 5, F	Core Study/ Maintenance	10 mg	154	Dental caries	13484	Moderate/ No	Dose Not Changed/ None	Resolved
	Extension/ Maintenance	10 mg	154	Influenza	183/--	Moderate/ No	Dose Not Changed/ None	Not Resolved
(b) (6) 5, M	Core Study/ Titration	4 mg	54	Acute respiratory failure	20/25	Moderate/ No	Dose Not Changed/ None	Resolved
		4 mg	54	Upper respiratory tract inflammation	33/43	Moderate/ No	Dose Not Changed/ None	Resolved
(b) (6) 10, F	Core Study/ Maintenance	12 mg	161	Gastroenteritis	99/102	Severe/ No	Dose Not Changed/ Treatment Given	Resolved
	Core Study/ Titration	4 mg	161	Gastroenteritis	14/36	Severe/ No	Dose Not Changed/ Treatment Given	Resolved
	Extension/ Maintenance	12 mg	161	Vomiting	187/220	Severe/ No	Dose Not Changed/ Treatment Given	Resolved
(b) (6) 7, F	Follow-Up	2 mg	20	Seizure cluster	45/46	Moderate/ No	Not Applicable/ Treatment Given	Resolved
Study 232								
(b) (6) 6, M	Titration	0.1 mg	75	Mental status changes	29/32	Severe/NR	Drug interrupted/ Treatment given	Resolved

Subj ID Age (y), Sex	Study Phase/ Period of AE Onset	Dose at SAE Onset	Duration of Treatment (Days)	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
(b) (6) 2, M	Titration	0.16 mg	55	Respiratory syncytial virus bronchiolitis	44/48	Moderate/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 11, F	Follow-up	0.18 mg	78	Hypoglycaemia	79/300	Moderate/Poss	Dose not changed/ Treatment given	Resolved
(b) (6) 5, M	Maintenance	0.17 mg	79	Developmental hip dysplasia	61/315	Severe/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 11, M	Titration	0.01 mg	6	Abnormal behaviour	6/7	Severe/Poss	Drug withdrawn/ Withdrawn from study	Resolved
(b) (6) 7, M	Maintenance	0.15 mg	77	Convulsion	61/66	Moderate/NR	Dose not changed/ Treatment given	Resolved
		0.15 mg	77	Gastroenteritis	64/66	Moderate/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 8, M	Titration	0.08 mg	82	Pneumonia	34/49	Moderate/NR	Dose not changed/ Treatment given	Resolved
		0.08 mg	82	Respiratory failure	34/49	Severe/NR	Dose not changed/ Treatment given	Resolved
		0.08 mg	82	Septic shock	35/38	Moderate/NR	Dose not changed/ Treatment given	Resolved
		0.09 mg	82	Hypotension	36/49	Moderate/NR	Dose not changed/ Treatment given	Resolved
		0.09 mg	82	Pleural effusion	37/49	Moderate/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 11, M	Titration	0.16 mg	77	Otitis externa	43/58	Severe/NR	Dose not changed/ Treatment given	Resolved
		0.16 mg	77	Otitis media acute	43/58	Severe/NR	Dose not changed/ Treatment given	Resolved
		0.16 mg	77	Mastoiditis	44/58	Severe/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 4, M	Extension/ Maintenance	0.183 mg	524	Convulsion	341/346	Severe/NR	Dose not changed/ Treatment given	Resolved

Subj ID Age (y), Sex	Study Phase/ Period of AE Onset	Dose at SAE Onset	Duration of Treatment (Days)	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
		0.183 mg	524	Cyclic vomiting syndrome	356/359	Moderate/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 11, F	Extension/ Maintenance	0.192 mg	364	Hypoglycaemia	79/300	Moderate/Poss	Dose not changed/ Treatment given	Resolved
(b) (6) 2, M	Extension/ Maintenance	0.195 mg	364	Otitis media	267/267	Severe/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 5, M	Core Study/ Maintenance	0.193 mg	365	Developmental hip dysplasia	61/315	Severe/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 11, M	Extension/ Maintenance	0.131 mg	373	Status epilepticus	262/263	Severe/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 3, M	Extension/ Maintenance	0.161 mg	189	Constipation	10310	Severe/Poss	Dose not changed/ None	Resolved
(b) (6) 7, M	Core Study/ Maintenance	0.156 mg	229	Convulsion	61/66	Moderate/NR	Dose not changed/ Treatment given	Resolved
		0.143 mg	229	Gastroenteritis	64/66	Moderate/NR	Dose not changed/ Treatment given	Resolved
	Extension/ Maintenance	0.143 mg	229	Convulsion	82/33	Moderate/Poss	Dose not changed/ Treatment given	Resolved
		0.143 mg	229	Gastroenteritis	84/86	Moderate/NR	Dose not changed/ None	Resolved
		0.143 mg	229	Convulsion	84/86	Moderate/Poss	Dose not changed/ Treatment given	Resolved
		0.143 mg	229	Gastroenteritis	13234	Moderate/NR	Dose not changed/ Treatment given	Resolved
		0.143 mg	229	Convulsion	13234	Moderate/NR	Dose not changed/ Treatment given	Resolved
		0.143 mg	229	Dehydration	13236	Moderate/NR	Dose not changed/ Treatment given	Resolved
		0.143 mg	229	Anticonvulsant drug level incr	14748	Mild/NR	Dose not changed/ None	Resolved

Subj ID Age (y), Sex	Study Phase/ Period of AE Onset	Dose at SAE Onset	Duration of Treatment (Days)	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Severity/ Relationship to Study Drug	Study Drug Action Taken/ Other Action Taken	Outcome
		0.143 mg	229	Dehydration	14748	Moderate/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 10, M	Extension/ Maintenance	0.197 mg	367	Muscle contracture	179/266	Mild/NR	Dose not changed/ Treatment given	Resolved
		0.197 mg	367	Foot deformity	179/266	Mild/NR	Dose not changed/ Treatment given	Resolved
(b) (6) 9, F	Extension/ Maintenance	0.177 mg	359	Status epilepticus	378/379	Severe/NR	Not applicable/ Treatment given	Resolved
(b) (6) 4, F	Extension/ Maintenance	0.091 mg	276	Cyanosis	202/203	Moderate/Poss	Dose not changed/ None	Resolved
		0.091 mg	276	Convulsion	202/203	Moderate/Poss	Dose not changed/ None	Resolved
		0.091 mg	276	Mental status changes	202/203	Moderate/Poss	Dose not changed/ None	Resolved
(b) (6) 8, F	Extension/ Maintenance	0.023 mg	119	Aggression	98/-	Moderate/Prob	Drug withdrawn/ Multiple	Not resolved
		0.023 mg	119	Suicidal ideation	11111	Severe/Poss	Drug withdrawn/ Withdrawn from study	Resolved

Source: Tables 2.7.4-35, 2.7.4-37, and 2.7.4-42 SCS and Table 14.3.2.2.4, CSR Study 311

8.5.3. Dropouts and/or Discontinuations Due to Adverse Effects

As seen in Table 10 below, a total of 24 patients (11.6%) experienced 38 adverse events leading to withdrawal from study participation during the core and extensions phases of both studies, 15 (10%) in Study 311 and 9 (18%) in Study 232. This rate differs slightly from that reported by the applicant in the SCS and in the CSRs for both studies. The data used to calculate the discontinuation rate due to AEs was derived from the SDTM datasets for each study, as well as listings from the CSR for each study and confirmed on review of the patients' disposition CRFs. The single study period in which discontinuations due to adverse events most commonly occurred was the titration period (14/24, 58.3%) with more of these patients in Study 311 (n=11) than in Study 232 (n=3).

