Common Drug Review
Clinical Review Report

May 2016

Drug	eslicarbazepine acetate (Aptiom) oral tablets
Indication	Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy who are not satisfactorily controlled with conventional therapy
Listing request	As per indication
Manufacturer	Sunovion Pharmaceuticals Canada Inc.

This review report was prepared by the Canadian Agency for Drugs and Technologies in Health (CADTH). In addition to CADTH staff, the review team included a clinical expert in Neurology who provided input on the conduct of the review and the interpretation of findings.

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ABBREVIATIONS

AED	antiepileptic drug
ANCOVA	analysis of covariance
CDR	CADTH Common Drug Review
CGI	Clinical Global Impression
CMH	Cochran-Mantel-Haenszel
CNS	central nervous system
CSR	Clinical Study Report
DE	daily entry
EE	event entry
ESL	eslicarbazepine acetate
FDA	US Food and Drug Administration
GCP	good clinical practice
GS	generalized seizures
HRQoL	health-related quality of life
ITT	intention-to-treat
LCS	lacosamide
LS	least squares
MIC	minimally important change
NMA	network meta-analysis
OR	odds ratio
PER	perampanel
POS	partial-onset seizure
QoL	quality of life
QOLIE-31	31-item Quality of Life in Epilepsy Inventory
RCT	randomized controlled trial
SAE	serious adverse event
SD	standard deviation
SSQ	Seizure Severity Questionnaire
SUDEP	sudden unexpected death in epilepsy
TEAE	treatment-emergent adverse event
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Epilepsy is a chronic neurological disorder characterized by recurrent epileptic seizures. Seizures may be classified into two broad categories: partial-onset seizures (POS) and generalized seizures. The goals of treatment in epilepsy are to control seizures, avoid side effects from treatment, and maintain or improve quality of life. Typically, 50% of patients with POS will respond to the first antiepileptic drug (AED) tried, and another 20% will respond to a combination of two or three AEDs. The remaining 30% of patients will be considered to have medication-refractory epilepsy and thus potential candidates for epilepsy surgery. While patients are awaiting surgery, or if they are not surgical candidates, the only option is to continue to treat medically with AEDs. There are limited AEDs available that are effective for patients with refractory epilepsy. Eslicarbazepine acetate (ESL) is an oral, once-daily AED indicated as adjunctive therapy in the management of POS in adult patients who are not satisfactorily controlled with conventional therapy.

Indication under review
Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy who are not satisfactorily controlled with conventional therapy
Listing criteria requested by sponsor
As per indication

The objective of this systematic review was to examine the beneficial and harmful effects of ESL at doses of 800 mg to 1,200 mg daily as adjunctive therapy for the treatment of POS in adult patients who are not satisfactorily controlled with conventional therapy.

Results and Interpretation

Included Studies

Four multi-centre, double-blind, parallel-group, randomized, placebo-controlled, phase 3 superiority trials met the inclusion criteria for this systematic review. Study 301 (N = 402), Study 302 (N = 395), Study 303 (N = 253), and Study 304 (N = 653) enrolled patients with uncontrolled POS with or without secondarily generalized seizures, despite receiving one to three AED treatments. Patients were randomized to once-daily placebo, ESL 800 mg, or ESL 1,200 mg. Studies 301 and 302 also had an ESL 400 mg group (the results for this dose are not presented in this review). Patients in studies 301, 302, and 303 remained on a fixed AED background regimen while in Study 304, patients were permitted the use of a benzodiazepine as a rescue medication and dose modifications of carbamazepine and phenytoin at the beginning of the double-blind period were also permitted. Double-blind treatment in all studies included a two-week titration period and 12-week maintenance period. Studies 301, 303, and 304 also included a tapering period after completion of the maintenance period. Patients who completed the randomized controlled trials (RCTs) had the option to enter a one-year open-label extension (OLE) trial. The primary outcome in all four studies was standardized seizure frequency (seizure frequency per four-week period) during the 12-week maintenance period.

A limitation of studies 301, 302, and 303 included the use of event-entry diaries rather than daily diaries to record seizures, which makes it difficult to differentiate missing entries from seizure non-occurrence. Study 303 was not considered a pivotal trial by Health Canada due to significant good clinical practice compliance issues that included improper activities relating to study conduct, inappropriate enrolment of randomized patients, absence of source documentation to verify data entry, and failure to assure patient safety. Other key limitations of the available evidence included the lack of trials assessing the comparative efficacy and safety of ESL with other clinically relevant AEDs (particularly lacosamide and perampanel, which are also indicated for refractory POS), and the relatively short duration of the trials, which hinders the assessment of durability of effect and long-term safety, although data from OLE trials of one year's duration were available.

Efficacy

The proportion of patients randomized to ESL who achieved seizure-free status over the maintenance phase of the trials ranged from 2.0% to 8.2%. There were no statistically significant differences compared with placebo, except for one comparison in one trial (ESL 1,200 mg versus placebo in Study 301; $P = 0.042$). As the trials were not designed nor adequately powered to detect differences for this outcome, these findings are largely inconclusive.

The primary efficacy analysis of seizure frequency per four-week period during the maintenance period consistently demonstrated statistically significant reductions across the four trials for both ESL 800 mg and ESL 1,200 mg compared with placebo, except for one comparison (ESL 800 mg versus placebo in Study 304). Least squares mean differences between ESL and placebo ranged from 1.6 to 2.7 seizures per four-week period in the 800 mg groups, and 1.9 to 2.8 seizures in the 1,200 mg groups. The subpopulation of patients with complex partial seizures also appeared to benefit from treatment with ESL, with differences achieving statistical significance at the 1,200 mg dose.

The clinical expert indicated that the proportion of responders (i.e., proportion of patients with seizure frequency reduction of 50% or more) is a more clinically useful outcome than standardized seizure frequency. In this respect, it was shown that approximately 30% to 40% of patients demonstrated a 50% or higher reduction in seizures, although differences were not statistically significant in all trials for the ESL 800 mg group. The number needed to treat for this outcome was eight with ESL 800 mg, and ranged from five to seven with ESL 1,200 mg.

The effects of seizures and adverse effects from medications on quality of life, daily function, and independence were identified by patient groups providing input on this submission as important outcomes. However, there were no statistically significant differences between ESL and placebo in the overall scores for the 31-item Quality of Life in Epilepsy Inventory (QOLIE-31), the Seizure Severity Questionnaire (SSQ), and the Clinical Global Impression (CGI) Global Improvement score. For the majority of patients, there was no change or minimal improvement in CGI. It is unclear why the reductions in seizure frequency with ESL did not translate into improvements in health-related quality of life on a disease-specific instrument such as the QOLIE-31 or other patient-reported outcomes, although the higher incidence of adverse effects in the ESL groups may partially explain this finding.

Other efficacy outcomes of interest were: change in standardized seizure frequency, time to seizure control, patient adherence to treatment, and health care utilization. The mean change from baseline in standardized seizure frequency ranged from 21% to 35% for ESL, with no apparent differences between doses, although no statistical comparisons were reported. The median time to seizure control (i.e., a 50% or greater reduction in seizures), measured only in Study 304, was 24.5 days for all groups. Patient

compliance with treatment was high (more than 96%) in all trials. Finally, no data were available pertaining to health care utilization.

In the absence of a direct comparative trial, it is difficult to evaluate the relative risk–benefit profile of ESL compared with other clinically relevant AEDs. Comparisons with lacosamide and perampanel are particularly relevant as all three drugs share the same clinical indication. A manufacturer-submitted network meta-analysis (NMA) compared the efficacy and tolerability of ESL with perampanel and lacosamide. It showed that the three AEDs were more effective than placebo in terms of proportion of responders; however, there were no significant differences between any of the comparators. The precision of the indirect estimates for ESL versus the other active comparators was low; hence, uncertainty remains regarding the comparative efficacy of these three drugs.

Harms

There were two deaths in the placebo groups: one patient died of hypothermia and one patient died of respiratory failure. One patient randomized to the ESL 800 mg group died of status epilepticus while taking ESL 400 mg in the titration phase. The deaths due to hypothermia and to status epilepticus may have been cases of sudden unexpected death in epilepsy.

Patients with at least one treatment-emergent adverse event (TEAE) ranged from 50% to 83% with ESL and appeared to be dose-related, although no formal statistical analyses were reported. The most common TEAEs were related to the central nervous system and included dizziness, headache, and somnolence. The incidence of serious adverse events (SAEs) was highest in the ESL 800 mg group. With ESL 800 mg, SAEs included vertigo, hyponatremia, and vomiting. With ESL 1,200 mg, SAEs included vertigo, exanthem, dizziness, and cerebellar syndrome. The proportion of patients withdrawing due to an adverse event (WDAE) ranged from 8% to 19% with ESL 800 mg, 11% to 26% with ESL 1,200 mg, and 3% to 8% with placebo. Dizziness, nausea, and vomiting were common reasons for stopping treatment. Cognitive disorder, an adverse event identified by a patient group as clinically important, was infrequently reported.

Notable harms identified by the clinical expert included hyponatremia, allergic reactions, skin reactions, and neutropenia. While no cases of allergic reactions were reported, hyponatremia was seen with ESL treatment at both doses, with two cases of severe hyponatremia reported in the ESL 800 mg groups. ESL is in the same pharmacological class as carbamazepine. Severe skin-related adverse events have been reported with carbamazepine, especially in patients who carry a specific human leukocyte antigen (HLA) protein. Although no cases of toxic epidermal necrolysis or Stevens–Johnson syndrome were reported in the four RCTs included, there were cases of skin reactions. One patient treated with ESL 800 mg and three patients treated with ESL 1,200 mg developed exanthem; one of those cases (with ESL 1,200 mg) was considered an SAE. There were also 15 ESL patients who developed rashes. One patient on ESL 800 mg treatment acquired leukocytoclastic vasculitis; he tested negative for the HLA protein.

Finally, the manufacturer-submitted NMA showed there were no statistically significant differences in TEAEs, WDAEs, and SAEs between ESL, lacosamide, and perampanel; however, the 95% credible intervals for comparisons of ESL with other drugs were wide, indicating a high degree of uncertainty regarding these findings.

Other Considerations

In April 2011, Vimpat (lacosamide) was recommended for listing by the Canadian Drug Expert Committee (CDEC) as adjunctive therapy in patients with refractory POS who meet all of the following criteria:

- They are under the care of a physician experienced in the treatment of epilepsy.
- They are currently receiving two or more AEDs.
- All other AEDs are ineffective or not appropriate for them.

In September 2013, CDEC recommended that Fycompa (perampanel) be listed as adjunctive therapy in the management of POS in patients with epilepsy who are not satisfactorily controlled with conventional therapy who meet all of the following criteria:

- They are under the care of a physician experienced in the treatment of epilepsy.
- They are currently receiving two or more AEDs.
- Less costly AEDs are ineffective or not appropriate for them.

Unlike carbamazepine, ESL is not a strong inducer of cytochrome P-450 and, as such, has a lower propensity to cause drug interactions.

Conclusions

In four RCTs of patients with uncontrolled POS despite treatment with one to three AEDs, ESL 800 mg and ELS 1,200 mg demonstrated statistically significant benefits relative to placebo on two key outcomes: seizure frequency per four-week period, and the proportion of patients with a 50% reduction in seizures. A small proportion of ESL-treated patients achieved seizure-free status, but the trials were of insufficient size for definitive assessment of this outcome. There was no difference in health-related quality of life between ESL and placebo. ESL 800 mg appeared to be as effective as ESL 1,200 mg, although the trials were not designed to test for differences between doses. However, there was an apparent dose-dependent increase in TEAEs and WDAEs, as patients in the ESL 1,200 mg group experienced more TEAEs and WDAEs compared with the ESL 800 mg group. The most frequently reported TEAEs with ESL were related to the central nervous system (e.g., dizziness, somnolence, and headache). There were three deaths, two of which may have been cases of sudden unexpected death in epilepsy. There was a lack of data comparing ESL with another clinically relevant AED for refractory POS. A manufacturer-submitted NMA suggested ESL, perampanel, and lacosamide have similar efficacy, although uncertainty remains in this regard due to a high degree of imprecision in the estimates of indirect effects.

TABLE 1: SUMMARY OF RESULTS

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL
Proportion of patients with a 100% reduction in seizures, MP												
N	98	98	102	100	97	100	84	77	84	200	183	212
n (%)	4 (4.1)	8 (8.2)	2 (2.0)	3 (3.0)	5 (5.2)	2 (2.0)	4 (4.8)	3 (3.9)	1 (1.2)	4 (2.0)	4 (2.2)	2 (0.9)
P value vs. PL	0.372	**0.042**	-	0.556	0.16	-	0.185	0.263	-	0.336	0.235	-
RR[a]	2.1	4.2	-	1.5	2.6	-	4.0	3.3	-	2.1	2.3	-
95% CI[a]	0.4 to 11.1	0.9 to 19.1	-	0.3 to 8.8	0.5 to 13.0	-	0.5 to 35.0	0.3 to 30.8	-	0.4 to 11.4	0.4 to 12.5	-
Seizure frequency per 4-week period, MP												
N	94	94	99	88	85	99	80	69	79	200	184	212
LS mean	5.7	5.4	7.6	7.1	7.0	9.8	5.7	5.5	7.3	6.5	6.0	7.9
95% CI	4.9 to 6.5	4.6 to 6.1	6.8, 8.6	6.2 to 8.2	6.0 to 8.1	8.7 to 11.1	4.9 to 6.7	4.6 to 6.5	6.3 to 8.5	5.8 to 7.4	5.3 to 6.8	7.0 to 8.9
LS mean diff. vs. PL	–1.9	–2.2	-	–2.7	–2.8	-	–1.6	–1.9	-	–1.4	–1.9	-
P value vs. PL	**0.0028**	**0.0003**	-	**0.002**	**0.001**	-	**0.048**	**0.021**	-	0.058	**0.004**	-
Proportion of patients with ≥ 50% reduction in seizures, MP												
N	98	98	102	100	97	100	84	77	84	200	183	212
n (%)	33 (33.7)	42 (42.9)	20 (19.6)	32 (32.0)	34 (35.1)	18 (18.0)	29 (34.5)	29 (37.7)	19 (22.6)	61 (30.5)	78 (42.6)	49 (23.1)
RR[a]	1.7	2.2	-	1.8	1.9	-	1.5	1.7	-	1.3	1.8	-
95% CI[a]	1.1 to 2.8	1.4 to 3.4	-	1.1 to 3.0	1.2 to 3.2	-	0.9 to 2.5	1.0 to 2.7	-	1.0 to 1.8	1.4 to 2.5	-
P value vs. PL	**0.0246**	**0.0004**	-	**0.005**	**< 0.001**	-	0.106	**0.02**	-	0.068	**< 0.001**	-
Clinical Global Impression, n (%)[b]												
N	98	98	102	NR	NR	NR	NR	NR	NR	215	205	220
Much improved	25 (26)	23 (24)	21 (21)	NR	NR	NR	NR	NR	NR	56 (28)	59 (30)	35 (17)
Minimally improved	31 (32)	29 (30)	34 (33)	NR	NR	NR	NR	NR	NR	64 (31)	54 (28)	66 (31)
No change	28 (29)	26 (27)	32 (31)	NR	NR	NR	NR	NR	NR	60 (29)	53 (27)	83 (39)
Patients with > 0 TEAEs												
n (%)	49 (50)	62 (61)	32 (31)	84 (83)	78 (80)	68 (68)	45 (53)	49 (61)	34 (39)	145 (67)	163 (78)	125 (56)

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL
Patients with > 0 SAEs												
n (%)	4 (4)	6 (6)	4 (4)	6 (6)	2 (2)	0	0	1 (1)	0	14 (7)	3 (1)	7 (3)
WDAEs												
n (%)	9 (9)	20 (20)	4 (4)	19 (19)	26 (27)	3 (3)	7 (8)	9 (11)	6 (7)	26 (12)	54 (26)	18 (8)
Deaths												
n (%)	0	0	1 (1)	0	0	0	0	0	0	1 (< 1)	0	1 (< 1)
Notable harms, n (%)												
Hyponatremia	0	1 (1)	0	1 (1)	2 (2)	0	0	1 (1)	0	4 (2)	7 (3)	0
Neutropenia	0	0	0	0	0	0	0	0	1 (1)	0	1 (< 1)	1 (< 1)
Exanthem	1 (1)	3 (3)	0	0	0	0	0	0	0	0	0	0
Rash	0	2 (2)	1 (1)	0	3 (3)	1 (1)	2 (2)	1 (1)	0	3 (1)	4 (2)	2 (1)
Leukocytoclastic vasculitis	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0

CDR = CADTH Common Drug Review; CI = confidence interval; diff. = difference; ESL = eslicarbazepine acetate; ITT = intention-to-treat; LS = least squares; MP = maintenance period; NR = not reported; PL = placebo; RR = relative risk; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event; vs. = versus.

[a] Calculated by CDR.

[b] Statistical significance not reported.

Source: Clinical Study Reports.[1-4]

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 (POS), which affect 60% of patients,[5] and generalized seizures (GS).[6] Partial seizures involve only a portion of the brain, typically one lobe of one hemisphere, while GS involve large parts of both hemispheres of the brain. Simple POS are not associated with loss of consciousness, while consciousness is affected in complex POS and GS.[7] A POS can evolve over seconds into a secondarily GS.[6] Many patients will experience more than one type of seizure (for example, simple partial seizures and complex POS with secondarily GS).[6]

It is estimated that approximately 1% of Canadians have epilepsy.[8] Each year in Canada, about 15,500 people are diagnosed with epilepsy.[5] Of these, 44% are diagnosed before the age of five years, 55% before the age of 10, 75% to 85% before 18, and 1.3% over the age of 60.[5] Approximately 60% of new patients are young children and seniors.[5]

1.2 Standards of Therapy

The treatment goals in epilepsy are to achieve seizure freedom and avoid treatment side effects.[9] Monotherapy with an antiepileptic drug (AED) is recommended in patients who are at high risk of recurrent seizures. AED selection is based on seizure type, the potential for adverse effects, drug interactions, comorbid conditions, age and gender, cost, and patient preferences.[6,9] Approximately 50% of patients will be treated successfully with the first AED.[6] If seizures recur with monotherapy, treatment may be augmented or replaced with another AED.[6] Non-pharmacological treatments for refractory epilepsy include vagal nerve stimulation or resective surgery.[6,10] For selected patients, primarily children, dietary therapies may also be used.

Patients with uncontrolled seizures, despite having tried two or more AEDs at a therapeutic dose and despite compliance with treatment, are considered to have medication-refractory epilepsy.[10] Approximately 30% of patients have refractory epilepsy.[7] While patients are awaiting surgery, or if they are not surgical candidates, medical treatment with AEDs is continued. Despite the availability of numerous AEDs with various mechanisms of action, some patients' epilepsy remains refractory; hence there is a need for additional treatment options.

1.3 Drug

Eslicarbazepine acetate (ESL) is a new chemical entity of the dibenzazepine carboxamide class of AEDs.[11] It is chemically related to the existing AEDs, carbamazepine and oxcarbazepine, and all three drugs share similar mechanisms of action.[12,13] ESL differs from oxcarbazepine in that it is almost exclusively converted to S(+) licarbazepine, an active metabolite, whereas oxcarbazepine is converted to both S(+) licarbazepine and R(–) licarbazepine, and 3% to 5% circulates as the parent compound. R(–) licarbazepine crosses the blood–brain barrier less efficiently than S(+) licarbazepine. [11] Furthermore, ESL is not metabolized into carbamazepine-10, 11-epoxide, a compound that may be responsible for some of the adverse events (AEs) seen with carbamazepine.[11] Hence, ESL was specifically developed for greater efficacy with fewer toxic effects through avoidance of toxic metabolites and impure enantiomers compared with carbamazepine.[13,14]

The precise mechanism by which ESL exerts its anticonvulsant action has not been fully elucidated, although it is believed that more than one mechanism of action may come into play.[14,15] ESL's active metabolite, S(+) licarbazepine, is primarily responsible for its pharmacologic action.[11,15] In vitro studies have shown that S(+) licarbazepine stabilizes the inactivated state of voltage-gated sodium channels, delaying their return to the activated state, resulting in an inhibition of repetitive neuronal firing. This is thought to be the main mechanism of the anticonvulsant effect.[11,14]

The starting dose of ESL is 400 mg once daily for one to two weeks, after which the dose is increased to a maintenance dose of 800 mg once daily. Therapy may be initiated at 800 mg once daily if the need for seizure control outweighs a potentially increased risk of AEs during initiation. Based on response and tolerability, the dose may be increased to a maximum of 1,200 mg once daily once the patient has been treated with 800 mg for at least one week.[15] Dose adjustment for renal or hepatic impairment is required.[12,15] ESL is not recommended for use in patients younger than 18 years of age.[12]

Indication under review
Adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy who are not satisfactorily controlled with conventional therapy
Listing criteria requested by sponsor
As per indication

The comparators for ESL with a similar Health Canada indication are perampanel (Fycompa) and lacosamide (Vimpat), which were approved by Health Canada in April 2013 and September 2010, respectively. As with ESL, both lacosamide and perampanel are indicated as adjunctive therapy in the management of POS in adult patients with epilepsy who are not controlled with conventional treatments. Both were recommended for listing with criteria by the Canadian Drug Expert Committee (CDEC; as detailed in section 4.3). A comparison of the key characteristics of ESL, perampanel, and lacosamide is provided in Table 2.

