Common Drug Review
Clinical Review Report

May 2016

Drug	Perampanel (Fycompa)
Indication	Indicated as adjunctive therapy in the management of primary generalized tonic-clonic (PGTC) seizures, in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy
Reimbursement request	As per indication
Dosage form(s)	2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg tablets
NOC date	December 2015
Manufacturer	Eisai Limited

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

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ABBREVIATIONS

AE	adverse event
AED	anti-epileptic drug
AMPA	alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
CGI-C	Clinical Global Impression of Change
CI	confidence interval
C-SSRS	Columbia-Suicide Severity Rating Scale
FAS	full analysis set
HRQoL	health-related quality of life
LOCF	last observation carried forward
MCID	minimum clinically important difference
MD	median difference
medDRA	Medical Dictionary for Regulatory Activities
PGTC	primary generalized tonic-clonic
QOLIE-31	Quality of Life in Epilepsy Inventory-31
QOLIE-31-P	Patient-Weighted Quality of Life in Epilepsy Inventory-31
SAE	serious adverse event
SD	standard deviation
SF-36	Short Form 36
SUDEP	sudden unexpected death in epilepsy
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Epilepsy is a chronic neurological disorder that manifests as a variety of seizure types and syndromes, often of unknown etiology. The estimated prevalence of epilepsy is 400 per 100,000 Canadians, and each year in Canada, about 15,500 people are diagnosed with epilepsy.[1,2] There are two broad categories of epileptic seizures: partial-onset seizures and generalized seizures.[3] Generalized seizures involve large parts of both hemispheres of the brain and are associated with loss of consciousness.[3] Tonic-clonic seizures may be considered the most serious seizure type and put the patient at risk for seizure-related injury. The impacts of epilepsy can vary widely in terms of frequency, severity, and duration. For some patients, epilepsy can have a significant impact on all aspects of life.

Perampanel is a first-in-class anti-epileptic drug (AED) that is thought to be a selective, non-competitive antagonist of the ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons, although the precise mechanism of action in epilepsy is not known.[4] The recommended dose of perampanel is 2 mg to 12 mg per day orally, and varies depending on the patient's concomitant use of enzyme-inducing AEDs.

Perampanel is approved in Canada as adjunctive therapy in adults for the management of primary generalized tonic-clonic (PGTC) seizures and partial-onset seizures not satisfactorily controlled with conventional therapy. It was reviewed by the Canadian Drug Expert Committee (CDEC) in 2013 for use in partial-onset seizures.[4] CDEC recommended that perampanel be listed for this population if the following clinical criteria and conditions were met:

- patients are currently receiving two or more AEDs
- less-costly AEDs are ineffective or not appropriate
- patients are under the care of a physician experienced in the treatment of epilepsy.[5]

Indication under review
Perampanel is indicated as adjunctive therapy in the management of primary generalized tonic-clonic (PGTC) seizures, in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.
Reimbursement criteria requested by sponsor
As per indication

The objectives of this review are to perform a systematic review of the beneficial and harmful effects of perampanel 2 mg to 12 mg tablets as adjunctive therapy in adults with epilepsy for the management of PGTC seizures not satisfactorily controlled with conventional therapy.

Results and Interpretation

Included Studies

One randomized, double-blind, placebo-controlled trial met the inclusion criteria.[6,7] Study 332 examined the efficacy and safety of adjunctive perampanel (up to 8 mg per day) versus placebo for the treatment of refractory PGTC seizures in patients ≥ 12 years of age with idiopathic generalized epilepsy (N = 164). All patients were treated with stable doses of one to three approved AEDs, and had at least three documented PGTC seizures during the eight weeks prior to randomization. Those enrolled had a mean

age of 28 years (85% ≥ 18 years of age), 56% were female, and had epilepsy, on average, for 17 years. The primary outcome was the per cent change in PGTC seizure frequency per 28 days (treatment period versus baseline), and the key secondary outcome was the proportion of patients with ≥ 50% reduction in PGTC seizure frequency. The key limitations of Study 332 were the short duration of the study (17 weeks in total, only 13 weeks for maintenance treatment), small sample size, lack of active comparator, lack of data on the 10 mg and 12 mg dosages approved for use in Canada during the randomized comparative phase, and no control of multiplicity of statistical testing.

Efficacy

In Study 332, perampanel showed statistically significant reductions in per cent change of PGTC seizure frequency per 28 days compared with placebo (median difference [MD] –30.8%; 95% CI, –45.5% to –15.2%) and all-seizure frequency (MD –23.5%; 95% CI, –40.7% to –8.5%). Statistically significantly more patients showed a ≥ 50% reduction in PGTC seizure frequency in the perampanel versus placebo group (64% versus 40%, *P* = 0.0019). Although more patients on perampanel (31%) were PGTC seizure-free than placebo (12%), Study 332 was not designed to test for differences in this outcome, which was identified by patients as one of the key goals of therapy.

Compared with the overall study population, the benefits in reduction of seizure frequency were similar for the adult subgroup (N = 139, representing 85% of the overall study population), which is the population approved for perampanel use in Canada. Likewise, the per cent change in PGTC seizure frequency or 50% responder rate was similar for perampanel subgroups based on concurrent AED use (lamotrigine, valproic acid, levetiracetam, or topiramate). However, the subgroup analyses should be interpreted with caution, given they were defined post hoc and the AED subgroups included a limited number of patients (25 to 64).

Though reductions in PGTC seizure frequency were detected with perampanel, no clinically important differences were found in health-related quality of life (HRQoL), based on the Patient-Weighted Quality of Life in Epilepsy Inventory-31 (QOLIE-31-P). Moreover, clinician-rated Clinical Global Impression of Change (CGI-C) showed few differences between treatment groups in the proportion of patients rated as improved, worsened, or showing no change after 12 weeks of therapy. These data suggest that perampanel is not associated with short-term differences in outcomes that patients report as affecting their day-to-day lives. However, the QOLIE-31-P and CGI-C data should be interpreted with caution, given that these were exploratory outcomes, [redacted]. No data were available on the number of missed work or school days.

Harms

In Study 332, most patients reported one or more adverse events during the trial (perampanel 83%, placebo 72%), with dizziness (32% versus 6%), fatigue (15% versus 6%), somnolence (11% versus 4%) and irritability (11% versus 2%) reported more frequently in those receiving perampanel. In addition, more patients who received perampanel reported a > 7% increase in body weight (11% versus 4%), and aggression or hostility-related adverse events (19% versus 5%) compared with placebo.

The frequency of serious adverse events was similar in the perampanel and placebo groups, 7% and 9%, respectively. Two patients in the perampanel group and none in the placebo group had serious adverse events related to suicide ideation or behaviour. More patients stopped treatment due to adverse events in the perampanel group (11%) than in the placebo group (6%), with dizziness and vomiting reported as the most frequent reasons among those who received perampanel.

The adverse events reported in Study 332 were consistent with those observed in the partial-onset seizure perampanel trials and Study 332 extension phase, as well as with post-marketing data reported to the Health Canada Pharmacovigilance program.[4,8-11] Data from partial-onset seizure trials suggest a dose response, with an increasing incidence of some adverse events associated with perampanel doses ≥ 8 mg per day.[4,9] Thus, the frequency of adverse events may be higher in clinical practice than in study 332 if more patients are prescribed doses greater than 8 mg per day.

Place in Therapy

The clinical expert involved in the review stated that there is an unmet treatment need in the management of patients with PGTC seizures who are not satisfactorily controlled with conventional therapy. According to the clinical expert, patients with "resistant" or "refractory" epilepsy are variably defined, but in essence, the terms are applied to those in whom seizures continue despite adequate trials of standard AEDs. There are no standardized guidelines for treatment of epilepsy, but in practice, an "adequate" trial of an AED usually means several months of phenytoin, carbamazepine, or valproic acid, either alone or in combination. In the total population of people with epilepsy, about 20% to 30% prove to be resistant or refractory,[12] and among these at least half would have resistant or refractory PGTC seizures. Thus, a substantial proportion of patients with epilepsy would require add-on therapy to manage their PGTC seizures.

Perampanel joins a substantial list of AEDs, any or several of which might be tried in a given patient with resistant or refractory PGTC seizures, according to the clinical expert consulted. Based on the Study 332, the efficacy of perampanel as an add-on AED appears to be similar to alternative new AEDs. However, the absence of direct or indirect evidence to support this makes it difficult to draw concrete conclusions about comparative efficacy and safety. One potential advantage of perampanel is that it can be given as a single daily dose, unlike all other available AEDs except phenytoin. In epilepsy, non-compliance with prescribed drugs is an important problem, and non-compliance tends to be more likely with medications requiring multiple daily doses. Perampanel is believed to exert its anti-seizure actions by antagonizing brain AMPA receptors. This mechanism of action is unique to perampanel among available AEDs, but whether this has important practical consequences is unclear. The rate of adverse events, particularly dizziness and somnolence, seems to be higher with perampanel compared with placebo. Although Study 332 did not show a negative impact on quality-of-life measures, these adverse events may become important when the drug is used in clinical practice.

Conclusions

Among patients with refractory idiopathic generalized epilepsy, adjunctive perampanel was associated with statistically significant short-term reductions in PGTC seizure frequency, and a higher seizure response rate (≥ 50%), compared with placebo. The impact of perampanel on HRQoL and other outcomes patients report as important is unclear, based on a single, double-blind randomized controlled trial.

Perampanel was associated with an increased frequency of dizziness, aggression or hostility, fatigue, or somnolence, and weight gain compared with placebo.

Uncertainty remains regarding the comparative effects of perampanel, given the lack of direct or indirect treatment comparisons, and additional data are needed to determine the long-term safety and efficacy of this first-in-class drug.

TABLE 1: SUMMARY OF RESULTS

Outcome	Study 332	
	Placebo N = 81	Perampanel N = 81
Proportion of patients PGTC seizure-free		
n (%)	10 (12)	25 (31)
RD (95% CI)		19% (6% to 31%)
PGTC seizure frequency per 28 days		
Baseline, median (min, max)	2.5 (1.0 to 11.7)	2.6 (1.4 to 18.5)
Per cent change from baseline, median (min, max)	–38.4% (–100.0 to 1,546.3)	–76.5% (–100.0to 184.5)
Median difference versus placebo (95% CI) *P* value		–30.8% (–45.5 to –15.2), *P* < 0.0001
Proportion of patients ≥ 50% reduction in PGTC seizures per 28 days		
n (%)	32 (40)	52 (64)
RD (95% CI), *P* value		25% (10% to 40%), *P* = 0.0019
Withdrawals		
n (%)	10 (12)	14 (17)
SAEs		
n (%)	7 (9)	6 (7)
WDAEs		
n (%)	5 (6)	9 (11)
Notable harms, n (%)		
Dizziness	5 (6)	26 (32)
Fatigue	5 (6)	12 (15)
Somnolence	3 (4)	9 (11)
Aggression or hostility	4 (5)	15 (19)
Weight gain > 7%	3 (4)	9 (11)

CI = confidence interval; PGTC = primary generalized tonic-clonic; RD = risk difference; SAE = serious adverse events; WDAE = withdrawals due to adverse events.
Source: Clinical Study Report.[7]

1. INTRODUCTION

1.1 Disease Prevalence and Incidence

Epilepsy is a chronic neurological disorder that manifests as a variety of seizure types and syndromes, often of unknown etiology. There are two broad categories of epileptic seizures: partial-onset seizures and generalized seizures.[3] Partial seizures involve only a portion of the brain, typically one lobe of one hemisphere, while generalized seizures involve large parts of both hemispheres of the brain.[3] Simple partial-onset seizures are not associated with loss of consciousness, while consciousness is affected in complex partial-onset seizures and generalized seizures.[3] Tonic-clonic seizures may be considered the most serious seizure type and put the patient at risk for seizure-related injury.

The estimated prevalence of epilepsy is 400 per 100,000 Canadians, based on data from the Canadian Community Health Survey 2010-2011.[2] Each year in Canada, about 15,500 people are diagnosed with epilepsy.[1] Of these, 44% are diagnosed before the age of 5, 55% before 10 years, 75% to 85% before 18 years, and 1.3% older than 60 years.[1]

The impacts of epilepsy can vary widely in terms of frequency, severity, and duration. For some patients, epilepsy can have a significant impact on all aspects of life. Patients with uncontrolled seizures are often placed in dangerous situations, for example, should a seizure occur while riding a bus, shopping, or crossing a street. In addition, those with uncontrolled epilepsy are not permitted by law to operate motor vehicles. Patients with epilepsy may face stigma and discrimination, including difficulty obtaining and retaining employment, and some patients who are housebound and socially isolated may have difficulties maintaining relationships and suffer a loss of independence.

1.2 Standards of Therapy

The goals of therapy are to control seizures, avoid treatment-related adverse events, and maintain or restore quality of life.[3] Approximately half of patients with a new diagnosis of epilepsy will become seizure-free with the first anti-epileptic drug (AED) prescribed.[3] Of those whose initial therapy is ineffective, about 10% to 20% will have a successful second drug trial.[3] Combination therapy may be required for some patients whose epilepsy is treatment-resistant. The selection of AEDs is usually based on several factors, including drug effectiveness for the patient's seizure type, potential adverse events and interactions with medications, comorbid medical conditions, age and gender (including childbearing plans), patient preference, and cost.[3]

There are several AEDs approved for use in Canada, and those drugs that may be used to treat primary generalized tonic-clonic (PGTC) seizures are summarized in Table 2. According to patient groups, effective anti-seizure medications are life-saving and can assist them in enjoying a fulfilled life. However, existing therapies are not effective for some patients and the adverse events associated with therapies can be debilitating and detrimental to the patient's well-being. Patient input suggests that novel treatment options are needed for those who have failed to achieve complete seizure elimination or who cannot tolerate the adverse events of existing AEDs.