A total of 38 adverse events led to discontinuation in these 24 patients, with several patients experiencing more than one AE leading to withdrawal from the study. AEs leading to discontinuation which occurred in more than one patient included irritability (n=4, 1.9%), seizure/convulsion (n=4, 1.9%), aggression (n=3, 1.4%), and gait disturbance (n=2, 1%). The rest of the events occurred in one patient each. Psychiatric events leading to discontinuation were notable, with 17 events occurring in 12 patients. Please see Section 8.5.4 for further discussion of these events. Eleven AEs leading to discontinuation in 8 patients had not resolved as of the time of the data cutoff.

Reviewer's comment:
The discontinuation rate due to adverse events during the core studies in the Applicant's submission differs from the rate I identified during my review. Based on the listings and disposition dataset (SDTM/DS), 14 patients (8.8%) not 11 (7.8%) in Study 311 and 3 (6%) not 2 (4%) of patients in Study 232 discontinued due to an adverse event. The reason for these discrepancies is not clear, but most likely the primary reason was miscoded as lack of efficacy or withdrawal of consent. The differences between the rates identified by the Applicant that those identified by me are small and do not impact the final conclusions.

The discontinuation rate for pediatric patients in the uncontrolled PK and safety studies was 11.6%, slightly higher than the rate in the treated patients the controlled phase 2 and phase 3 epilepsy trials (8.4%). Most of the AEs leading to discontinuation in Studies 311 and 232 were reported as AEs in the controlled epilepsy trials in adults and adolescents. Several of the AEs causing discontinuation in Studies 311 and 232 also caused patients to withdraw from the controlled epilepsy trials (including suicidal ideation, aggression, anger, seizure, and irritability).

The discontinuations due to AEs more commonly occurred early in the treatment, rather than later with 58% occurring during the titration period. Discontinuation of treatment during titration due to adverse events is a common occurrence with AEDs and is not excessive in

these Studies 311 and 232.

The rate of discontinuation due to AEs and the types of AEs that led to withdrawal from the studies were similar to those in the controlled epilepsy trials. Any further conclusions cannot be drawn because of the lack of a placebo comparator in Studies 311 and 232.

Table 10: Adverse events leading to discontinuation, Studies 311 and 232

Subj ID Age (y), Sex	Study Phase/ Period of AE Onset	Dose/Days Since Last Dose to AE Onset	Treatment Duration (Days)	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Serious	Severity/ Relationship to Study Drug	Outcome
(b) (6) 8, F	Core Study/ Maintenance	8 mg/1	108	Balance Disorder	78/130	No	Severe/ Yes	Resolved
(b) (6) 4, M	Core Study/ Titration	8 mg / 2	67	Viral myocarditis	68/68	Yes	Severe/ No	Fatal
(b) (6) 8, M	Core Study/ Titration	2 mg / 1	10	Aggression	13/14	No	Moderate/ Yes	Resolved
		2 mg / 1	10	Anger	13/14	No	Moderate/ Yes	Resolved
		2 mg / 1	10	Anxiety	13/14	No	Moderate/ Yes	Resolved
(b) (6) 11, M	Core Study/ Titration	4 mg / 1	34	Dizziness	14/36	No	Mild/ Yes	Resolved
		2 mg / 1	34	Rasmussen's encephalitis	31/--	Yes	Moderate/ No	Not Resolved
(b) (6) 8, F	Core Study/ Titration	4 mg / 1	54	Drug eruption	53/80	No	Moderate/ Yes	Resolved
(b) (6) 6, F	Core Study/ Titration	6 mg / 1	56	Irritability	37/45	No	Mild/ Yes	Resolved
(b) (6) 8, M	Core Study/ Titration	14 mg / 1	138	Bradyphrenia	64/--	No	Mild/ Yes	Not Resolved
(b) (6) 11, M	Core Study/ Titration	6 mg / 1	86	Seizure	72/79	No	Moderate/ Yes	Resolved
(b) (6) 6, F	Core Study/ Maintenance	6 mg / 1	100	Irritability	38/--	No	Mild/ Yes	Not Resolved
(b) (6) 4, M	Core Study/ Maintenance	7 mg / 5	98	Gait disturbance	102	Yes	Moderate/ Yes	Resolving
		7 mg / 5	98	Dysarthria	102	Yes	Moderate/ Yes	Resolving

Subj ID Age (y), Sex	Study Phase/ Period of AE Onset	Dose/Days Since Last Dose to AE Onset	Treatment Duration (Days)	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Serious	Severity/ Relationship to Study Drug	Outcome
(b) (6) 11, M		7 mg / 5	98	Seizure	102/109	Yes	Moderate/ Yes	Resolved
	Core Study/ Titration	4 mg / 1	36	Irritability	9/38	No	Mild/ Yes	Resolved
(b) (6) 8, M	Core Study/ Titration	12 mg / 1	48	Disruptive mood dysregulation disorder	38/--	Yes	Severe/ Yes	Not Resolved
(b) (6) 10, F	Core Study/ Titration	8 mg / 1	72	Cognitive disorder (cognitive slowing)	65/86	No	Mild/ Yes	Resolved
		8 mg / 1	72	Mood altered	22/87	No	Mild/ Yes	Resolved
(b) (6) 11, F	Core Study/ Titration	2 mg / 1	51	Seizure	8/55	No	Moderate/ Yes	Resolved
(b) (6) 8, F	Extension/ Maintenance	16 mg / 1	213	Ataxia	206/--	No	Mild/ Yes	Not Resolved
(b) (6) 11, M	Core Study/ Titration	0.01 mg/kg / 0	6	Abnormal behavior (suicidal ideation?)	6/7	Yes	Severe/ Possible	Resolved
(b) (6) 7, M	Core Study/ Titration	0.02 mg / 1	4	Emotional distress	3/6	No	Moderate/ Yes	Resolved
		0.02 mg / 1	4	Psychomotor hyperactivity	3/8	No	Moderate/ Yes	Resolved
		0.02 mg / 1	4	Irritability	3/10	No	Moderate/ Yes	Resolved
		0.02 mg / 1	4	Tremor	3/10	No	Moderate/ Yes	Resolved
		0.02 mg / 1	4	Gait disturbance	4/5	No	Mild/ Yes	Resolved
(b) (6) 6, M	Core Study/ Titration	0.05 mg / 1	41	Grand mal convulsion	41/42	No	Mild/ Yes	Resolved
(b) (6) 8, F	Extension/ Maintenance	0.023 mg/kg / 1	119	Aggression	98/--	No	Moderate/ Yes	Not Resolved