TABLE 2: KEY CHARACTERISTICS OF ESLICARBAZEPINE ACETATE, LACOSAMIDE, AND PERAMPANEL

	Eslicarbazepine Acetate	Lacosamide	Perampanel
Trade Name	Aptiom	Vimpat	Fycompa
Mechanism of Action	Stabilizes the inactivated state of voltage-gated sodium channels	Enhancement of slow inactivation of voltage-gated sodium channels	AMPA receptor antagonist
Indication[a]	Adjunctive therapy in the treatment of POS in patients with epilepsy who are not satisfactorily controlled with conventional therapy	Adjunctive therapy in the management of POS in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy	
Route of Administration	Tablets: 200 mg, 400 mg, 600 mg, and 800 mg	Film-coated tablets: 50 mg, 100 mg, 150 mg, and 200 mg Injection solution: 10 mg/mL	Tablets: 2 mg, 4 mg, 6 mg, 8 mg, 10 mg, and 12 mg
Recommended Dose	Start with 400 mg q.d. × 1 week or 2 weeks. Some patients may have therapy initiated at 800 mg q.d. × 1 week. Based on response and tolerability, the dose may be increased to a maximum of 1,200 mg q.d.	Titration: Start with 50 mg b.i.d. × 1 week, then 100 mg b.i.d. × 1 week and, depending on response and tolerability, increase to 150 mg b.i.d. × 1 week, then to 200 mg b.i.d. The maximum recommended dose is 400 mg daily.	In the presence of EIAEDs[b]: Start with 4 mg q.d. and, based on response and tolerability, increase by increments of 2 mg q.d. at 1-week intervals to a maximum dose of 12 mg q.d. In the absence of EIAEDs: Start with 2 mg q.d. and, based on response and tolerability, increase by increments of 2 mg q.d. at 2-week intervals to 8 mg q.d. If 8 mg q.d. is well tolerated and clinical response is lacking, may increase to a maximum dose of 12 mg q.d.
Serious Side Effects/Safety Issues	Hyponatremia and skin reactions	Cardiac rhythm and conduction abnormalities	Serious psychiatric and behavioural reactions

AMPA = ionotropic alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; b.i.d. = twice daily; EIAED = enzyme-inducing antiepileptic drug; POS = partial-onset seizures; q.d. = once daily.
[a] Health Canada indication.
[b] EIAEDs include carbamazepine, oxcarbazepine, and phenytoin.
Source: Product monographs.[15-17]

2. OBJECTIVES AND METHODS

2.1 Objective

To perform a systematic review of the beneficial and harmful effects of ESL at doses of 800 mg to 1,200 mg daily as adjunctive therapy for the treatment of POS in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.

2.2 Methods

All studies identified by Health Canada as pivotal trials for ESL were included in the systematic review. Other 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 with POS who are not satisfactorily controlled with conventional therapy (i.e., one or more AEDs) Subgroups of interest: age (≥ 18 years to < 65 years; ≥ 65 years), seizure type (simple POS, complex POS, secondarily generalized seizure), background AED use (number of AEDs, enzyme inducers[a] versus non-inducers)
Intervention	Eslicarbazepine acetate 800 mg to 1,200 mg daily (in combination with at least one other AED)
Comparators	In combination with at least one or other AED: • carbamazepine • clobazam • gabapentin • lacosamide • lamotrigine • levetiracetam • oxcarbazepine • perampanel • phenytoin • topiramate • valproic acid/divalproex • vigabatrin • placebo
Outcomes	**Key efficacy outcomes*:*** • seizure-free status (proportion of patients who are seizure free) • health-related quality of life • patient or clinician global impression of change. **Other efficacy outcomes*:*** • change in seizure frequency • proportion of responders (e.g., patients with ≥ 50% or ≥ 75% reduction in seizure frequency) • time to reduction in seizure frequency • reduction in use of concomitant AEDs • patient adherence to treatment • health care resource utilization. **Harms outcomes:** Mortality (SUDEP), AEs, SAEs, WDAEs, AEs of special interest (hyponatremia, allergic reactions, skin reactions, neutropenia)
Study Design	Published and unpublished Phase 3 RCTs

AED = antiepileptic drug; AE = adverse event; POS = partial-onset seizure; RCT = randomized controlled trial; SAE = serious adverse event; SUDEP = sudden unexpected death in epilepsy; WDAE = withdrawal due to adverse event.
[a] Includes carbamazepine, oxcarbazepine, and phenytoin.

The literature search was performed by an information specialist using a peer-reviewed search strategy. Published literature was identified by searching the following bibliographic databases: MEDLINE (1946–) with in-process records and daily updates via Ovid; Embase (1974–) via 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 Aptiom (eslicarbazepine acetate).

Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and controlled clinical trials. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results.

The initial search was completed on November 11, 2014. Regular alerts were established to update the search until the meeting of the Canadian Drug Expert Committee on March 18, 2015. 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 CADTH Grey Matters checklist (www.cadth.ca/en/resources/finding-evidence-is/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), 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.

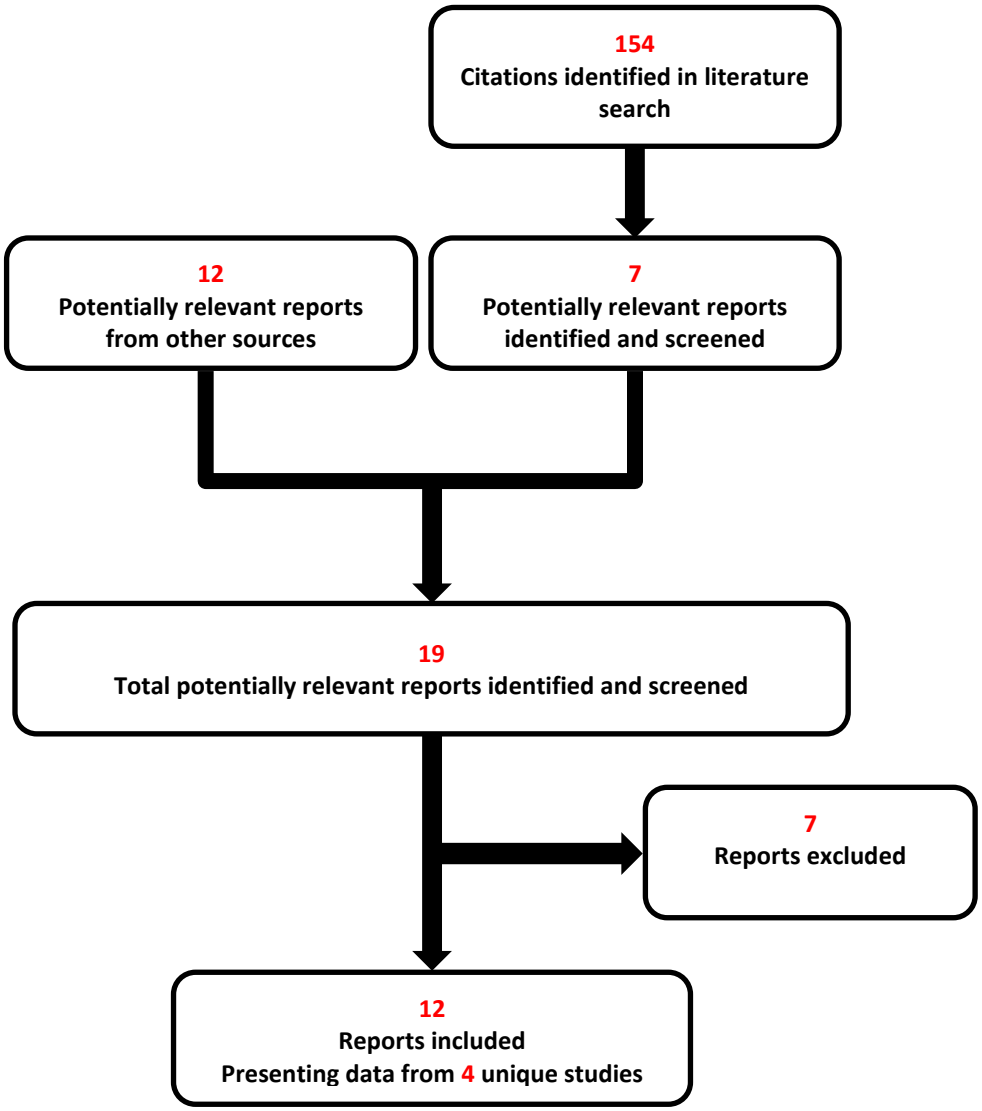
Two CADTH Common Drug Review (CDR) clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers 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: Excluded Studies.

3. RESULTS

3.1 Findings From the Literature

A total of four studies were identified from the literature for inclusion in the systematic review (Figure 1). The included studies are summarized in Table 4 and described in Section 3.2. A list of excluded studies is presented in Appendix 3: Excluded Studies.

FIGURE 1: QUOROM FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES



QUOROM = Quality of Reporting of Meta-analyses.

TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 301	Study 302	Study 303	Study 304
DESIGNS AND POPULATIONS	**Study Design**	Multi-centre, double-blind, placebo-controlled phase 3 RCT			
	Locations	40 centres in 11 countries (Austria, Croatia, Czech Republic, Germany, Hungary, Lithuania, Poland, Romania, Russia, Switzerland, Ukraine)	46 sites in 13 countries (Argentina, Australia, Belgium, Brazil, Denmark, Germany, the Netherlands, Portugal, Romania, South Africa, Spain, Sweden, United Kingdom)	39 sites in 3 countries (Portugal, Spain, Mexico)	173 sites in 19 countries (Argentina, Australia, Belgium, Brazil, Canada, Cypress, France, Germany, Greece, Hungary, India, Italy, Poland, Romania, South Africa, South Korea, Turkey, Ukraine, United States)
	Randomized (N)	402	395	253	653
	Inclusion Criteria	≥ 18 years			≥ 16 years
		Simple or complex POS with or without secondary generalization since at least 12 months before screening			
		At least 4 POS in each of the two 4-week periods prior to screening as well as during each of the two 4-week periods of the 8-week baseline period, and no seizure-free interval > 21 consecutive days			At least 4 POS in the 28 days prior to screening and ≥ 8 POS at baseline with at least 3 POS in each 4-week period of the 8-week baseline period, and no seizure-free interval exceeding 28 consecutive days
		Treated with 1 to 2 AEDs in a stable dose regimen for ≥ 2 months prior to screening	Treated with 1 to 3 concomitant AEDs in a stable dose regimen for ≥ 2 months prior to screening	Treated with 1 to 2 AEDs in a stable dose regimen ≥ 2 months before screening	Treated with 1 or 2 AEDs in a stable dose regimen ≥ 1 month prior to screening
		Patients using vigabatrin were required to have been on the medication for at least 1 year with no deficit in visual field identified			
	Exclusion Criteria	Simple POS without motor symptoms; primarily generalized epilepsy; progressive neurologic disorder; status epilepticus or cluster seizures within three months before screening; seizures of psychogenic origin within the last two years; history of schizophrenia or suicide attempt; AV blockade not corrected with a pacemaker, relevant clinical laboratory abnormalities			
		Received OXC or felbamate within one month of screening			Seizures that were too close in frequency to count accurately, seizures of non-epileptic origin, major psychiatric disorders, currently treated with OXC

		Study 301	Study 302	Study 303	Study 304
DRUGS	**Intervention**	ESL 400 mg, ESL 800 mg, or ESL 1,200 mg once daily for 12 weeks		ESL 800 mg or ESL 1,200 mg once daily for 12 weeks	
	Comparator(s)	Placebo			
DURATION	**Phase**				
	Baseline	8 weeks (patient-blinded, placebo run-in)	8 weeks (observational)		
	Titration	2 weeks			
	Maintenance	12 weeks			
	Tapering	4 weeks	None	4 weeks	2 weeks
	Extension	12 months			
OUTCOMES	**Primary end point**	Seizure frequency per four-week period			
	Other end points	• Proportion of responders (patients with a ≥ 50% reduction in seizure frequency) • Proportion of seizure-free patients (100% seizure reduction) • Proportion of patients with a ≥ 25% increase in seizure frequency • Treatment compliance • CGI • QOLIE-31 • MADRS • SSQ and MOS-SS for Study 304 only			
NOTES	**Publications**	Elger et al.[18]	Ben-Menachem et al.[19]	Gil-Nagel et al.[20]	Sperling et al.[21]

AED = antiepileptic drug; AV = atrioventricular; CDR = CADTH Common Drug Review; CGI = Clinical Global Impression; ESL = eslicarbazepine acetate; MADRS = Montgomery–Åsberg Depression Rating Scale; MOS-SS = Medical Outcomes Study–Sleep Scale; OXC = oxcarbazepine; PL = placebo; POS = partial-onset seizures; QOLIE-31 = 31-item Quality of Life in Epilepsy Inventory; RCT = randomized controlled trial; SSQ = Seizure Severity Questionnaire.
Five additional reports were included: CDR submission,[11] Statistical Report for Study 301,[22] FDA Medical and Statistical Reports,[23,24] and Health Canada Reviewer's Report.[12]
Source: Clinical Study Reports.[1-4]

3.2 Included Studies

3.2.1 Description of Studies

Four multi-centre, double-blind, parallel-group, randomized, placebo-controlled, phase 3 superiority trials were included in the systematic review: Study 301 (N = 402),[3,18] Study 302 (N = 395),[4,19] Study 303 (N = 253)[1,20] and Study 304 (N = 653).[2,21] All studies investigated the efficacy, safety, and tolerability of ESL given as adjunctive therapy (i.e., added onto a background regimen of one to two, or one to three AEDs) for the treatment of POS with or without secondarily GS as detailed in Table 4. There were three study sites in Canada (Study 304) for a total of seven patients. The other trials did not have Canadian sites. Of note, Study 303 was not considered a pivotal trial by Health Canada; however, it met the inclusion criteria outlined in the protocol for the review.

Following an eight-week pre-randomization (baseline) phase, patients were randomized on a 1:1:1:1 basis to once-daily treatment with ESL 400 mg, ESL 800 mg, ESL 1,200 mg, or placebo (studies 301 and 302) and to ESL 800 mg, ESL 1,200 mg, or placebo, also in a 1:1:1 ratio (studies 303 and 304). Patients were treated in a double-blind manner that included a two-week titration phase and a 12-week maintenance phase. All patients in studies 301 and 303 were tapered off treatment at the end of the maintenance phase over a four-week period with the first two weeks of tapering being double-blinded. Patients in Study 304 not entering an extension trial were tapered off in a double-blinded manner over two weeks. Study 302 did not include a tapering phase.

a) Open-Label Extension Trials

Patients who completed the randomized controlled trials (RCTs), including patients who had received placebo, had the option to enter a one-year open-label extension (OLE) trial. Additional information on the OLE trials is available in Appendix 6: Summary of Open-Label Extension Studies.

3.2.2 Populations

b) Inclusion and Exclusion Criteria

Studies 301, 302, and 303 enrolled patients 18 years of age or older. In Study 304, patients were considered for enrolment if they were 16 years of age or older. Patients were required to have a documented diagnosis of simple or complex partial seizures, with or without secondary generalization, within 12 months of screening. In studies 301, 302, and 303, patients were considered for enrolment if they had experienced at least four partial seizures in each four-week period during the last eight weeks immediately preceding screening. Patients were also required to have had at least four partial seizures during each of the two four-week periods of the eight-week baseline period, and no seizure-free interval exceeding 21 consecutive days. In Study 304, a minimum of four partial seizures within four weeks prior to screening was required. A minimum of eight or more partial seizures was also required in the baseline period, with at least three partial seizures in each four-week period of the eight-week baseline period, and no seizure-free interval exceeding 28 consecutive days. All trials required that seizures experienced in the baseline period be documented in a diary.

Patients were required to be currently treated with stable doses of one to two AEDs for at least two months before screening (studies 301 and 303), or at least one month before screening (Study 304), or currently treated with stable doses of one to three AEDs at least two months before screening (Study 302). Vagal nerve stimulation was considered a concomitant AED in studies 301, 302, and 303, but not in Study 304. There was no indication as to whether AED dosing was optimized to achieve maximum efficacy and tolerability.

Key exclusion criteria included the presence of seizure types other than POS (e.g., primary GS), status epilepticus or cluster seizures within three months before screening, history of schizophrenia or suicide attempt, and relevant clinical laboratory abnormalities (e.g., low sodium levels, low white blood cell counts). In Study 304, patients of Asian descent testing positive for HLA-B*15:02 were also excluded.

c) Baseline Characteristics

Patient characteristics are detailed in Table 5 and Table 6. The median age of included patients ranged from 33 to 42 years. There was equal representation of male and female patients in all treatment groups across the studies. Patients were predominantly white, although Study 303 included a high proportion of patients classified as “other” (approximately 60%). Study 304 included a higher proportion of Asian and Chinese patients (approximately 20%) compared with none in Study 301 and less than 5% in studies 302 and 303.

The mean duration of epilepsy ranged from 18 to 23 years across treatment groups in the four trials. The most common seizure type was complex POS (69% to 85%). In studies 302 and 303, 25% to 38% of patients had unclassified seizures. Of note, patients could have presented with more than one seizure type at baseline. The median number of seizures during the baseline period ranged from six to nine seizures per four-week period, with some patients experiencing no seizures and others experiencing a high number of seizures (for example, a maximum of 412 seizures per four-week period in the baseline period).

TABLE 5: SUMMARY OF BASELINE PATIENT CHARACTERISTICS, STUDIES 301 AND 302

	Study 301				Study 302			
	ESL 400 mg	ESL 800 mg	ESL 1,200 mg	PL	ESL 400 mg	ESL 800 mg	ESL 1,200 mg	PL
Safety population, N	100	98	102	102	96	101	98	100
Age, years								
Mean (SD)	37.8 (11.4)	41.3 (12.0)	38.4 (11.7)	37.0 (11.9)	37.6 (11.2)	36.4 (12.6)	36.9 (11.6)	36.7 (12.2)
Median (min, max)	38.1 (18, 71)	42.2 (18, 75)	36.8 (19, 65)	35.8 (18, 68)	37.0 (18, 67)	33.0 (18, 65)	35.5 (18, 69)	36.0 (18, 68)
> 65 years, n (%)	NR	NR	NR	NR	NR	NR	NR	NR
Gender, n (%)								
Male	50 (50)	54 (55)	44 (43)	48 (47)	39 (41)	51 (51)	52 (53)	52 (52)
Race, n (%)								
White	100 (100)	98 (100)	102 (100)	102 (100)	87 (91)	91 (90)	81 (83)	87 (87)
Black	0	0	0	0	2 (2)	6 (6)	9 (9)	6 (6)
Asian	0	0	0	0	2 (2)	0	5 (5)	0
Other	0	0	0	0	5 (5)	4 (4)	3 (3)	7 (7)
Duration of epilepsy, years								
Mean (SD)	21.0 (11.7)	23.1 (13.5)	20.4 (11.9)	19.4 (12.6)	24.7 (11.5)	22.4 (11.6)	23.0 (12.9)	25.4 (13.1)
Median (min, max)	19.6 (1, 55)	20.5 (1, 53)	18.8 (1, 46)	18.0 (1, 54)	23.3 (1, 59)	22.3 (2, 58)	20.9 (2, 66)	23.1 (2, 66)
Seizure type at baseline,[a] n (%)								
Simple partial	43 (43)	43 (44)	46 (45)	45 (44)	51 (53)	58 (57)	55 (56)	59 (59)
Complex partial	69 (69)	70 (71)	70 (71)	71 (70)	77 (80)	77 (76)	80 (82)	84 (84)
Secondarily GS	40 (40)	39 (40)	39 (40)	48 (47)	29 (30)	32 (32)	39 (40)	34 (34)
Unclassified	4 (4)	5 (5)	5 (5)	4 (4)	26 (27)	27 (27)	24 (25)	28 (28)
Number of seizures per 4 weeks during baseline period								
Mean (SD)	11.4 (9.7)	11.2 (11.2)	11.6 (15.9)	12.4 (17.9)	14.2 (16.9)	16.5 (19.6)	14.8 (16.0)	14.3 (16.6)
Median (min, max)	7.5 (3, 56)	7.9 (3, 71)	7.4 (4, 142)	6.7 (2, 154)	8.0 (3, 94)	9.0 (3, 125)	9.0 (1, 90)	8.0 (3, 114)

ESL = eslicarbazepine acetate; GS = generalized seizures; max = maximum; min = minimum; PL = placebo; SD = standard deviation.

[a] Patients could have more than one seizure type at baseline.

Source: Elger et al.,[18] Ben-Menachem et al.[19]

TABLE 6: SUMMARY OF BASELINE CHARACTERISTICS, STUDIES 303 AND 304

	Study 303			Study 304		
	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL
Safety population, N	85	80	87	216	210	223
Age, years						
Mean (SD)	36.8 (10.7)	36.0 (11.4)	37.7 (12.1)	38.8 (12.1)	38.0 (12.0)	39.0 (12.7)
Median (min, max)	36.0 (18, 64)	34.0 (17, 68)	37.0 (17, 77)	38.5 (16, 71)	38.0 (16, 69)	39.0 (16, 67)
> 65 years, n (%)	NR	NR	NR	3 (1)	2 (1)	3 (1)
Gender, n (%)						
Male	35 (41)	35 (44)	43 (49)	109 (51)	105 (50)	112 (50)
Race, n (%)						
White	32 (38)	27 (34)	33 (38)	137 (63)	134 (64)	142 (63)
Black	0	0	0	8 (4)	8 (4)	8 (4)
Asian	1 (1)	0	0	41 (19)	39 (19)	46 (21)
Other[a]	52 (61)	53 (66)	54 (62)	30 (14)	29 (14)	28 (13)
Duration of epilepsy, years						
Safety population, N	85	80	87	215	210	224
Mean (SD)	22.5 (11.8)	23.0 (13.0)	23.8 (13.0)	21.6 (13.0)	21.2 (13.0)	21.3 (14.6)
Median (min, max)	23.5 (0.6, 51)	22.2 (1, 53)	23.6 (1, 63)	19.6 (1, 54)	18.3 (1, 57)	18.3 (1, 63)
Seizure type at baseline (Study 303, safety) or 4 weeks prior to screening (Study 304, ITT), n (%)[b]						
Safety or ITT population, N	85	80	87	215	205	220
Simple partial	47 (55)	46 (58)	56 (64)	84 (39)	66 (32)	81 (37)
Complex partial	72 (85)	64 (80)	62 (71)	170 (79)	170 (83)	175 (80)
SG	24 (28)	29 (36)	31 (36)	59 (28)	63 (31)	57 (26)
Unclassifiable	32 (38)	25 (31)	30 (35)	0	3 (2)	2 (1)
Other	0	0	0	1 (< 1)	0	2 (1)
Missing	0	0	0	1 (< 1)	0	0
Number of seizures per 4 weeks during baseline period						
ITT population, N	84	77	84	215	204	220
Mean (SD)	12.8 (18.2)	11.7 (12.3)	12.6 (17.9)	18.2 (34.5)	17.2 (21.1)	16.3 (19.3)
Median (min, max)	7.7 (1, 150)	6.0 (0, 71)	6.4 (0, 130)	8.6 (2, 412)	8.9 (4, 164)	9.0 (2, 132)

ESL = eslicarbazepine acetate; ITT = intention-to-treat; max = maximum; min = minimum; NR = not reported; PL = placebo; SD = standard deviation; SG = secondarily generalized seizures.