1.3 Drug

Perampanel is indicated as adjunctive therapy in adult patients with epilepsy for the management of PGTC seizures that are not satisfactorily controlled with conventional therapy.[4] The recommended dose of perampanel is 4 mg to 12 mg per day orally in patients receiving concomitant enzyme-inducing AEDs (e.g., carbamazepine, oxcarbazepine, phenytoin) or 2 mg to 8 mg per day in all other patients.[4] The dose

should be started at the lowest dose and may be increased at weekly or biweekly intervals, based on clinical response and tolerability, by 2 mg increments up to the daily maximum.[4] Perampanel appears to be a selective, non-competitive antagonist of the ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) glutamate receptor on post-synaptic neurons. However, the precise mechanism of action in epilepsy is not known.[4]

Indication under review
As adjunctive therapy in the management of primary generalized tonic-clonic (PGTC) seizures, in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy
Reimbursement criteria requested by sponsor
As per indication

Perampanel is also approved in Canada as adjunctive therapy in adults for the management of partial-onset seizures not satisfactorily controlled with conventional therapy, and was reviewed by the Canadian Drug Expert Committee (CDEC) in 2013 for this indication.[4] CDEC recommended that perampanel be listed for this population if the following clinical criteria and conditions were met:

- Patients are currently receiving two or more AEDs.
- Less-costly AEDs are ineffective or not appropriate.
- Patients are under the care of a physician experienced in the treatment of epilepsy.[5]

TABLE 2: KEY CHARACTERISTICS OF COMMONLY USED DRUGS USED FOR THE MANAGEMENT OF GENERALIZED TONIC-CLONIC SEIZURES

Drug name	Perampanel	Valproic Acid (Sodium Valproate/ Divalproex Sodium)	Lamotrigine	Topiramate	Carbamazepine	Phenytoin	Levetiracetam
Mechanism of Action	Appears to be a selective antagonist of the ionotropic AMPA glutamate receptor on post-synaptic neurons.	May be related to increased brain concentrations of GABA.	Thought to act at voltage-sensitive sodium channels.	Thought to reduce the frequency of action potentials when neurons are subjected to a sustained depolarization; enhances the activity of GABA; and antagonizes the activation of the kainate/AMPA subtype of glutamate receptors.	Affects voltage-dependent sodium channels.	Primary site of action appears to be the motor cortex where spread of seizure activity is inhibited.	Not known.
Indication[a]	Adjunctive therapy in adult patients with epilepsy for the management of partial-onset seizures and primary generalized tonic-clonic seizures not satisfactorily controlled with conventional therapy.	For use as sole or adjunctive therapy in the treatment of simple or complex absence seizures, including petit mal, and is useful in primary generalized seizures with tonic-clonic manifestations. For use adjunctively in patients with multiple seizure types that include either absence or tonic-clonic seizures.	Adjunctive therapy for the management of epilepsy seizures not satisfactorily controlled by conventional therapy. For use as monotherapy following withdrawal of concomitant anti-epileptic drugs. Adjunctive therapy for the management of the seizures associated with Lennox-Gastaut syndrome.	Monotherapy for the management of patients (adults and children six years and older) with newly diagnosed epilepsy. Adjunctive therapy for the management of patients (adults and children two years and older) with epilepsy seizures not satisfactorily controlled with conventional therapy.	For use as an anticonvulsant drug, either alone or in combination with other anticonvulsant drugs.	For the control of generalized tonic-clonic and psychomotor (grand mal and temporal lobe) seizures and prevention and treatment of seizures occurring during or following neurosurgery.	Adjunctive therapy in the management of patients with epilepsy seizures not satisfactorily controlled by conventional therapy.
Route of Administration	Oral	Oral	Oral	Oral	Oral	Oral	Oral

Drug name	Perampanel	Valproic Acid (Sodium Valproate/ Divalproex Sodium)	Lamotrigine	Topiramate	Carbamazepine	Phenytoin	Levetiracetam
Recommended Dose in Adults	2 mg to 12 mg once daily	15mg/kg/day to 60 mg/kg/day (in 2 or 3 divided doses)	50 mg to 250 mg twice daily	50 mg to 200 mg twice daily	800 mg to 1,600 mg daily (in 2 or 3 divided doses)	300 mg to 600 mg daily (in 3 divided doses)	500 mg to 1,500 mg twice daily
Serious Side Effects and Safety Issues	Serious psychiatric and behavioural adverse reactions (aggression, hostility, irritability). Common: dizziness, disturbance in gait or coordination and falls, somnolence and fatigue-related events, vision-related adverse events. Contraindications: hypersensitivity to perampanel.	Hepatotoxicity, pancreatitis, hyperammonemia, hypothermia, thrombocytopenia, teratogenic. Common: CNS and gastrointestinal adverse events, weight gain. Contraindications: hepatic disease, urea cycle disorder, mitochondrial disorders, hypersensitivity.	Serious dermatologic adverse events, DRESS, aseptic meningitis. Common: dizziness, ataxia, somnolence. Contraindications: hypersensitivity to lamotrigine.	Kidney stones, hyperammonemia, hypothermia, oligohidrosis and hyperthermia, metabolic acidosis, ophthalmic adverse events. Common: CNS- related adverse events.	Hematologic adverse events (e.g., agranulocytosis, aplastic anemia), serious dermatologic events (SJS, TEN, DRESS), hyponatremia. Common: CNS or gastrointestinal disturbances, rash, blurred vision. Contraindications: hepatic disease, history of bone-marrow depression or hepatic porphyria, serious blood disorder, hypersensitivity, atrioventricular heart block, use with MAOI, itraconazole and voriconazole.	Dermatologic events (hypersensitivity syndrome, DRESS, SJS, TEN), acute hepatoxicity, hematopoietic complications. Common: nystagmus, ataxia, slurred speech, decreased coordination, and mental confusion, rash. Contraindications: hypersensitivity, use with delavirdine.	Serious dermatologic events (SJS, TEN, DRESS), hematologic adverse events. Common: somnolence, asthenia, dizziness, behavioural and psychiatric symptoms (aggression, agitation). Contraindications: hypersensitivity to levetiracetam.
Use During Pregnancy	Unknown risk.	Increased risk of severe birth defects such as neural tube defects, craniofacial defects, cleft palate, cardiovascular malformations, and hypospadias.	Increased risk of cleft lip or cleft palate.	Increased risk of cleft lip or cleft palate.	Increased risk of spina bifida, and other congenital anomalies, e.g., craniofacial defects, cardiovascular malformations, hypospadias, and anomalies involving various body systems.	Increased risk of birth defects including cleft lip or palate and heart malformations and fetal hydantoin syndrome.	Unknown risk.

AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CNS = central nervous system; DRESS = drug reaction with eosinophilia and systemic symptoms; GABA = gamma-aminobutyric acid; MAOI = monoamine oxidase inhibitor; SJS = Steven's-Johnson Syndrome; TEN = toxic epidermal necrolysis.

[a] Health Canada indication.

Source: Product monographs.[4,13-18]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of perampanel 2 mg to 12 mg tablets as adjunctive therapy for the management of PGTC seizures in adults with epilepsy that are not satisfactorily controlled with conventional therapy.

2.2 Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase 3 studies were selected for inclusion based on the selection criteria presented in Table 3.

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years) with PGTC seizures not satisfactorily controlled with conventional therapy. **Subgroups:** Age (e.g., ≥ 18 years to < 65 years, ≥ 65 years) Background AED use (e.g., number of AEDs, enzyme inducers[a] versus non-inducers, etc.)
Intervention	Perampanel 2 mg to 12 mg once daily in combination with at least one other AED
Comparators	AEDs available in Canada (used alone or in combination) • carbamazepine • clobazam • eslicarbazepine acetate • gabapentin • lacosamide • lamotrigine • levetiracetam • placebo (with at least one other AED) • oxcarbazepine • phenobarbital • phenytoin • primidone • topiramate • valproic acid/divalproex • vigabatrin
Outcomes	**Key efficacy outcomes:** • Seizure-free status (proportion of patients who are seizure-free)b • HRQoLb • Change in seizure frequency[b] **Other efficacy outcomes:** • Proportion of responders (e.g., patients with ≥ 50% or ≥ 75% reduction in seizure frequency) • Patient or clinician global impression of change • Reduction in use of concomitant AEDs • Patient adherence to treatment • Health care resource utilization • Missed work or school days[b] **Harms outcomes:** [b] Mortality (SUDEP), AEs, SAEs, WDAEs, AEs of special interest (ophthalmologic, hepatotoxicity, weight gain, dermatologic, CNS-related events in the following categories: aggression-related events; somnolence and fatigue; or coordination difficulties, dizziness and falls)
Study Design	Published and unpublished phase 3 RCTs

AE = adverse events; AED = anti-epileptic drug; CNS = central nervous system; HRQoL = health-related quality of life; RCT = randomized controlled trial; SAE = serious adverse events; SUDEP = sudden unexpected death in epilepsy; WDAE = withdrawal due to adverse events.

[a] Includes carbamazepine, oxcarbazepine and phenytoin.

[b] Outcomes that patients reported as being important, based on the patient group input.

An information specialist using a peer-reviewed search strategy performed the literature search.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates through Ovid; Embase (1974–) through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was Fycompa (perampanel).

No filters were applied to limit retrieval by study type. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on January 5, 2016. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee (CDEC) on April 20, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters): health technology assessment agencies, health economics, clinical practice guidelines, drug and device regulatory approvals, advisories and warnings, drug class reviews, databases (free), and Internet search. Google and other Internet search engines were used to search for additional web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CADTH Common Drug Review clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 4; excluded studies (with reasons) are presented in Appendix 3.

3. RESULTS

3.1 Findings from the Literature

A total of one study was identified from the literature for inclusion in the systematic review (Figure 1). The included study is summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in Appendix 3.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

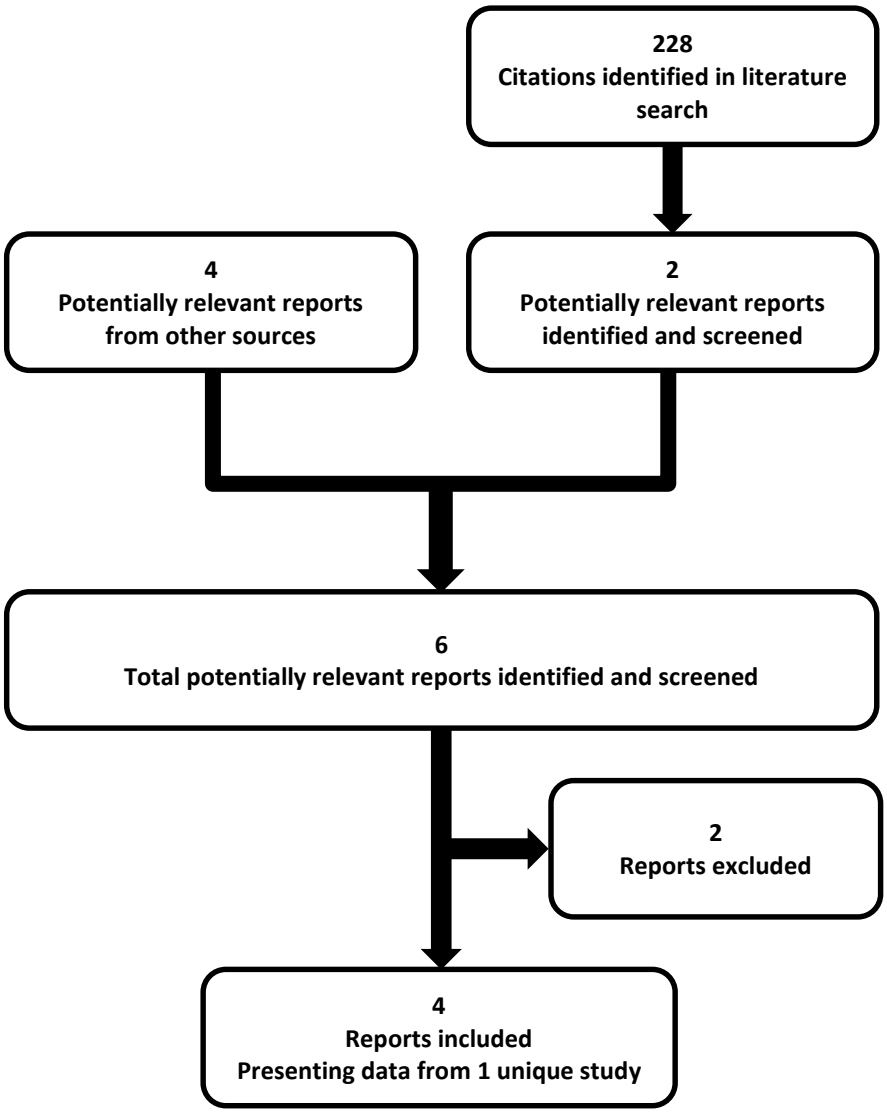


TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 332
DESIGNS & POPULATIONS	**Study Design**	DB RCT
	Locations	Europe, Asia, Australia, US
	Randomized (N)	164
	Inclusion Criteria	• Patients ≥ 12 years of age with PGTC seizures and IGE (confirmed diagnosis based on ILAE classification) • Three or more PGTC seizures during the eight weeks prior to randomization • Taking stable doses of one to three approved AEDs (only one AED could be an enzyme inducer [i.e., carbamazepine, oxcarbazepine, or phenytoin])
	Exclusion Criteria	• History of status epilepticus that required hospitalization in past year • Concomitant diagnosis of partial-onset seizures • Progressive neurologic disease or Lennox-Gastaut syndrome • Seizure clusters where individual seizures could not be counted • Clinically significant disease that could affect safety or study conduct • Alcohol or drug dependency in past two years • Suicidal ideation with intent within past six months
DRUGS	**Intervention**	Perampanel: initial dose 2 mg daily, increased weekly in 2 mg increments, as tolerated, to a maximum of 8 mg daily.
	Comparator(s)	Placebo
DURATION	**Phase**	3
	Pre-randomization (baseline)	Eight weeks
	Double-blind	Titration: four weeks Maintenance: 13 weeks
	Safety follow-up	Four weeks
OUTCOMES	**Primary End Point**	• Per cent change in PGTC seizure frequency per 28 days (titration plus maintenance phase versus baseline)
	Other End Points	• Responder – PGTC seizures (per cent with ≥ 50% reduction PGTC seizure frequency for maintenance phase versus baseline, LOCF) • Per cent change in seizure frequency — all seizures • Responder —all seizures • Proportion PGTC seizure-free • Proportion seizure-free • Clinical Global Impression of Change (CGI-C) • Patient-Weighted Quality of Life in Epilepsy Inventory-31 • Health care resource utilization • Adherence • Harms
NOTES	**Publications**	French 2015[6]