Subj ID Age (y), Sex	Study Phase/ Period of AE Onset	Dose/Days Since Last Dose to AE Onset	Treatment Duration (Days)	MedDRA Preferred Term	Study Day SAE Started/ Stopped	Serious	Severity/ Relationship to Study Drug	Outcome
		0.023 mg/kg / 1	119	Suicidal Ideation	111/111	No	Severe/ Yes	Resolved
(b) (6) 3, M	Extension/ Maintenance	0.177 mg/kg / 1	189	Gingival recession	176/--	No	Moderate/ Possibly	Not Resolved
		0.177 mg/kg / 1	189	Oral mucosal discoloration	176/--	No	Moderate/ Possibly	Not Resolved
(b) (6) 5, M	Extension/ Follow-up	0.129 mg/kg	94	Incoherent	195/195	No	Mild/ No	Resolved
(b) (6) 11, M	Extension/ Maintenance	0.191 mg/kg / 1	271	Blood alkaline phosphatase increased	245/--	No	Mild/ Possibly	Not Resolved
		0.191 mg/kg / 1	271	Total bile acids increased	245/--	No	Mild/ Possibly	Not Resolved
		0.191 mg/kg / 1	271	Urine bilirubin increased	245/--	No	Mild/ Possibly	Not Resolved
(b) (6) 4, F	Extension/ Maintenance	0.091 mg/kg / 1	276	Lethargy	275/293	No	Moderate/ Probable	Resolved
(b) (6) 3, M	Extension/ Maintenance	0.094 mg/kg / 1	281	Aggression	233/--	No	Moderate/ Probable	Resolving

Source: SDTM DS (JMP), Listing 16.2.7.1 in CSR S31, Listing 16.2.7.1 CSR Study 232 (core), Listing 16.2.1.1, CSR Study 232 (ext), review of relevant CRFs

8.5.4. Significant Adverse Events and Submission Specific Issues

The Applicant specifically analyzed the data for adverse events of special interest during both studies. These AEs were predefined as those related to abuse, dependence, or withdrawal; hostility/aggression; cognition; suicidality; and falls.

TEAEs Related to Hostility/Aggression

During the controlled POS trials, patients on perampanel experienced more hostility- and aggression-related adverse reactions compared to patients who received placebo. Therefore, TEAEs related to hostility and aggression were examined using narrow and broad SMQ searches. The Applicant's broad search identified the following TEAEs (irritability, aggression, agitation, laceration, psychomotor hyperactivity, abnormal behavior, anger, affect lability, defiant behavior, disruptive mood dysregulation disorder, oppositional defiant disorder, and personality change). Laceration was excluded from the analysis below, as it is difficult to lacerations are commonly experienced by patients with seizures and it is difficult to differentiate the underlying cause of the laceration.

Overall, 92 hostility- and aggression-related TEAEs were reported in 65 (31.4%) patients. The most common TEAEs in this category were irritability (27 patients, 13%), aggression (21 patients, 10%), agitation (10 patients, 4.8%), and abnormal behavior (6 patients, 2.9%). The other events occurred in 5 or fewer patients (Table 11 below). Overall incidence and incidences of most of the TEAEs were greater in Study 232 than in Study 311. The reason for this difference is unclear but is likely due to the small sample size in Study 232.

Table 11: TEAEs related to Hostility or Aggression, pooled Studies 311 and 232

	Overall N=207		Study 311 N=157		Study 232 N=50	
Hostility/Aggression TEAEs (by PT)	n	%	n	%	n	%
All Hostility/Aggression TEAEs	65	31.4%	45	28.7%	20	40%
Irritability	27	13%	18	11%	9	18%
Aggression	21	10%	13	8.3%	8	16%
Agitation	10	4.8%	8	5.1%	2	4%
Abnormal behavior	6	2.9%	3	1.9%	3	6%
Psychomotor hyperactivity	5	2.4%	3	1.9%	2	4%
Oppositional defiant disorder	4	1.9%	1	0.6%	3	6%
Anger	3	1.4%	2	1.3%	1	2%
Affect lability	1	0.5%	1	0.6%	0	0%
Defiant behavior	1	0.5%	1	0.6%	0	0%
Disruptive mood dysregulation disorder	1	0.5%	1	0.6%	0	0%
Personality change	1	0.5%	1	0.6%	0	0%

Source: Pooled safety dataset, ADAE ([STUDYID, USUBJID, AEDECOD] by AEDECOD), excluding Laceration (denominator, total safety population)

Two-thirds of the events occurred in the older patients (≥7 years of age), and one third in the younger patients (<7 years). This finding, although complicated by the lack of a control group and small population, suggests that these behavioral effects may be more prominent in older children than younger ones.

Three of the events were SAEs (aggression, abnormal behavior, and disruptive mood dysregulation disorder), 2 of which led to discontinuation:

- Subj (b) (6) is an 11 year-old male with POS on lacosamide, rufinamide, clonazepam, zonisamide, diazepam, and VNS and a history of abnormal behavior, cognitive disorder, and oppositional defiant disorder. On day 6, he experienced an SAE of abnormal behavior at titration dosage 0.01 mg. It was reported that he ran into the street in front of cars. After he was brought home, he ran into the house and threatened to kill himself with a butcher knife. The knife was confiscated and he began to 'trash the house.' This was a new behavior. The mother reported that during previous outbursts, the subject would get angry and run away but returned home within a few minutes. The study drug was withdrawn due to this event (abnormal behavior). The SAE resolved on Study Day 7.
- Subj (b) (6) 8 year-old with POS and a history of disruptive mood dysregulation disorder, abnormal behavior, and oppositional defiant disorder on oxcarbazepine and risperidone. On Study Day 38, at titration dosage 24 mL PO QD perampanel, he experienced worsening of disruptive mood dysregulation disorder. He was hospitalized due to increased anger and aggression, and the perampanel was decreased to 20 mg PO on Study Day 44. He was discontinued from the drug and the study due to the event of disruptive mood dysregulation disorder on Study Day 48. The event of disruptive mood dysregulation disorder was ongoing at the time of study discontinuation. The investigator classified the event of disruptive mood dysregulation disorder to be related to the study drug.

Five of these 65 patients (7.7%) experienced 5 severe behavioral TEAEs: abnormal behavior in 2 patients, and aggression, agitation, and disruptive mood dysregulation disorder in 1 patient each. Thirty-two patients (53.3%) experienced 41 moderate TEAEs, and 42 patients (70%) had a total of 47 mild events. Most of the events resolved, with only one reported as ongoing (disruptive mood dysregulation disorder).

Eleven of the 92 hostility- and aggression-related TEAEs (12%) led either singly or in combination to discontinuation in 9 patients (13.8%). Twenty-four patients (36.9%) had their perampanel dose reduced due to 36 events (39.1%), and 35 patients (53.8%) experienced 44 events (47.8%) leading to no change in the perampanel dosing. One patient (1.5%) experienced aggression during down-titration of the perampanel in the follow-up period. Down-titration was continued with no other action; thus, this patient is not included in the above dose adjustment categories.