[a] In Study 303, Hispanic patients were reported as "other" in Mexico; in Portugal and Spain, Hispanic patients were reported as white.

[b] Patients could have more than one seizure type at baseline or at screening.

Source: Clinical Study Reports.,[1,2] Gil-Nagel et al.[20]

A summary of the concomitant AEDs used at baseline is provided in Table 7 and Table 8. The majority of patients were on a background regimen of two AEDs (60% to 79%), followed by a single AED (15% to 39%) across treatment groups. Only a minority of patients received a regimen of three AEDs at baseline (up to 10% in Study 302 as per the inclusion criteria). Carbamazepine was the most commonly used AED, ranging from 34% to 69%. Other commonly used AEDs included lamotrigine, levetiracetam, and valproic acid, although there were variations across studies in background use of these drugs. No information was provided on the total number or types of AEDs used by the patient in the past.

TABLE 7: SUMMARY OF ANTIEPILEPTIC DRUGS AT BASELINE, STUDIES 301 AND 302

	Study 301				Study 302			
	ESL 400 mg	ESL 800 mg	ESL 1,200 mg	PL	ESL 400 mg	ESL 800 mg	ESL 1,200 mg	PL
Safety population, N	100	98	102	102	96	101	98	100
AEDs at baseline, n (%)								
1 AED	39 (39)	31 (31)	39 (38)	34 (33)	22 (23)	17 (17)	20 (20)	15 (15)
2 AEDs	60 (60)	67 (68)	63 (62)	67 (66)	68 (71)	73 (72)	68 (69)	76 (76)
3 AEDs	1 (1)	0	0	1 (1)	6 (6)	10 (10)	8 (8)	9 (9)
4 AEDs	0	0	0	0	0	1 (1)	2 (2)	0
AEDs at baseline (> 15% patients), n (%)								
Carbamazepine	56 (56)	59 (60)	57 (56)	63 (62)	59 (62)	61 (60)	58 (59)	58 (58)
Clobazam	2 (2)	0	0	1 (1)	19 (20)	21 (21)	13 (13)	16 (16)
Lamotrigine	25 (25)	26 (27)	27 (27)	27 (27)	21 (22)	17 (17)	21 (21)	24 (24)
Levetiracetam	8 (8)	8 (8)	11 (11)	7 (7)	15 (16)	14 (14)	19 (19)	16 (16)
Phenytoin	3 (3)	3 (3)	3 (3)	3 (3)	11 (12)	15 (15)	12 (12)	14 (14)
Topiramate	9 (9)	19 (19)	11 (11)	16 (16)	11 (12)	11 (11)	15 (15)	12 (12)
Valproic acid	26 (26)	22 (22)	26 (26)	29 (28)	12 (13)	21 (21)	20 (20)	26 (26)
Phenobarbital	4 (4)	12 (12)	9 (9)	8 (8)	11 (12)	13 (13)	9 (9)	18 (18)

AED = antiepileptic drug; ESL = eslicarbazepine acetate; PL = placebo.
Source: Elger et al.,[18] Ben-Menachem et al.,[19] Clinical Study Report.[3]

TABLE 8: SUMMARY OF ANTIEPILEPTIC DRUGS AT BASELINE, STUDIES 303 AND 304

	Study 303			Study 304		
	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL
Safety population, N	85	80	87	216	210	224
AEDs at baseline, n (%)						
1 AED	22 (26)	12 (15)	16 (18)	60 (28)	59 (28)	64 (29)
2 AEDs	58 (68)	63 (79)	66 (76)	153 (71)	151 (72)	158 (71)
3 AEDs	4 (5)	5 (6)	5 (6)	0	0	1 (< 1)
4 AEDs	1 (1)	0	0	0	0	0
AEDs at baseline (> 15% patients), n (%)						
Carbamazepine	43 (51)	39 (49)	60 (69)	84 (39)	89 (42)	77 (34)
Lamotrigine	9 (11)	12 (15)	12 (14)	51 (24)	57 (27)	57 (25)
Levetiracetam	17 (20)	14 (18)	22 (25)	58 (27)	43 (21)	66 (30)
Phenytoin	18 (21)	14 (18)	10 (12)	18 (8)	28 (13)	26 (12)
Topiramate	14 (17)	15 (19)	9 (10)	18 (8)	22 (11)	24 (11)
Valproic acid	23 (27)	28 (35)	27 (31)	46 (21)	41 (20)	42 (19)

AED = antiepileptic drug, ESL = eslicarbazepine acetate, PL = placebo.
Source: Clinical Study Report,[2] Gil-Nagel et al.[20]

3.2.3 Interventions

The trials consisted of a baseline period, a titration period, and a maintenance period. Studies 301, 303, and 304 included a tapering period. The titration period, maintenance period, and the first two weeks of the tapering period were double-blinded. Patients assigned to placebo received placebo in all study periods. The shape, colour, and size of the placebo tablets matched the shape, colour, and size of the 400 mg, 600 mg, or 800 mg ESL tablets.

a) Baseline Period

The baseline period was eight weeks in duration. It was used to assess patient compliance with respect to completion of seizure diaries, and to measure the number of seizures and interval between seizures. Patients were to maintain their concomitant AEDs at a constant dosage. At the end of the baseline period, patients were reassessed for eligibility to enter the trial. In Study 301 only, all patients were treated with placebo in a blinded fashion during the baseline period (in addition to their one to two AEDs).

Patients who met the inclusion criteria set for the baseline period were randomized to once-daily ESL or once-daily placebo. In studies 301 and 302, patients were randomized in a 1:1:1:1 ratio to one of four treatment groups: ESL 1,200 mg, ESL 800 mg, ESL 400 mg, or matching placebo. In studies 303 and 304, patients were randomized in a 1:1:1 ratio to one of three treatment groups: ESL 1,200 mg, ESL 800 mg, or matching placebo. The randomization was stratified by region in Study 304: North America (US and Canada), and the rest of the world.

b) Titration and Maintenance Periods

The titration period occurred over two weeks and the duration of the maintenance period was 12 weeks:

- Study 301: Patients randomized to ESL 1,200 mg received ESL 400 mg once daily in the first week and ESL 800 mg once daily in the second week, then 1,200 mg once daily for the 12-week maintenance period. Patients assigned to ESL 800 mg received ESL 400 mg once daily in the first week and ESL 800 mg once daily in the second week of titration and remained on this dose for the maintenance period. Patients assigned to ESL 400 mg received this dose for both the titration and maintenance periods.
- Study 302: Patients assigned to ESL 1,200 mg started with ESL 800 mg once daily for two weeks before increasing the dose to 1,200 mg once daily for the 12-week maintenance period. Patients assigned to ESL 400 mg or ESL 800 mg received those doses for both the titration and maintenance periods.
- Study 303: Patients randomized to ESL 1,200 mg received ESL 600 mg once daily during the two-week titration period before increasing the dose to 1,200 mg once daily for the 12-week maintenance period. Patients assigned to ESL 800 mg received ESL 400 mg once daily during the two-week titration period before increasing the dose to 800 mg once daily for the 12-week maintenance period.
- Study 304: Patients assigned to ESL 800 mg received ESL 400 mg once daily for two weeks before increasing the dose to 800 mg once daily for the 12-week maintenance period. Patients assigned to ESL 1,200 mg received ESL 800 mg once daily for two weeks before increasing the dose to 1,200 mg once daily for the 12-week maintenance period.

During the maintenance period, dose adjustments of the study drugs were not permitted in any treatment group, and patients were to be withdrawn if a dose adjustment was required (for example due to intolerable AEs).

c) Tapering Period

In studies 301, 303, and 304, the 12-week maintenance period was followed by a tapering period. Down-titration occurred over two weeks (followed by two weeks of placebo) in studies 301 and 303 irrespective of whether or not the patient entered the extension trial, whereas in Study 304, titration occurred only for patients who did not enter the OLE trial. There was no tapering period in Study 302.

Patients who completed the RCTs (including patients who had received placebo) had the option to enter a one-year OLE trial. Additional information on the OLE trials is available in Appendix 6: Summary of Open-Label Extension Studies.

d) Concomitant Medications

In all four trials, any concomitant therapy required for supportive care was allowed. Changes in AED regimens were prohibited in studies 301, 302, and 303. In Study 304, benzodiazepines were permitted for use as rescue medication for seizure control no more than twice per week. Also in Study 304, patients on concomitant carbamazepine or phenytoin could decrease their dose by up to 25% or 15%, respectively, in the last week of the titration period or in the first week of the maintenance period in case of intolerable AEs.

3.2.4 Outcomes

a) Efficacy

Primary Outcome

The primary outcome for all included trials was seizure frequency over the 12-week maintenance period, standardized to frequency per four-week period (mean daily frequency multiplied by 28) in the intention-to-treat (ITT) population. Natural logarithm transformation was applied to standardized seizure frequency in order to meet the assumptions of analysis of covariance (ANCOVA) and to be consistent with sample size calculation. For studies 301, 302, and 303, a constant of +4 was added to avoid log zero (i.e., Ln[standardized seizure frequency + 4]) and, in Study 304, a constant of 0.333 was added.

The occurrence of a seizure and the type of seizure were recorded by the patient (or caregiver) in an event-entry (EE) seizure diary. In the absence of seizure, no entry was recorded. Partway through Study 304 (after 168 patients were randomized and received treatment), the EE seizure diary was changed to a daily entry (DE) seizure diary. Patients subsequently randomized into the trial were to complete the DE diary daily whether or not they had experienced a seizure.

For Study 304, the primary analysis of the primary outcome was performed on two populations in two ordered stages: the ITT population (stage 1 of the type I error-control strategy) and the DE diary ITT population (stage 2 of the type I error-control strategy).

In all trials, the diaries were reviewed at randomization (visit 2), two weeks (visit 3), eight weeks (visit 4), and 14 weeks (visit 5). Visit schedules had a three-day window.

Secondary Outcomes

Secondary outcomes related to seizure included:

- Standardized seizure frequency during the titration period and every four weeks during the maintenance period
- Seizure frequency during each week
- Standardized seizure frequency by seizure type
- Percentage change from baseline in standardized seizure frequency
- Proportion of patients with a 50% or greater reduction in seizure frequency compared with baseline
- Distribution of seizure reduction (seizure reduction of less than 50%; from 50% to 75%; and greater than 75%) compared with baseline
- Proportion of seizure-free patients (100% seizure reduction) compared with baseline

- Proportion of patients with a 25% or greater increase in seizure frequency compared with baseline
- Time to seizure control (Study 304); seizure control was defined as a 50% or greater reduction in standardized seizure frequency.

Other secondary outcomes included:

- Treatment retention time (time to withdrawal due to lack of efficacy or AEs) in studies 301, 302, and 303.
- Proportion of patients remaining on treatment for the duration of the study in Study 304.
- Adherence to treatment, assessed by returned tablet count.
- Health-related quality of life (HRQoL): HRQoL was measured with the 31-item Quality of Life in Epilepsy Inventory (QOLIE-31), an instrument that is described in detail in Appendix 5: Validity of Outcome Measures. The QOLIE-31 is a self-reported questionnaire comprising seven subscales and 31 items. It measures emotional well-being, social functioning, energy and fatigue, cognitive functioning, seizure worry, medication effects, and overall quality of life in the previous 28 days. The instrument also includes a single item that assesses overall health. Items are measured on a four- to six-point Likert scale. The overall score is a weighted average of the multi-item scale scores. The maximum score per subscale and overall is 100. Higher scores indicate a better quality of life. The QOLIE-31 has established responsiveness and the minimal clinically important difference ranges between 4.73 points and 11.8 points.
- Clinical Global Impression (CGI): The CGI scale, described in Appendix 5: Validity of Outcome Measures, consists of three components: Severity of Illness (CGI-S), Global Improvement (CGI-I), and the Efficacy Index (CGI-E). Scores on the CGI-S subscale range from 1 (not ill at all) to 7 (among the most extremely ill). The CGI-I subscale ranges from 1 (very much improved) to 7 (very much worse). The CGI-E involves locating a rating on a matrix of therapeutic versus AEs. Scores range from 0 (marked improvement and no AEs) to 4 (unchanged or worse and AEs outweigh therapeutic effects). The CGI instrument does not yield a global score as each component of the CGI is rated separately. A minimal clinically important difference has not been specified for CGI.
- Seizure Severity Questionnaire (SSQ): The SSQ was not a prespecified outcome in the CDR protocol. However, given that this is an important outcome for patients, the SSQ results (measured in Study 304 only; see Appendix 5: Validity of Outcome Measures for description) are reported in the systematic review. The SSQ was developed to evaluate seizure severity as a treatment response by characterizing changes in bothersomeness and severity of specific seizure characteristics (e.g., shifts from complex to simple partial seizures, or cognitive effects). It is a 24-item questionnaire with three sections. The first section deals with frequency and helpfulness of warning signs. The second section focuses on bothersomeness and severity of ictal movement and loss of consciousness. The third section examines the emotional, cognitive, and physical aspects of postictal recovery. There are seven response categories for each of these three sections. The responses for the frequency questions range from 1 (never) to 7 (always). The responses for the bothersomeness questions range from 1 (no bother at all) to 7 (very bothersome). The responses for the severity questions range from 1 (very mild) to 7 (very severe). The summary score comprises the warning, activity, and recovery phases of the seizure. The minimally important change (MIC) thresholds for the SSQ within-group differences were determined to be 0.50, 0.39, and 0.48 for the three composite scores evaluated (i.e., activity during seizures, overall recovery, and overall severity, respectively). The MIC thresholds for the physical, cognitive, and emotional components of recovery were 0.34, 0.48, and 0.42, respectively. The MIC threshold for the total score was 0.48.

b) Harms

In Study 301 and in Study 304, AEs could be symptoms, signs, or clinically relevant laboratory abnormalities occurring during the course of the study and causing an undesirable change in the function, structure, or chemistry of the body, whether or not the change was considered related to the study drug. A worsening of a pre-existing condition occurring during the study was also an adverse event. A serious adverse event (SAE) was any untoward adverse event that a patient suffered during the course of the study that resulted in death or: was life-threatening; required hospitalization or prolonged hospitalization; resulted in persistent or significant disability or incapacity; or was a congenital anomaly, birth defect, or other medically important condition.

Safety assessments in studies 302 and 303 included monitoring for AEs, SAEs, laboratory data, concomitant medications, vital signs, electrocardiograms, and other physical findings, and determining whether these were related to the study medication, were serious, led to permanent discontinuation of study participation, or led to death. Other safety end points included withdrawal or rebound effects during the tapering-off period.

3.2.5 Statistical Analysis

a) Sample Size and Power

The estimation of sample size was carried out for the primary outcome; i.e., the natural log transformation of the seizure frequency in a four-week period:

- For studies 301, 302, and 303, the assumed change for placebo from baseline to the end of the maintenance period using the log of the seizure frequency was assumed to be –0.05, and the change for the active groups was assumed to be –0.30. These assumptions were derived from the US Food and Drug Administration's (FDA) review of the Keppra (levetiracetam) submission by averaging the results of three trials. The assumed standard deviation (SD) was 0.50, based on one of the levetiracetam studies.
- For studies 301 and 302, the alpha level was set at 0.017 based on a Bonferroni adjustment for comparisons of three doses of an active drug with placebo (each at the alpha = 0.05 level). These assumptions yielded a required sample size of 86 patients per treatment group. Assuming that approximately 15% of randomized patients would be dropped from the efficacy population, a total of 400 patients were required in each study.
- For Study 303, the alpha level was 0.025, based on a Bonferroni adjustment for comparisons of two doses of active drug with placebo (each at the alpha = 0.05 level).These assumptions yielded a sample size of 71 patients per treatment group. Assuming that approximately 15% of randomized patients would be dropped from the efficacy population, a total of 252 patients was required.
- For studies 302 and 303, power was set at 80% (not reported in Study 301).
- Originally, in Study 304, the assumed change for placebo from baseline to the end of the maintenance period using the natural log transformation of the standardized seizure frequency was –0.08, and the assumed change for the active groups was 0.30. The assumed SD was 0.50. The alpha level was 0.025, based on a Bonferroni adjustment for comparisons of two doses of an active drug with placebo (each at the alpha = 0.05 level). These assumptions yielded a sample size of 100 patients per treatment group to achieve a power of 80%. Assuming that approximately 15% of randomized patients would be dropped from the double-blind period, a total of 360 patients was required. However, this plan was revised to obtain the required number of patients for the assessment of the primary efficacy variable collected in a DE seizure diary instead of an EE diary. The sample size was recalculated to detect a treatment difference (in standardized seizure frequency during the maintenance period) of 0.174 in the DE diary group, with an SD of 0.4. Assuming a dropout rate of 10% (based on the actual dropout rates observed in studies 301 and 302), a total of 435 patients

using the DE diary (145 patients in each of the three groups) was required to achieve 89.4% power, in addition to those patients already randomized and using the EE seizure diary (n = 168).

b) Statistical Tests Used in the Efficacy Analyses

Efficacy analyses were conducted using data collected over the 12-week maintenance period for the ITT and per-protocol populations. Additional analyses that combined data from the two-week titration period and the 12-week maintenance period were conducted for some variables in studies 301, 302, and 303. For statistical comparison of the active treatment and placebo groups, Dunnett's or Bonferroni methods were used. For secondary outcomes, no hierarchical testing or statistical adjustments were performed to account for multiple testing. Subgroup analyses and sensitivity analyses were considered exploratory.

Primary Outcome

Standardized seizure frequency (natural log-transformed) was compared among treatment groups by ANCOVA with baseline seizure frequency as a covariate and treatment as a fixed effect. Study 304 added diary version (EE versus DE) as a covariate.

Other analyses of seizure frequency were performed using ANCOVA, with additional factors and their interaction with treatment added to the model as applicable (region, race, age, gender, carbamazepine use, carbamazepine dose reduction, phenytoin dose reduction, or use of rescue medication). The statistical significance of interactions was assessed at an alpha level of 0.10.

In Study 304, to control for type I error for the analysis of the primary efficacy variable in the ITT population and DE diary ITT population, a two-stage gate-keeping procedure was used. First, each of the two pair-wise comparisons of ESL 800 mg and 1,200 mg with placebo in the ITT population was conducted using an alpha level of 0.025 (stage 1). If both comparisons were statistically significant, the Dunnett's method was conducted at an alpha level of 0.05 for the DE diary population (stage 2). If only one of two pair-wise comparisons was statistically significant in stage 1, an alpha level of 0.025 was carried over to stage 2 testing. If neither of the two pair-wise comparisons was statistically significant in stage 1, the procedure would stop and no further analyses would be performed for the DE diary ITT population.

Secondary Outcomes

The proportion of patients with a 50% or greater reduction in seizure frequency, the proportion of seizure-free patients (100% reduction in seizure frequency), the distribution of seizure reduction (seizure reduction less than 50%; from 50% to 75%; and greater than 75%), and the proportion of patients with a 25% or greater increase in seizure frequency were compared between each active treatment group and the placebo group using: a Cochran-Mantel-Haenszel (CMH) test (Study 301); a CMH test stratified by region (studies 302 and 303); and a CMH test stratified by region and by diary version (Study 304).

The percentage changes in standardized seizure frequency and the standardized seizure frequency by seizure type were analyzed as per the primary efficacy outcome.

Kaplan-Meier methods were used to estimate median time to seizure control in Study 304. The comparisons between active treatment groups and placebo were performed using the log-rank test.

Patient-Reported Outcomes

In Study 301, CGI scores at the last assessment were tested using the CMH test, adjusting for baseline score. In studies 302 and 303, each active treatment group was compared with the placebo group using an ANCOVA that modelled each CGI score at the last observed value (post-baseline) as a function of baseline CGI-S score and treatment. No statistical testing was done for CGI in Study 304.

QOLIE-31 and SSQ (in Study 304) results were analyzed using ANCOVA models as a function of baseline score and treatment (and diary version in Study 304).

Handling of Missing Data and Early Dropouts

In studies 301, 302, and 303, patients who discontinued the study prematurely were not replaced. For patients who discontinued prematurely, seizure data were analyzed up to the time of discontinuation in the ITT analysis. It was unclear from the Clinical Study Reports (CSRs) how missing diaries were handled in the primary efficacy analysis; presumably, days for which no diaries were returned were excluded from the calculation of standardized seizure frequency (i.e., zero seizures were not assumed). Various sensitivity analyses were apparently performed to account for missing data, but results were not reported in the CSRs.

In Study 304, if patients discontinued during the two-week titration period, before the start of the 12-week maintenance period, they were treated as missing in the primary efficacy analysis. Although it is not made clear in the Study 304 CSR, it appears that seizure data up to the time of discontinuation were included in the ITT analysis for patients who discontinued from the maintenance period prematurely. For seizure data that were missing due to unreturned EE diaries, the number of days in the specific period was not included in the calculation of the average daily seizure frequency for that period. Zero seizures were entered only in cases where the diary card was returned. If there were no seizure data for a specific day in the DE diaries, it was assumed the patient had missing seizure data and the day was excluded from the calculation of the standardized seizure frequency. Various imputation scenarios were conducted as part of secondary and sensitivity analyses to account for missing data and early withdrawals.

c) Analysis Populations

The ITT population was the primary population for the analysis of efficacy. Patients were analyzed according to the treatment to which they had been randomized, regardless whether they actually received the assigned treatment.