AEDs = anti-epileptic drugs; CGI-C = Clinical Global Impression of Change; C-SSRS = Columbia-Suicide Severity Rating Scale; DB = double blind; IGE = idiopathic generalized epilepsy; ILAE = International League Against Epilepsy; LOCF = last observation carried forward; PGTC = primary generalized tonic-clonic; QOLIE-31-P = Patient-Weighted Quality of Life in Epilepsy Inventory-31; RCT = randomized controlled trial.
Note: Two additional reports were included (CADTH Common Drug Review submission,[19] Health Canada Reviewer's Report[11]).
Source: Clinical Study Report,[7] French.[6]

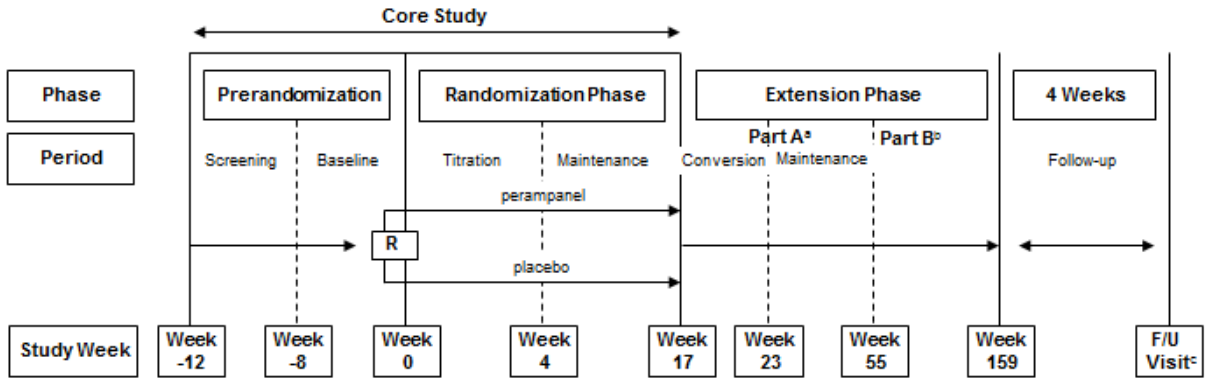
3.2 Included Studies

3.2.1 Description of Studies

Study 332 was a randomized, controlled, double-blind trial, designed to test the superiority of adjunctive perampanel versus placebo for the treatment of refractory PGTC seizures in patients with idiopathic generalized epilepsy. The study consisted of three main periods: the baseline, titration, and maintenance phases (Figure 2). After screening, the baseline rate of PGTC seizures was determined during the eight weeks prior to randomization. Those with three or more PGTC seizures during the baseline period were randomized in a 1:1 ratio to perampanel or placebo, using a computer-generated randomization scheme (stratified by country) and interactive voice response system. Double-blind treatments were titrated over four weeks to the maximum tolerated dose (up to 8 mg/day of perampanel), and then the maximum tolerated dose was continued for 13 weeks during the maintenance period.

Patients who completed the randomization period were eligible to enter the extension phase and receive open-label perampanel. See Appendix 6 for a summary of the extension phase.

FIGURE 2: STUDY 332 DESIGN DIAGRAM



F/U = follow-up; R = random.
[a] All subjects should be retained in the study through the last visit of Extension Part A.
[b] Subjects only need to complete Part B if perampanel is not made available free of charge according to the appropriate local country-specific mechanism (revised per Amendment 03).
[c] The follow-up visit should be conducted for all subjects 4 weeks after their last on-treatment visit.
Source: Clinical Study Report, p. 24.[7]

3.2.2 Populations

a) Inclusion and Exclusion Criteria

The study enrolled patients aged 12 years and older with a clinical diagnosis of drug-refractory PGTC seizures in idiopathic generalized epilepsy (with or without other subtypes of primary generalized seizures). The accuracy of the seizure diagnosis was confirmed for all patients by an independent review by the Epilepsy Study Consortium.

All patients were receiving one to three concomitant AEDs at stable doses for at least 30 days prior to the baseline period. Despite AED therapy, patients had to experience three or more PGTC seizures during the eight-week baseline period in order to meet the inclusion criteria. Key exclusion criteria were partial-onset seizures, recent status epilepticus, pregnancy, suicidal ideation, drug or alcohol dependence, and positive status for HIV or hepatitis A, B, or C.

Study protocol changes included increasing the minimum number of baseline PGTC seizures from two to three and increasing the maximum number of concurrent AEDs from two to three drugs.

b) Baseline Characteristics

Of the 162 patients enrolled in Study 332, 86% of patients were adults (N = 140), and 14% (N = 22) were younger than 18 years of age (mean age per group 27.3 to 29.5 years). The majority of patients were female (56%) and the mean time from diagnosis of epilepsy ranged from 15.7 to 18.6 years. All patients had tonic-clonic seizures; however, 40% also experienced myoclonic seizures and 52% reported absence seizures. [redacted].[11] More patients reported taking one (34%) or two (46%) AEDs than those using three (20%) or four AEDs (< 1%). Besides their seizure disorder, the large majority of patients in both groups had no other neurological disorders. No substantial between-group differences were noted in the baseline characteristics.

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS — STUDY 332

	Overall Population		Subgroup (Age ≥ 18 to < 65 Years)	
	Placebo	Perampanel	Placebo	Perampanel
FAS	N = 81	N = 81	N = 71	N = 68
Age (years), mean (SD)	29.5 (12.2)	27.3 (10.5)	[redacted]	[redacted]
Age group, n (%)			NA	NA
< 18 years	9 (11)	13 (16)		
≥ 18 to < 65 years	71 (88)	68 (84)		
≥ 65 years	1 (1)	0		
Male, n (%)	36 (44)	35 (43)	[redacted]	[redacted]
Safety set	N = 82	N = 81	N = 72	N = 68
Time since diagnosis (years), mean (SD)	18.6 (12.6)	15.7 (10.8)	[redacted]	[redacted]
Seizure type, n (%)				
Tonic-clonic[a]	82 (100)	81 (100)	[redacted]	[redacted]
Myoclonic	33 (40)	32 (40)	[redacted]	[redacted]
Absence	41 (50)	42 (52)	[redacted]	[redacted]
Clonic	1 (1)	0	[redacted]	[redacted]
Tonic	2 (2)	0	[redacted]	[redacted]
Atonic	1 (1)	0	[redacted]	[redacted]
Number of AEDs at baseline			NR	NR
1 AED	29 (35)	26 (32)		
2 AEDs	36 (44)	39 (48)		
3 AEDs	16 (20)	16 (20)		
4 AEDs	1 (1)	0		

AED = anti-epileptic drug; FAS = full analysis set ; NA = not applicable; NR = not reported; SD = standard deviation.
[redacted].[11]
Source: Clinical Study Report.[7]

3.2.3 Interventions

Patients were randomized to perampanel (up to 8 mg daily at bedtime) or identical-looking placebo. The initial dose was perampanel 2 mg daily, which was titrated weekly, as tolerated, in 2 mg increments to a maximum daily dose of 8 mg (titration period four weeks). During the 13-week maintenance phase, patients remained on the maximum dose reached during the titration period unless patients experienced intolerable adverse events, then a one-time 2 mg decrement in dose was allowed. For patients who were not on the maximum daily dose, a one-time 2 mg dose increment was allowed, at the investigator's clinical judgment, for patients with inadequate seizure control.

Patients continued on background AED therapy during the study. Therapy consisted of one to three approved AEDs, of which only one could be a hepatic enzyme inducer (i.e., carbamazepine, oxcarbazepine, or phenytoin). No dose adjustments, addition or deletion of AEDs, were allowed during the trial. In emergencies, additional AEDs could be administered as rescue medications to treat status epilepticus, uncontrolled seizures or seizure clusters. Concomitant use of medications that induced cytochrome P450 hepatic enzyme 3A (other than carbamazepine, oxcarbazepine, or phenytoin) was not allowed. Patients with a vagal nerve stimulator implanted five or more months prior to baseline were allowed to participate in the study. A ketogenic diet was allowed, provided patients had been on the diet for five weeks prior to randomization.

The proportion of patients using specific AEDs is listed in Table 6. There were more patients using an enzyme inducer in the placebo (22%) than in the perampanel (11%) group. Levetiracetam and topiramate were used more frequently, and zonisamide (unavailable in Canada) was used less frequently in the perampanel than placebo groups.

TABLE 6: KEY ANTI-EPILEPTIC DRUG UTILIZATION AT BASELINE

	Study 332	
	Placebo N = 82	Perampanel N = 81
Inducer, n (%)	18 (22)	9 (11)
Carbamazepine	9 (11)	4 (5)
Oxcarbazepine	3 (4)	2 (3)
Phenytoin	6 (7)	3 (4)
Non-inducer, n (%)[a]	73 (89)	79 (98)
Lamotrigine	31 (38)	33 (41)
Valproic acid	28 (34)	27 (33)
Ergenyl chrono[b]	7 (9)	8 (10)
Levetiracetam	21 (26)	30 (37)
Topiramate	7 (9)	18 (22)
Zonisamide[c]	13 (16)	6 (7)
Clonazepam[d]	10 (12)	4 (5)

[a] Includes drugs used by at least 5% of patients enrolled in Study 332.
[b] Prolonged-release valproic acid product not available in Canada.
[c] Not available in Canada.
[d] Patients on clonazepam were taking other AEDs for the treatment of PGTC seizures.
Source: Clinical Study Report.[7]

3.2.4 Outcomes

The primary outcome was the per cent change in PGTC seizure frequency per 28 days for the titration plus maintenance phase versus the baseline period. The primary efficacy outcome for the EU registration was the 50% responder rate (per cent with ≥ 50% reduction PGTC seizure frequency per 28 days) for the maintenance phase versus the baseline period.

Other relevant secondary outcomes included the following:

- Per cent change in seizure frequency per 28 days for all seizures (titration plus maintenance phase versus baseline).
- 50% responder rate per 28 days for all seizures (maintenance phase versus baseline).

Exploratory outcomes included the following:

- Proportion of patients who were PGTC seizure-free during the maintenance period
- Proportion of patients who were seizure-free during the maintenance period
- Clinical Global Impression of Change (CGI-C)
- Patient-Weighted Quality of Life in Epilepsy Inventory-31 (QOLIE-31-P)
- Health care resource utilization

Data on adherence to treatment were collected as part of the study procedures and were reported descriptively.

Seizure count data were recorded by the patient or caregiver using a paper seizure diary. Prior to randomization, at least eight weeks of consecutive seizure diary data were required to determine the baseline seizure frequency. Of these eight weeks, four weeks could be the patient's own retrospective seizure diary if it contained all the information required for the study. Seizure frequency per 28 days (as determined from patient diaries) was calculated as the number of seizures divided by the number of days in the interval and multiplied by 28.

The CGI-C questionnaire was completed by the investigator at the end of the pre-randomization baseline period, at week 12, and at the follow-up visit, to assess the patient's clinical status over the past four weeks. Patients were evaluated on a seven-point Likert scale (1 = very much improved, 7 = very much worse). No evidence was found regarding the validity of the CGI-C for patients with epilepsy (Appendix 5).

The QOLIE-31-P was completed by patients older than 18 years of age at baseline and week 17, and was used to assess changes in quality of life over the previous four weeks. The QOLIE-31-P contains 39 items, including eight subscales (energy, mood, daily activities, cognition, medication effects, seizure worry, distress, and overall quality of life) and an overall QOLIE-31-P score, each scored from 0 (worst) to 100 (best). The inventory was used in countries where a validated translation existed for the spoken language and in the age groups for which it had been validated. In Study 332, the scoring of the QOLIE-31-P was calculated according to the scoring manual (v.2) except for one item, regarding the health state of the patient, which was not scored as designated by the developer's official scoring algorithm. In total, 37 items were used to calculate the eight subscales. Although no data on the minimum clinically important difference were identified for the QOLIE-31-P, the parent instrument, QOLIE-31, has minimum clinically important difference (MCID) estimates ranging from 5.2 to 11.8 points using anchor-based methods, and from 4.7 to 8.5 points using statistical methods (Appendix 5).[20,21]

Health care resource utilization data were collected from patients every four weeks after randomization (week 4, 8, 12, 17, or early discontinuation). Data collected included the number of unscheduled physician visits due to seizures, emergency room visits, and emergency room visits that resulted in hospitalization.

Assessment of adverse events was completed at each study visit (baseline to end of follow-up) and included recording any adverse events, serious adverse events, discontinuation from treatment, suicide ideation and behaviour (based on the Columbia-Suicide Severity Rating Scale [C-SSRS]), concomitant medication usage and laboratory and vital-sign measurements. A serious adverse event was defined as a medical occurrence that resulted in death, was life-threatening, required hospitalization, resulted in persistent disability or incapacity, or was a congenital anomaly. A withdrawal questionnaire was used to assess potential withdrawal signs and symptoms associated with discontinuation of perampanel.

3.2.5 Statistical Analysis

The study was powered to test the superiority of perampanel versus placebo in the change in PGTC seizure frequency per 28 days, and the proportion of patients with at least a 50% reduction in PGTC seizures (i.e., 50% responder rate). With 82 patients per treatment group, the study was estimated to have > 85% power to detect a 30% difference between treatments for the per cent change in PGTC seizure frequency (assuming a common standard deviation [SD] of 60%) based on the Wilcoxon rank-sum test, and > 80% power to detect a 22% difference in the responder rates (assuming a 35% response rate for placebo) using the chi-square test (alpha 0.05, two-sided significance level).

The per cent change in seizure frequency per 28 days was analyzed using a rank analysis of covariance (ANCOVA) model for the full analysis set (FAS) population. The baseline and end point seizure frequency data were first rank-transformed. An ANCOVA was then conducted on the rank-transformed per cent change data, with treatment and pooled country as factors, and ranked baseline seizure frequency as a covariate. The median per cent change between treatments was used due to the expected irregular distribution of seizure frequency. The Hodges-Lehmann estimator and 95% confidence interval were reported for between-treatment differences. The analysis compared the per cent change for the titration plus maintenance period with the baseline (pre-randomization) period. The 50% responder rate was analyzed using the Cochran–Mantel–Haenszel test (stratified by pooled country), comparing the proportion of patients who achieved a 50% or greater reduction in seizure frequency in the maintenance period with the baseline for perampanel versus placebo (FAS), and using last observation carried forward (LOCF) for missing data. The same models were used for the primary outcome (PGTC seizures) and other secondary seizure frequency or responder outcomes.