Reviewer's comment: The overall incidence of hostility and aggression TEAEs in the 2

uncontrolled studies was 32%, notably greater than that seen in the controlled adult/adolescent epilepsy studies (14.5%). Five of these events were serious, and five were deemed to be severe. Nine patients discontinued the drug due to hostility or aggressive events, which was 37.5% of the total number of patients who discontinued due to AEs. The incidence of hostility and aggression related TEAEs was greater in Studies 311 and 232 than in the controlled POS trials; however, because of the lack of a controlled comparator, it is difficult to generate any significant conclusions about these data. In general, these data so not raise any new clinical concerns and support the box warning in the currently approved PI.

Adverse Events Related to Abuse Potential

A total of 3 patients overall experienced AEs that the Applicant deemed possibly related to abuse potential. In Study 311, 3 patients reported accidental overdose. None of the patients were withdrawn from the study drug as a result of the accidental overdose and all patients recovered completely. The concurrent AEs reported in these patients include irritability, somnolence, and balance disorder.

Adverse Events Related to Rash

Overall, 29 (14%) patients experienced TEAEs related to any type of rash. The most common TEAEs related to rash were rash (8 [3.9%] patients), eczema (5 [2.4%] patients), contact dermatitis (5 [2.4%] patients), and urticaria (5 [2.4%] patients). The other TEAEs related to rash were dermatitis, dermatitis diaper, erythema, rash papular (each reported in 2 patients), and drug eruption, viral rash (each in 1 patient). TEAEs related to rash are presented in Table 12. One patient discontinued the study drug and withdrew from the study due to rash (drug eruption). No patient reported an SAE related to rash.

Table 12: All rash TEAEs, pooled Studies 311 and 232

	Overall (N=207)		Study 311 (N=157)		Study 232 (N=50)	
AEDECOD	n	%	n	%	n	%
All rash types	29	14%	17	10.8%	12	24%
Rash	8	3.9%	5	3.2%	3	6%
Eczema	5	2.4%	3	1.9%	2	4%
Urticaria	5	2.4%	3	1.9%	2	4%
Dermatitis contact	4	1.9%	1	0.6%	3	6%
Erythema	2	1%	1	0.6%	1	2%
Rash papular	2	1%	1	0.6%	1	2%
Rash maculopapular	1	0.5%	1	0.6%	0	
Dermatitis	1	0.5%	1	0.6%	0	
Dermatitis diaper	1	0.5%	1	0.6%	0	
Drug eruption	1	0.5%	1	0.6%	0	

Source: ADAE (pooled dataset)

Reviewer's comment: The incidence of rash of any type in Studies 311 and 232 is somewhat greater than in the controlled POS trial. Only one patient discontinued the drug due to rash and no rash-related SAEs were reported. Any conclusions as to increased likelihood of rash in children on perampanel as compared to adolescents or adults cannot be made due to the lack of a placebo comparator in Studies 311 and 232. No new clinical concerns are raised by the rash-related TEAEs.

Adverse Events Related to Suicidality

The Applicant used the following PTs to identify TEAEs related to suicidal ideation and behavior: completed suicide, depression suicidal, intentional overdose, intentional self-injury, poisoning deliberate, self-injurious behavior, self-injurious ideation, suicidal behavior, suicidal ideation, suicide attempt. Four patients (1.9%) reported 5 TEAEs related to suicidality (PT of suicidal ideation). No patient reported a suicidality-related SAE. One patient discontinued perampanel due to a severe suicidality TEAE (see below)

- Subject (b) (6) in Study 311 reported two separate episodes of suicidal ideation. After the first episode, his dose was decreased from 10 mg to 8 mg at the time of the first event and not changed after the second episode. The first episode resolved and the second was ongoing at the time of data cutoff (extension phase). Suicidal thinking for this patient was identified through Columbia-Suicide Severity Rating Scale (C-SSRS) questionnaire. These TEAEs were categorized as mild and considered related to the study drug by the investigator.
- Subject (b) (6) in Study 232 (core) developed suicidal ideation and behavior which was characterized as mild and did not lead to dose adjustment or drug discontinuation. The event was not an SAE and resolved without sequelae.
- Subject (b) (6) developed suicidal ideation on Study Day 226 (0.197 mg/kg). The event was classified as mild and nonserious. The study drug was temporarily interrupted due to this event, and no treatment was reported. The event resolved on Study Day 227.
- Subject (b) (6) in Study 232 (extension) experienced suicidal ideation on Study Day 111 (dosage 0.023 mg/kg. The event was classified as severe and nonserious. The study drug was discontinued in response to this event. No treatment was reported, and the event resolved on the same day (Study Day 111).

Reviewer's comment: Four patients developed suicidal ideation during these uncontrolled studies. This rate of 1.9% is notably greater than the incidence in the controlled POS trials (0.3%). While this incidence is greater, the lack of a concurrent control group for comparison and the overall small sample size make it difficult to draw any conclusion with respect to a greater incidence in the younger pediatric population. The PI for Fycompa currently contains a warning about suicidality, as AEDs in general have been linked with an increased risk of suicidal thoughts or behavior in patients taking these drugs for any indication. The findings in

Studies 311 and 232 do not raise new concerns at this point and support the current warning in the PI.

8.5.5. Treatment Emergent Adverse Events and Adverse Reactions

Treatment emergent adverse events (TEAEs) occurred in 177/207 (85.5%) of patients in the pooled safety database. A summary of the percentages of subjects with TEAEs that occurred in at least 2% of patients overall are presented in Table 13 below. The most frequently reported TEAEs were in the system organ classes (SOC) of nervous system disorders, infections and infestations, and psychiatric disorders, all of which are commonly reported in this patient population.

The most common TEAEs in Studies 311 and 232 were somnolence/sedation and nasopharyngitis, which occurred in 24% and 19% of patients, respectively. TEAEs that occurred in at least 5% of patients in the pooled dataset were somnolence and sedation, somnolence, nasopharyngitis/pharyngitis, pyrexia, rash, ataxia/balance disorder/gait disturbance, irritability, dizziness and vertigo, vomiting, all upper respiratory tract infection, aggression/anger, aggression, all seizures, fatigue, headache, diarrhea, weight increased, gastroenteritis, ear infection, increased appetite, and insomnia.

As noted by the Applicant in the submission, these findings may represent an underestimation of TEAEs since the studies were ongoing at time of data cutoff. When the pooled data was analyzed with inclusion of 23 more patients in Study 311, the AE incidence rates were slightly greater, but raised no new clinical concerns.

Reviewer's comment: In general, the frequently reported TEAEs are consistent both with commonly observed illnesses in this age population and TEAEs observed in the trials in adults and adolescents.