The populations were defined as follow:

- Intention-to-treat (ITT): All randomized patients with at least one administration of study medication and at least one post-baseline seizure-frequency assessment
- Per-protocol: All ITT patients who completed the 12-week maintenance period without major protocol violations
- Safety: All patients who received at least one dose of study medication after randomization.

Study 301 had two modified ITT populations, including or excluding 20 patients with missing diary cards from two sites in Poland.

Study 304 included two other ITT populations, one with patients who completed the EE diary and one with patients who completed the DE diary.

3.3 Patient Disposition

Across the studies, discontinuations ranged from 6% to 33% in individual treatment groups as detailed in Table 9 and Table 10. Overall, the primary reason for discontinuation was the occurrence of AEs, which ranged from 2% to 25% in individual treatment groups, with the highest proportion in the ESL 1,200 mg groups of Study 301 (20%), Study 302 (25%) and Study 304 (21%).

TABLE 9: PATIENT DISPOSITION, STUDIES 301 AND 302

	Study 301				Study 302			
	ESL 400 mg	ESL 800 mg	ESL 1,200 mg	PL	ESL 400 mg	ESL 800 mg	ESL 1,200 mg	PL
Screened, N	468				503			
Randomized, N	100	98	102	102	96	101	98	100
Discontinued, N (%)								
Total withdrew	10 (10)	13 (13)	31[a] (30)	18[b] (18)	12 (13)	20 (20)	30 (31)	6 (6)
At end of baseline	2 (2)	2 (2	7 (7)	1 (1)	0	1 (1)	0	0
Titration period	2 (2)	4 (4)	13 (13)	5 (5)	0	8 (8)	6 (6)	0
Maintenance period	6 (6)	7 (7)	10 (10)	10 (10)	12 (13)	11 (11)	24 (25)	6 (6)
Taper period	0	0	0	0	0	0	0	0
Reasons, N (%)								
Withdrew consent	4 (4)	2 (2)	4 (4)	8 (8)	1 (1)	2 (2)	2 (2)	1 (1)
Poor compliance	0	0	1 (1)	2 (2)	0	0	2 (2)	2 (2)
Adverse events	4 (4)	8 (8)	20 (20)	4 (4)	8 (8)	14 (14)	25 (25)	2 (2)
Protocol violation	0	0	2 (2)	1 (1)	0	1 (1)	0	0
Pregnancy	0	1 (1)	0	0	0	0	0	0
Investigator decision	0	0	0	0	0	1 (1)	0	0
Exacerbations of seizures	0	0	0	0	2 (2)	0	0	1 (1)
Other[c]	2 (2)	2 (2)	4 (4)	3 (3)	1 (1)	1 (1)	1 (1)	0
Missing	0	0	0	0	0	0	0	0
ITT, N (%)	94 (94)	93 (95)	97 (95)	98 (96)	96 (100)	101 (100)	98 (100)	100 (100)
m-ITT[d], N (%)	93 (93)	93 (95)	93 (91)	98 (96)	96 (100)	100 (99)	97 (99)	100 (100)
m-ITT plus Poland[e], N (%)	99 (99)	98 (100)	98 (96)	102 (100)	NA	NA	NA	NA
PP, N (%)	81 (81)	83 (85)	78 (76)	86 (84)	63 (66)	74 (73)	70 (71)	75 (75)
Safety, N (%)	100 (100)	98 (100)	102 (100)	102 (100)	96 (100)	101 (100)	98 (100)	100 (100)

CDR = CADTH Common Drug Review; ESL = eslicarbazepine acetate; ITT = intention-to-treat; m-ITT = modified intention-to-treat analysis; NA = not applicable; PL = placebo; PP = per-protocol.

[a] One ESL 1,200 mg patient finished the tapering period but did not complete visits 3 to 6.

[b] Two placebo patients finished the tapering period but did not complete visits 3 to 6.

[c] "Other" not defined.

[d] Five patients in Study 301 and two patients in Study 302 were excluded from the ITT analysis because they did not provide a valid post-baseline assessment.

[e] All randomized patients with at least one dose of randomized study medication who had at least one post-baseline seizure-frequency assessment, including patients from two sites in Poland (this was the population used in the analyses).

Source: CDR submission,[11] Clinical Study Reports,[3,4] FDA Statistical Review.[24]

TABLE 10: PATIENT DISPOSITION, STUDIES 303 AND 304

	Study 303			Study 304		
	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL
Screened, N	85	80	88	936		
Randomized, N	85	80	88	216	211	226
Discontinued, N (%)						
Total withdrawn	15 (18)	21 (26)	22 (25)	43 (20)	69 (33)	37 (16)
At end of baseline	0	0	2 (2)	NR	NR	NR
Titration period	3 (4)	4 (5)	2 (2)	NR	NR	NR
Maintenance period	9 (11)	15 (19)	11 (13)	NR	NR	NR
Taper period	3 (4)	2 (3)	7 (8)	NR	NR	NR
Reasons, N (%)						
Withdrew consent	2 (2)	2 (3)	4 (5)	7 (3)	12 (6)	7 (3)
Poor compliance	2 (2)	5 (6)	1 (1)	1 (< 1)	3 (1)	5 (2)
Adverse events	7 (8)	9 (11)	5 (6)	21 (10)	45 (21)	9 (4)
Protocol violation	0	0	2 (2)	3 (1)	3 (1)	4 (2)
Pregnancy	0	0	0	1 (< 1)	0	2 (1)
Investigator decision	0	0	0	0	3 (1)	1 (< 1)
Administrative reasons	0	0	0	2 (1)	1 (< 1)	1 (< 1)
Lack of efficacy	0	0	0	0	1 (< 1)	0
Other[a]	4 (5)	5 (6)	10 (11)	8 (4)	1 (< 1)	8 (4)
Missing	0	0	1 (1)	0	0	0
ITT, N (%)	84 (99)	77 (96)	84 (95)	215 (99)	205 (97)	220 (97)
EE ITT, N (%)	NA	NA	NA	67 (31)	56 (27)	62 (27)
DE ITT, N (%)	NA	NA	NA	148 (69)	149 (71)	158 (70)
PP, N (%)	47 (55)	35 (44)	51 (58)	184 (85)	175 (83)	188 (83)
Safety, N (%)	85 (100)	80 (100)	87 (99)	216 (100)	210 (99)	224 (99)

CDR = CADTH Common Drug Review; DE = daily-event diary; EE = event-entry diary; ESL = eslicarbazepine acetate; ITT = intention-to-treat; NA = not applicable; NR = not reported; PL = placebo; PP = per-protocol.
[a] Not defined.
Source: CDR submission,[11] Clinical Study Reports,[1,2] Gil-Nagel et al.,[20] FDA Statistical Review.[24]

3.4 Exposure to Study Treatments

Table 11 and Table 12 summarize the extent of treatment exposure in the included trials. The mean duration of exposure was lower in the ESL 1,200 mg groups compared with the lower-dose groups. This is consistent with the higher overall withdrawals observed in the ESL 1,200 mg groups.

TABLE 11: EXPOSURE TO STUDY TREATMENT DURING DOUBLE-BLIND PERIOD, STUDIES 301 AND 302, SAFETY POPULATION

	Study 301				Study 302			
	ESL 400 mg (N = 100)	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 102)	PL (N = 102)	ESL 400 mg (N = 96)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)
N	100	98	102	102	96	101	98	100
Mean (SD), days	120.0 (24.8)	116.2 (31.7)	100.0 (44.2)	116.4 (27.3)	94.5 (15.4)	83.3 (33.6)	75.6 (37.1)	95.2 (17.5)
Median (min, max)	126.0 (1.0, 148.0)	126.0 (2.0, 154.0)	126.0 (1.0, 135.0)	126.0 (1.0, 135.0)	98 (4.9, 112)	98 (0.7, 112)	98 (2.1, 111)	98 (13.3, 116)

ESL = eslicarbazepine acetate; max = maximum; min = minimum; PL = placebo; SD = standard deviation.
Source: Clinical Study Reports.[3,4]

TABLE 12: EXPOSURE TO STUDY TREATMENT, STUDIES 303 AND 304, SAFETY POPULATION

	Study 303			Study 304		
	ESL 800 mg (N = 85)	ESL 1,200 mg (N = 80)	PL (N = 87)	ESL 800 mg (N = 216)	ESL 1,200 mg (N = 210)	PL (N = 224)
N	85	80	87	200	183	211
Mean (SD), days	115.5 (39.2)	106.4 (49.0)	112.7 (39.2)	77.7 (17.8)	72.6 (23.0)	79.6 (15.5)
Median (min, max)	126.0 (0.7, 198.1)	126.7 (0.7, 226.8)	126.0 (0.7,175.7)	83.0 (2, 102)	83.0 (1, 95)	84.0 (4, 99)

ESL = eslicarbazepine acetate; ITT = intention-to-treat; max = maximum; min = minimum; NR = not reported; PL = placebo; SD = standard deviation.
Source: Clinical Study Reports.[1,2]

3.5 Critical Appraisal

3.5.1 Internal Validity

All included studies were randomized and double-blinded. Matching placebo tablets were used. Randomization codes were prepared by an independent agency by means of computerized techniques. Allocation was concealed through individual sealed patient envelopes provided to the investigators.

Sample size calculations were performed based on the results of three levetiracetam trials. The patients in these trials had 1.7 to 2.6 seizures per week at baseline (equal to approximately 7 to 10 seizures per four-week period), which is comparable to the patients in the ESL trials who had a median of approximately 6 to 9 seizures per four-week period at baseline. Hence, the use of these trials to estimate the sample sizes for the ESL trials appears reasonable; however, validation of statistical parameters against trials for another drug indicated for refractory POS, such as lacosamide or perampanel, could have augmented the robustness of the power calculations.

Natural logarithm transformation was applied to standardize seizure frequency (SSF) in order to meet the assumptions of ANCOVA and to be consistent with sample size calculation. For studies 301, 302, and 303, a constant of +4 was added to avoid log zero (i.e., Ln[SSF + 4]). The levetiracetam trials used Ln(SSF + 1) and Study 304 added a constant of 0.333. However, the FDA states that Ln(SSF + 1) approximates the normal distribution better than Ln(SSF + 4). When the constant used in the logarithm

transformation is large (4 versus 1), the percentage reduction in seizure frequency over placebo may be underestimated.[24]

While adjustments were made for multiple groups, adjustments for multiple secondary outcomes were not done.

In studies 301, 302, and 303, good clinical practice (GCP) audits by the FDA revealed GCP non-compliance and data-quality issues.[23] For example, inadequate record keeping, poor source documentation of safety data, and discrepancies between source documents and case report forms were noted through FDA inspections. Diary cards were completed but source documents were not maintained and seizure data could not be verified in Study 301 (20 patients). In studies 301 and 302, some patients' eligibility for inclusion in the trial could not be confirmed; other patients did not meet strict eligibility criteria (see next paragraph). Furthermore, an audit of seizure data found additional seizure-diary pages and an additional 115 seizures (equally distributed across groups) were added to the database.[23] When the seizure-frequency data were reanalysed[24] to exclude the 20 patients without original diary cards and to include the additional seizures, the *P* value for ESL 800 mg in Study 301 changed from 0.0028 to 0.047 (compared with placebo), and the *P* value for ESL 1,200 mg in Study 302 changed from 0.001 to 0.042 (also compared with placebo; original data in Table 20, Appendix 4: Detailed Outcome Data). FDA reviewers were divided as to whether or not the study conduct and documentation issues were subsequently addressed adequately by the investigators.[23] Study 303 had significant GCP compliance deficiencies which, according to the submitter, included improper activities relating to study conduct, inappropriate enrolment of randomized patients, absence of source documentation to verify data entry, and failure to assure patients safety. As such, Study 303 was not considered by the FDA or Health Canada in their review; i.e., both bodies considered it a supportive rather than pivotal trial.

Some patients in studies 301, 302, and 303 did not meet the inclusion criteria for frequency of seizures at baseline. There were 12 patients (3.0%), 35 patients (8.9%), and 39 patients (15.4%) included in studies 301, 302, and 303, respectively, who had a baseline seizure frequency of less than four per four-week period. It is unlikely that this would substantially affect the observed effect sizes as patients were equally distributed between groups. If anything, the inclusion of patients with less frequent POS in these studies would likely tend to obscure the difference between ESL and placebo.

In studies 302 and 303, 25% to 38% of patients had seizures at baseline that were "unclassified" as to type. All unclassified seizures were within the diagnosis of POS, in keeping with the inclusion criteria.[25] These may have been events in which the patient lost consciousness during the seizure and could not differentiate between a complex POS and a secondarily GS.[25]

Withdrawals occurred in approximately 20% of patients treated with ESL 800 mg and approximately 30% of patients treated with ESL 1,200 mg, compared with 6% to 25% of patients given placebo. Particularly in Study 302, the differences between ESL and placebo in terms of the proportion of patients withdrawing were 14% with ESL 800 mg and 24% with ESL 1,200 mg. Across all trials, most of the withdrawals occurred in the maintenance period; the most common reasons were AEs in the active groups and a variety of reasons in the placebo groups. Greater withdrawals from the active treatment groups before the end of the trial may compromise randomization to some degree; i.e., treatment groups may be less comparable in terms of baseline characteristics or prognoses, potentially biasing results. As well, higher continuation rates with placebo may tend to underestimate differences in adverse event rates between ESL and placebo due to the lower overall exposure in the ESL groups. Nonetheless, these discontinuation rates are similar to those for other AEDs such as lacosamide and perampanel; the

manufacturer-submitted network meta-analysis (NMA) showed no significant differences in discontinuation rates between these three drugs (Appendix 7: Summary and Critical Appraisal of the Manufacturer-Submitted Network Meta-Analysis).

Patients in studies 301, 302, and 303, and the first 168 patients in Study 304 recorded a seizure event in a diary when a seizure occurred. As such, there was no means of differentiating whether the absence of a seizure entry for a particular day was due to non-occurrence of seizure, or because a seizure was not recorded by the patient or caregiver. This likely resulted in some seizures being missed in the analysis. However, the impact on the observed treatment effects may be small, as failure to record a seizure is likely to occur with equal probability across treatment groups. In Study 304, the EE diary was changed to a DE diary where patients were required to maintain daily records whether or not a seizure event had occurred. With a DE diary, the absence of a seizure could be differentiated from missing data. The 168 patients in Study 304 were asked to continue using the EE diary, whereas the subsequent patients used the DE diary. Study 304 increased its sample size from 360 patients to 615 patients to have a sufficient number of patients using the DE diary.

Study 304 reported outcomes only for the 12-week maintenance period, whereas studies 301, 302, and 303 did secondary analyses based on combined data from the titration period plus the maintenance period. Reporting outcomes only for the 12-week maintenance period is appropriate, as guidelines by the European Medicines Agency recommend that only calculations based on the maintenance period be considered.[26] This approach has been shown to provide more conservative results, as responder rates with placebo — but not with the active medication — are significantly higher in the maintenance period compared with the entire treatment period. Hence, the relative effect of the active treatment is lower when response is assessed over the maintenance period compared with the entire treatment period.[26]

3.5.2 External Validity

The clinical expert consulted for this review affirmed that baseline demographic and disease characteristics (age, duration of epilepsy, and number of seizures) of patients enrolled in the trials were representative of patients with refractory epilepsy encountered in clinical practice in Canada. Carbamazepine, the most commonly used AED at baseline in the included trials, is a first-line therapy in clinical practice; it is particularly common in the countries that were included in the trials.

Health Canada restricts the use of ESL to adult patients (≥ 18 years old). In Study 304, patients aged 16 years or older qualified for enrolment; it was unclear how many patients in the trial were 16 or 17 years old and if there were differences in response to treatment in this younger population. However, it is unlikely the inclusion of slightly younger patients in the ESL trials compared with the approved indication would have substantively impacted the results or their generalizability.

Patients in the included trials were predominantly white. The clinical expert consulted for this review stated it is possible there are racial differences in drug metabolism. This may affect the generalizability of the results to non-white patients. Of note, Study 303 included a high proportion of patients in the "other" race category (approximately 60%). This was due to reporting differences between Mexico (where Hispanic patients were reported as "other") and Portugal and Spain (where Hispanic patients were reported as white).

Studies 301 and 302 had no North American study sites and Study 303 had Mexico as a North American centre. Study 304 had North American sites, including three Canadian sites, for a total of only seven Canadian patients, which may limit generalizability to the Canadian population.

The choice of primary end point (seizure frequency per 28 days) is a less clinically relevant end point according to the clinical expert consulted for this review. The proportion of responders (patients with a 50% reduction in seizures) is a more useful measure of effectiveness. These were captured as secondary end points in the included trials.

All trials were placebo-controlled and no active-controlled trials were identified. The use of placebo in a refractory population does not reflect clinical practice since such patients would likely be considered for adjunctive therapy with newer AEDs. Furthermore, an active comparator trial would have permitted an assessment of the relative benefit-risk profile of ESL compared with other AEDs indicated for refractory epilepsy. It would have been especially beneficial to have a head-to-head comparison with perampanel or lacosamide as both are new AEDs with similar indications targeting the same patient population. The manufacturer conducted a network meta-analysis of ESL with lacosamide and perampanel used as adjunctive therapy in patients with refractory POS with or without secondarily GS. That analysis is summarized in Appendix 7: Summary and Critical Appraisal of the Manufacturer-Submitted Network Meta-Analysis.

In three of the four trials (studies 301, 302, and 303), patients continued throughout the trial on the same background AED regimen they were on at baseline, and dosage adjustment and the use of rescue medication were not permitted. In Study 304, dose reduction of carbamazepine or phenytoin was permitted in the last week of the titration period or in the first week of the maintenance period in case of intolerable AEs, and benzodiazepines could be used as rescue medication no more than twice per week. In clinical practice, background AED regimens would be modified or doses adjusted to maximize treatment success. Limiting the use of rescue medications can cause significant risk to patients, including risk of death.

CDR recommendations for lacosamide and perampanel specify, as part of the listing criteria for these medications, that patients be on two or more AEDs and that other AEDs be ineffective or inappropriate.[27,28] This implies that more than two AEDs would have been tried by most patients eligible for reimbursement with perampanel or lacosamide. At baseline, approximately 15% to 40% of patients in the ESL trials were on one concomitant AED and approximately 60% to 80% were on two concomitant AEDs. No information was provided in the submission as to whether the included patients' epilepsy was refractory despite optimization of existing treatment, and there were also no data on the lifetime use of AEDs. Subsequent information provided by the manufacturer revealed that the median number of AEDs ever used by patients prior to enrolment was five (range 1 to 22), and 96% of patients had used two or more AEDs in their lifetime.[29] These data mitigate to an extent the concern that patients in the ESL trials were not as treatment-refractory as the target population reflected in the listing criteria of the CDR recommendations for perampanel and lacosamide. Furthermore, when efficacy outcomes were analyzed by number of concomitant AEDs in the ESL trials, there were no differences in relative reduction in seizure frequency or in responder rates in patients taking one concomitant AED compared with those taking two AEDs.[29]

The duration of double-blind treatment was up to 16 weeks (two weeks of titration, 12 weeks of maintenance, and two weeks of tapering off in studies 301, 303, and 304), which is insufficient to characterize long-term efficacy and safety of ESL in light of the fact that AEDs are intended for chronic use. However, the duration of these trials is in line with those for other AEDs approved for refractory POS, such as lacosamide and perampanel.[27,28] Supplementary data from open-label extension trials of ESL are summarized in Appendix 4: Detailed Outcome Data.

3.6 Efficacy

See Appendix 4: Detailed Outcome Data for detailed efficacy data. Only those efficacy outcomes identified in the review protocol (section 2.2, Table 3) are reported.

As 400 mg is not a Health Canada–approved dose, only the results for the 800 mg and 1,200 mg doses are reported in this section.

For some outcomes in studies 301, 302, and 303, combined results from the titration period and maintenance period are reported in Appendix 4: Detailed Outcome Data. However, only data from the maintenance period are discussed below.

3.6.1 Seizure-Free Status

Seizure-free status was a secondary outcome in all trials. A higher proportion of ESL patients achieved a 100% reduction in seizures compared with placebo patients (Table 15). Statistical significance was reached for only one comparison: 8% of ESL 1,200 mg patients were seizure free compared with 2% of placebo patients in Study 301 ($P = 0.042$). All other comparisons between active treatments and placebo were not statistically significant.

3.6.2 Health-Related Quality of Life

In studies 301, 302, and 303, baseline median QOLIE-31 overall scores were approximately 55 out of a possible 100 points (Table 16). A higher score indicates a better quality of life. For Study 304, baseline values were greater than 100 points, most likely because the raw data were not standardized on a 0 to 100 scale. Median scores increased from baseline by 0.2 points to 5.6 points across treatment groups. The largest increase was seen in Study 304, with an increase in the median overall score of 5.4 points and 5.6 points from baseline for ESL 800 mg and ESL 1,200 mg, respectively. For all four trials, there were no statistically significant differences between active treatments and placebo in the QOLIE-31 overall scores (Table 16).

3.6.3 Seizure Severity Questionnaire

SSQ was measured only in Study 304 (Table 17). The change from baseline in the median SSQ overall severity score was –3.0 (ESL 800 mg), –7.0 (ESL 1,200 mg), and –1.0 (placebo). There were no statistically significant differences between active treatments and placebo in SSQ overall severity score (Table 17).

3.6.4 Clinical Global Impression

In studies 301 and 304, 24% to 30% of ESL patients were considered “much improved” compared with 17% and 21% of placebo patients (Table 18). Approximately 28% of ESL patients reported “no change” compared with 31% to 39% of placebo patients.

There were no statistically significant differences between active treatments and placebo in CGI-I score (Table 19), CGI-S score (data not shown), and CGI-E score (data not shown) across studies, except that patients administered ESL 1,200 mg in Study 301 had a higher CGI-E score compared with placebo ($P = 0.0326$).