The treatment group difference in the CGI-C (an exploratory outcome) was analyzed using [redacted]. No adjustments for multiplicity were made for the secondary or exploratory outcomes.

Descriptive statistics were used to summarize the proportion of patients who were seizure-free (categorized by per cent change in PGTC seizure frequency per 28 days), the absolute and per cent change from baseline in QOLIE-31-P domains, and total score. Descriptive statistics were also used to summarize the accumulated number of patients at each visit with each health care resource utilization visit type (i.e., unscheduled physician or emergency room visit) and the number of each type of visits per 28 days averaged across all visits since baseline. For the analysis of the proportion of patients seizure-free, any patient who did not complete the maintenance period was assumed to have failed treatment (i.e., was not seizure-free).

Post-hoc subgroup analyses were conducted based on the following: age group (< 18 years, 18 to < 65 years, and ≥ 65 years), sex, race, country, region, and the most commonly used AEDs at baseline (lamotrigine, valproic acid, levetiracetam, topiramate, zonisamide [not available in Canada], and ergenyl chrono [a prolonged-release valproic acid product not available in Canada]).

No description was provided on how missing data were handled for the QOLIE-31-P. The seizure diary data used to estimate seizure frequency included all valid days reported (either no seizure occurred was recorded or the number and type of seizures was recorded), with no imputation for missing days. Both the analyses of seizure frequency during the maintenance period (a sensitivity analysis of the primary outcome) and the 50% responder analyses used the LOCF for patients who dropped out early. If the overall duration of the maintenance period was less than eight weeks, but treatment duration (titration plus maintenance) was more than eight weeks, the diary data from the last eight weeks were used to calculate seizure frequency. If the treatment duration was less than eight weeks, all diary data were used to calculate the seizure frequency. LOCF was used for missing data for CGI-C. There was no imputation of missing data for the health care resource utilization outcomes.

a) Analysis Populations

The safety set included all randomized patients who received at least one dose of study drug and had at least one post-baseline safety assessment. Patients were analyzed according to the treatment actually received.

The FAS included all randomized patients who received at least one dose of study drug and had at least one post-baseline record of seizure frequency. Patients were analyzed in the treatment groups to which they were randomized.

The per protocol set included patients in the FAS who did not have any major protocol violations and were at least 80% adherent to study medications and to completing seizure diary data.

3.3 Patient Disposition

Of the 307 patients screened for the study, 164 (53%) were randomized to either placebo or perampanel (82 patients per group) (Table 7). Twelve per cent of patients discontinued the study, compared with 17% of patients, in the placebo and perampanel groups, respectively. More patients withdrew due to adverse events in the perampanel group (11%) than in the placebo group (6%).

TABLE 7: PATIENT DISPOSITION

	Study 332	
	Placebo	Perampanel
Screened, N	307	
Randomized, N (%)	164 (53)[a]	
	82	82
Discontinued, N (%)	10 (12)	14 (17)
Withdrew before receiving study drug	0	1 (1)
Adverse event	5 (6)	9 (11)
Patient's choice	2 (2)	3 (4)
Inadequate efficacy	2 (2)	0
Lost to follow-up	1 (1)	1 (1)
FAS, N	81[b]	81

	Study 332	
	Placebo	Perampanel
PP, N	76	75
Safety, N	82	81

FAS = full analysis set; PP = per protocol.
[a] A total of 143 patients (47%) did not meet screening criteria due to failure to meet inclusion/exclusion criteria (n = 117), withdrawal of consent (n = 15) lost to follow-up (n = 7), other reasons (n = 4).
[b] One patient was excluded from the FAS because they did not have any post-baseline seizure data. This patient died as a result of convulsions on day 11, prior to the first post-baseline seizure diary assessment.
Source: Clinical Study Report.[7]

3.4 Exposure to Study Treatments

In Study 332, the median duration of exposure was 17 weeks in both the placebo and perampanel groups (mean 16.2 weeks placebo, 15.7 weeks perampanel). The median daily perampanel dose was 8 mg (range 4 mg to 8 mg; mean 7.5 mg).

3.5 Critical Appraisal

3.5.1 Internal Validity

The study used accepted methods to randomize patients and conceal allocation (interactive voice response system) and patient groups appeared similar at the start of the double-blind period. A matched- placebo was used to maintain blinding. Some unblinding may have occurred due to the frequency of adverse events, such as dizziness and somnolence, in the perampanel group, and this potentially may have biased the reporting of outcomes. Numerically more patients withdrew in the perampanel (n = 14, 17%) than placebo (n = 10, 12%) group, including more withdrawals due to adverse events (11% versus 6%, respectively), although the absolute differences were small. The diagnosis of idiopathic generalized epilepsy was confirmed for all patients by an independent review committee.

The primary end point (i.e., seizure frequency per 28 days or 50% responder rate) was clinically relevant and consistent with US Food and Drug Administration or European Medicines Agency requirements. However, the study was not powered to detect differences in the proportion of patients who were seizure-free, or to detect changes in HRQoL, which are important outcomes to patients. QOLIE-31-P data were reported for [redacted]

The analysis of seizure frequency data were based on a modified intention-to-treat population that included randomized patients who had received at least one dose of the study drug and had post-baseline seizure data recorded. Seizure frequency data were derived from patient or caregiver reports using seizure diaries. Although this is a standard method of recording seizure-frequency–related outcomes in clinical trials of AEDs, self- or caregiver-reporting is subject to individual variability in reporting accuracy and completion.[22-25] Not all seizures may be reported as patients may forget or may not be aware of all seizures, and seizures may not be witnessed by caregivers.[23,24] The seizure type may also be inaccurately classified and compliance with completing seizure diaries may vary.[23,25] Given the severe nature of PGTC seizures, misclassification or failure to report a seizure event may be less likely with PGTC seizures than other types. Also the variability in reporting of seizure events is likely to be similar in both treatment groups and thus any bias would be non-differential. However, the possibility of differential bias cannot be ruled out, given the increased frequency of neurocognitive adverse events in the perampanel group that may affect recall or may have led to unblinding to treatment allocation. In Study 332, any days with no information reported in seizure diaries were excluded from the analyses; however, compliance with completing seizure diaries was reported to be high (> 99% in both groups).

Statistical testing was performed for the primary, secondary, and some exploratory outcomes with no control of multiplicity. Thus, the interpretation of statistically significant results for secondary and exploratory outcomes should be made with caution due to the inflated type I error.

No subgroup analyses were specified in the protocol, thus those presented are assumed to be post hoc. As well, although perampanel is only indicated in Canada for use in adults, Study 332 was not designed to make inferences regarding treatment effects within age groups, and enrolled a mixed population of pediatric and adult patients.

The treatment period was of limited duration (four weeks titration, 13 weeks maintenance therapy) and was considered by the consulting clinical expert to be the absolute minimum duration that could show a treatment effect. Considering the irregular and unpredictable occurrence of PGTC seizures, a longer duration of therapy would likely provide stronger evidence of clinically important treatment effects.

3.5.2 External Validity

According to the clinical expert consulted for this review, the baseline demographic, disease characteristics, and patterns of background AED use of the patients enrolled in Study 332 appear to be representative of those with refractory PGTC seizures in Canadian clinical practice. The clinical expert would classify the patients in Study 332 as difficult to treat as they had at least three PGTC seizures in the eight-week baseline period, despite ongoing AED therapy. Of note, no Canadian centres were included in this multi-national trial, though 24% of those enrolled were from the US.

The Health Canada indication for perampanel is for patients older than 18 years. Study 332 enrolled patients > 12 years of age, and those < 18 years of age comprised 14% of the total study population (n = 22). As a result, there are no trials of perampanel conducted in an adult-only population. Nonetheless, given the relatively small proportion of patients < 18 years of age, and the similarity of treatment effects in pediatric and adult patients, it is unlikely that inclusion of pediatric patients had a substantial impact on generalizability of efficacy results to adults. It is noteworthy that no subgroup data by age were available for harms. The consulting clinical expert indicated that perampanel, like other AEDs, is likely to be used in children despite the lack of an approved indication for this population. Therefore, the limited availability of data in pediatric patients could be considered a limitation. Furthermore, data are lacking in patients older than 65 years of age as only one such person was enrolled in Study 332.

The maximum dosage of perampanel was restricted to 8 mg per day, and thus there is a lack of comparative blinded data for the 10 mg and 12 mg dose approved for use in Canada. Furthermore, no adjustments to concomitant AED therapy was allowed during Study 332, which is not consistent with clinical practice.

Study 332 was placebo-controlled, and no active-controlled trials or indirect treatment comparisons of perampanel in patients with PGTC seizures were identified. The use of placebo in this refractory population does not reflect clinical practice, because such patients would likely be considered for adjunctive therapy with newer AEDs. An active comparator trial would have permitted an assessment of the relative benefit-risk profile of perampanel compared with other AEDs used for refractory epilepsy.

The duration of double-bind treatment (17 weeks) is inadequate to characterize long-term efficacy and safety. The clinical expert advised that this is not unique among trials of AEDs, as the treatment phase in most AED trials is short, even though these therapies are intended for chronic use.

3.6 Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Section 2.2, Table 3). See Appendix 4 for detailed efficacy data.

No data were available for two outcomes of interest in this review: the number of work or school days missed due to epilepsy; and reduction in the use of concomitant AEDs. Study 332 was not designed to evaluate the impact of perampanel on the use of background AED therapies. In Study 332, patients were to remain on pre-existing background therapies during the study period and any change in background therapy was considered a major protocol violation.

The mean seizure diary compliance was reported to be > 99% for both groups.

3.6.1 Seizure-Free Status

In Study 332, the proportion of patients who achieved seizure-free status during the 13-week maintenance period was reported as an exploratory outcome and no statistical testing was conducted. More patients in the perampanel group were PGTC seizure-free than in the placebo group (31% versus 12%, respectively) (Table 8). Similar absolute differences were noted between treatments for the proportion of patients who were free of all seizures (24% versus 5%).

TABLE 8: PROPORTION OF PATIENTS SEIZURE-FREE

	Study 332		
	Placebo N = 81	Perampanel N = 81	Risk Difference (95% CI)
Seizure-free during maintenance period, n (%)[a]			
PGTC seizures	10 (12)	25 (31)	19% (6% to 31%)[a]
All seizures	4 (5)	19 (24)	19% (8% to 29%)[a]

CI = confidence interval; PGTC = primary generalized tonic-clonic.
[a] Calculated by CADTH using Review Manager v. 5.3.
Source: Clinical Study Report.[7]

3.6.2 Health-Related Quality of Life

Data on HRQoL, assessed using the QOLIE-31-P instrument, [redacted]. The median QOLIE-31-P overall score at baseline was 58.1 and 55.5 points, and the change from baseline to week 17 was –1.2 and 3.3 points in the placebo and perampanel groups, respectively (Table 9). Although no formal statistical testing was performed for this exploratory outcome, the between-group differences were small and did not exceed the MCID estimates available for the parent instrument (QOLIE-31), which range from 4.7 to 11.8 points in the literature.

The change from baseline to week 17 scores for the eight QOLIE-31-P domains showed values ranging from [redacted] (Appendix 4, Table 15). The clinical importance of the differences is unclear.

TABLE 9: QOLIE-31-P OVERALL SCORE

	Study 332					
QOLIE-31-P	**Placebo N = 81**			**Perampanel N = 81**		
	Baseline	**Week 17[a]**	**Absolute Change From Baseline**	**Baseline**	**Week 17[a]**	**Absolute Change From Baseline**
Overall Score[b], N	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	58.1 [redacted]	57.7 [redacted]	–1.2 [redacted]	55.5 [redacted]	60.6 [redacted]	3.3 [redacted]

max = maximum; min = minimum; QOLIE-31-P = Patient-Weighted Quality of Life in Epilepsy Inventory-31.
[a] Measured at week 17 or early termination visit.
[b] Overall Score is the mean of the eight subscales with a range from 0 (worst) to 100 (best). Positive change from baseline suggests improvement.
Source: Clinical Study Report.[7]

3.6.3 Seizure Frequency

Over the baseline period, the median PGTC seizure rate was 2.5 and 2.6 seizures per 28 days, and over the treatment period the rate was 1.6 and 0.7 seizures per 28 days, in the placebo and perampanel groups, respectively (Table 10). The median per cent change from baseline was –38% and –77% in the placebo and perampanel groups, respectively, and the differences between groups was statistically significant (-31%; 95% CI, –46% to –15%; $P < 0.0001$).

The PGTC seizure frequency was similar at baseline and the end of treatment for the adult subgroup (≥ 18 to < 65 years, N = 139) as in the overall study population. The PGTC seizure frequency rate was [redacted] seizures per 28 days during treatment, in the placebo and perampanel groups, respectively. In adults, the median per cent change from baseline was –38% for placebo and –74% perampanel (no statistical testing performed) (Appendix 4, Table 16). [redacted]

PGTC seizure frequency data for subgroups based on concomitant use of lamotrigine (N = 64), valproic acid (N = 54), levetiracetam (N = 50) and topiramate (N = 25) are summarized in Appendix 4 , Table 17. The median baseline PGTC seizure frequency rate ranged from [redacted] seizures per 28 days in the subgroups on placebo, and [redacted] for subgroups on perampanel. During treatment, [redacted] PGTC seizures per 28 days were observed in the placebo subgroups, with a median per cent change of [redacted]. In the subgroups receiving perampanel, the PGTC seizure frequency during treatment ranged from [redacted] seizures per 28 days, and the median per cent change from baseline ranged from [redacted]. No statistical testing was performed.