Table 13: TEAEs in ≥2% of patients, Studies 311 and 232

Treatment-emergent Adverse Event (Preferred Term)	Overall N=207		Study 311 N=157		Study 232 N=50	
	n	%	n	%	n	%
Any TEAE	**177**	**85.5%**	**128**	**81.5%**	**49**	**98%**
Somnolence and Sedation	49	23.7%	40	25.5%	9	18%
Somnolence	47	22.7%	39	25%	8	16%
Nasopharyngitis	39	18.8%	33	21.0%	6	12%
Pyrexia	31	15%	14	8.9%	17	34%
Rash	28	13.5%	16	10.2%	12	24%

Treatment-emergent Adverse Event (Preferred Term)	Overall N=207		Study 311 N=157		Study 232 N=50	
	n	%	n	%	n	%
Ataxia/Balance disorder/ Gait disturbance	27	13%	19	12.1%	8	16%
Gait disturbance	10	4.8%	7	4.5%	3	6%
Ataxia	9	4.3%	7	4.5%	2	4%
Balance disorder	8	3.9%	5	3.2%	3	6%
Irritability	27	13%	18	11.5%	9	18%
Dizziness and vertigo	27	13%	21	13.3%	6	12%
Vomiting	26	12.6%	15	9.6%	11	22%
All upper respiratory tract infection	26	12.6%	14	8.9%	12	24%
Aggression/Anger	24	11.5%	15	9.6%	9	18%
Aggression	21	10.1%	13	8.3%	8	16%
All seizures*	23	11.1%	16	10.2%	7	14%
Status epilepticus	4	1.9%	2	1.3%	2	4%
Ear infection	21	10.1%	4	2.5%	17	34%
Fatigue	18	8.7%	9	5.7%	9	18%
Pharyngitis	18	8.7%	11	7.0%	7	14%
Headache	16	7.7%	11	7%	5	10%
Diarrhea	13	6.3%	8	5.1%	5	10%
Abdominal pain	13	6.3%	6	3.8%	7	14%
Weight increased	12	5.8%	7	4.5%	5	10%
Gastroenteritis	12	5.8%	8	5.1%	4	8%
Increased appetite	11	5.3%	6	3.8%	5	10%
Insomnia	11	5.3%	6	3.8%	5	10%
Agitation	10	4.8%	8	5.1%	2	4%
Cough	10	4.8%	4	2.5%	6	12%
Decreased appetite	9	4.3%	5	3.2%	4	8%
Lethargy	9	4.3%	2	1.3%	7	14%
Rhinorrhea	9	4.3%	5	3.2%	4	8%
Anxiety	8	3.9%	5	3.2%	3	6%
Constipation	8	3.9%	5	3.2%	3	6%
Nausea	8	3.9%	4	2.5%	4	8%
Weight decreased	7	3.4%	4	2.5%	3	6%
Influenza	7	3.4%	5	3.2%	2	4%
Rhinitis	7	3.4%	5	3.2%	2	4%
Abnormal behavior	6	2.9%	3	1.9%	3	6%
Disturbance in attention	6	2.9%	6	3.8%	0	
Urinary incontinence	6	2.9%	6	3.8%	0	
Sinusitis	6	2.9%	3	1.9%	3	6%
Bradyphrenia	5	2.4%	5	3.2%	0	
Eczema	5	2.4%	3	1.9%	2	4%
Fall	5	2.4%	2	1.3%	3	6%
Psychomotor hyperactivity	5	2.4%	3	1.9%	2	4%

Treatment-emergent Adverse Event (Preferred Term)	Overall N=207		Study 311 N=157		Study 232 N=50	
	n	%	n	%	n	%
Toothache	5	2.4%	4	2.5%	1	2%

Source: Pooled dataset, ADAE (JMP), TEAE flag
*All seizures include the following preferred terms: Seizure, Status epilepticus, Epilepsy, Petit mal epilepsy, Seizure cluster, Atonic seizures, Generalized tonic-clonic seizure

TEAEs Resulting in Discontinuation or Dosage Adjustment

TEAEs resulting in interruption of the study drug or dose adjustment were reported in 90 (43.5%) patients. Seventy-two patients (35%) had their dose reduced due to a TEAE, 24 (12%) had the drug withdrawn in response to a TEAE and 2 patients each (1%) had their dose increased or the dosing temporarily interrupted due to TEAEs.

The TEAEs most commonly resulting in reduction of study drug dose are summarized in Table 14 below. The most common TEAEs leading to decrease in dose were related to aggression and anger, occurring in 23 patients (11.1%), followed closely by somnolence/sedation (21 [10.1%] patients). Please see Section 8.5.3 for discussion of AEs leading to discontinuation of the drug.

Table 14: Most common TEAEs leading to dosage reduction (≥2% patients), pooled Studies 311 and 232

TEAE by PT	Overall (N=207)	
	n	%
Aggression/Anger/Agitation/Irritability	23	11.1%
Irritability	9	4.3%
Aggression	8	3.9%
Agitation	5	2.4%
Somnolence/Sedation	21	10.1%
Somnolence	19	9.2%
Dizziness/Vertigo	12	5.3%
Balance disorder/Gait disturbance/Ataxia	10	4.8%
Fatigue	8	3.9%

Source: ADAE (JMP)

Reviewer's comment: The TEAEs leading to reduction of the perampanel dose during Studies 311 and 232 are adverse reactions/events that have been associated with AEDs in general and were reported in the controlled POS trials. No further conclusions can be drawn, and these findings raise no new clinical concerns.

8.5.6. 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 patients had AST/ALT ≥ 2x upper limit of normal (ULN) or met criteria for Hy's law. A few patients had elevated bilirubin > 2x ULN. There were no TEAEs related to elevated liver function tests reported.

Eight patients (3.9%) developed hematologic abnormalities (7 with low neutrophil count and 1 with low platelet count). All of these patients recovered completely, and none had the perampanel discontinued due to the lab findings.

Reviewer's comment: There was no evidence of any new safety concerns in the laboratory data. Potentially clinically significant low neutrophil counts were reported in 2.2% of patients in the controlled POS trials. Review of the laboratory data included in the 120-day safety update did not identify any safety signal in laboratory testing.

8.5.7. Vital Signs

Vital signs and weight were collected at all visits, including the early termination and final visits. Mean systolic blood pressure (SBP), diastolic blood pressure (DBP), and heart rate were analyzed by mean change from baseline for each study, and vital signs were also reviewed for markedly abnormal values. Overall, mean systolic and diastolic BP, body temperature, pulse rate, and respiratory rate were within the normal range and similar at baseline and end-of-study for the core phases of both studies.

No TEAEs were reported for changes in blood pressure, pulse or respiratory rate. Of note, 16.4% of patients reported a TEAE of pyrexia, primarily in the setting of illness.

Reviewer's comment: Analysis of vital signs data did not raise any new clinical concerns.

Weight

In Study 311, 66 patients (42%) had a >7% increase in weight, while 8 patients (5.1%) experienced a >7% decrease in weight as compared to baseline. In Study 232, 5 patients (10%) had a >7% decrease in weight, while 33 patients (66%) had a >7% increase in weight compared to baseline. Most of the clinically significant weight gain was reported at ≥28 weeks.

Reviewer's comment: It is difficult to generate any meaningful conclusions from the weight data, other than to state that some patients may gain weight and some may lose weight. Longer exposure may lead to greater changes in weight, but the long-term data is confounded

by the fact that patients were not specifically restricted to perampanel monotherapy, and other AEDs have been linked to weight changes. Additionally, weight gain was reported in the controlled POS trials and is included in the PI.

8.5.8. Electrocardiograms (ECGs)

In Study 311, ECGs were performed at baseline, end of maintenance period (week 23), follow-up (week 27, if not transitioning to the LTE phase), week 52 (end of LTE), and early termination. During Study 232, ECGs were obtained at baseline, weeks 3, 7, 11, 15, 28, 52, and at early termination.