3.6.5 Seizure Frequency

a) Standardized Seizure Frequency

Standardized seizure frequency was the primary outcome for all four trials. Seizure frequency per four-week period was statistically significantly lower in the active groups compared with placebo, except

for one comparison in Study 304 that was not statistically significant (LS mean 6.5 for ESL 800 mg and LS mean 6.0 for placebo; *P* value = 0.058) (Table 20).

In Study 304, the results for the DE diary ITT population analysis were consistent with those observed in the ITT population (LS means of 7.54 for placebo, 6.32 for the ESL 800 mg group, and 5.96 for the ESL 1,200 mg group). Assessed at the 0.025 level of significance, the difference from placebo was not statistically significant for either of the ESL groups (data not shown).

In adjusted analyses, there were no statistical interactions reported for any of the covariates tested. The results of subgroup analyses are presented below.

b) Change in Standardized Seizure Frequency

The mean change from baseline in standardized seizure frequency was +2.5% for the placebo group in one trial and –5% to –9% in the other trials, whereas it was –21% to –31% for ESL 800 mg and –21% to –35% for ESL 1,200 mg across trials (Table 21). No *P* values were reported.

c) Subgroup Analyses

Standardized Seizure Frequency by Seizure Type

Standardized seizure frequency by seizure type was measured in studies 302, 303, and 304 (Table 22).

- Simple partial: In Study 302, patients with a diagnosis of simple partial seizure experienced statistically less frequent seizures with ESL 800 mg and ESL 1,200 mg compared with placebo. In studies 303 and 304, there were no statistically significant differences between ESL (both doses) and placebo.
- Complex partial: Patients with complex partial seizures had statistically significantly less frequent seizures with ESL 1,200 mg compared with placebo, but not with ESL 800 mg in all three trials.
- Partial evolving to GS: There were no statistically significant differences between ESL (both doses) and placebo in seizure frequency in POS evolving to GS.

Standardized Seizure Frequency by AED Use

Standardized seizure frequency by AEDs was reported in Study 304 (Table 23).

- Carbamazepine use during baseline period: For patients who used carbamazepine during the baseline period, there were no statistically significant differences between ESL (both doses) and placebo in standardized seizure frequency. For patients who did not use carbamazepine during the baseline period, Least squares (LS) means were lower with ESL 800 mg and ESL 1,200 mg compared with placebo (LS mean 6.6 and LS mean 5.1, respectively, versus LS mean 8.3 [unadjusted *P* values 0.038 and < 0.001, respectively]). The treatment by carbamazepine use interaction was statistically significant.
- Subgroup analyses according to use of other AEDs at baseline were considered exploratory (data not shown). With levetiracetam, results were similar to those reported for carbamazepine; there were no statistical differences between ESL and placebo for patients who used levetiracetam, whereas those who did not use levetiracetam had statistically fewer seizures with ESL versus placebo. For valproic acid and lamotrigine, both patients who used and did not use either of these drugs at baseline had significantly lower LS means with ESL compared with placebo.
- Carbamazepine or phenytoin dose reduction during maintenance period: Very few patients required a carbamazepine dose reduction in the maintenance period. No patients required a phenytoin dose reduction in the maintenance period.
- Use of rescue medication during maintenance period: Patients who used rescue medication during the maintenance period had no statistically significant difference in standardized seizure frequency when comparing ESL (both doses) and placebo. Patients who did not use rescue medication had

statistically significantly fewer seizures with ESL 800 mg and ESL 1,200 mg compared with placebo (LS mean 6.3 and LS mean 5.8, respectively, versus LS mean 7.6 [unadjusted *P* values 0.029 and 0.003, respectively]).

d) Sensitivity Analyses

The submitter reported that various sensitivity analyses were carried out in studies 301, 302, and 303 (data not reported in CSRs), and that missing data did not have a meaningful impact on results.[25] Several sensitivity analyses were also carried out for Study 304 to account for missing data or early discontinuations and results were similar to those of the main analyses (data not shown). The FDA also conducted additional sensitivity analyses for all four included trials to account for missing seizure data and early withdrawals. These analyses showed that the results were still favourable to ESL.[24]

3.6.6 Responders

a) Proportion of Responders

Approximately 18% to 23% of placebo patients achieved a 50% reduction in seizures compared with 31% to 35% of ESL 800 mg patients and 35% to 43% of ESL 1,200 mg patients (Table 24). Findings were statistically significant, except for ESL 800 mg compared with placebo in Study 303 and Study 304.

b) Distribution of Responders

The proportion of patients achieving less than 50% seizure reduction ranged from 42% to 62% with ESL 800 mg, 34% to 53% with ESL 1,200 mg, and 51% to 81% with placebo. Approximately 15% to 21% of ESL 800 mg patients, 19% to 26% of ESL 1,200 mg patients, and 10% to 17% of placebo patients achieved 50% to 75% seizure reduction. The proportion of patients achieving a greater than 75% seizure reduction ranged from 11% to 16% with ESL 800 mg, 17% to 20% with ESL 1,200 mg, and 6% to 10% with placebo. The distribution of seizure reduction was statistically significantly different for all but two comparisons: ESL 800 mg compared with placebo in studies 303 and 304.

c) Seizure Exacerbations

There were no statistically significant differences in the proportion of patients with a seizure frequency increase of 25% or greater between active and placebo groups except for one comparison: the proportion of placebo patients with seizure exacerbations was higher than the proportion of ESL 800 mg patients (28% versus 10%, respectively; *P* = 0.004) in Study 302 (Table 26).

3.6.7 Time to Reduction in Seizure Frequency

In Study 304, median time to onset of ≥ 50% reduction in standardized seizure frequency was 24.5 days for all groups (Table 27).

3.6.8 Use of Rescue Medication

In Study 304, 8% of ESL 800 mg patients and 6% of patients in the ESL 1,200 mg group required the use of at least one rescue medication compared with 7% of placebo patients (Table 28).

3.6.9 Patient Adherence to Treatment

The mean percentage intake of study medication was balanced across treatment groups and across trials, ranging from 96% to 100% (Table 29).

3.6.10 Health Care Resource Utilization

This was not an outcome of interest in the included trials.

TABLE 13: KEY EFFICACY OUTCOMES, INTENTION-TO-TREAT POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL
Proportion of patients seizure free, MP												
N	98	98	102	100	97	100	84	77	84	200	183	212
n (%)	4 (4.1)	8 (8.2)	2 (2.0)	3 (3.0)	5 (5.2)	2 (2.0)	4 (4.8)	3 (3.9)	1 (1.2)	4 (2.0)	4 (2.2)	2 (0.9)
P value vs. PL	0.372	0.042	-	0.556	0.16	-	0.185	0.263	-	0.336	0.235	-
RR[a]	2.1	4.2	-	1.5	2.6	-	4.0	3.3	-	2.1	2.3	-
95% CI[a]	0.4 to 11.1	0.9 to 19.1	-	0.3 to 8.8	0.5 to 13.0	-	0.5 to 35.0	0.3 to 30.8	-	0.4 to 11.4	0.4 to 12.5	-
Seizure frequency per 4-week period, MP												
N	94	94	99	88	85	99	80	69	79	200	184	212
LS mean	5.7	5.4	7.6	7.1	7.0	9.8	5.7	5.5	7.3	6.5	6.0	7.9
95% CI	4.9 to 6.5	4.6 to 6.1	6.8 to 8.6	6.2 to 8.2	6.0 to 8.1	8.7 to 11.1	4.9 to 6.7	4.6 to 6.5	6.3 to 8.5	5.8 to 7.4	5.3 to 6.8	7.0, 8.9
LS mean diff. versus PL	–1.9	–2.2	-	–2.7	–2.8	-	–1.6	–1.9	-	–1.4	–1.9	-
P value vs. PL	0.0028	0.0003	-	0.002	0.001	-	0.048	0.021	-	0.058	0.004	-
Proportion of patients with ≥ 50% reduction in seizures, MP												
N	98	98	102	100	97	100	84	77	84	200	183	212
n (%)	33 (33.7)	42 (42.9)	20 (19.6)	32 (32.0)	34 (35.1)	18 (18.0)	29 (34.5)	29 (37.7)	19 (22.6)	61 (30.5)	78 (42.6)	49 (23.1)
RR[a]	1.7	2.2	-	1.8	1.9	-	1.5	1.7	-	1.3	1.8	-
95% CI[a]	1.1 to 2.8	1.4 to 3.4	-	1.1 to 3.0	1.2 to 3.2	-	0.9 to 2.5	1.0 to 2.7	-	1.0 to 1.8	1.4 to 2.5	-
P value vs. PL	0.0246	0.0004	-	0.005	< 0.001	-	0.106	0.02	-	0.068	< 0.001	-
Clinical Global Impression[b], n (%)												
N	98	98	102	NR	NR	NR	NR	NR	NR	215	205	220
Much improved	25 (26)	23 (24)	21 (21)	NR	NR	NR	NR	NR	NR	56 (28)	59 (30)	35 (17)

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL	ESL 800 mg	ESL 1,200 mg	PL
Minimally improved	31 (32)	29 (30)	34 (33)	NR	NR	NR	NR	NR	NR	64 (31)	54 (28)	66 (31)
No change	28 (29)	26 (27)	32 (31)	NR	NR	NR	NR	NR	NR	60 (29)	53 (27)	83 (39)

CDR = CADTH Common Drug Review; CI = confidence interval; diff. = difference; ESL = eslicarbazepine acetate; ITT = intention-to-treat; LS = least squares; MP = maintenance period; NR = not reported; PL = placebo; RR = relative risk.

[a] Calculated by CDR.

[b] Statistical significance not reported.

Source: Clinical Study Reports.[1-4,18,22]

3.7 Harms

Only those harms identified in the review protocol (see 2.2.1, Protocol) are reported in this section. (For detailed harms data, see Appendix 4: Detailed Outcome Data.)

3.7.1 Adverse Events

In studies 301, 303, and 304, the proportion of patients who experienced at least one treatment-emergent adverse event (TEAE) ranged from 50% to 67% in the ESL 800 mg groups and 61% to 78% in the ESL 1,200 mg groups. The proportion was lower in the placebo groups, ranging from 31% to 56%. Study 302 reported a higher incidence of events compared with the other trials, with 83% (ESL 800 mg), 80% (ESL 1,200 mg), and 68% (placebo) of patients reporting at least one TEAE (Table 14).

Dizziness was the most common TEAE associated with ESL, occurring in 14% to 44% of patients, compared with less than 10% of patients given placebo (Table 30). Other common TEAEs in the active groups were related to the central nervous system (CNS) and included headache (6% to 19% with ESL versus 6% to 12% with placebo), somnolence (7% to 21% with ESL versus 2% to 17% with placebo), diplopia (1% to 15% with ESL versus 0% to 4% with placebo), nausea (4% to 15% with ESL versus 1% to 5% with placebo), and vomiting (1% to 13% with ESL versus 0% to 3% with placebo). Study 302 also had a relatively high proportion of patients with blurred vision (8% and 7% for ESL 800 mg and 1,200 mg, respectively, versus 2% with placebo) and abnormal coordination (13% and 11% for ESL 800 mg and 1,200 mg, respectively, versus 5% with placebo). Considering ESL 800 mg and ESL 1,200 mg, a number of AEs occurred in a similar proportion of patients regardless of dose (i.e., dizziness in Study 301; headache in Study 301 and 304; somnolence in studies 301 and 303; nausea in studies 301 and 302; and blurred vision and fatigue in all trials). In Study 302, the rate of AEs was higher with ESL 800 mg compared with ESL 1,200 mg for diplopia, vomiting, and abnormal coordination.

3.7.2 Serious Adverse Events

The proportion of patients with at least one SAE was highest with ESL 800 mg in two trials (studies 302 and 304), with 6% and 7% patients experiencing at least one SAE compared with 1% and 2% with ESL 1,200 mg, and 0% and 3% with placebo. Study 301 had 4% of patients experiencing at least one SAE with ESL 800 mg and placebo compared with 6% for the ESL 1,200 mg group. In Study 303, it was reported that only one patient (in the ESL 1,200 mg group) experienced an SAE (cerebellar syndrome) (Table 14).

The types of SAEs varied, with an incidence of 1% or less for each SAE. With ESL 800 mg, SAEs included vertigo, hyponatremia, and vomiting. With ESL 1,200 mg, SAEs included vertigo, exanthem, dizziness, and cerebellar syndrome (Table 31).

3.7.3 Withdrawals Due to Adverse Events

The proportion of patients withdrawing due to adverse events (WDAEs) ranged from 8% to 19% with ESL 800 mg, 11% to 26% with ESL 1,200 mg, and 3% to 8% with placebo across trials (Table 14). The reasons for WDAEs varied across trials. Common reasons for stopping ESL treatment included: dizziness (1% to 7% with ESL 800 mg and 4% to 14% with ESL 1,200 mg, versus 0% to 2% with placebo), nausea (1% to 4% with ESL 800 mg and 3% to 7% with ESL 1,200 mg versus 0% with placebo) and vomiting (1% to 7% with ESL 800 mg and 3% to 7% with ESL 1,200 mg versus less than 1% with placebo) (Table 32). ESL 1,200 mg was associated with higher proportions of WDAEs than ESL 800 mg in all four included trials, particularly in studies 301 and 304 where the difference was more than two-fold.

3.7.4 Mortality

In the included trials, three deaths were reported. In Study 301, one patient in the placebo group died due to hypothermia. In Study 304, one patient randomized to the ESL 800 mg group died of status epilepticus while taking ESL 400 mg in the titration phase, and one patient in the placebo group died due to respiratory failure (Table 33).

3.7.5 Notable Harms

Notable harms identified in consultation with the clinical expert and occurring in the included trials were hyponatremia, neutropenia, and skin reactions (Table 14 and Table 33). Across trials, a total of 16 patients (five patients with ESL 800 mg [one in Study 302, and four in Study 304] and 11 patients with ESL 1,200 mg [one in each of studies 301 and 304, two in Study 302, and one in Study 303]) experienced hyponatremia with ESL treatment compared with zero patients on placebo. Neutropenia was seen in one patient receiving ESL 1,200 mg (in Study 304) and in two placebo patients (one patient in Study 303 and one in Study 304). With active treatment, exanthem was reported in four patients (one patient with ESL 800 mg and three patients with ESL 1,200 mg in Study 301) and rash was reported in 15 patients (two and three ESL 800 mg patients in Study 303 and Study 304, respectively; and with ESL 1,200 mg, two patients in Study 301, three patients in Study 302, one patient in Study 303, and four patients in Study 304). Rash was also reported in four placebo patients. One patient treated with ESL 800 mg developed leukocytoclastic vasculitis (Study 304).

TABLE 14: SUMMARY OF HARMS, SAFETY POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 102)	PL (N = 100)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 85)	ESL 1,200 mg (N = 80)	PL (N = 87)	ESL 800 mg (N = 216)	ESL 1,200 mg (N = 210)	PL (N = 224)
TEAEs												
Patients with > 0 TEAEs, N (%)	49 (50)	62 (61)	32 (31)	84 (83)	78 (80)	68 (68)	45 (53)	49 (61)	34 (39)	145 (67)	163 (78)	125 (56)
SAEs												
Patients with > 0 SAEs, N (%)	4 (4)	6 (6)	4 (4)	6 (6)	2 (2)	0	0	1 (1)	0	14 (7)	3 (1)	7 (3)
WDAEs												
N (%)	9 (9)	20 (20)	4 (4)	19 (19)	26 (27)	3 (3)	7 (8)	9 (11)	6 (7)	26 (12)	54 (26)	18 (8)
Deaths												
N (%)	0	0	1 (1)	0	0	0	0	0	0	1 (< 1)	0	1 (< 1)
Notable harms												
Hyponatremia	0	1 (1)	0	1 (1)	2 (2)	0	0	1 (1)	0	4 (2)	7 (3)	0
Neutropenia	0	0	0	0	0	0	0	0	1 (1)	0	1 (< 1)	1 (< 1)
Skin reaction:												
• exanthem	1 (1)	3 (3)	0	0	0	0	0	0	0	0	0	0
• rash	0	2 (2)	1 (1)	0	3 (3)	1 (1)	2 (2)	1 (1)	0	3 (1)	4 (2)	2 (1)
• leukocytoclastic vasculitis	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0

ESL = eslicarbazepine acetate; PL = placebo; SAE = serious adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports.[1-4]

4. DISCUSSION

4.1 Summary of Available Evidence

Four multi-centre, double-blind, parallel-group, randomized, placebo-controlled, phase 3 superiority trials met the inclusion criteria for this systematic review. Study 301 (N = 402), Study 302 (N = 395), Study 303 (N = 253), and Study 304 (N = 653) enrolled patients with uncontrolled POS with or without secondarily GS, despite receiving AEDs. Patients were randomized to once-daily placebo, ESL 800 mg, or ESL 1,200 mg. Studies 301 and 302 also had an ESL 400 mg group. Patients in studies 301, 302, or 303 remained on a fixed AED background regimen while in Study 304, patients were permitted the use of benzodiazepines as a rescue medication and dose modifications of carbamazepine and phenytoin at the beginning of the double-blind period. The duration of the double-blind treatment in all studies was 16 weeks (two weeks of titration, 12 weeks of maintenance, and two weeks of tapering) for studies 301, 303, and 304, while Study 302 did not have a tapering period. The primary outcome was standardized seizure frequency (seizure frequency per four-week period) during the 12-week maintenance period. Results of three open-label extension trials are summarized in Appendix 6: Summary of Open-Label Extension Studies.

A limitation of studies 301, 302, and 303 included the use of EE diaries rather than DE diaries to record seizures, which makes it difficult to differentiate missing entries from seizure non-occurrence. Study 303 was not considered a pivotal trial by Health Canada due to significant GCP compliance issues; nevertheless, the results of this study were in line with those of the other trials. Other key limitations of the available evidence included the lack of trials to assess the comparative efficacy and safety of ESL with other clinically relevant AEDs, the short duration of the controlled trials (which precludes assessment of durability of effect and long-term safety), and the high proportion of withdrawals in the ESL 1,200 mg groups.

4.2 Interpretation of Results

4.2.1 Efficacy

The ultimate goal of epilepsy treatment is to achieve seizure-free status.[9] While this outcome was evaluated in each of the four trials, only a small proportion of patients achieved seizure-free status during the maintenance period. Statistically significant differences between placebo and ESL were demonstrated only in the 1,200 mg ESL group in Study 301. According to the clinical expert consulted for this review, this was not surprising, as few patients from a refractory population would be expected to become seizure free.

The primary efficacy analysis of seizure frequency per four-week period during the maintenance period demonstrated statistically significant and consistent results across the four trials for both ESL 800 mg and ESL 1,200 mg compared with placebo, except for one comparison: ESL 800 mg versus placebo in Study 304. However, the clinical expert indicated that the proportion of responders (proportion of patients with seizure frequency reduction of 50% or more) is a more clinically useful outcome than standardized seizure frequency. In this respect, it was shown that approximately 30% to 40% of patients demonstrated a ≥ 50% reduction in seizures and all findings were statistically significant compared with placebo, except in two instances when ESL 800 mg was compared with placebo in studies 303 and 304. Numbers needed to treat for this outcome were eight with ESL 800 mg, and ranged from five to seven with ESL 1,200 mg. According to the clinical expert, the percentage of responders seen in the included trials is in keeping with what is seen in randomized placebo-controlled trials with other AEDs.

Seizure frequency was also evaluated according to seizure types in studies 302, 303, and 304. Across the three trials, findings were statistically significant for ESL 1,200 mg compared with placebo for patients with complex partial seizures. Findings were statistically significant for ESL 800 mg compared with placebo, and for ESL 1,200 mg compared with placebo for patients with simple partial seizures in Study 302, but not in studies 303 and 304. For all treatment groups in all three trials, there were no statistically significant differences in seizure frequency for patients with secondarily GS. These findings must be interpreted in light of the fact that sample sizes for each subgroup were relatively small and *P* values are descriptive only.

Carbamazepine was the most commonly used AED at baseline. In trials conducted exclusively outside of North America, the use of carbamazepine was highest (approximately 60%) whereas in Study 304, approximately 30% of patients used carbamazepine at baseline. A subgroup analysis in this trial showed that patients who had not used carbamazepine at baseline demonstrated a statistically significant result when comparing ESL with placebo for the primary outcome. Conversely, no statistically significant difference was seen in patients who had used carbamazepine. Considering that ESL and carbamazepine belong to the same class of drugs and share similar mechanisms of action, it is possible that the addition of ESL to carbamazepine does not augment effectiveness to the same degree as when it is added to drugs with a different mechanism of action. Or perhaps, if patients have failed to obtain seizure control with carbamazepine, they are unlikely to respond to ESL. However, the findings must be interpreted in light of the fact that sample sizes for each subgroup were relatively small.

Less than 10% of patients required rescue medications (similar across treatment groups) in the maintenance period. Patients who did not use a rescue medication demonstrated a statistically significant result when comparing ESL with placebo for the primary outcome. This result was not surprising as it would be expected that patients with a good response to treatment would not require rescue medications.

In the absence of a direct comparison, it is difficult to evaluate the relative risk-benefit profile of ESL compared with other clinically relevant AEDs used in patients with refractory epilepsy, such as lacosamide and perampanel. Published meta-analyses of placebo-controlled RCTs of AEDs as adjunctive treatment for refractory POS reported similar response rates (i.e., ≥ 50% reduction in seizure frequency) for ESL and other AEDs against placebo.[30-32] In an indirect comparison, Costa et al. found that topiramate was more effective than other AEDs (including ESL), but patients on topiramate treatment also had a higher withdrawal rate.[30] In the same review, gabapentin and lacosamide were the least effective.[30] A manufacturer-submitted NMA is summarized in Appendix 7: Summary and Critical Appraisal of the Manufacturer-Submitted Network Meta-Analysis. The NMA compared ESL with lacosamide and perampanel. It showed that the three AEDs were more effective than placebo in terms of proportion of responders (≥ 50% reduction in seizure frequency); there were no significant differences in this efficacy outcome between any of the comparators. Although the NMA demonstrated sufficient methodological rigour for a number of criteria, there were some important limitations. In particular, the wide credible intervals associated with the NMA estimates rendered uncertain the comparative efficacy and safety of ESL against lacosamide and perampanel.