TABLE 10: SEIZURE FREQUENCY

Outcome	Study 332					
	Placebo N = 81			Perampanel N = 81		
	Baseline Phase	Treatment Phase	Per Cent Change	Baseline Phase	Treatment Phase	Per Cent Change
PGTC seizure frequency per 28 days						
Mean (SD)	3.2 (2.0)	2.9 (4.7)	–5.9% (184.6)	3.5 (2.6)	1.9 (3.3)	–56.9% (50.8)
Median (min, max)	2.5 (1.0 to 11.7)	1.6 (0 to 39.1)	–38.4% (–100.0 to 1,546.3)	2.6 (1.4 to 18.5)	0.7 (0 to 22.8)	–76.5% (–100.0 to 184.5)
Median difference versus placebo (95% CI)						–30.8% (–45.5 to –15.2)
P value						< 0.0001
All-seizure frequency per 28 days						
Mean (SD)	33.6 (97.0)	30.2 (85.2)	–13.1% (57.1)	64.4 (197.7)	44.9 (121.9)	–9.3% (192.1)
Median (min, max)	4.6 (1.3 to 589.5)	3.3 (0 to 498.6)	–22.9% (–100.0 to 125.7)	5.5 (1.4 to 1,404.5)	3.3 (0 to 687.9)	–43.4% (–100.0 to 1,366.7)
Median difference versus placebo (95% CI)						–23.5% (–40.7 to –8.5)
P value						0.0018

CI = confidence interval; max = maximum; min = minimum; PGTC = primary generalized tonic-clonic; SD = standard deviation.
Source: Clinical Study Report.[7]

The frequency distribution of all-seizure events was highly skewed, with a baseline rate ranging from 1.3 to 590 seizures in the placebo group and 1.4 to 1,405 seizures per 28 days in the perampanel group (Table 10). The median rate was 4.6 and 5.5 seizures per 28 days during the baseline period, and 3.3 and 3.3 during the treatment period, in the placebo and perampanel groups, respectively. For the placebo group the median per cent change from baseline was –23%, and for perampanel it was –43%, for a between-group difference of –24% (95% CI, –41% to –9%; *P* = 0.0018) (secondary outcome).

3.6.4 Response Rate

The proportion of patients who achieved a 50% or greater reduction in PGTC seizure frequency was statistically significantly higher in the perampanel group (64%) versus the placebo group (40%), *P* = 0.0019 (Table 11).

TABLE 11: RESPONDER ANALYSIS

	Study 332			
50% Responder Rate[a]	**Placebo N = 81**	**Perampanel N = 81**	**Risk Difference (95% CI)**	***P* Value Versus Placebo**
PGTC seizures, n (%)	32 (40)	52 (64)	25% (10%, 40%)[b]	0.0019
All seizures, n (%)	28 (35)	37 (46)	11% (-4%, 26%)[b]	0.18

CI = confidence interval; PGTC = primary generalized tonic-clonic.
[a] Proportion of patients with 50% or greater reduction in seizure frequency per 28 days during the maintenance versus baseline phase (LOCF).
[b] Calculated by CADTH using Review Manager v. 5.3.
Source: Clinical Study Report.[7]

Among the adult subgroup (≥ 18 to < 65 years, N = 139), [redacted] in the placebo group compared with [redacted] in the perampanel group achieved a 50% or greater reduction in PGTC seizure frequency (Appendix 4, Table 18). [redacted] Data for all adults are presented in Figure 3.

The proportion of patients with a 50% PGTC seizure response rate [redacted] in subgroups based on concomitant AED (Figure 3, Appendix 4, Table 18).

FIGURE 3: PROPORTION OF PATIENTS WITH ≥ 50% REDUCTION IN PGTC SEIZURE FREQUENCY BY SUBGROUP

Figure redacted at the request of the manufacturer

PGTC = primary generalized tonic-clonic
Source: Clinical Study Report.[7]

Descriptive data on the categorized per cent change in PGTC seizure frequency is presented in Figure 4 and Appendix 4, Table 19. [redacted]

FIGURE 4: CATEGORIZED PER CENT CHANGE IN PGTC SEIZURE FREQUENCY

Figure redacted at the request of the manufacturer

PGTC = primary generalized tonic-clonic.
Source: Clinical Study Report.[7]

The differences between placebo and perampanel in the proportion of patients with a 50% or greater reduction in all seizures was not statistically significant (35% versus 46%, *P* = 0.18) (secondary outcome) (Table 11).

3.6.5 Clinical Global Impression of Change

The CGI-C was reported for 150 patients as an exploratory outcome (Appendix 4, Table 20). After 12 weeks of treatment, [redacted]

[redacted]

FIGURE 5: CGI-C RATING AT WEEK 12

Figure redacted at the request of the manufacturer

CGI-C = Clinical Global Impression of Change.
Source: Clinical Study Report.[7]

3.6.6 Treatment Adherence

Based on pill counts, one patient (1%) in the placebo and perampanel groups had < 80% treatment adherence and 98% to 99% had compliance rates between 80% and 120%. There were no patients with suspected abuse or diversion of the study drug.

3.6.7 Health Care Resource Utilization

During the 17-week treatment period, 5% and 6% of patients had an unscheduled physician visit, and 12% and 2% had an emergency room visit in the placebo and perampanel groups, respectively (Appendix 4, Table 21). The median rate of unscheduled physician visits, emergency room visits and emergency room visits resulting in hospitalization was 0 visits per 28 days for all outcomes in both treatment groups. No statistical testing was performed on this exploratory outcome.

3.7 Harms

Only those harms identified in the review protocol are reported below (see 2.2.1, Protocol). See Appendix 4 for detailed harms data.

3.7.1 Adverse Events

In Study 332, 72% and 83% of patients in the placebo and perampanel groups, respectively, reported one or more adverse events (Table 12). Dizziness (32%), fatigue (15%), headache (12%), somnolence (11%), and irritability (11%) were the most common adverse events and these were reported more frequently in the perampanel than placebo group (2% to 10%). No events related to overdose, misuse, or abuse were reported during the study.

TABLE 12: ADVERSE EVENTS REPORTED IN ≥ 5% OF PATIENTS IN PERAMPANEL GROUP

	Study 332	
Adverse Events	**Placebo N = 82**	**Perampanel N = 81**
Patients with ≥ 1 adverse event, N (%)	59 (72)	67 (83)
Most common adverse events[a]		
Dizziness	5 (6)	26 (32)
Fatigue	5 (6)	12 (15)
Headache	8 (10)	10 (12)
Adverse Events	**Placebo N = 82**	**Perampanel N = 81**
Somnolence	3 (4)	9 (11)
Irritability	2 (2)	9 (11)
Nasopharyngitis	7 (9)	7 (9)

	Study 332	
Vomiting	2 (2)	7 (9)
Vertigo	2 (2)	7 (9)
Weight increased	3 (4)	6 (7)
Nausea	4 (5)	5 (6)
Contusion	3 (4)	5 (6)
Anxiety	3 (4)	4 (5)
Abdominal pain	1 (1)	4 (5)

Source: Clinical Study Report.[7]

3.7.2 Serious Adverse Events

Serious adverse events were reported in seven (9%) and six (7%) patients in the placebo and perampanel groups, respectively (Table 13). A total of four patients in placebo and two patients in the perampanel group reported convulsion-related serious adverse events, including one case of status epilepticus in each treatment group.

TABLE 13: SERIOUS ADVERSE EVENTS, WITHDRAWALS DUE TO ADVERSE EVENT AND DEATHS

	Study 332	
Adverse Events	**Placebo N = 82**	**Perampanel N = 81**
SAEs		
Patients with at least one SAE, N (%)	7 (9)	6 (7)
Most common SAEs[a]		
Convulsion N (%)	2 (2)	1 (1)
SAE reported in one patient per group	Status epilepticus, grand mal convulsion, nausea, fall, thermal burn	Status epilepticus, suicidal ideation, suicide attempt, constipation, drowning, chronic cholecystitis
WDAEs		
Adverse events leading to treatment discontinuation, N (%)	5 (6)	9 (11)
Most common reasons[a]		
Vomiting	0	2 (2)
Dizziness	0	2 (2)
Suicidal ideation N (%)	2 (2)	1 (1)
Reason reported in one patient per group	Gait disturbance, muscular weakness, musculoskeletal stiffness, convulsion, agitation, confusional state, depression	Lacrimation increased, abdominal discomfort, drowning, fatigue, irritability, decreased appetite, myalgia, sedation, status epilepticus, abnormal behaviour, aggression, anxiety, insomnia, mood swings, suicide attempt
Adverse events leading to dose reduction or interruption, N (%)	6 (7)	9 (11)
Deaths		
Number of deaths, N (%)	1 (1)	1 (1)
Reason for death	Convulsion (likely SUDEP)	Drowning

SAE = serious adverse event; SUDEP = sudden unexpected death in epilepsy; WDAE = withdrawals due to adverse events.
[a] Reported in more than one patient per group.
Source: Clinical Study Report.[7]

3.7.3 Withdrawals Due to Adverse Events

More patients in the perampanel group stopped treatment due to adverse events than in the placebo group (11% versus 6%, respectively) (Table 13). The most common reasons for stopping treatment in the perampanel group were dizziness and vomiting.

Eleven per cent of patients in the perampanel group reported an adverse event that led to a dose reduction or treatment interruption, compared with 7% of patients in the placebo group.

3.7.4 Mortality

Two deaths were reported during Study 332. One patient in the placebo group died as the result of convulsions (likely sudden unexpected death in epilepsy [SUDEP]), and one patient in the perampanel group died of accidental drowning (Table 13).

3.7.5 Notable Harms

In Study 332, standardized queries were run using Medical Dictionary for Regulatory Activities (medDRA) terms for adverse events of special interest (Table 14). Adverse events related to alertness or cognition were reported more frequently in the perampanel than placebo groups (20% versus 15%), mainly due to increased somnolence among those on perampanel (11%). Aggression or hostility-related adverse events were reported in 19% of patients on perampanel compared with 5% of those on placebo. Within this group of adverse events, irritability was the most commonly reported event for perampanel (11%) versus placebo (2%).

More patients on perampanel reported an increase in body weight than in the placebo group (15% versus 5%), including the proportion of patients with a > 7% increase in body weight (11% versus 4%, respectively, Table 14). Dermatologic (15% versus 9%) and ophthalmologic adverse events (7% versus 2%), as well as accidents or injuries (15% versus 11%), were also reported more frequently in patients in the perampanel versus placebo group, respectively.

TABLE 14: NOTABLE HARMS

	Study 332	
Adverse Events	**Placebo N = 82**	**Perampanel N = 81**
Notable harms, n (%)		
Body weight increased	4 (5)	12 (15)
Weight gain > 7%	3 (4)	9 (11)
Dermatologic adverse events	7 (9)	12 (15)
Ophthalmologic adverse events	2 (2)	6 (7)
Hepatic disorder[a]	1 (1)	2 (2)
Fatigue	5 (6)	12 (15)
Accidents or injuries[a]	9 (11)	12 (15)
Falls	1 (1)	2 (2)
Dizziness	5 (6)	26 (32)
CNS-related events[c], n (%)		
Suicide ideation or behaviour	3 (4)	2 (2)
Psychosis or psychotic disorder	3 (4)	6 (7)
Alertness or cognition-related adverse events	12 (15)	16 (20)
Aggression or hostility-related	4 (5)	15 (19)

CNS = central nervous system; medDRA = Medial Dictionary for Regulatory Activities. [a] Based on a standardized MedDRA query of adverse events.
Source: Clinical Study Report.[7]

Based on data from the C-SSRS, two patients (2%) in the perampanel group reported positive suicide-related behaviour (one actual and one aborted suicide attempt), and three patients (4%) reported suicide ideation (Appendix 4, Table 22). No patients in the placebo group reported suicide behaviour but five patients (6%) reported positive suicide ideation. Two events in the perampanel group and none in the placebo group were considered serious adverse events (Table 13). One patient in the perampanel group and two patients in the placebo group stopped treatment due to suicide ideation (Table 13).

4. DISCUSSION

4.1 Summary of Available Evidence

One randomized, double-blind, placebo-controlled trial met the inclusion criteria.[6,7] Study 332 examined the efficacy and safety of adjunctive perampanel (up to 8 mg per day) versus placebo for the treatment of refractory PGTC seizures in patients ≥ 12 years of age with idiopathic generalized epilepsy (N = 164). The primary outcome was the per cent change in PGTC seizure frequency per 28 days (treatment period versus baseline), and the key secondary outcome was the proportion of patients with ≥ 50% reduction in PGTC seizure frequency. The key limitations were the short duration of the study (17 weeks), small sample size (N = 162), lack of active comparator, lack of comparative data on the 10 mg and 12 mg dosages approved for use in Canada, and no control of multiplicity of statistical testing.

4.2 Interpretation of Results

4.2.1 Efficacy

Perampanel showed statistically significant reductions in PGTC seizure frequency (median difference [MD] –30.8%; 95% CI, –45.5% to –15.2%) and all-seizure frequency (MD –23.5%; 95% CI, –40.7% to –8.5%) over the short-term (17 weeks), with statistically significantly more patients showing a ≥ 50% reduction in PGTC seizure frequency compared with placebo (64% versus 40%). Although more patients on perampanel (31%) were PGTC seizure-free than placebo (12%), Study 332 was not designed to test for differences in this outcome, which was identified by patients as one of the key goals of therapy. The clinical expert consulted for this review agreed that elimination of seizures with minimal treatment-related adverse events is the ideal outcome of AED therapy. However, reductions in seizure frequency may be an important alternate goal, particularly for those patients with refractory epilepsy. The reductions in PGTC seizure frequency observed with perampanel in Study 332 were considered to be clinically important by the consulting expert, in this difficult-to-treat population.

Compared with the overall study population, the seizure frequency data were similar for the adult subgroup (N = 139, 85% of patients enrolled), which is the population approved for use in Canada. The per cent change in PGTC seizure frequency or 50% responder rate was similar for perampanel subgroups based on concurrent AED use (lamotrigine, valproic acid, levetiracetam, or topiramate). However, the subgroup analyses should be interpreted with caution, given they were defined post hoc, and the AED subgroups included a limited number of patients (25 to 64).

Though reductions in PGTC seizure frequency were detected with perampanel, data are lacking to show if perampanel improves outcomes that patients report as affecting their day-to-day lives. No clinically important differences were found in HRQoL, based on the QOLIE-31-P. Moreover, clinician-rated change (CGI-C scale) showed few differences between treatment groups in the proportion of patients rated as improved, worsened, or showing no change after 12 weeks of therapy. The QOLIE-31-P and CGI-C data were limited in that they were exploratory outcomes, and [redacted]. No data were available on the number of missed work or school days, which patients report as having an important impact on their lives.