There were no changes of clinical importance in mean ECG parameters over time in either study. The shift analyses revealed no shifts of clinical concern for ECG parameters for either study. One patient in Study 311 (core) had a shift from normal at Baseline to abnormal, clinically significant at EOT of the Core Study, but this was not considered a TEAE. QT abnormalities were observed in 14 patients in Studies 311 and 232. No patient had on-treatment increase of QTcF >60 msec, and none of these events were considered TEAEs.

Reviewer's comment: No ECG signal was identified in Studies 311 and 232.

8.5.9. QT

A formal QT study that examined the effect of perampanel on cardiac repolarization was reviewed as part of the original NDA. The FDA Interdisciplinary Review Team (IRT) for QT studies reviewed these data, which are already summarized in the PI.

8.5.10. Immunogenicity

Not applicable

8.6. Analysis of Submission-Specific Safety Issues

See Section 8.5.4 for discussion of Adverse Events of Special Interest and submission-specific safety issues.

8.7. Safety Analyses by Demographic Subgroups

TEAEs by age

TEAEs were examined by age subgroup (2 to <7 years and 7 to < 12 years) in the pooled dataset. Sixty-one (29.5%) of patients who received at least one dose of perampanel in Studies 311 and 232 were 2 to < 7 years of age and 146 (71.5%) were 7 to < 12 years of age. A total of 5 patients under age 4 received perampanel in Study 232. Although the overall incidence of TEAEs was greater in the younger group (96.7%) than in the older group (80.8%), not all specific TEAEs were more frequent in the younger age group. As seen in Table 15, somnolence, pyrexia, gait disturbance/ataxia/balance disorder, ear infections, and seizures occurred notably more frequently patients < 7 years of age, while fatigue, headache, abdominal pain, and weight gain were more frequently seen in the older patients.

Table 15: TEAEs by age in ≥3% patients, pooled Studies 311 and 232

	Overall N=207		2 to < 7 years* N=61		7 to < 12 years N=146	
TEAE (Preferred Term)	n	%	n	%	n	%
All TEAEs	**177**	**85.5%**	**59**	**96.7%**	**118**	**80.8%**
Somnolence and Sedation	49	23.7%	19	31.1%	30	20.5%
Somnolence	47	22.7%	17	27.9%	30	20.5%
Nasopharyngitis and pharyngitis	45	21.7%	14	23%	31	21.2%
Pyrexia	31	15.0%	17	27.9%	14	9.6%
Rash	29	14%	11	18%	18	12.3%
Dizziness and vertigo	27	13.1%	8	13.1%	19	13%
Irritability	27	13.0%	10	16.4%	17	11.6%
Gait disturbance/Ataxia/Balance	27	13%	13	21.3%	14	9.6%
Vomiting	26	12.6%	8	13.1%	18	12.3%
Upper respiratory tract infection	26	12.6%	10	16.4%	16	11%
Aggression/Anger	24	11.6%	9	14.8%	15	10.3%
All seizures	23	11.1%	10	16.4%	13	8.9%
Ear infection	20	9.7%	11	18%	9	7.1%
Fatigue	18	8.7%	3	4.9%	15	10.3%
Headache	16	7.7%	3	4.9%	13	8.9%
Diarrhea	13	6.3%	6	9.8%	7	4.8%
Abdominal pain	13	6.3%	1	1.6%	12	8.2%
Weight increased	12	5.8%	1	1.6%	11	7.5%
Gastroenteritis	12	5.8%	6	9.8%	6	4.1%
Increased appetite	11	5.3%	3	4.9%	8	5.5%
Agitation	10	4.8%	2	3.3%	8	5.5%
Cough	10	4.8%	5	8.2%	5	3.4%
Decreased appetite	9	4.3%	3	4.9%	6	4.1%
Insomnia	9	4.3%	2	3.3%	7	4.8%
Lethargy	9	4.3%	5	8.2%	4	2.7%

TEAE (Preferred Term)	Overall N=207		2 to < 7 years* N=61		7 to < 12 years N=146	
	n	%	n	%	n	%
Rhinorrhea	9	4.3%	4	6.6%	5	3.4%
Anxiety	8	3.9%	3	4.9%	5	3.4%
Constipation	8	3.9%	3	4.9%	5	3.4%
Nausea	8	3.9%	3	4.9%	5	3.4%
Bronchitis	7	3.4%	1	1.6%	6	4.1%
Epistaxis	7	3.4%	4	6.6%	3	2.1%
Weight decreased	7	3.4%	4	6.6%	3	2.1%

*Patients < 4 years of age enrolled in Study 232 only
Source: pooled ADAE (AEDECOD by USUBJID and AGE)

Reviewer's comment: Although some differences in the incidence of AEs were observed between age groups, the clinical significance of these differences is unclear, due to the small sample size of the younger age group and the lack of a placebo comparator.

TEAEs by dose

As these were single arm, open-label studies with a multitude of doses administered, assessment of TEAEs by dose was not possible.

8.8. Specific Safety Studies/Clinical Trials

8.8.1. Additional Safety Explorations Human Carcinogenicity or Tumor Development

Not applicable

8.8.2. Human Reproduction and Pregnancy

No pregnancies or exposure to study drug through breastfeeding were reported, as would be expected given the age range of subjects in the studies.

8.8.3. Pediatrics and Assessment of Effects on Growth

The effects of perampanel on growth was assessed via height, weight, insulin-like growth factor-1 (IGF-1), and thyroid tests in both studies. In Study 311, at Week 23, the mean change from baseline (SD) for IGF-1 was 2.52 (8.68). There were minimal or no changes from Baseline for thyrotropin, free thyroxine, and free triiodothyronine. At Week 23, the mean change from baseline (SD) for body weight was 2.06 (3.28) kg. At the end of the extension phase of Study

232 (Week 52), the mean change from baseline (SD) for IGF-1 was 2.75 (6.99). There were minimal or no changes from Baseline for thyrotropin, free thyroxine, and free triiodothyronine. At Week 52, the mean change from baseline (SD) for body weight was 0.58 (10.14) kg.

Reviewer's comment: There were no clinically significant changes in growth parameters in either study.

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

See discussion of overdose in Section 8.5.4.

8.8.5. Safety in the Postmarket Setting Safety Concerns Identified Through Postmarket Experience

Tendon/ligament rupture, ventricular arrhythmias/cyanosis, pancreatitis/cholelithiasis, and incarceration were included as TEAEs of interest based on findings in the controlled POS trials. There were no above-mentioned TEAEs reported in Studies 311 and 232.

8.8.6. Expectations on Safety in the Postmarket Setting

I expect that the safety issues in the pediatric population (4 to <12 years) will be similar to those seen in the adolescent and adult population. There may eventually be suicides in the younger pediatric patients, as the risk of suicide is greater with AEDs as a class. SUDEP is also likely to occur, as this is a known yet uncommon adverse sequela of epilepsy.

8.8.7. Additional Safety Issues From Other Disciplines

Not applicable

8.9. Integrated Assessment of Safety

Fycompa (perampanel) is already approved for adjunctive and monotherapy use as treatment for partial onset seizures in patients 12 years and older in the US. It is also approved for adjunctive treatment of primary generalized tonic-clonic seizures in patients 12 years and older. To support the indication for adjunctive and monotherapy use in treatment of POS in patients 4 to <12 years, perampanel was studied in two open-label, single arm PK and safety studies in patients with refractory epilepsy who were 2 to <12 years of age {Studies 311 and 232).