Based on input received on this submission from a patient group, key outcomes for patients with uncontrolled POS include quality of life, reduced seizure frequency, and AEs compared with other AEDs. While quality of life was assessed in the included trials using QOLIE-31, there were no statistically significant differences between ESL and placebo. These findings were corroborated with CGI-I score, for which there was also no statistically significant differences between ESL and placebo. For the majority of

patients, there was no change or minimal improvement in CGI. No test of statistical significance was done for between-group comparisons. It is unclear why the reductions in seizure frequency with ESL did not translate into improvements in HRQoL on a disease-specific instrument such as the QOLIE-31, although benefits on HRQoL were also not apparent in trials of perampanel and lacosamide.[27,28] The higher incidence of adverse effects in the ESL groups may partially explain this finding.

Finally, the duration of the double-blind phase (14 to 16 weeks) is insufficient to assess the durability of the treatment effect for a drug such as ESL that is intended for chronic administration. The controlled data for ESL are supplemented by data from three open-label extension trials summarized in Appendix 6: Summary of Open-Label Extension Studies. In the one-year OLE period, 2.5% of patients achieved seizure-free status in studies 302 and 303, while 37.2% and 52.6% of patients had a 50% or greater reduction in seizure frequency, respectively (results not reported for Study 301). In all three OLE trials, patients had statistically significant improvements from baseline in the QOLIE-31 overall scores of between 2.1 points and 6.7 points. It should be noted that 20% to 30% of patients who entered the extension trials discontinued treatment before the end of the one-year period due to withdrawal of consent, lack of efficacy, or the occurrence of unacceptable AEs. Moreover, it is possible that patients in the RCTs who found ESL treatment to be tolerable and efficacious were more likely to enrol in the extension trials. Over time, it is likely that the remaining cohort increasingly represented patients who had the greatest benefit and lowest incidence of AEs because such patients self-selected to continue treatment in the OLE trials. Hence, the reduction in seizures and improvements in HRQoL observed with ESL is likely overestimated in these studies.

4.2.2 Harms

A meta-analysis published in 2011[33] showed that patients with uncontrolled seizures enrolled in double-blind RCTs of adjunctive AEDs were less likely to die due to sudden unexplained death in epilepsy (SUDEP) if allocated to the treatment group rather than placebo. Being on active treatment resulted in an over seven-fold reduction in the incidence of definite or probable SUDEP.[33] In the CDR review, one patient died of hypothermia and one patient died of respiratory failure, both in the placebo group. One patient randomized to the ESL 800 mg group died of status epilepticus in the titration phase while taking ESL 400 mg. Both the case of hypothermia and the case of status epilepticus may have been SUDEPs.[23]

The most common TEAEs were CNS-related and included dizziness, headache, and somnolence. According to the clinical expert, CNS-related AEs are common with AEDs. The clinical expert commented that the incidence of dizziness seemed particularly high with ESL, which could affect adherence to treatment in clinical practice. Furthermore, TEAEs appeared to be dose-related, with a higher incidence occurring with the higher dose. As such, WDAEs were highest with ESL 1,200 mg and dizziness was a common reason for stopping treatment. The incidence of SAEs was higher in the ESL 800 mg group compared with the ESL 1,200 mg group in studies 302 and 304. This could be a chance finding in light of the higher overall incidence of AEs in the ESL 1,200 mg groups; the fact that more patients in the ESL 1,200 mg group discontinued treatment prematurely, resulting in longer overall exposure to ESL 800 mg, may also have contributed to this observation.

A patient group commented that it hoped ESL would cause less cognitive dysfunction than other AEDs, with the expectation that the drug would improve overall day-to-day functioning and ability to be employed or go to school. In the included trials, few patients reported cognitive disorder, disturbance in attention, or memory impairment as a TEAE. Hence, it is uncertain whether ESL has advantages over other AEDs in this respect.

A meta-analysis of neurological AEs found that ESL was associated with increased dizziness at the 800 mg dose and increased diplopia, nausea, and vertigo at the 1,200 mg dose compared with placebo.[34] Risk of withdrawals due to AEs was related to dose for all AEDs.[34] An indirect comparison in the same publication showed that neurological AEs were more frequently reported with oxcarbazepine than with lacosamide or ESL.[34] The manufacturer-submitted NMA showed there were no statistically significant differences in TEAEs, WDAEs, and SAEs between ESL, lacosamide, and perampanel (Appendix 7: Summary and Critical Appraisal of the Manufacturer-Submitted Network Meta-Analysis). However, the 95% credible intervals for comparisons of ESL with other drugs were wide, indicating a high degree of uncertainty regarding these findings.

Notable harms of AEDs identified by the clinical expert included hyponatremia, allergic reactions, skin reactions, neutropenia, and teratogenicity. While no cases of allergic reaction were reported, two cases of severe hyponatremia were reported in the ESL 800 mg group. Study 304 included a higher proportion of Asian patients (approximately 20%) compared with none in Study 301 and less than 5% in studies 302 and 303. Carbamazepine is associated with skin-related AEs, which can range from mild skin rash to more serious skin reactions such as Stevens–Johnson syndrome.[35] The frequency of severe skin-related AEs has been estimated at one to six cases per 10,000 new users of carbamazepine.[36] The presence of HLA proteins (HLA-B*1502/HLA-B75 alleles) in patients of Asian descent (more so in patients of Chinese or Thai origin) is a strong risk factor for carbamazepine-induced skin reactions, including toxic epidermal necrolysis and Stevens-Johnson syndrome.[35,36] More recently, it has been shown that the presence of HLA-A*3101 in people of Asian (most commonly Japanese) or European descent is also associated with carbamazepine-induced skin reactions, but not as strongly as HLA-B*1502.[35] ESL and oxcarbazepine were developed as safer alternatives to carbamazepine, although there have been reports of oxcarbazepine-induced severe skin reactions.[35] Due to limited long-term data, it is too early to tell if ESL could potentially cause severe skin reactions, but the possibility of such reactions exists since ESL has the same active metabolite as oxcarbazepine. In the included trials, four patients (one with ESL 800 mg and three with ESL 1,200 mg) reported exanthem as an adverse event, of which one was considered an SAE (with ESL 1,200 mg); it was not specified if the cause of the exanthem was infection or if it was drug-induced. There were also five ESL 800 mg patients, 10 ESL 1,200 mg patients, and four placebo patients with rashes. One patient on ESL 800 mg developed leukocytoclastic vasculitis (drug hypersensitivity cutaneous vasculitis syndrome). The patient tested as a non-carrier of HLA-B*1502. Finally, there were no reports of teratogenicity as pregnant women were excluded from entering the ESL trials. Health Canada's product monograph states that the administration of ESL to animals has resulted in fetal malformations and growth retardation.[15]

In the OLE trials (Appendix 6: Summary of Open-Label Extension Studies), the safety profile was similar overall to that observed in the double-blind RCTs, except that WDAEs were less frequent than in the RCTs. The investigators attributed one death to the study drug, with the cause of death described as prolonged and recurrent seizures. There were also three cases of drowning, one patient dying due to severe coronary atherosclerosis, and one other death due to a recurrent tumour.

4.3 Other Considerations

In April 2011, Vimpat (lacosamide) was recommended for listing by the Canadian Expert Drug Committee as adjunctive therapy in patients with refractory POS who meet all of the following criteria:

- They are under the care of a physician experienced in the treatment of epilepsy.
- They are currently receiving two or more AEDs.
- All other AEDs are ineffective or not appropriate for them.[28]

In September 2013, the Canadian Drug Expert Committee recommended that Fycompa (perampanel) be listed as adjunctive therapy in the management of POS in patients with epilepsy who are not satisfactorily controlled with conventional therapy who meet all of the following criteria:

- They are under the care of a physician experienced in the treatment of epilepsy.
- They are currently receiving two or more AEDs.
- Less costly AEDs are ineffective or not appropriate for them.[8]

Unlike carbamazepine, ESL is not a strong inducer of cytochrome P-450 and, as such, has a lower propensity to cause drug interactions.[11]

5. CONCLUSIONS

In four RCTs of patients with uncontrolled POS despite treatment with one to three AEDs, ESL 800 mg and 1,200 mg demonstrated statistically significant benefits relative to placebo on two key outcomes: seizure frequency per four-week period, and the proportion of patients with a 50% reduction in seizures. A small proportion of ESL-treated patients achieved seizure-free status, but the trials were of insufficient size for definitive assessment of this outcome. There was no difference in HRQoL between ESL and placebo. ESL 800 mg appeared to be as effective as ESL 1,200 mg, although the trials were not designed to test for differences between doses. However, there was an apparent dose-dependent increase in TEAEs and WDAEs as patients in the ESL 1,200 mg group experienced more TEAEs and WDAEs compared with the ESL 800 mg group. The most frequently reported TEAEs with ESL were CNS-related (e.g., dizziness, somnolence, and headache). There were three deaths, two of which may have been SUDEP. There was a lack of data comparing ESL with other clinically relevant AEDs for refractory POS. A manufacturer-submitted NMA suggested similar efficacy for ESL, perampanel, and lacosamide, although uncertainty remains in this regard due to a high degree of imprecision in the indirect-effect estimates.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was summarized by CADTH Common Drug Review staff based on the input provided by patient groups. It has not been systematically reviewed.

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

Four patient groups submitted input regarding Aptiom.

Epilepsy Newfoundland and Labrador has a mission to share information, educate the public, and to adopt any measures necessary to improve the health, strength, and well-being of the 10,000 men, women, and children living with epilepsy in the province of Newfoundland and Labrador. Epilepsy Newfoundland and Labrador declared no conflict of interest whatsoever and no current relationship with Sunovion.

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. Epilepsy Nova Scotia declared no conflict of interest whatsoever and no current relationship with Sunovion.

Epilepsy Ontario includes 13 community-based epilepsy agencies that provide direct services to children, youth, and adults who have epilepsy and their family members in southern and northeastern Ontario, and provides support in areas where there are no agencies. Epilepsy Ontario is dedicated to promoting independence and optimal quality of life for those living with seizure disorders through providing information and education, raising public awareness, engaging and empowering people who live with epilepsy, advocating for supports and services to improve the quality of life for people living with epilepsy, and providing provincial programs, including summer camps and scholarships. Epilepsy Ontario has received funding from UCB Canada, Eisai, Sunovion, Rx&D, and Baylis Medical. The author of the submission from Epilepsy Ontario received funding to attend the 2012 American Epilepsy Society meeting from UCB Pharma, and a consultantship from Shoppers Drug Mart.

The BC Epilepsy Society is a non-profit charitable organization providing education, advocacy, and support for those affected by epilepsy. The BC Epilepsy Society offers educational events, multi-language information materials, support groups, school outreach, and newsletters. The BC Epilepsy Society also provides seizure-awareness workshops, funds children to attend accessible camps, awards post-secondary scholarships, and funds research in BC. The BC Epilepsy Society has previously received funding from UCB and Lundbeck. It declares no conflict of interest with Sunovion and no conflict of interest in the preparation of its submission.

2. Condition and Current Therapy-Related Information

Information was gathered through personal experience as a caregiver, from patient group members, executives of patient groups, one-on-one conversations, and through an online survey that was completed by 72 Canadians (54 adults with epilepsy, 11 caregivers, one individual who no longer has epilepsy, and six staff).

Epilepsy is most aptly characterized as a spectrum with individuals experiencing different types of seizures with different frequency, severity, and duration. Partial-onset seizures can affect almost every aspect of a person's day-to-day life; in particular, patients who achieve only partial or no seizure control

on anti-seizure medications are affected in almost every aspect of day-to-day life. This includes loss of independence; a reduced ability to seek or maintain employment or to participate in exercise or educational programs; social isolation; a reduced ability to ride a bus, shop for groceries, or cross a street; and not being able to operate a motor vehicle. Financial difficulties caused by unemployment or underemployment and medical costs can lead to a need for financial assistance from government programs. Not knowing when a seizure could occur can result in excessive anxiety or other mood disorders. The following table presents some responses to the survey from adults living with epilepsy.

Survey Feedback From Patients With Epilepsy	
• Due to epilepsy, I have no life.	• Epilepsy took simple things from me: being able to cook, drive, breastfeed my children, carry my babies around the house.
• Epilepsy has made me realize how much I took independence for granted.	• I am restricted where I can live, where I can shop, where I can work.
• I put my infant son in harm during a seizure.	• Epilepsy has rattled my confidence and self-esteem.

Societal attitudes have a significant impact on people with epilepsy; people with this condition often face stigma and discrimination. People experiencing seizures or the aftermath of seizures have been "tasered" or arrested for being "intoxicated" in public. Children with epilepsy may not be invited to friends' houses due to fear of not knowing how to handle a seizure.

When a person has epilepsy, the entire family is affected. There is anxiety regarding when the next seizure will occur and what impact it will have. A husband might fear his wife will have a seizure and drop their baby or burn herself while cooking; a wife might fear her husband taking a bath alone and drowning; parents are nervous about their child attending a birthday party and worry about who will care for him or her when they are gone. A child might be concerned over their parent driving or feeling suicidal. Some caregivers cannot bring themselves to leave their loved one alone, contributing to a loss of independence and self-esteem in the person with seizures, and compassion fatigue or sleep deprivation in the caregiver. Many of the side effects of anti-seizure medications affect family life. The financial burden on the family can also be immense. The following table presents some responses to the survey from the 11 Canadian caregivers whose family member(s) with epilepsy were 18 years of age or older.

Survey Feedback From Caregivers of Patients With Epilepsy	
• I quit working for the first three years.	• The uncertainty of not knowing when the next seizure will be is a source of great stress on us all.
• I am constantly worried, terrified, or on edge that my husband will die.	• It has been difficult to ensure balance among work, family, and especially to ensure that my other children get equal care.
• We can no longer afford our home.	• The drugs all seem to have horrific side effects.

There is no cure for epilepsy; however, approximately 70% of persons with epilepsy can achieve full seizure control by taking the anti-seizure medications currently available. These medications have adverse effects, some of which may be intolerable to the patient, including the inability to concentrate, memory problems, turbulent mood swings, fatigue, kidney and liver failure, depression, suicidal ideation, cognitive problems, behavioural problems, excessive growth of body hair, gum overgrowth, sexual dysfunction, and thinning of the bones.

3. Related Information About the Drug Being Reviewed

No patient group reported members having experience with Aptiom. Although no anti-seizure medication is expected to be beneficial for everyone, it is hoped that Aptiom 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 Aptiom if it can help reduce their seizure frequency — even without full control — and have fewer side effects compared with other drug treatments.

Patient groups understand that Aptiom has a different mechanism of action. One patient group referred to materials from published medical journal studies and noted that Aptiom could stop or reduce the number of partial-onset seizures. It could cause less cognitive dysfunction than other epilepsy medications. This would greatly improve patients' overall day-to-day functioning and ability to participate in employment and educational opportunities.

People with intractable epilepsy are often unemployed or underemployed and are living on very restricted incomes, most often without private insurance plans. New medications that are not covered by public formularies will thus not be accessible to most people with intractable epilepsy, the very ones who need the opportunity to try new treatment options the most.

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:	November 11, 2014
Alerts:	Weekly search updates until (date of CDEC meeting)
Study types:	Systematic reviews; meta-analyses; technology assessments; randomized controlled trials; controlled clinical trials.
Limits:	No date or language limits were used 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
adj	Requires words are adjacent to each other (in any order)
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.pt	Publication type
.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	
Database: Embase < 1974 to 2014 November 10> , Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) < 1946 to Present> Search Strategy:	
1	eslicarbazepine.ti,ot,ab,sh,rn,hw,nm.
2	(Aptiom or Eslify or Eslizen or Exalief or Normictal or Zebinix or Zefretol).ti,ot,ab,sh,rn,hw,nm.
3	ESL.ti,ot,ab,sh,rn,hw,nm.
4	*eslicarbazepine acetate/
5	(236395-14-5 or BIA 2-093 or Pazzul or "Sep 0002093" or Stedesa or BEA68ZVB2K).ti,ot,ab,sh,rn,hw,nm.
6	or/1-5
7	(Randomized Controlled Trial or Controlled Clinical Trial).pt.

MULTI-DATABASE STRATEGY	
8	Randomized Controlled Trial/
9	Randomized Controlled Trials as Topic/
10	"Randomized Controlled Trial (topic)"/
11	Controlled Clinical Trial/
12	Controlled Clinical Trials as Topic/
13	"Controlled Clinical Trial (topic)"/
14	Randomization/
15	Random Allocation/
16	Double-Blind Method/
17	Double Blind Procedure/
18	Double-Blind Studies/
19	Single-Blind Method/
20	Single Blind Procedure/
21	Single-Blind Studies/
22	Placebos/
23	Placebo/
24	Control Groups/
25	Control Group/
26	(random* or sham or placebo*).ti,ab,hw.
27	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
28	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.
29	(control* adj3 (study or studies or trial*)).ti,ab.
30	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.
31	allocated.ti,ab,hw.
32	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.
33	or/7-32
34	6 and 33
35	meta-analysis.pt.
36	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/
37	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab.
38	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab.
39	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab.
40	(data synthes* or data extraction* or data abstraction*).ti,ab.
41	(handsearch* or hand search*).ti,ab.
42	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab.
43	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab.
44	(meta regression* or metaregression*).ti,ab.
45	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
46	(MEDLINE or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
47	(cochrane or (health adj2 technology assessment) or evidence report).jw.
48	(meta-analysis or systematic review).md.
49	(comparative adj3 (efficacy or effectiveness)).ti,ab.
50	(outcomes research or relative effectiveness).ti,ab.
51	((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab.
52	or/35-51
53	6 and 52

MULTI-DATABASE STRATEGY	
54	34 or 53
55	remove duplicates from 54
56	55 not conference abstract.pt.
57	56 use pmez
58	56 use oemezd
59	55 not conference abstract.pt.

OTHER DATABASES	
PubMed	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:	November, 2014
Keywords:	Aptiom (eslicarbazepine acetate)
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 evidence-based searching" (http://www.cadth.ca/en/resources/finding-evidence-is/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
Halasz P, Cramer JA, Hodoba D, Czlonkowska A, Guekht A, Maia J, et al. Long-term efficacy and safety of eslicarbazepine acetate: results of a one-year open-label extension study in partial-onset seizures in adults with epilepsy. Epilepsia. 2010 Oct;51(10):1963-9.	Open-label extension study
Hufnagel A, Ben-Menachem E, Gabbai AA, Falcao A, Almeida L, Soares-da-Silva P. Long-term safety and efficacy of eslicarbazepine acetate as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy: results of a one-year open-label extension study. Epilepsy Res. 2013 Feb;103(2-3):262-9.	Open-label extension study
Clinical Study Report: part II of PRA/BIA-2093-303. Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multi-centre clinical trial [**CONFIDENTIAL** internal manufacturer's report]. S. Mamede do Coronado, Portugal: BIAL - Portela & Ca, SA; 2008 Sep 15.	Open-label extension study
Clinical Study Report: part II of PRA/BIA-2093-302. Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multi-centre clinical trial [**CONFIDENTIAL** internal manufacturer's report]. S. Mamede do Coronado, Portugal: BIAL - Portela & Ca, SA; 2008 Sep 15.	Open-label extension study
Clinical Study Report: part II of SCO/BIA-2093-301. Efficacy and safety of BIA 2-093 as adjunctive therapy for refractory partial seizures in a double-blind, randomized, placebo-controlled, parallel-group, multi-centre clinical study [**CONFIDENTIAL** internal manufacturer's report]. S. Mamede do Coronado, Portugal: BIAL - Portela & Ca, SA; 2007 Jun 30.	Open-label extension study
Elger C, Bialer M, Cramer JA, Maia J, Almeida L, Soares-da-Silva P. Eslicarbazepine acetate: a double-blind, add-on, placebo-controlled exploratory trial in adult patients with partial-onset seizures. Epilepsia. 2007 Mar;48(3):497-504.	Phase 2 study
Gil-Nagel A, Elger C, Ben-Menachem E, Halasz P, Lopes-Lima J, Gabbai AA, et al. Efficacy and safety of eslicarbazepine acetate as add-on treatment in patients with focal-onset seizures: integrated analysis of pooled data from double-blind phase 3 clinical studies. Epilepsia. 2013 Jan;54(1):98-107.	Pooled analysis

APPENDIX 4: DETAILED OUTCOME DATA

TABLE 15: PROPORTION OF PATIENTS WITH 100% REDUCTION IN SEIZURES, INTENTION-TO-TREAT POPULATION

	Study 301[a]			Study 302				Study 303		Study 304		
	ESL 800 mg (N = 98	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Maintenance period												
N	98	98	102	100	97	100	84	77	84	200	183	212
n (%)	4 (4.1)	8 (8.2)	2 (2.0)	3 (3.0)	5 (5.2)	2 (2.0)	4 (4.8)	3 (3.9)	1 (1.2)	4 (2.0)	4 (2.2)	2 (0.9)
P value vs. PL	0.372[b]	0.042[b]	-	0.556[c]	0.16[c]	-	0.185[c]	0.263[c]	-	0.336[d]	0.235[d]	-
RR[e] (95% CI)[e]	2.1 (0.4 to 11.1)	4.2 (0.9 to 19.1)	-	1.5 (0.3 to 8.8)	2.6 (0.5 to 13.0)	-	4.0 (0.5 to 35.0)	3.3 (0.3 to 30.8)	-	2.1 (0.4 to 11.4)	2.3 (0.4 to 12.5)	-
NNT[e]	48	17	-	100	32	-	28	37	-	95	81	-
Titration plus maintenance period												
N	98	98	102	100	97	100	84	77	84	NA	NA	NA
n (%)	3 (3.1)	5 (5.1)	0	8 (8.0)	4 (4.1)	1 (1.0)	3 (3.6)	1 (1.3)	1 (1.2)	NA	NA	NA
P value vs. PL	0.075[a]	0.021[a]	-	0.019[b]	0.168[b]	-	0.319[b]	0.977[b]	-	NA	NA	NA

ANOVA = analysis of variance; CDR = CADTH Common Drug Review; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; ESL = eslicarbazepine acetate; ITT = intention-to-treat; m-ITT = modified intention-to-treat; NA = not applicable; NNT = number needed to treat; PL = placebo; RR = relative risk; vs. = versus.