Adherence to treatment was high in Study 332. However, this cannot be used to estimate adherence in clinical practice, as adherence is often optimized during clinical trials by the selection of motivated patients, as well as the close monitoring that is part of the study procedures. In clinical practice, suboptimal treatment adherence contributes to poor treatment response to AED therapy. Post-marketing

data are required to assess if the once-daily dosing of perampanel translates to improved treatment adherence in the community.

The data available to support the use of perampanel for treatment of PGTC seizures has a number of limitations. First, there is no direct or indirect evidence available that compares perampanel with other second-line AEDs. Study 332 compared perampanel with placebo and did not include an active control group. The manufacturer did not supply an indirect treatment comparison as part of the CADTH Common Drug Review (CDR) submission and none were identified in a CDR literature search. Given the lack of comparative data it is difficult to determine perampanel's place in therapy. Second, Study 332 enrolled a limited number of patients (N = 162) and assessed only the 8 mg dose, although the drug is approved for up to 12 mg per day in patients with PGTC seizures. Health Canada has stated that the small sample size was acceptable given that perampanel has been approved for partial-onset seizures (based on data from a larger number of patients), and that type of seizure was anticipated to have little effect on the core efficacy or adverse event profile.[11] With regards to the higher doses of perampanel, the Health Canada reviewer stated that partial-onset data and the open-label extension of Study 332, where 19 of 140 patients received the 12 mg dose, support the same dosing instructions for the PGTC seizure population as for the partial-onset seizure population, including dosing to 12 mg/day as needed and tolerated.[11] Other limitations include the short duration of Study 332 (17 weeks). Although longer-term data are available as part of the extension phase of Study 332, these data have limited utility as seizure frequency was analyzed in 13-week blocks. As analyzed, it does not show, in a way that is meaningful to patients, if reductions in seizure frequency are maintained over the longer-term. Furthermore, the number of patients with longer-term exposure was limited (60 patients at one year) and it was a non-randomized, uncontrolled clinical trial. Thus, uncertainty remains about the longer-term efficacy and safety of perampanel. Lastly, Study 332 did not institute any procedures to control for multiplicity, thus the interpretation of statistically significant results for secondary or exploratory outcomes should be made with caution due to the potential for inflated type I error.

4.2.2 Harms

In Study 332, most patients reported one or more adverse events during the trial (perampanel 83%, placebo 72%), with dizziness (32% versus 6%), fatigue (15% versus 6%), somnolence (11% versus 4%) and irritability (11% versus 2%) reported more frequently in those receiving perampanel. In addition, more patients who received perampanel reported a weight gain > 7% (11% versus 4%) and aggression or hostility-related adverse events (19% versus 5%) compared with placebo. The frequency of serious adverse events was similar in the perampanel and placebo groups, 7% and 9%, respectively. Two patients in the perampanel group and none in the placebo group had serious adverse events related to suicide ideation or behaviour. More patients stopped treatment due to adverse events in the perampanel group (11%) than in the placebo group (6%), with dizziness and vomiting reported as the most frequent reasons among those who received perampanel.

The adverse events reported in Study 332 were consistent with those observed in the partial-onset seizure perampanel trials, Study 332 extension phase, as well as post-marketing data reported to the Health Canada Pharmacovigilance program.[4,8-11] The most frequently reported post-marketing adverse events included seizure; somnolence; hostility, aggression, irritability or anger; dizziness; and suicide ideation or self-injurious behaviour.[8]

Although only one perampanel dose was tested in Study 332, data from partial-onset seizure trials suggest a dose response, with an increasing incidence of some adverse events associated with perampanel doses greater than or equal to 8 mg per day.[9] Thus, the frequency of adverse events may be

higher in clinical practice than observed in Study 332 if more patients are prescribed doses greater than 8 mg per day. Uncertainty remains about the comparative safety of perampanel, given the lack of direct or indirect comparisons.

4.3 Potential Place in Therapy[1]

The clinical expert involved in the review stated that there is an unmet treatment need in the management of patients with PGTC seizures that are not satisfactorily controlled with conventional therapy. According to the clinical expert, patients with "resistant" or "refractory" epilepsy are variably defined, but in essence, the terms are applied to those in whom seizures continue despite adequate trials of standard AEDs. There are no standardized guidelines for treatment of epilepsy, but in practice, an "adequate" AED trial usually means several months of phenytoin, carbamazepine, or valproic acid, either alone or in combination. In the total population of people with epilepsy, about 20% to 30% prove to be resistant or refractory,[12] and among these at least half would have resistant or refractory PGTC seizures. Thus, a substantial proportion of patients with epilepsy would require add-on therapy to manage their PGTC seizures.

Perampanel joins a substantial list of AEDs, any or several of which might be tried in a given patient with resistant or refractory PGTC seizures, according to the clinical expert consulted. Based on Study 332, the efficacy of perampanel as an add-on AED appears to be similar to alternative new AEDs. However, the absence of direct or indirect evidence to support this makes it difficult to draw concrete conclusions about comparative efficacy and safety. One potential advantage of perampanel is that it can be given as a single daily dose, unlike all other available AEDs except phenytoin. In epilepsy, non-compliance with prescribed drugs is an important problem, and non-compliance tends to be more likely with medications requiring multiple daily doses. Perampanel is believed to exert its anti-seizure actions by antagonizing brain AMPA receptors. This mechanism of action is unique to perampanel among available AEDs, but whether this has important practical consequences is unclear. The rate of adverse events, particularly dizziness and somnolence, seems to be higher with perampanel compared with placebo. Although Study 332 did not show a negative impact on quality-of-life measures, these adverse events may become important when the drug is used in clinical practice.

[1] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

5. CONCLUSIONS

Among patients with refractory idiopathic generalized epilepsy, adjunctive perampanel was associated with statistically significant short-term reductions in PGTC seizure frequency, and a higher seizure response rate (≥ 50%), compared with placebo. The impact of perampanel on HRQoL and other outcomes patients report as important is unclear, based on a single, double-blind randomized controlled trial.

Perampanel was associated with an increased frequency of dizziness, aggression or hostility, fatigue, or somnolence, and weight gain compared with placebo.

Uncertainty remains regarding the comparative effects of perampanel, given the lack of direct or indirect treatment comparisons, and additional data are needed to determine the long-term safety and efficacy of this first-in-class drug.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two patient groups submitted input.

Epilepsy Nova Scotia supports individuals with epilepsy in Nova Scotia, New Brunswick, and Prince Edward Island through personal and public education, client-based services, and the support of research. Programs and services include an epilepsy awareness campaign, provision of epilepsy education and information, scholarships, research grants, advocacy and counselling services, and social and recreational programs for adults and children with epilepsy. Epilepsy Nova Scotia declares no relationship or conflict of interest regarding Eisai in terms of funding or the preparation of this submission; however, they intend to pursue a relationship with Eisai in future.

Epilepsy Toronto supports individuals with epilepsy in Toronto by addressing all aspects of epilepsy from the first diagnosis to adult needs, such as employment and relationships. Their programs include counselling, advocacy, support groups, employment workshops, and outreach programs, as well as publishing educational materials. Epilepsy Toronto's membership includes people with epilepsy, their caregivers, donors, and other stakeholders. With regards to possible conflicts of interest in the preparation of this submission, Epilepsy Toronto declares that Bayliss, Sunovion, and Natus have provided funding support to their agency during the past 12 months.

2. Condition-Related Information

The information in this submission was gathered through consultation with executive directors, directors, association members, and board members from Epilepsy Nova Scotia and Epilepsy Toronto.

Epilepsy is a general term for many different types of seizure disorders. It can manifest in an array of symptoms, making it difficult to generally characterize between individuals. At one end of the spectrum are seizures involving the entire brain, in which a person can lose consciousness, convulse, lose bowel control, foam at the mouth, and become temporarily disoriented. At the other end of the spectrum are localized seizures, which can briefly cause a person to become mentally immobile and is often mistaken for "day dreaming." Within this spectrum are seizures that manifest in random, repetitive actions and mental disorientation; however, patients remain continuously conscious during the episodes. Others suffering from epilepsy can experience developmental delays due to the severity of their seizures, which often brings with it comorbidities that complicate treatment. The impacts of epilepsy can vary widely in terms of frequency, severity and duration; and for some patients, epilepsy can have a significant impact on all aspects of life. Some of those suffering from frequent and generalized seizures have to wear a helmet at all times to protect their head. Others require medication resulting in significant negative adverse events. Patients with uncontrolled seizures are often placed in dangerous situations, for example, should a seizure occur while riding a bus, shopping, or crossing a street. In addition, those diagnosed with epilepsy are not permitted by law to operate motor vehicles. These consequences require some patients to be housebound and leave them socially isolated, leading to difficulties in maintaining relationships and a loss of independence.

Professional development can be extremely challenging for those suffering from epilepsy. Current statistics indicate that people with epilepsy have a lower income than people living with other chronic conditions. Obtaining and retaining employment is difficult for those suffering from epilepsy, commonly due to the employer's misinformation, on-the-job safety issues and employee absence. Educational development can also pose overwhelming challenges; learning while managing memory loss due to seizures has been well documented and leads to negative associations with education. Public seizures often lead to taunting, ostracism, stigma, and discrimination. People experiencing seizures have been "tasered" or arrested for being "intoxicated" in public.

When a person has epilepsy, the entire family is affected. Loved ones feel anxiety around when the next seizure will occur and what impact it will have. Caregivers are constantly worried and stressed about who will care for those suffering from epilepsy when they are away. Some caregivers cannot bring themselves to leave their loved one alone, contributing to a loss of independence and self-esteem in the patient. Financial concerns are a common issue for caregivers of a person highly affected by epilepsy. Adverse events associated with medications also affect caregivers, who must deal with mood swings, sexual dysfunction, suicidal thoughts, difficulty concentrating, fatigue, and depression in those with epilepsy. Caring for a person with epilepsy may be a lifetime commitment that can result in sleep deprivation, compassion, and empathy fatigue in the caregiver.

3. Current Therapy-Related Information

The main objective of epilepsy treatment is to completely eliminate seizures. However, many patients only experience a reduction in the absolute number of seizures and continue to have uncontrolled episodes despite treatment. According to patient groups, effective anti-seizure medications are life-saving and can assist them in enjoying a fulfilled life. Other treatment options used to eliminate or reduce certain types of seizures include brain surgery and a ketogenic diet. Approximately 50% to 70% of people with epilepsy are able to control their seizures with currently available treatment options. However, the treatment regimens can be quite varied due to the individual nature of seizures and how patients respond to their treatment. Some of the adverse events associated with anti-seizure medications include memory loss, drowsiness, fatigue, weakness, clumsiness, dizziness, appetite loss, hyperirritability, insomnia, depression, hyperactivity, confusion, mood swings, sexual dysfunction, suicidal thoughts, and exhaustion. Another adverse event associated with anti-seizure treatment often mentioned by patients is impairment of the ability to concentrate or focus. The adverse events caused by anti-seizure medication can be detrimental to the patient's well-being and their personal relationships.

4. Expectations About the Drug Being Reviewed

Approximately 30% of patients suffering from epilepsy continue to have uncontrolled seizures despite currently available treatments, and new treatment options are required to fulfill this unmet need. Patient groups suggest that novel treatment options provide hope for those who have failed to achieve complete seizure elimination. One patient with experience with perampanel reported that it was an easy-to-use once-daily tablet and that it stopped daily seizures almost immediately. The patient reported being seizure-free for two years. Adverse events reported by the patient included dizziness and sleepiness; both were considered acceptable as the drug was taken before bed.

Although no anti-seizure medication is expected to be beneficial for everyone, it is hoped that perampanel will change the lives of some of the 30% of patients who currently suffer uncontrolled or partially controlled seizures. The expectation is that the quality of life of some of these patients will be improved by perampanel, and that they will experience fewer adverse events when compared with other drug treatments.

One of the concerns with treatment as expressed by patient groups is treatment (medication or long-term care) affordability. Many people suffering from epilepsy are either unemployed or underemployed, which can cause financial distress. Under these circumstances treatment cost or reimbursement criteria become extremely important in terms of accessibility. Patient groups express the need for affordable and accessible treatment options for those suffering from intractable epilepsy.

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of search:	January 05, 2016
Alerts:	Biweekly (twice monthly) search updates until April 20, 2016
Study types:	No search filters were applied
Limits:	No date or language limits were used Human filter was applied Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
.sh	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.kw	Keyword heading
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.po	Population group [PsycInfo only]
.rn	CAS registry number
.nm	Name of substance word
pmez	Ovid database code; MEDLINE In-Process & Other Non-Indexed Citations, MEDLINE Daily and Ovid MEDLINE 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY

#	Searches
1	(H821664NPK or 380917-97-5).rn,nm.
2	(Fycompa* or perampanel* or E 2007 or E2007).ti,ab,ot,kw,hw,rn,nm.
3	or/1-2
4	3 use pmez
5	*perampanel/
6	(Fycompa* or perampanel* or E 2007 or E2007).ti,ab.
7	or/5-6
8	7 use oemezd

MULTI-DATABASE STRATEGY	
#	**Searches**
9	conference abstract.pt.
10	8 not 9
11	4 or 10
12	exp animals/
13	exp animal experimentation/ or exp animal experiment/
14	exp models animal/
15	nonhuman/
16	exp vertebrate/ or exp vertebrates/
17	animal.po.
18	or/12-17
19	exp humans/
20	exp human experimentation/ or exp human experiment/
21	human.po.
22	or/19-21
23	18 not 22
24	11 not 23
25	remove duplicates from 24

OTHER DATABASES	
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.