The total number of pediatric patients 4 to <12 years of age who were exposed to perampanel during Studies 311 and 232 was 225 (including patients enrolled into Study 311 after the original data cutoff and included in the 120-Day Safety Update). The Applicant performed safety analyses on Studies 311 and 232 separately. However, all FDA analyses were performed on the integrated, pooled dataset submitted on July 13, 2018, which included 207 patients who had been exposed to perampanel during Studies 311 and 232. The FDA safety analyses pooled safety data from the core and extension phases from both studies.

There was 1 death during Studies 311 and 232. The cause of death (viral myocarditis) was not deemed due to the study drug and does not raise clinical concerns. Please see Section 8.5.1 for further information on this patient.

The overall incidence of treatment-emergent SAEs was 14.5% in the perampanel-treated patients. The most-commonly reported SAE was seizures in 9 patients (4.3%). Each remaining SAE was reported by only 1 or 2 patients.The types of SAEs reported in Studies 311 and 232 were similar to those in the controlled POS studies, and the incidence was similar to that seen in the entire epilepsy study pool (including controlled and uncontrolled safety data) in the original NDA submission for POS.

A total of 24 patients (11.6%) discontinued perampanel due to a TEAE in Studies 311 and 232, which was higher than that seen in the patients taking permapanel in the controlled POS trials (8.4%). The reason for this higher rate is unclear, but as there was no control group for comparison, further conclusions cannot be drawn. The most common causes of discontinuation due to TEAE were irritability (n=4, 1.9%), seizure/convulsion (n=4, 1.9%), and aggression (n=3, 1.4%). Discontinuations due to TEAEs were more likely to occur earlier in the treatment with 58% (14/24) occurring during the titration period.

Certain adverse events of special interest were specifically evaluated. TEAEs related to to hostility or aggression were of special interest due to the greater incidence seen in patients taking permapanel in the controlled POS trials. Overall, 92 hostility- and aggression-related TEAEs were reported in 65 (31.4%) patients in Studies 311 and 232. The most common TEAEs in this category were irritability (27 patients, 13%), aggression (21 patients, 10%), agitation (10 patients, 4.8%), and abnormal behavior (6 patients, 2.9%). Two-thirds of the hostility- or aggression-related TEAEs occurred in the older age group (7 to < 12 years). This finding, although complicated by the lack of a control group and small population, suggests that these behavioral effects may be more prominent in older children than younger. Three of these events were SAEs (aggression, abnormal behavior, and disruptive mood dysregulation disorder), two of which led to discontinuation, and five of the events were characterized as severe. Hostility- or aggression-related TEAEs led to drug discontinuation in nine patients and dose reduction in 24 patients. As in the controlled trials, hostility- and aggression-related TEAEs occurred in a sizable minority of patients, leading to discontinuation or dose reduction, supporting the continued need for the warning in the PI.

Rash occurred in 14% of patients, leading to discontinuation in only one patient. No patients reported a SAE related to rash.

Four patients were reported as exhibiting suicidality (3 with suicidal ideation and 1 with suicidal ideation and behavior). Only one patient was discontinued from the drug due to suicidality, and one had a dosage reduction. None of these cases were deemed serious or severe. The rate of suicidality (1.9%) is greater than that in the controlled POS trials (0.3%). Potential reasons for this include enrollment of patients with significant underlying behavioral problems, small sample size, and careful attention to suicidality during the studies. These findings do not raise new clinical concerns.

No new safety signals were identified during review of the laboratory data. There were no cases of drug-induced liver injury. No patient met Hy's law criteria. No patients discontinued treatment due to LFT abnormalities or liver dysfunction. Although 8 patients (3.9%) developed hematologic abnormalities on laboratory testing (neutropenia or thrombocytopenia), all recovered completely without discontinuation of perampanel.

TEAEs occurred in 85.5% of patients in Studies 311 and 232. The most common TEAEs overall in Studies 311 and 232 were somnolence (22.7%), nasopharyngitis (18.8%), pyrexia (15%), rash (13.5%), irritability (13%), dizziness and vertigo (13%), vomiting (12.6%), all upper respiratory tract infection (12.6%), aggression/anger (11.5%), all seizures (11.1%), and ear infection (10.1%). In the absence of a concurrent placebo comparator, any conclusions regarding clinical meaningfulness of the AE incidences must be regarded with care.

In summary, review of the safety data from the studies of perampanel in pediatric patients with epilepsy demonstrated no new safety signals. The safety profile was generally consistent with that of the adolescent and adult epilepsy safety profile in the current Fycompa label.

9. Advisory Committee Meeting and Other External Consultations

The Division did not present this sNDA to an Advisory Committee.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

Edits to the prescribing information have been proposed, but the labeling has not been finalized at the time of this review.

10.2. Nonprescription Drug Labeling

Not applicable

11. Risk Evaluation and Mitigation Strategies (REMS)

The need for a REMS has not been determined at the time of this review.

12. Postmarketing Requirements and Commitments

One new PMR will be issued for a PK study in patients 2 to > 4 years of age in order to generate sufficient dose-exposure data for extrapolation of efficacy in pediatric patients 2 to <4 years of age with POS. Two current PMRs will be released/reissued with changes to the planned age range of the study population. Current, former, and proposed PMRs are summarized in Table 16 below.

In a Type C/Guidance meeting on December 18, 2017, the Division noted that based on the review of the clinical safety data, addition of the following language to Section 9.3 Dependence in the prescribing information will be sufficient to address PMR 1932-9: “FYCOMPA may cause dependence and withdrawal symptoms that may include anxiety, nervousness, irritability, fatigue, lethargy, asthenia, mood swings, and insomnia.” The Applicant included this language in Section 9.3 of the PI, and thus PMR 1932-9 should be released.