[a] Study 301: ITT = m-ITT plus Poland (all randomized patients with at least one dose of randomized study medication who had at least one post-baseline seizure-frequency assessment, including patients from two sites in Poland).

[b] CMH test.

[c] CMH test stratified by region using the ANOVA statistic for ordinal data.

[d] CMH test stratified by region and diary version.

[e] Calculated by CDR.

Source: Clinical Study Reports.[1-4,22]

TABLE 16: QOLIE-31, INTENTION-TO-TREAT POPULATION[A]

	Study 301			Study 302				Study 303		Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Baseline overall score												
N	97	95	100	89	86	87	64	57	64	214	205	220
Mean (SD)	53.0 (16.5)	53.3 (16.0)	55.9 (15.6)	56.0 (15.3)	52.9 (17.4)	54.8 (15.6)	59.4 (15.8)	55.0 (19.3)	56.3 (15.1)	118.9 (33.5)	117.4 (32.3)	120.5 (30.0)
Median	52.2	52.0	53.5	53.3	52.3	53.7	62.1	54.4	53.1	118.0	119.2	120.6
Min, max	21.3, 92.1	20.7, 86.9	20.7, 95.8	30.8, 92.4	8.4, 100.0	23.0, 89.3	21.6, 93.0	19.1, 93.7	24.8, 86.6	21.4, 198.8	20.7, 191.6	46.6, 195.7
Change from baseline in overall score at last observed value or at last assessment[b]												
N	89	90	93	89	86	87	64	57	64	195	190	209
Mean (SD)	NR	NR	NR	2.6 (13.3)	–1.6 (14.9)	1.9 (14.6)	6.1 (12.9)	3.6 (13.5)	4.3 (15.1)	5.4 (23.8)	4.6 (25.7)	2.2 (25.4)
Median	NR	NR	NR	2.7	0.2	0.3	4.1	3.6	1.2	5.4	5.6	3.4
Min, max	NR	NR	NR	–51.6, 32.7	–88.9, 26.9	–38.1, 42.3	–26.8, 50.9	–23.3, 39.6	–34.8, 40.2	–76.3, 84.8	–94.2, 89.0	–100.3, 79.2
LS mean total score	55.1	52.9	55.0	57.7	52.6	56.6	63.9	59.9	61.1	NR	NR	NR
95% CI for mean	53.0 to 57.2	50.8 to 55.0	52.9 to 57.1	55.1 to 60.4	49.9 to 55.3	53.9 to 59.3	60.7 to 67.0	56.5 to 63.2	57.9 to 64.2	NR	NR	NR
Diff. in LS mean vs. PL	0.1	–2.1	-	1.1	–4.1	-	2.8	–1.2	-	2.8	1.9	-
P value vs. PL	0.9998[c]	0.3729[c]	-	0.892[c]	0.092[c]	-	0.360[c]	0.826[c]	-	0.241[c]	0.433[c]	-

ANCOVA = analysis of covariance; CI = confidence interval; diff. = difference; ESL = eslicarbazepine acetate; ITT = intention-to-treat; LS = least squares; max = maximum; min = minimum; NR = not reported; PL = placebo; QOLIE-31 = 31-item Quality of Life in Epilepsy Inventory; SD = standard deviation; vs. = versus.

[a] Higher QOLIE-31 score = better quality of life.

[b] Study 301: ANCOVA. Studies 302 and 303: ANCOVA; treatment as a factor and baseline score as covariate. Study 304: ANCOVA; baseline overall score and diary version as covariates and treatment as a fixed effect.

[c] Dunnett's test (unadjusted *P* value for Study 304).

Source: Clinical Study Reports.[1-4,22]

TABLE 17: SEIZURE SEVERITY QUESTIONNAIRE, INTENTION-TO-TREAT POPULATION

	Study 304		
	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Baseline overall severity score			
N	32	33	36
Mean (SD)	23.6 (12.2)	25.0 (11.6)	24.5 (10.0)
Median	21.5	23.0	26.5
Min, max	5, 55	6, 51	3, 43
Change from baseline in overall severity score at last assessment[a]			
N	12	20	19
Mean (SD)	–6.5 (10.7)	–4.8 (9.2)	–2.8 (6.8)
Median	–3.0	–7.0	–1.0
Min, max	–23, 11	–22, 17	–16, 8
LS mean (95% CI)	–6.6 (–11.7 to –1.5)	–4.8 (–8.6 to –1.0)	–2.8 (–6.7 to 1.1)
Diff. in LS mean vs. PL	–3.8	–2.0	-
Unadjusted *P* value vs. PL	0.235	0.462	-

ANCOVA = analysis of covariance; CI = confidence interval; diff. = difference; ESL = eslicarbazepine acetate; LS = least squares; max = maximum; min = minimum; PL = placebo; SD = standard deviation.
[a] ANCOVA baseline severity score and diary version as covariates and treatment as a fixed effect.
Higher SSQ score = higher severity.
Source: Clinical Study Report.[2]

TABLE 18: CLINICAL GLOBAL IMPRESSION, INTENTION-TO-TREAT POPULATION

	Study 301[a]			Study 304[a]		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Global Improvement score at last assessment, n (%)						
Very much improved	4 (4)	7 (7)	2 (2)	14 (7)	12 (6)	9 (4)
Much improved	25 (26)	23 (24)	21 (21)	56 (28)	59 (30)	35 (17)
Minimally improved	31 (32)	29 (30)	34 (33)	64 (31)	54 (28)	66 (31)
No change	28 (29)	26 (27)	32 (31)	60 (29)	53 (27)	83 (39)
Minimally worse	4 (4)	3 (3)	6 (6)	8 (4)	11 (6)	13 (6)
Much worse	2 (2)	3 (3)	3 (3)	2 (1)	7 (4)	6 (3)
Very much worse	0	1 (1)	0	0	0	0
Missing	4 (4)	6 (6)	4 (4)	11 (NR)	9 (NR)	8 (NR)

ESL = eslicarbazepine acetate; NR = not reported; PL = placebo.
[a] Number of patients based on patients with non-missing data; N not reported.
Source: Clinical Study Reports.[2,3,22]

TABLE 19: CGI GLOBAL IMPROVEMENT SCORE, INTENTION-TO-TREAT POPULATION[A]

	Study 301			Study 302[a]				Study 303[a]	
	ESL 800 mg (N =98)	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)
Global Improvement score at last observed value									
N	98	98	102	93	85	97	79	67	77
Mean (SD)	NR	NR	NR	3.1 (1.2)	3.0 (1.3)	3.3 (1.0)	2.6 (1.4)	2.5 (1.3)	2.9 (1.1)
Median	NR	NR	NR	3.0	3.0	3.0	2.0	2.0	3.0
Min, max	NR	NR	NR	1, 6	1, 6	1, 7	1, 7	1, 6	1, 6
LS mean	NA	NA	NA	3.2	3.0	3.3	2.6	2.5	2.9
95% CI for mean	NA	NA	NA	2.9 to 3.4	2.7 to 3.2	3.1 to 3.6	2.3 to 2.9	2.2 to 2.8	2.6 to 3.2
Diff. in LS mean vs. PL[b]	NA	NA	NA	–0.2	–0.4	-	–0.3	–0.4	-
P value vs. PL[c]	0.306	0.250	-	0.632	0.081	-	0.280	0.110[c]	-

ANCOVA = analysis of covariance; CGI = Clinical Global Impression; CI = confidence interval; diff. = difference; ESL = eslicarbazepine acetate; LS = least squares; max = maximum; min = minimum; NA = not applicable; NR = not reported; PL = placebo; SD = standard deviation.

[a] Score: 1 = very much improved; 7 = very much worse.

[b] Studies 302 and 303: ANCOVA; treatment as a factor and baseline score as covariate.

[c] Dunnett's test.

Source: Clinical Study Reports.[1,3,4,22]

TABLE 20: ANALYSIS OF COVARIANCE FOR STANDARDIZED SEIZURE FREQUENCY, INTENTION-TO-TREAT POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Maintenance period												
N	94	94	99	88	85	99	80	69	79	200	184	212
LS mean (back-transformed)	5.7	5.4	7.6	7.1	7.0	9.8	5.7	5.5	7.3	6.5	6.0	7.9
95% CI for mean	4.9 to 6.5	4.6 to 6.1	6.8 to 8.6	6.2 to 8.2	6.0 to 8.1	8.7 to 11.1	4.9 to 6.7	4.6 to 6.5	6.3 to 8.5	5.8 to 7.4	5.3 to 6.8	7.0 to 8.9
LS mean diff. vs. PL[a]	–1.9	–2.2	-	–2.7	–2.8	-	–1.6	–1.9	-	–1.4	–1.9	-
LS mean log-transformed[b]	2.27	2.24	2.45	2.41	2.40	2.60	2.27	2.25	2.42	1.92	1.85	2.11
LS mean log diff. vs. PL[c]	–0.19	–0.22	-	–0.19	–0.20	-	–0.15	–0.17	-	–0.18	–0.26	-
P value vs. PL	0.0028[d]	0.0003[d]	-	0.002[d]	0.001[d]	-	0.048 [d]	0.021[d]	-	0.058[e]	0.004[e]	-
Titration plus maintenance period												
N	98	98	102	100	97	100	84	77	84	NA	NA	NA
LS mean (back-transformed)	6.1	5.9	8.1	7.1	7.4	10.9	6.2	6.1	8.0	NA	NA	NA
95% CI for mean	5.3 to 6.9	5.2 to 6.7	7.3 to 9.1	6.2 to 8.1	6.4 to 8.4	9.6 to 12.2	5.4 to 7.2	5.3 to 7.1	7.0 to 9.1	NA	NA	NA
LS mean diff. vs. PL[a]	–2.0	–2.2	-	–3.8	–3.5	-	–1.8	–1.8	-	NA	NA	NA
LS mean log diff. vs. PL[c]	–0.19	–0.20	-	–0.29	–0.27	-	–0.16	–0.16	-	NA	NA	NA
P value vs. PL	0.002[d]	0.0006[d]	-	< 0.001[d]	< 0.001[d]	-	0.025[d]	0.020[d]	-	NA	NA	NA

ANCOVA = analysis of covariance; CDR = CADTH Common Drug Review; CI = confidence interval; diff. = difference; ESL = eslicarbazepine acetate; LS = least squares; NA = not applicable; PL = placebo.

ANCOVA model: treatment as fixed effect and log-transformed baseline seizure frequency (plus diary version in Study 304) as covariate.

[a] Difference calculated by CDR for studies 301 and 304.

[b] [Ln(LS mean + 4)] for studies 301, 302, and 303 and [Ln(LS mean + 0.333)] for Study 304, calculated by CDR.

[c] Difference calculated by CDR for studies 302 and 303.

[d] Dunnett's test.

[e] Bonferroni's test.

Source: Elger,[18] Clinical Study Reports.[2-4]

TABLE 21: CHANGE IN STANDARDIZED SEIZURE FREQUENCY, INTENTION-TO-TREAT POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 98)	PL (N =102)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N =84)	ESL 1,200 mg (N =77)	PL (N =84)	ESL 800 mg (N =215)	ESL 1,200 mg (N =205)	PL (N =220)
Percentage relative change from baseline (MP)												
N	94	94	99	88	85	99	80	68	78	200	183	212
Mean (SD)	–30.8 (43.8)	–34.5 (48.4)	–6.9 (64.1)	–25.2 (59.4)	–25.4 (56.2)	+2.5 (63.5)	–21.1 (73.0)	–21.1 (106.8)	–5.1 (68.8)	–23.5 (53.9)	–28.6 (51.9)	–8.7 (121.5)
Median	–36.1	–45.3	–16.4	–32.6	–32.9	–5.0	–37.9	–41.9	–17.0	–29.7	–35.6	–21.8
Min, max	–100, 147	–100, 87	–100, 367	–290.7, 100.0	–150.5, 100.0	–323.6, 100.0	–386.3, 100.0	–717.2, 100.0	–306.6, 100.0	–100.0, 261.3	–100.0, 168.4	–100.0, 1,521.0

ESL = eslicarbazepine acetate; max = maximum; min = minimum; MP = maintenance period; PL = placebo; SD = standard deviation.
Source: Clinical Study Reports.[1-4,22]

TABLE 22: ANALYSIS OF COVARIANCE FOR STANDARDIZED SEIZURE FREQUENCY BY SEIZURE TYPE, ITT POPULATION

	Study 302				Study 303		Study 304		
	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Simple partial (MP)									
N	52	49	58	46	42	53	98	88	101
LS mean	3.8	4.4	6.8	3.3	3.8	4.1	4.0	4.1	4.8
95% CI for mean	2.9 to 5.0	3.3 to 5.6	5.6 to 8.3	2.3 to 4.3	2.7 to 5.0	3.1 to 5.2	3.2 to 4.9	3.3 to 5.2	3.8 to 5.9
LS mean diff. vs. PL[a,c]	–3.0	–2.5	-	–0.8	–0.3	-	–0.1	–0.7	-
LS mean log diff. vs. PL[b,c]	–0.33	–0.25	-	–0.1	–0.04	-	–0.17	–0.13	-
P value vs. PL[d]	0.002	0.017	-	0.458	0.923	-	0.23	0.343	-
Complex partial (MP)									
N	68	73	83	69	58	59	158	148	164
LS mean	4.4	3.6	5.3	3.1	2.3	3.9	4.7	4.2	5.2
95% CI for mean	3.5, 5.3	2.9, 4.4	4.5, 6.2	2.4, 3.9	1.6, 3.1	3.0, 4.8	4.2, 5.4	3.7, 4.9	4.6, 5.9

	Study 302				Study 303			Study 304		
	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)		PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
LS mean diff. vs. PL[a,c]	–1.0	–1.7	-	–0.7	–1.5		-	–0.5	–1.0	-
LS mean log diff. vs. PL[b,c]	–0.1	–0.2	-	–0.11	–0.23		-	–0.08	–0.19	-
P value vs. PL[d]	0.318	0.012	-	0.356	0.018		-	0.343	0.031	-
Partial evolving to GS (MP)										
N	29	35	33	23	28		31	58	56	71
LS mean	2.3	1.0		1.7	1.1	1.6	1.5	2.0	1.6	2.1
95% CI for mean	1.6, 3.1	0.5, 1.6		1.1, 2.4	0.5, 1.8	1.0, 2.3	0.9, 2.1	1.6, 2.5	1.2, 2.1	1.7, 2.6
LS mean diff. vs. PL[a,c]	0.6	–0.7		-	–0.4	0.1	-	–0.1	–0.5	-
LS mean log diff. vs. PL[b,c]	0.1	–0.13		-	–0.07	0.02	-	–0.05	–0.23	-
P value vs. PL[d]	0.494	0.308		-	0.653	0.933	-	0.726	0.091	-

CDR = CADTH Common Drug Review; CI = confidence interval; diff. = difference; ESL = eslicarbazepine acetate; GS = generalized seizures; ITT = intention-to-treat; LS = least squares; MP = maintenance period; PL = placebo.

[a] Difference calculated by CDR for Study 304.

[b] Difference calculated by CDR for studies 302 and 303, based on difference in [Ln(LS mean +4)].

[c] ANCOVA model: treatment as factor and log-transformed baseline seizure frequency (plus diary version in Study 304) as covariate.

[d] Dunnett's test (unadjusted *P* values for Study 304).

Note:

Source: Clinical Study Reports.[1,2,4]

TABLE 23: ANALYSIS OF COVARIANCE FOR STANDARDIZED SEIZURE FREQUENCY BY AEDS, ITT POPULATION

	Study 304					
Standardized Seizure Frequency During MP	**ESL 800 mg (N = 215)**	**ESL 1,200 mg (N = 205)**	**PL (N = 220)**	**ESL 800 mg (N = 215)**	**ESL 1,200 mg (N = 205)**	**PL (N = 220)**
Carbamazepine used during baseline period	**Yes**			**No**		
N	77	77	73	132	107	139
LS mean	6.5	7.4	7.2	6.6	5.1	8.3
95% CI for mean	5.5 to 7.7	6.2 to 8.8	6.0 to 8.7	5.5 to 7.8	4.3 to 6.2	7.1 to 9.7
LS mean log diff. vs. PL[a]	–0.1	0.02	-	–0.22	–0.46	-
Unadjusted *P* value vs. PL	0.407	0.889	-	0.038	< 0.001	-
Carbamazepine dose reduction during MP	**Yes**			**No**		
N	6	12	0	71	65	73
LS mean	NA	NA	NA	6.4	7.6	7.1
95% CI for mean	NA	NA	NA	5.3 to 7.6	6.3 to 9.2	5.9 to 8.5
LS mean log diff. vs. PL[a]	NA	NA	NA	–0.10	0.07	-
Unadjusted *P* value vs. PL	NA	NA	NA	0.413	0.576	-
Phenytoin dose reduction during MP	**Yes**			**No**		
N	0	0	0	18	23	23
LS mean	NA	NA	NA	7.1	5.6	8.1
95% CI for mean	NA	NA	NA	4.4 to 11.3	3.6 to 8.6	5.3 to 12.1
LS mean log diff. vs. PL[a]	NA	NA	NA	–0.12	–0.34	-
Unadjusted *P* value vs. PL	NA	NA	NA	0.672	0.226	-
Use of rescue medication during MP	**Yes**			**No**		
N	18	13	15	182	171	197
LS mean	11.1	9.1	12.1	6.3	5.8	7.6
95% CI for mean	7.6 to 16.1	5.6 to 14.5	7.9 to 18.5	5.5 to 7.1	5.0 to 6.6	6.7 to 8.6
LS mean log diff. vs. PL[a]	–0.09	–0.28	-	–0.19	–0.26	-
Unadjusted *P* value vs. PL	0.721	0.323	-	0.029	0.003	-

AED = antiepileptic drug; CI = confidence interval; diff. = difference; ESL = eslicarbazepine acetate; ITT = intention-to-treat; LS = least squares; MP = maintenance period; NA = not applicable; PL = placebo; vs. = versus.

[a] ANCOVA model with log-transformed baseline standardized frequency and diary version as covariates and treatment as a fixed effect.

Source: Clinical Study Report.[2]

TABLE 24: PROPORTION OF RESPONDERS, INTENTION-TO-TREAT POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 100)	ESL 1,200 mg (N = 97)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Proportion of patients with seizure frequency reduction ≥ 50% (MP)												
N	98	98	102	100	97	100	84	77	84	200	183	212
n (%)	33 (33.7)	42 (42.9)	20 (19.6)	32 (32.0)	34 (35.1)	18 (18.0)	29 (34.5)	29 (37.7)	19 (22.6)	61 (30.5)	78 (42.6)	49 (23.1)
P value vs. PL	0.0246[a]	0.0004[a]	-	0.005[b]	< 0.001[b]	-	0.106[b]	0.02[b]	-	0.068[c]	< 0.001[c]	-
RR[d] (95% CI)[d]	1.7 (1.1 to 2.8)	2.2 (1.4 to 3.4)	-	1.8 (1.1 to 3.0)	1.9 (1.2 to 3.2)	-	1.5 (0.9 to 2.5)	1.7 (1.0 to 2.7)	-	1.3 (1.0 to 1.8)	1.8 (1.4 to 2.5)	-
NNT[d]	8	5	-	8	6	-	9	7	-	14	6	-
Proportion of patients with seizure frequency reduction ≥ 50% (TP plus MP)												
N	98	98	102	100	97	100	84	77	84	NA	NA	NA
n (%)	31 (31.6)	37 (37.8)	15 (14.7)	40 (40.0)	36 (37.1)	13 (13.0)	24 (28.6)	28 (36.4)	20 (23.8)	NA	NA	NA
P value vs. PL	0.0046[a]	0.0002[a]	-	< 0.001[b]	< 0.001[b]	-	0.515[b]	0.078[b]	-	NA	NA	NA

ANOVA = analysis of variance; CI = confidence interval; CMH = Cochran–Mantel–Haenszel; ESL = eslicarbazepine acetate; MP = maintenance period; NA = not applicable; NNT = number needed to treat; PL = placebo; RR = relative risk; TP = titration period.

[a] CMH test (not adjusted for multiple testing).

[b] CMH test stratified by region using the ANOVA statistic for ordinal data.

[c] CMH test stratified by region and diary version.

[d] Calculated by the CADTH Common Drug Review.