Grey Literature

Dates for Search:	December 2015
Keywords:	Fycompa (perampanel), PGTCS
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist, "Grey matters: a practical tool for searching health-related grey literature" (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

APPENDIX 3: EXCLUDED STUDIES

Reference	Reason for Exclusion
Clinical Study Report: E2007-G000-332. A double-blind, randomized, placebo-Controlled, multicenter, parallel-group study with an open-label extension phase to evaluate the efficacy and safety of adjunctive perampanel in primary generalized tonic-clonic seizures [CONFIDENTIAL internal manufacturer's report]. Bunkyo-ku (JP): Eisai Inc.; 2015 May 12.	Wrong study design
Glauser T, Laurenza A, Yang H, Williams B, Ma T, Fain R. Efficacy and tolerability of adjunct perampanel based on number of antiepileptic drugs at baseline and baseline predictors of efficacy: A phase III post hoc analysis. Epilepsy Res. 2016 Jan;119:34-40.	Wrong population

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 15: CHANGE IN QOLIE-31-P DOMAIN SCORES

QOLIE-31-P Domain	Study 332					
	Placebo (N = 81)			Perampanel (N = 81)		
	Baseline	Week 17[a]	Absolute Change From Baseline[b]	Baseline	Week 17[a]	Absolute Change From Baseline[b]
Overall QoL, N	[redacted]					
Median (min, max)	[redacted]					
Energy, N	[redacted]					
Median (min, max)	[redacted]					
Mood, N	[redacted]					
Median (min, max)	[redacted]					
Daily activities, N	[redacted]					
Median (min, max)	[redacted]					
Cognition, N	[redacted]					
Median (min, max)	[redacted]					
Medication effects, N	[redacted]					
Median (min, max)	[redacted]					
Seizure worry, N	[redacted]					
Median (min, max)	[redacted]					
Distress, N	[redacted]					
Median (min, max)	[redacted]					

max = maximum; min = minimum; QoL = quality of life; QOLIE 31-P = Patient-Weighted Quality of Life in Epilepsy Inventory-31.
[a] Measured at week 17 or early termination visit.
[b] Each domain scored from 0 (worst) to 100 (best); positive change from baseline suggests improvement.
Source: Clinical Study Report.[7]

TABLE 16: SEIZURE FREQUENCY IN ADULT SUBGROUP

Outcome	Study 332 Adults ≥ 18 to < 65 Years					
	Placebo (N = 71)			Perampanel (N = 68)		
	Baseline Phase	Treatment Phase	Per cent Change	Baseline Phase	Treatment Phase	Per Cent Change
PGTC seizure frequency per 28 days						
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	**–38.4% (–100.0, 1,546.3)**	[redacted]	[redacted]	**–74.4% (–100.0, 108.8)**

max = maximum; min = minimum; PGTC = primary generalized tonic-clonic; SD = standard deviation.
Source: Clinical Study Report.[7]

TABLE 17: SEIZURE FREQUENCY — SUBGROUP BASED ON CONCOMITANT ANTI-EPILEPTIC DRUGS

	Study 332					
PGTC Seizure Frequency per 28 Days	Placebo (N = 81)			Perampanel (N = 81)		
	Baseline Phase	Treatment Phase	Per Cent Change	Baseline Phase	Treatment Phase	Per Cent Change
Lamotrigine		N = 31			N = 33	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Valproic acid		N = 27			N = 27	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Levetiracetam		N = 20			N = 30	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Topiramate		N = 7			N = 18	
Mean (SD)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Median (min, max)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

max = maximum; min = minimum; PGTC = primary generalized tonic-clonic; SD = standard deviation.
Source: Clinical Study Report.[7]

TABLE 18: SUBGROUP ANALYSIS FOR 50% RESPONSE RATE

50% Responder Rate,[a] PGTC Seizures, n/N (%)	Study 332	
	Placebo	Perampanel
Subgroup		
Adults (≥ 18 to < 65 years)	[redacted]	[redacted]
Adults (≥ 65 years)	[redacted]	[redacted]
Baseline concomitant AED		
Lamotrigine	[redacted]	[redacted]
Valproic acid	[redacted]	[redacted]
Levetiracetam	[redacted]	[redacted]
Topiramate	[redacted]	[redacted]

AED = anti-epileptic drug; PGTC = primary generalized tonic-clonic.
[a] Proportion of patients with 50% or greater reduction in seizure frequency per 28 days during the maintenance versus pre-randomization phase (last observation carried forward).
Source: Clinical Study Report.[7]

TABLE 19: OTHER SEIZURE OUTCOMES

	Study 332	
Categorized Per Cent Change in PGTC Seizure Frequency per 28 Days (Maintenance, LOCF)	Placebo N = 81	Perampanel N = 81
–100% to –75%	[redacted]	[redacted]
> –75% to –50%	[redacted]	[redacted]
> –50% to –25%	[redacted]	[redacted]
> –25% to 0%	[redacted]	[redacted]
> 0% to 25%	[redacted]	[redacted]
> 25% to 50%	[redacted]	[redacted]
> 50% to 75%	[redacted]	[redacted]
> 75% to 100%	[redacted]	[redacted]
> 100%	[redacted]	[redacted]

LOCF = last observation carried forward; PGTC = primary generalized tonic-clonic.
[a] Patients who did not complete the study were considered not to have achieved seizure-free status.
Source: Clinical Study Report.[7]

TABLE 20: CGI-C RATING

	Study 332		
CGI-C Rating	Placebo	Perampanel	*P* Value Versus Placebo
At baseline, n (%)	[redacted]	[redacted]	
Very much improved	[redacted]	[redacted]	NR
Much improved	[redacted]	[redacted]	
Minimally improved	[redacted]	[redacted]	
No change	[redacted]	[redacted]	
Minimally worse	[redacted]	[redacted]	
Much worse	[redacted]	[redacted]	
Very much worse	[redacted]	[redacted]	

	Study 332		
CGI-C Rating	**Placebo**	**Perampanel**	***P* Value Versus Placebo**
At week 12 (LOCF) compared with baseline, n (%)	[redacted]	[redacted]	
Very much improved	[redacted]	[redacted]	0.56[a]
Much improved	[redacted]	[redacted]	
Minimally improved	[redacted]	[redacted]	
No change	[redacted]	[redacted]	
Minimally worse	[redacted]	[redacted]	
Much worse	[redacted]	[redacted]	
Very much worse	[redacted]	[redacted]	

CGI-C = Clinical Global Impression of Change; LOCF = last observation carried forward; NR = not reported.
[a] Based on Cochran–Mantel–Haenszel test stratified by pooled country for patients with non-missing baseline and post-baseline data.
Source: Clinical Study Report.[7]

TABLE 21: HEALTH CARE RESOURCE UTILIZATION

Week 17[a]	Study 332	
	Placebo (N = 82)	**Perampanel (N = 81)**
Unscheduled physician visits since baseline		
Yes, *n (%)*	[redacted] (5)	[redacted] (6)
No, n (%)	[redacted]	[redacted]
Missing, n (%)	[redacted]	[redacted]
Number of visits per 28 days since baseline, median (min, max)	[redacted]	[redacted]
Emergency room visits since baseline		
Yes, *n (%)*	[redacted] (12)	[redacted] (2)
No, n (%)	[redacted]	[redacted]
Missing, n (%)	[redacted]	[redacted]
Number of visits per 28 days since baseline, median (min, max)	[redacted]	[redacted]
Number of visits resulting in hospitalization per 28 days since baseline, median (min, max)	0.0 [redacted]	0.0, [redacted]

[a] Measured at week 17 or early termination visit. Data were averaged across all treatment visits (approximately every four weeks). Of note: the questionnaire covers the previous 28 days. If more than 28 days had passed since the previous visit or the subject did not answer the questionnaire at a visit, there may be gaps in the data collected.
Source: Clinical Study Report.[7]

TABLE 22: COLUMBIA-SUICIDE SEVERITY RATING SCALE

	Study 332	
	Placebo N = 82	Perampanel N = 81
Patients with at least one positive suicide behaviour	**0**	**2 (2)**
Preparatory acts or behaviour	0	0
Interrupted attempt	0	0
Aborted attempt	0	1(1)
Actual attempt	0	1 (1)
Patients with at least one positive suicide ideation	**5 (6)**	**3 (4)**
Wish to be dead	5 (6)	2 (2)
Non-specific active thoughts	5 (6)	3 (4)
Active thoughts with intent to act	2 (2)	1 (1)
Active thoughts with some intent – no plan	1 (1)	1 (1)
Active thoughts with plan and intent	1 (1)	1 (1)
All patients with suicidal ideation or behaviour	**5 (6)**	**3 (4)**

Source: Clinical Study Report.[7]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Patient-Weighted Quality of Life in Epilepsy Inventory-31 (QOLIE-31-P)
- Clinical Global Impression Scale (CGI-C)

Findings

QOLIE-31-P

The QOLIE-31 is an epilepsy-specific health-related quality-of-life (HRQoL) scale,[26] derived from the longer QOLIE-89, which was developed and validated in 1995.[27] The QOLIE-89 is an epilepsy-focused scale that comprises 17 subscales, including the entire generic HRQoL measure, the Short Form 36 (SF-36). Four dimensions of health scores (epilepsy-targeted, mental health, physical health, and cognitive distress) plus an overall QOLIE-89 score are obtained from the QOLIE-89.

The QOLIE-31 was developed by an expert panel (QOLIE Development Group) in 1998. The group selected the most relevant HRQoL subscales of the QOLIE-89 based on empirical evidence of the most commonly reported issues by patients with epilepsy.[26] This selection resulted in seven subscales (seizure worry, overall quality of life, emotional well-being, energy/fatigue, medication effects, work/driving/social limits, and cognitive functioning) and one overall item, creating the 31-item questionnaire rated on a 4- to 6-point Likert scale, the QOLIE-31, version 1.1. Scoring of the QOLIE-31 requires the conversion of raw data to a scale of 0 to 100 for each subscale, with higher scores reflecting higher quality of life and lower scores worse quality of life. The total score is calculated as a weighted mean of the subscale scores. The subscales showed an adequate range of variability, with mean scores ranging from 55 to 67. The maximum total score is 100 per subscale and total score.[26]

A factor analysis of the seven subscales revealed two factors. The first factor relates to emotional and psychological issues and includes seizure worry, overall quality of life, emotional well-being, and energy or fatigue. The second factor relates to mental efficiency and includes medication effects, work/driving/social limits, and cognitive functioning.[26]

Internal consistency reliability coefficients (Cronbach's alpha) demonstrated adequate to high internal consistency within each subscale, ranging from alpha = 0.77 (social functioning) to alpha = 0.85 (cognitive functioning).[26] Intra-rater reliability was demonstrated for all of the subscales; correlation coefficients between test and re-test data (with a re-test date from one to 21 days after the initial date) ranged from r = 0.64 (medication effects) to r = 0.85 (cognitive functioning), demonstrating adequate to high intra-rater reliability.[26]

Construct validity of the QOLIE-31 was established through concurrent administration of the QOLIE-31 and the QOLIE-89, plus several widely used measures for patients with epilepsy: the VA Systemic and Neurotoxicity Scales (designed to assess signs of epilepsy), symptoms reported by patients, a neuropsychological test battery (measures of attention, memory/language, cognitive speed, motor speed, and mood), plus the Profile of Mood States (POMS), which measures tension, depression, anger, vigour, fatigue, and confusion.[26] As expected, the correlations between the systemic toxicity scores and the QOLIE-31 subscales were low (range [r] = 0.00 to r = 0.006). Six of the scales were statistically significantly correlated with neurotoxicity with $P < 0.0001$ (r = 0.24 to 0.36) and one scale (seizure/worry) was significant with $P < 0.03$ (r = 0.12). The number of anti-epileptic drugs (AEDs) used was statistically

significantly correlated with the work/driving/social limits subscale (r = –0.72, *P* = 0.004); and health care utilization was correlated with total QOLIE score (r = –0.146, *P* = 0.016) and two of the subscales (work/driving/social limits r = –0.182, *P* = 0.002; medical r = –0.136, *P* = 0.020).[26]

A minimum clinically important difference (MCID) has also been established for the QOLIE-31 in a study of 136 consecutive adult patients with refractory focal epilepsy with or without secondary generalization who were being evaluated for epilepsy surgery. Patients completed two epilepsy-specific quality-of-life scales, the QOLIE-31 and QOLIE-89, and two HRQoL scales, the SF-36 and the Health Utility Index III (HUI-III), two times each, six months apart. Concurrent with completion of the quality-of-life scales, patients were also asked to rate changes on the following five domains during the previous six months: overall HRQoL, general health, social activities and work, seizures, and drug side effects. These domains were rated using a 15-point scale ranging from –7 (a very great deal worse) to 0 (no change) to +7 (a very great deal better). A summary global rating was derived from the average score across the five domains. Regression analysis was used to assess the relationship between patients' assessment of overall change and change in quality of life as per the QOLIE-89, QOLIE-31, SF-36 and HUI-III. The MCID for QOLIE-31 was determined to be 11.8, and for QOLIE-89, 10.1.[20]

The MCID in QOLIE-31 was also established using an anchor-based approach and distribution-based approach using data from one phase 2 and two phase 3 trials of adjunctive lacosamide in subjects with partial seizures with or without secondary generalization. Three distribution-based statistics were calculated to estimate the MCID. One method (Effect Size [ES]) combined the change in scores with the standard deviation (SD) of baseline scores as a measure of variability. The other methods (standard error of measurement [SEM], and reliable change index [RCI]) used reliability estimates of the scale scores. For the anchor-based methods, the Patient Global Impression of Change data from the two phase 3 lacosamide trials were used as an anchor. The MCID threshold based on ES varied between 4.73 and 7.88. The SEM and RCI yielded MCID thresholds of 6.01 and 8.50, respectively. The anchor-based MCID threshold ranged between 5.19 and 5.31.[21]

The QOLIE-31-P is a variant of the original QOLIE-31, in which an extra item was added to each of the seven subscales asking the patient to grade their overall distress with respect to the subscale in question. An additional item was also added asking respondents to rank the importance of each subscale topic for a total of 39 items and 8 subscales.[28] The newly added items related to distress were rated using a 5-point scale (not at all, somewhat, moderately, a lot, and very much), in which the ratings were converted to a scale of 0 to 100, with higher scores reflecting higher distress, and lower scores lower distress.[28] No information on the validity of the QOLIE-31-P in patients with epilepsy was identified. An MCID was also not found.

No information was found suggesting that the validity and the MCID identified for the QOLIE-31 are transferable to the QOLIE-31-P.