Table 16: Fulfilled, Current, and Proposed PMRs

CURRENT PREA PMRs	PROPOSED and UNCHANGED PREA PMRs
Ongoing PREA PMRs	
1932-1 A pharmacokinetic study in pediatric patients with partial-onset seizures aged 1 month to < 24 months. At least 2 maintenance dose levels of FYCOMPA (perampanel) should be evaluated to characterize pharmacokinetic parameters following multiple administration of oral perampanel. Pharmacokinetic data can be obtained and analyzed using either conventional pharmacokinetics methods with intensive sampling or using a population PK approach by collecting sparse samples. Subjects should be balanced among age cohorts. Effort should also be made to balance the gender distributions within each age cohort. Final Protocol Submission: February 2014 Core Study Completion: January 2016 Extension Study Completion November 2016 Final Core Report Submission: July 2016 Final Extension Report Submission: May 2017 Final Extension Report Submission: March 2022 [DE granted 7/1/15]	**1932-1** A pharmacokinetic study in pediatric patients with partial-onset seizures aged 1 month to < 24 months. At least 2 maintenance dose levels of FYCOMPA (perampanel) should be evaluated to characterize pharmacokinetic parameters following multiple administration of oral perampanel. Pharmacokinetic data can be obtained and analyzed using either conventional pharmacokinetics methods with intensive sampling or using a population PK approach by collecting sparse samples. Subjects should be balanced among age cohorts. Effort should also be made to balance the gender distributions within each age cohort. **(UNCHANGED)** Final Protocol Submission: February 2014 Core Study Completion: January 2016 Extension Study Completion November 2016 Final Core Report Submission: July 2016 Final Extension Report Submission: May 2017 Final Extension Report Submission: March 2022 [DE granted 7/1/15]
1932-4 Deferred pediatric study under PREA: A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) for the adjunctive treatment of partial onset seizures in children ages 1 month to < 4 years with a long-term safety extension. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data. Safety will be evaluated during the controlled phase and long-term extension. **(Plan to RELEASE/REISSUE new PMR in combination with 3076-1→)** Final Protocol Submission: April 2016 Core Study Completion: October 2018 Extension Study Completion: September 2019 Final Core Report Submission: July 2019 Final Extension Report Submission: March 2020	**XXXX-X** Deferred pediatric study under PREA: A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) for the adjunctive treatment of partial onset seizures in children ages **1 month to < 2 years** with a long-term safety extension. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon Video/EEG data. Safety will be evaluated during the controlled phase and long-term extension. In the long-term extension, a minimum of 25 patients must be exposed to study drug for 6 months at or above the dose or doses identified as effective. Final Protocol Submission: (b) (4)

3076-1 A long-term, open-label, safety study of adjunctive therapy in patients from 1 month to less than 12 years of age with epilepsy. The purpose of this study is to evaluate the long-term safety of FYCOMPA (perampanel) as adjunctive therapy in the treatment of partial-onset seizures (ages 1 month to less than 12 years) or primary generalized tonic-clonic seizures in pediatric patients (ages 2 to less than 12 years). Doses for this study must be at or above those doses determined to be efficacious by Study 1932-4 (patients 1 month to less than 4 years of age with partial-onset seizures), Study 2922-1 (patients 2 to less than 12 years of age with primary generalized tonic-clonic seizures), and the pharmacokinetic analyses used for the extrapolation of efficacy in pediatric patients 4 to less than 12 years of age with partial-onset seizures. This study may include subjects enrolled in the extension phases of Studies 1932-1, 1932-2, 1932-4, and 2922-1, and may be supplemented as necessary. A minimum of 100 patients must be exposed to study drug for one year at or above the dose or doses identified as effective. Subjects should be balanced among age cohorts to allow for adequate conclusions to be drawn. Final Protocol Submission: 09/2016 Study Completion: 09/2021 Final Report Submission: 03/2022 **(Will be partially FULFILLED. Plan to RELEASE/REISSUE new PMR in combination with 1932-4→)**	Core Study Completion: (b) (4) Extension Study Completion: Final Core Report Submission: Final Extension Report Submission
Previously Fulfilled or Released PMRs	**New PMR**
1932-2 A pharmacokinetic study in pediatric patients with partial-onset seizures aged 2 to < 12 years. At least 2 maintenance dose levels of perampanel should be evaluated to characterize pharmacokinetic parameters following multiple administration of oral FYCOMPA (perampanel). Pharmacokinetic data can be obtained and analyzed using either conventional pharmacokinetic methods with intensive sampling or using a population PK approach by collecting sparse samples. Subjects should be balanced among age cohorts. Effort should also be made to balance the gender distributions within each age cohort. **[PMR Fulfilled per 7/26/17 communication]** Final Protocol Submission: November 2011 Core Study Completion: November 2013 Extension Study Completion: September 2014 Final Core Report Submission: May 2014 Final Extension Report Submission: March 2015 Final Extension Report Submission: July 2015 [DE granted 2/11/15] Final Extension Report Submission: July 2016 [DE granted 7/1/15]	**####-#** A pharmacokinetic (PK) study in children with epilepsy who are 2 years to less than 4 years of age to characterize pharmacokinetic parameters following multiple administration of oral perampanel. This study should include patients taking perampanel with and without concomitant CYP3A4 inducers. Final Protocol Submission: (b) (4) Study Completion: Final Report Submission: **(This is a new PREA PMR to address the need for more PK data in patients 2 to <4 years of age to allow for adequate characterization of dose-exposure and ultimately safety in this population)**

1932-3 A prospective, randomized, controlled, double-blind, efficacy and safety study of FYCOMPA (perampanel) in children ages 2 years to < 12 years for the adjunctive treatment of partial onset seizures with a long term safety extension. The primary efficacy endpoint during the controlled phase will examine seizure frequency based upon diary data. Safety will be evaluated during the controlled phase and long term extension. **[PMR Released per 7/27/16 communication]** Final Protocol Submission: February 2014 Core Study Completion: February 2017 Extension Study Completion: September 2017 Final Core Report Submission: August 2017 Final Extension Report Submission: March 2018	
2922-1 Conduct a multiple-dose pharmacokinetic (PK) and tolerability study to explore the range of tolerated doses of FYCOMPA (perampanel) in patients from 2 to less than 12 years of age with epilepsy. A sufficient proportion of subjects must be on background therapy that includes enzyme-inducing AEDs, such as carbamazepine, oxcarbazepine, or phenytoin, which are known to induce perampanel metabolism and decrease its plasma concentrations. PK data will be obtained using a sparse sampling approach. Sufficient PK and tolerability data must be generated from this study before conducting the efficacy and safety study, to inform the dose selection for that study. Sampling must be optimized to ensure adequate characterization of perampanel PK. Using information from the PK study, conduct an adequately powered, controlled, and blinded trial that examines the efficacy and safety of FYCOMPA (perampanel) in the treatment of primary generalized tonic-conic (PGTC) seizures in a pediatric population. Because PGTC seizures are less common in this age group, the study population may include the full range of pediatric patients (e.g., patients less than 17 years old). This study must include a minimum of 60% of patients that are 2 to 12 years of age. Information from the PK/tolerability part of this postmarketing requirement, and its resulting protocol-specified dosing, should be provided to the Division prior to the initiation of the efficacy trial, and agreements on dosing should be reached with the Division before the efficacy trial is initiated. **[PMR Released per 8/8/17 communication]** Final Protocol Submission (PK and tolerability study): 11/2011 Study Completion (PK and tolerability study): 05/2015 Final Report Submission (PK and tolerability study): 06/2016 Final Protocol Submission (Efficacy and safety study) 09/2016 Study Completion (Efficacy and safety study): 09/2020 Final Report Submission (Efficacy and safety study): 03/2021	

13. Appendices

13.1. References

See footnotes throughout review.

13.2. Financial Disclosure

Nine investigators had disclosable financial arrangements, ranging in amounts from $35,379.38 to $208,837.42. All of the disclosed arrangements were significant payments of other sorts. The Applicant noted that any potential bias from disclosed arrangement is minimized by the fact that both Studies 311 and 232 are open-label, nonrandomized studies with safety and PK as primary endpoints.

Covered Clinical Study (Name and/or Number): E2007-G000-232, E2007-G000-311

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 376		
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): 9		
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: 0 Significant payments of other sorts: 9 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
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) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

NATALIE B GETZOFF
09/26/2018

PHILIP H SHERIDAN
09/27/2018