CGI-C

The CGI-C scale consists of three components: Severity of Illness (CGI-S), Global Improvement (CGI-I), and the Efficacy Index (CGI-E). Scores on the Severity of Illness subscale range from 1 = "not ill at all" to 7 = "among the most extremely ill." The Global Improvement subscale also ranges from 1 = very much improved to 7 = very much worse. The Efficacy Index involves locating a rating on a matrix of therapeutic versus adverse events. Scores range from 0 = marked improvement and no adverse events to 4 = unchanged or worse and adverse events outweigh therapeutic effects.[29] No information on the validity of the CGI-C in patients with epilepsy was identified. An MCID was also not found.

Conclusion

The QOLIE-31-P consists of eight subscales and 39 items rated on a 4 to 6-point Likert scale. No information on the validity of the QOLIE-31-P in patients with epilepsy was identified. The CGI-C scale consists of three components: Severity of Illness (CGI-S), Global Improvement (CGI-I), and the Efficacy Index (CGI-E); the first two components are rated using a 7-point ordinal scale, and the third using a 4-point scale. No information on the validity of CGI in patients with epilepsy was identified.

APPENDIX 6: SUMMARY OF OTHER STUDIES

1. Objective

To summarize the results of the open-label extension phase of Study 332.

2. Findings

Study Design

The purpose of the open-label extension phase of Study 332 was to evaluate the long-term safety, tolerability and efficacy of perampanel. Patients participating in Study 332 were eligible to participate in the open-label extension phase only if they met the following criteria:

- Completed visit 8 (week 17) of Study 332
- Continued to be treated with a stable dose of one to a maximum of three approved anti-epileptic drugs (AEDs)
- Were themselves or had a legal guardian capable of recording seizure or adverse event information
- Females had a negative urine pregnancy test at visit 8 of Study 332 and were willing to use appropriate contraception for at least 30 days after the administration of the last dose of the study drug in the extension phase

The extension phase consisted of two parts depicted in Section 3.2.1 Figure 2; Part A was a six-week blinded conversion period where patients and investigators remained blinded to the treatment. Patients treated with placebo in Study 332 started a blinded treatment of perampanel 2 mg/day in the extension phase. They were subsequently up-titrated in increments of 2 mg/week to an optimal dose (maximum 12 mg per day) as per the investigator's discretion. Patients treated with perampanel in Study 332 remained blinded and continued to receive the same maintenance dose as they received during Study 332. However, the treatment dose could be increased (up to 12 mg) or decreased as per the investigator's judgment. The conversion period was followed by a 32-week maintenance period in which patients were unblinded to the treatment. Part B was a maximum of a 104-week maintenance period. A four-week follow-up was required by all participants after the last on-treatment visit of the extension phase. Data from an interim analysis were summarized in this report (data cutoff date March 2015).[10]

Assessment

Safety was assessed by monitoring adverse events, treatment discontinuation, suicidal ideation and behaviour, prior and concomitant medication usage, clinical laboratory tests (chemistry, hematology, and urinalysis), vital signs, and changes in physical and neurological examinations. In addition, a withdrawal questionnaire was administered to assess potential withdrawal signs and symptoms that might be associated with the discontinuation of perampanel. Efficacy assessment was derived from seizure counts from patient diaries.

Efficacy analyses were based on data from the core and extension phase for patients originally randomized to the perampanel group, and on the extension phase for those who had previously been assigned to placebo. Efficacy data were analyzed in 13-week blocks starting with the first dose o perampanel. Seizure data were only completed for days on which a seizure occurred on and after visit 15; therefore, all days with no entries during this period were imputed with zero. For this reason, diary compliance was only assessed up to visit 15.

Two approaches were used to analyze the efficacy data using different baselines for evaluating change. The first examined seizure data using the pre-perampanel phase as baseline for evaluating change. For patients who had received placebo, the baseline seizure frequency was based on all valid seizure diaries during Study 332. For those randomized to perampanel, baseline seizure data were based on the pre-randomization phase plus four weeks prior to Study 332. The second approach examined seizure data using the pre-randomization phase of Study 332 as the baseline for evaluating change and examined results stratified by treatment received in Study 332.

Results

Of the 164 patients who were randomized in Study 332, 140 completed it [redacted] Patient demographics and baseline characteristics are detailed in Table 23 and are similar across Study 332 and extension phase. Patient disposition is detailed in Table 24.

TABLE 23: BASELINE CHARACTERISTICS —EXTENSION PHASE (SAS)

Category	Total N = [redacted] n (%)
Age (years), mean (SD) min, max	[redacted]
Age group, n (%)	
< 18 years	[redacted]
≥ 18 to < 65 years	[redacted]
≥ 65 years	[redacted]
Male, n (%)	[redacted]
Seizure type, n (%)	
Tonic-clonic	[redacted]
Myoclonic	[redacted]
Absence	[redacted]
Clonic	[redacted]
Tonic	[redacted]
Atonic	[redacted]

max = maximum; min. = minimum; SAS= safety analysis set; SD= standard deviation.
Note: Age at informed consent in Study 332. All other demographics and characteristics are as of baseline in Study 332.
Source: Interim synoptic Clinical Study Report extension phase.[10]

TABLE 24: PATIENT DISPOSITION — EXTENSION PHASE (SAS)

Category	Modal Daily Perampanel Dose				Total
	< 4 mg/day	4 mg/day	> 4 mg to 8 mg/day	> 8 mg to 12 mg/day	
Treated, n	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Completed extension phase, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Discontinued from extension phase, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Ongoing in extension phase, n (%)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Primary reason for discontinuation, n (%)					
Adverse event	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Lost to follow-up	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subject choice	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Inadequate efficacy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Withdrawal of consent	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Pregnancy	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

SAS = safety analysis set.
Source: Interim synoptic Clinical Study Report extension phase.[10]

Safety

[redacted]

Detailed data of the most common (≥ 5% of patients) adverse events are presented in Table 25.

[redacted] Detailed data about adverse events of special interest experienced during the extension phase are presented in Table 26.

[redacted] Complete detailed harms data are presented in Table 27.

[redacted]

[redacted]

TABLE 25: MOST COMMON TREATMENT-EMERGENT ADVERSE EVENT (≥ 5%) — EXTENSION PHASE (SAS)

MedDRA Preferred Term	Modal Daily Perampanel Dose				Total N = [redacted] n (%)
	< 4 mg/day N = [redacted] n, (%)	4 mg/day N = [redacted] n, (%)	> 4 mg to 8 mg/day N = [redacted] n, (%)	> 8 mg to 12mg/day N = [redacted] n, (%)	
Subjects with any AE	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Upper respiratory tract infection	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irritability	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Somnolence	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Headache	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Fatigue	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Weight increased	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Contusion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nausea	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Abdominal pain	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Anxiety	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; MedDRA= Medical Dictionary for Regulatory Activities; SAS= safety analysis set.
Reported adverse events include data on AEs from Study 332 and extension phase for some patients (those in the treatment arm in Study 332). Includes treatment-emergent adverse events considered to be possibly or probably related to perampanel by the investigator or with unknown cause.
Source: Interim synoptic Clinical Study Report extension phase.[10]

TABLE 26: TEAES OF SPECIAL INTEREST — EXTENSION PHASE (SAS)

MedDRA Preferred Term	Total (N = [redacted]) n, (%)
Dizziness	[redacted]
Vertigo	[redacted]
Fatigue	[redacted]
Weight INCREASED	[redacted]
Status epilepticus and convulsions	[redacted]
Cardiac and ECG	[redacted]
Fall	[redacted]
Hepatic disorder abnormalities	[redacted]
Acute pancreatitis	[redacted]
Alertness or cognition	[redacted]
Somnolence	[redacted]
Aggression	[redacted]
Agitation	[redacted]
Mood swings	[redacted]
Mood altered	[redacted]

MedDRA Preferred Term	Total (N = [redacted]) n, (%)
Hostility/aggression	[redacted]
Irritability	[redacted]
Psychosis and psychotic disorders	[redacted]
Abnormal behaviour	[redacted]
Suicidal ideation and behaviour	[redacted]
Suicidal ideation	[redacted]
Attempted suicide	[redacted]
Self-injurious behaviour	[redacted]

ECG = electrocardiogram; MedDRA= Medical Dictionary for Regulatory Activities; SAS= safety analysis set; TEAE = treatment-emergent adverse event.
Reported adverse events include data on AEs from Study 332 and extension phase for some patients (those in the treatment arm in Study 332). Includes TEAEs considered to be possibly or probably related to perampanel by the investigator or TEAE with unknown cause.
Source: Interim synoptic Clinical Study Report extension phase.[10]

TABLE 27: TEAE SUMMARY — EXTENSION PHASE (SAS)

Category	Modal Daily Perampanel Dose				Total N = [redacted] n (%)
	< 4 mg/day N = [redacted] n, (%)	4 mg/day N = [redacted] n, (%)	> 4 mg to 8 mg/day N = [redacted] n, (%)	> 8 mg to 12 mg/day N = [redacted] n, (%)	
TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Severe TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Serious TEAEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Deaths	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other serious AEs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Life-threatening	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Requiring inpatient hospitalization or prolongs existing hospitalization	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Persistent or significant disability or incapacity	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Congenital anomaly/birth defect	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Important medical events	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TEAEs leading to dose adjustment	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leading to withdrawal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leading to dose increase	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Leading to dose reduction	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
eading to dose interruption	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

AE = adverse event; SAS= safety analysis set; TEAE = treatment-emergent adverse event.
Reported adverse events include data on AEs from Study 332 and extension phase for some patients (those in the treatment arm in Study 332). Includes TEAEs considered to be possibly or probably related to perampanel by the investigator or TEAE with unknown cause.
Source: Interim synoptic Clinical Study Report extension phase.[10]

Efficacy

The data detailed in Figure 6 and Figure 7 represents the efficacy relative to the pre-perampanel baseline [redacted]

FIGURE 6: MEDIAN PER CENT CHANGE FROM PRE-PERAMPANEL BASELINE IN PGTC SEIZURE FREQUENCY PER 29 DAYS BY 13-WEEK INTERVALS — EXTENSION PHASE (FAS)

Figure contained confidential information and was redacted at the request of the manufacturer

FAS = full analysis set; PGTC = primary generalized tonic-clonic.
Source: Interim synoptic Clinical Study Report extension phase.[10]

FIGURE 7: PGTC SEIZURE 50% RESPONDER RATE BY 13-WEEK INTERVALS — EXTENSION PHASE (FAS)

Figure contained confidential information and was redacted at the request of the manufacturer

FAS = full analysis set; PGTC = primary generalized tonic-clonic.
Source: Interim synoptic Clinical Study Report extension phase.[10]

The data detailed in Table 28 represent the efficacy relative to the pre-randomization baseline [redacted]

TABLE 28: PGTC SEIZURE FREQUENCY OUTCOMES — EXTENSION PHASE (FAS)

Analysis Window Parameter[a]	Median Per Cent Change in PGTC Seizure Frequency per 28 Days		50% Responder Rate PGTC Seizures, n (%)	
	Prior Placebo	Prior Perampanel	Prior Placebo	Prior Perampanel
Treated — pre-randomization phase, N	[redacted]	[redacted]	[redacted]	[redacted]
Median seizure frequency	[redacted]	[redacted]	[redacted]	[redacted]
Core study maintenance period, N	[redacted]	[redacted]	[redacted]	[redacted]
Median % change or responder rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Extension conversion period, N	[redacted]	[redacted]	[redacted]	[redacted]
Median % change or responder rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

Analysis Window Parameter[a]	Median Per Cent Change in PGTC Seizure Frequency per 28 Days		50% Responder Rate PGTC Seizures, n (%)	
	Prior Placebo	Prior Perampanel	Prior Placebo	Prior Perampanel
Extension maintenance weeks 1–13, N	[redacted]	[redacted]	[redacted]	[redacted]
Median % change or responder rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Extension maintenance weeks 14–26, N	[redacted]	[redacted]	[redacted]	[redacted]
Median % change or responder rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Extension maintenance weeks 27–39, N	[redacted]	[redacted]	[redacted]	[redacted]
Median % change or responder rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Extension maintenance weeks 40–52, N	[redacted]	[redacted]	[redacted]	[redacted]
Median % change or responder rate, n (%)	[redacted]	[redacted]	[redacted]	[redacted]

FAS = full analysis set; NA = not applicable; PGTC = primary generalized tonic-clonic.
[a] Week 1 begins on the date of the first dose of perampanel treatment in either Study 332 (for prior perampanel) or the extension phase (for prior placebo).
Source: Interim synoptic Clinical Study Report extension phase.[10]

Limitations

There are many important limitations related to the extension phase study, the main ones being that it was an open-label, non-randomized study with no control group. In addition, during the maintenance period of the extension phase, patients on concomitant AED medications are able to add, delete, or dose-adjust their treatment regimen; this makes it difficult to ascertain the absolute safety and efficacy of perampanel alone. Moreover, patients were eligible to receive higher doses of perampanel (up to 12 mg daily) during this phase versus what was allowed during the randomized placebo-controlled phase (≤ 8 mg daily), thereby making it difficult to draw concrete comparisons between effects and harms observed between the two phases. Efficacy results for the per cent change in PGTC seizure frequency and the 50% responder rate were reported; however, it should be noted that data on patients diminished with time, as this is an interim analysis of an ongoing study, therefore, there were fewer patients exposed to perampanel at later time points in the extension phase. There is potential for an overestimation of the efficacy and underestimation of the adverse events results due to the fact that the patients who discontinued may not have been doing well on perampanel, leaving only those able to tolerate and subsequently do well long-term. Also, efficacy results (per cent change in PGTC seizure frequency and the 50% responder rate) were analyzed in 13-week blocks instead of the entirety of the extension phase as a whole. This method of analysis also has the potential for an overestimation of the efficacy results, as it shortens the period of time required to show efficacious results, and more patients will show improvement.

3. Summary

The safety and tolerability of perampanel was reported as being similar in both Study 332 and the extension phase at a dose of > 4 mg to 8 mg/day, with no new safety signals identified. However, while the data suggest no new safety concerns and that the reduction in the frequency of PGTC seizures was maintained with longer-term treatment, caution is required for the interpretation of all outcomes, given the high degree of uncertainty resulting from the key limitations of this uncontrolled, non-randomized, open-label, extension phase with a small and highly select patient population.

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