Source: Elger,[18] Clinical Study Reports.[1-4,22]

TABLE 25: DISTRIBUTION OF SEIZURE REDUCTION, INTENTION-TO-TREAT POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 97)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Proportion of patients with seizure reduction per 4-week period (MP), n (%)												
N	98	98	102	100	97	100	84	77	84	200	183	212
< 50%	61 (62.2)	52 (53.1)	79 (77.5)	56 (56.0)	51 (52.6)	81 (81.0)	51 (60.7)	39 (50.6)	59 (70.2)	83 (41.5)	62 (33.9)	107 (50.5)
50% to 75%	19 (19.4)	22 (22.4)	10 (9.8)	21 (21.0)	18 (18.6)	12 (12.0)	17 (20.2)	15 (19.5)	14 (16.7)	30 (15.0)	47 (25.7)	31 (14.6)
> 75%	14 (14.3)	20 (20.4)	10 (9.8)	11 (11.0)	16 (16.5)	6 (6.0)	12 (14.3)	14 (18.2)	5 (6.0)	31 (15.5)	31 (17.0)	18 (8.5)
P value	0.0277[a]	0.0004[a]	-	0.008[b]	< 0.001[b]	-	0.059[b]	0.008[b]	-	0.156[c]	0.002[c]	-

ANOVA = analysis of variance; CMH = Cochran–Mantel–Haenszel; ESL = eslicarbazepine acetate; MP = maintenance period; PL = placebo.
[a] CMH test.
[b] CMH test stratified by region using the ANOVA statistic for ordinal data.
[c] CMH test stratified by region and diary version.
Source: Clinical Study Reports.[1-4,22]

TABLE 26: SEIZURE EXACERBATIONS, INTENTION-TO-TREAT POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 97)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Proportion of patients with seizure frequency increase ≥ 25% (MP)												
N	98	98	102	100	97	100	84	77	84	200	183	212
n (%)	9 (9.2)	12 (12.2)	22 (21.6)	10 (10.0)	14 (14.4)	28 (28.0)	14 (16.7)	10 (13.0)	19 (22.6)	26 (13.0)	24 (13.1)	31 (14.6)
P value vs. PL	NR	NR	-	0.004[a]	0.052[a]	-	0.292[a]	0.141[a]	-	0.514[b]	0.647[b]	-
Proportion of patients with seizure frequency increase ≥ 25% (TP plus MP)												
N	98	98	102	100	97	100	84	77	84	NA	NA	NA
n (%)	12 (12.2)	13 (13.3)	22 (21.6)	14 (14.0)	18 (18.6)	30 (30.0)	13 (15.5)	10 (13.0)	25 (29.8)	NA	NA	NA
P value vs. PL	NR	NR	-	0.006[a]	0.05[a]	-	0.025[a]	0.011[a]	-	NA	NA	NA

ANOVA = analysis of variance; CMH = Cochran–Mantel–Haenszel; ESL = eslicarbazepine acetate; MP = maintenance period; NR = not reported; PL = placebo; TP = titration period.
[a] CMH test stratified by region using the ANOVA statistic for ordinal data.
[b] CMH test stratified by region and diary version.
Source: Clinical Study Reports.[1-4,22]

TABLE 27: TIME TO SEIZURE CONTROL, INTENTION-TO-TREAT POPULATION

	Study 304		
	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Days to onset of ≥ 50% reduction in standardized seizure frequency (MP)			
N	186	171	191
Mean (SD)	31.4 (19.7)	29.8 (17.9)	32.9 (19.3)
Median	24.5	24.5	24.5
Min, max	15, 103	15, 104	14, 105
Kaplan-Meir estimates			
N	215	205	220
Median (95% CI)	24.5 (21.5 to 29.5)	24.5 (22.5 to 24.5)	30.5 (24.5 to 31.5)
Patients censored, n (%)	29 (13.5)	34 (16.6)	29 (13.2)
P value[a]	0.252	0.069	-

CI = confidence interval; ESL = eslicarbazepine acetate; MP = maintenance period; PL = placebo; SD = standard deviation.
[a] One-sided *P* value from the log-ranked test comparing time to onset of seizure control between ESL and PL.
Source: Clinical Study Report.[2]

TABLE 28: USE OF RESCUE MEDICATION, INTENTION-TO-TREAT POPULATION

	Study 304		
	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 205)	PL (N = 220)
Use of rescue medication (MP), n (%)			
Patients with at least one rescue medication	18 (8.4)	13 (6.3)	15 (6.8)

ESL = eslicarbazepine acetate; MP = maintenance period; PL = placebo; TP = titration period.
Source: Clinical Study Reports.[2]

TABLE 29: ADHERENCE TO TREATMENT

	Study 301			Study 302				Study 303		Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 98)	PL (N = 102)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 97)	PL (N = 100)	ESL 800 mg (N = 84)	ESL 1,200 mg (N = 77)	PL (N = 84)	ESL 800 mg (N = 215)	ESL 1,200 mg (N = 210)	PL (N = 224)
Percentage intake of study medication												
	ITT population, MP			**ITT population, period NR**			**ITT population, period NR**			**Safety population, MP**		
N	92	92	96	95	88	98	72	57	62	195	180	208
Mean (SD)	100.0 (3.7)	99.5 (4.8)	99.3 (6.0)	98.5 (6.2)	98.4 (10.7)	99.5 (5.3)	97.1 (10.6)	98.4 (43.4)	95.7 (11.3)	98.1 (6.1)	97.4 (8.7)	97.8 (10.1)
Median	100.0	100.0	100.0	100.0	100.0	100.0	99.0	99.5	98.6	100.0	100.0	100.0
Min, max	87.6, 127.3	76.6, 125.0	52.9, 126.7	63.2, 125.0	8.2, 125.0	73.3 133.3	60.0, 132.0	51.2, 405.3	56.1, 124.7	56.3, 116.9	42.1, 147.4	25.3, 150.0

ESL = eslicarbazepine acetate; ITT = intention-to-treat; max = maximum; min = minimum; MP = maintenance period; NR = not reported; PL = placebo; SD = standard deviation.
Source: Clinical Study Reports.[1-4]

TABLE 30: TREATMENT-EMERGENT ADVERSE EVENTS, SAFETY POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 102)	PL (N = 100)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 85)	ESL 1,200 mg (N = 80)	PL (N = 87)	ESL 800 mg (N = 216)	ESL 1,200 mg (N = 210)	PL (N = 224)
Patients with > 0 TEAEs												
N (%)	49 (50)	62 (61)	32 (31)	84 (83)	78 (80)	68 (68)	45 (53)	49 (61)	34 (39)	145 (67)	163 (78)	125 (56)
Most common TEAEs,[a] N (%)												
Dizziness	14 (14)	14 (14)	2 (2)	30 (30)	43 (44)	10 (10)	16 (19)	24 (30)	9 (10)	34 (16)	55 (26)	19 (9)
Headache	9 (9)	11 (11)	6 (6)	15 (15)	19 (19)	9 (9)	5 (6)	8 (10)	10 (12)	20 (9)	24 (11)	17 (8)
Somnolence	9 (9)	10 (10)	2 (2)	17 (17)	21 (21)	17 (17)	11 (13)	11 (14)	8 (9)	16 (7)	36 (17)	12 (5)
Diplopia	7 (7)	11 (11)	0	15 (15)	10 (10)	4 (4)	1 (1)	3 (4)	1 (1)	14 (7)	22 (11)	4 (2)
Nausea	4 (4)	5 (5)	1 (1)	12 (13)	15 (15)	4 (4)	5 (6)	8 (10)	1 (1)	16 (7)	32 (15)	11 (5)
Vertigo	2 (2)	6 (6)	1 (1)	1 (1)	2 (2)	0	2 (2)	3 (4)	0	6 (3)	15 (7)	1 (< 1)
Influenza	4 (4)	4 (4)	0	2 (2)	3 (3)	4 (4)	0	1 (1)	2 (2)	4 (2)	1 (< 1)	6 (3)
Complex PS	1 (1)	3 (3)	2 (2)	0	0	0	0	0	0	0	0	0
Vomiting	1 (1)	4 (4)	0	13 (13)	10 (10)	3 (3)	4 (5)	6 (8)	3 (3)	6 (3)	23 (11)	3 (1)
Abnormal coordination	1 (1)	0	0	13 (13)	11 (11)	5 (5)	2 (2)	4 (5)	1 (1)	1 (< 1)	3 (1)	0
Blurred vision	2 (0)	2 (0)	0	8 (8)	7 (7)	2 (2)	1 (1)	2 (3)	1 (1)	10 (5)	9 (4)	2 (1)
Fatigue	0	2 (2)	1 (1)	5 (5)	7 (7)	5 (5)	0	0	2 (2)	8 (4)	11 (5)	6 (3)

ESL = eslicarbazepine acetate; PL = placebo; PS = partial seizure; TEAE = treatment-emergent adverse event.

[a] Frequency > 2% for Study 301; frequency > 5% for studies 302, 303, and 304.

Source: Clinical Study Reports.[1-4]

TABLE 31: SERIOUS ADVERSE EVENTS, SAFETY POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 102)	PL (N = 100)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 85)	ESL 1,200 mg (N = 80)	PL (N = 87)	ESL 800 mg (N = 216)	ESL 1,200 mg (N = 210)	PL (N = 224)
Patients with > 0 SAEs												
N (%)	4 (4)	6 (6)	4 (4)	6 (6)	2 (2)	0	0	1 (1)	0	14 (7)	3 (1)	7 (3)
Reasons												
Angina	1 (1)	0	0	0	0	0	0	0	0	0	0	0
Vertigo	1 (1)	1 (1)	0	0	0	0	0	0	0	0	0	0
Constipation	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Gastric disorder	1 (1)	1 (1)	0	0	0	0	0	0	0	0	0	0
Pneumonia	0	0	1 (1)	0	0	0	0	0	0	0	0	0
Drug toxicity	0	1 (1)	0	1 (1)	0	0	0	0	0	0	1 (< 1)	0
Breast adenoma	0	0	1 (1)	0	0	0	0	0	0	0	0	0
Convulsion	1 (1)	0	0	0	0	0	0	0	0	0	0	0
Paresthesia	0	0	1 (1)	0	0	0	0	0	0	0	0	0
Exanthem	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Hypertensive crisis	0	1 (1)	0	0	0	0	0	0	0	0	0	0
Dizziness	0	0	0	0	1 (1)	0	0	0	0	0	0	0
Ataxia	0	0	0	0	1 (1)	0	0	0	0	0	0	0
Vomiting	0	0	0	2 (2)	0	0	0	0	0	0	0	0
Hyponatremia	0	0	0	1 (1)	0	0	0	0	0	1 (< 1)	0	0
Endometriosis	0	0	0	1 (1)	0	0	0	0	0	0	0	0
Lymphoma	0	0	0	1 (1)	0	0	0	0	0	0	0	0
Cerebellar syndrome	0	0	0	0	0	0	0	1 (1)	0	0	1 (< 1)	0
Pancreatitis	0	0	0	0	0	0	0	0	0	0	0	1 (< 1)
Status epilepticus	0	0	0	0	0	0	0	0	0	1 (< 1)	0	1 (< 1)
TIA	0	0	0	0	0	0	0	0	0	0	0	1 (< 1)
Partial seizure	0	0	0	0	0	0	0	0	0	5 (2)	0	0
Suicide attempt	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0
Hemorrhage	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0
Vasculitis	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0
Malaria	0	0	0	0	0	0	0	0	0	0	1 (< 1)	0
Overdose	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 102)	PL (N = 100)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 85)	ESL 1,200 mg (N = 80)	PL (N = 87)	ESL 800 mg (N = 216)	ESL 1,200 mg (N = 210)	PL (N = 224)
Contusion	0	0	0	0	0	0	0	0	0	0	0	1 (< 1)
Fracture	0	0	0	0	0	0	0	0	0	2 (1)	0	1 (< 1)
Hematoma	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0
Head injury	0	0	0	0	0	0	0	0	0	0	0	1 (< 1)
Encephalopathy	0	0	0	0	0	0	0	0	0	0	0	1 (< 1)
Disc protrusion	0	0	0	0	0	0	0	0	0	1 (< 1)		0
Respiratory failure	0	0	0	0	0	0	0	0	0	0	0	1 (< 1)
Radiculopathy	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0
Aneurysm	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0

ESL = eslicarbazepine acetate; PL = placebo; SAE = serious adverse event; TIA = transient ischemic attack.
Source: Clinical Study Reports.[1-4]

TABLE 32: WITHDRAWALS DUE TO ADVERSE EVENTS, SAFETY POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 102)	PL (N = 100)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 85)	ESL 1,200 mg (N = 80)	PL (N = 87)	ESL 800 mg (N = 216)	ESL 1,200 mg (N = 210)	PL (N = 224)
WDAEs												
N (%)	9 (9)	20 (20)	4 (4)	19 (19)	26 (27)	3 (3)	7 (8)	9 (11)	6 (7)	26 (12)	54 (26)	18 (8)
Most common reasons (some patients may have had more than one reasons to discontinue treatment)												
Ataxia	0	1 (1)	0	0	0	0	0	0	0	1 (< 1)	8 (4)	0
Somnolence	2 (2)	4 (4)	0	2 (2)	3 (3)	0	1 (1)	0	2 (2)	2 (1)	5 (2)	2 (1)
Diplopia	1 (1)	4 (4)	0	0	0	0	0	0	0	2 (1)	2 (1)	0
Dizziness	4 (4)	4 (4)	0	7 (7)	14 (14)	1 (1)	1 (1)	3 (4)	2 (2)	11 (5)	19 (9)	1 (< 1)
Vomiting	1 (1)	4 (4)	0	7 (7)	7 (7)	1 (1)	2 (2)	2 (3)	0	0	8 (4)	0
Nausea	2 (2)	4 (4)	0	3 (3)	7 (7)	0	3 (4)	2 (3)	0	3 (1)	13 (6)	0
Headache	1 (1)	0	0	0	4 (4)	2 (2)	1 (1)	2 (2)	2 (2)	0	2 (1)	1 (< 1)
Abnormal coordination	0	0	0	7 (7)	6 (6)	0	0	4 (5)	1 (1)	0	2 (1)	0
Blurred vision	1 (1)	1 (1)	0	2 (2)	3 (3)	0	0	0	0	2 (1)	3 (1)	0
Fatigue	0	0	0	0	5 (5)	0	0	0	0	0	2 (1)	0
Vertigo	0	3 (3)	0	0	0	0	1 (1)	2 (3)	0	2 (1)	3 (1)	1 (< 1)

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 102)	PL (N = 100)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 85)	ESL 1,200 mg (N = 80)	PL (N = 87)	ESL 800 mg (N = 216)	ESL 1,200 mg (N = 210)	PL (N = 224)
Asthenia	1 (1)	1 (1)	0	0	0	0	0	0	0	1 (< 1)	4 (2)	0
Dysarthria	0	0	0	0	0	0	0	0	0	0	5 (2)	0
Partial seizure	0	1 (1)	0	0	0	0	0	0	0	0	1 (< 1)	6 (3)
Rash	0	0	0	0	0	0	0	0	0	1 (< 1)	2 (1)	0

ESL = eslicarbazepine acetate; PL = placebo; WDAE = withdrawal due to adverse event.
Source: Clinical Study Reports.[1-4]

TABLE 33: DEATHS AND NOTABLE HARMS, SAFETY POPULATION

	Study 301			Study 302			Study 303			Study 304		
	ESL 800 mg (N = 98)	ESL 1,200 mg (N = 102)	PL (N = 100)	ESL 800 mg (N = 101)	ESL 1,200 mg (N = 98)	PL (N = 100)	ESL 800 mg (N = 85)	ESL 1,200 mg (N = 80)	PL (N = 87)	ESL 800 mg (N = 216)	ESL 1,200 mg (N = 210)	PL (N = 224)
Deaths												
N (%)	0	0	1 (1)	0	0	0	0	0	0	1 (< 1)	0	1 (< 1)
Cause of death												
Hypothermia	0	0	1 (1)	0	0	0	0	0	0	0	0	0
Respiratory failure	0	0	0	0	0	0	0	0	0	0	0	1 (< 1)
Status epilepticus	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0
Notable harms												
Hyponatremia	0	1 (1)	0	1 (1)	2 (2)	0	0	1 (1)	0	4 (2)	7 (3)	0
Neutropenia	0	0	0	0	0	0	0	0	1 (1)	0	1 (< 1)	1 (< 1)
Skin reaction												
• Exanthem	1 (1)	3 (3)	0	0	0	0	0	0	0	0	0	0
• Rash	0	2 (2)	1 (1)	0	3 (3)	1 (1)	2 (2)	1 (1)	0	3 (1)	4 (2)	2 (1)
• Leukocytoclastic vasculitis	0	0	0	0	0	0	0	0	0	1 (< 1)	0	0

ESL = eslicarbazepine acetate; PL = placebo.
Source: Clinical Study Reports.[1-4]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Objective

To summarize the validity and the minimal clinically important difference of the following outcome measures:

- Seizure Severity Questionnaire (SSQ)
- 31-item Quality of Life in Epilepsy Inventory (QOLIE-31)
- Clinical Global Impression (CGI).

Findings

The SSQ, QOLIE-31, Montgomery-Åsberg Depression Rating Scale, and CGI are briefly summarized in Table 34.

TABLE 34: VALIDITY AND MINIMAL CLINICALLY IMPORTANT DIFFERENCE OF OUTCOMES MEASURES

Instrument	Type	Evidence of Validity	MCID	References
SSQ	The SSQ was developed to evaluate seizure severity as a treatment response by characterizing changes in bothersomeness and severity of specific seizure characteristics. The SSQ is a 24-item questionnaire with three sections that address frequency and helpfulness of warning signs; bothersomeness and severity of ictal movement and loss of consciousness; and frequency, bothersomeness, and severity of the emotional, cognitive, and physical aspects of postictal recovery. Item scores range from 1 to 7, with higher scores indicating greater severity.	Yes	0.48	Borghs, 2014[37] Cramer, 2014[38] Cramer, 2002[39]
QOLIE-31	Derived from the longer version QOLIE-89, the QOLIE-31 is a valid and reliable measure of QoL in patients with epilepsy.[40] It is a self-reported questionnaire comprising two factors (emotional and psychological effects, and medical and social effects), seven subscales, and 31 items. Items are measured on 4- to 6-point Likert scales, with a maximum total score of 100. Higher scores indicate a better QoL.	Yes	4.73 to 11.8	Cramer, 1998[40] Devinsky, 1995[41] Wiebe, 2002[42] Borghs, 2012[43]
CGI	The CGI scale consists of three components: Severity of Illness (CGI-S), Global Improvement (CGI-I), and the Efficacy Index (CGI-E). Scores on the CGI-S subscale range from 1 (not ill at all) to 7 (among the most extremely ill). The CGI-I subscale also ranges from 1 (very much improved) to 7 (very much worse). The CGI-E involves locating a rating on a matrix of therapeutic versus AEs. Scores range from 0 (marked improvement and no AEs) to 4 (unchanged or worse and AEs outweigh therapeutic effects). The CGI instrument does not yield a global score, as each component of the CGI is rated separately.	Not validated in patients with epilepsy	Unspecified	Guy, 2000[44]

AEs = adverse events; CGI = Clinical Global Impression; MCID = minimal clinically important difference; QoL = quality of life; QOLIE-31 = 31-item Quality of Life in Epilepsy Inventory; SSQ = Seizure Severity Questionnaire.

Seizure Severity Questionnaire

The SSQ was developed to evaluate seizure severity as a treatment response by characterizing changes in bothersomeness and severity of specific seizure characteristics (e.g., shifts from complex to simple partial seizures, or cognitive effects). The SSQ is expected to differentiate among seizure types.[39] The SSQ is a 24-item questionnaire with three sections. Frequency and helpfulness of warning signs are reflected in the items in the first section. Items in the second section address bothersomeness and severity of ictal movement and loss of consciousness. The third section is subdivided into three components (emotional, cognitive, and physical aspects of postictal recovery), and each is rated for frequency, severity, and bothersomeness.[37,38] Seven response categories are provided for. There are frequency questions (ranging from 1 [never] to 7 [always]), bothersomeness questions (ranging from 1 [no bother at all] to 7 [very bothersome]), and severity questions (ranging from 1 [very mild] to 7 [very severe]). There are also yes/no responses for some questions.[37,38] The summary score comprises the warning, activity, and recovery phases of the seizure. Few details were reported on how it is calculated, although it appears to represent an average across questions.[39]

Inter-rater reliability of the SSQ was assessed using data from 91 patients. The cross-sectional inter-rater reliability coefficient was 0.76. Test-retest reliability was assessed using data from 63 patients. The cross-sectional test-retest reliability coefficient was 0.74. There were statistically significant correlations with the Liverpool Seizure Severity scale, the Veterans Administration Seizure Frequency and Severity Rating, and the National Hospital Seizure Severity scale. The highest correlation was between the SSQ and the Liverpool Seizure Severity questionnaire (0.48).[39]

Minimally important change (MIC) thresholds for the SSQ were established using the anchor-based method and the Patient Global Impression of Change score as the anchor. Patient data (N = 776) were pooled from two phase 3 study trials of adjunctive lacosamide in adult patients with partial-onset seizures with or without secondary generalization. Analyses were based on total score (across all questions except the warning question), three composite scores (activity during seizures [based on two questions on movement of action]; overall recovery [based on six questions asking about severity and bothersomeness during postictal recovery]; and overall severity [based on five questions asking about severity]); and three recovery component scores (physical, cognitive, and emotional components based on three questions rating frequency, severity, and bothersomeness for each component). The MIC thresholds for the SSQ within groups were 0.50, 0.39, and 0.48 for the three composite scores evaluated (i.e., activity during seizures, overall recovery, and overall severity, respectively). The MIC thresholds for the physical, cognitive, and emotional components of recovery were 0.34, 0.48, and 0.42, respectively. The MIC threshold for the total score was 0.48.[38]

Quality of Life in Epilepsy Inventory

The QOLIE-31 is an epilepsy-specific health-related quality of life (HRQoL) scale.[40] It is derived from the longer QOLIE-89, which was developed and validated in 1995.[41] The QOLIE-89 is an epilepsy-focused scale comprising 17 subscales, including the entire generic HRQoL measure, the Short-Form 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, the QOLIE Development Group, in 1998. The group selected the most relevant health-related quality of life subscales of the QOLIE-89 based on empirical evidence on the issues most commonly reported by patients with epilepsy.[40] This selection resulted in seven subscales (seizure worry, overall quality of life [QoL], emotional well-being, energy and fatigue, medication effects, work/driving/social limits, and cognitive functioning) and one overall item, creating a

31-item questionnaire, 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 QoL and lower scores, worse QoL. 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 score per subscale and overall is 100.[40]

A factor analysis of the seven subscales revealed two factors. The first factor relates to emotional and psychological issues and includes seizure worry, overall QoL, emotional well-being, and energy and fatigue. The second factor relates to mental efficiency and includes medication effects, work/driving/social limits, and cognitive functioning.[40]

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).[40] Intra-rater reliability was demonstrated for all of the subscales; correlation coefficients between test and retest data (with retest 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.[40]

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 Veterans Administration 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, which measures tension, depression, anger, vigour, fatigue, and confusion.[40] As expected, the correlations between the systemic toxicity scores and the QOLIE-31 subscales were low (range r = 0.00 to 0.006). Six of the scales were 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 antiepileptic drugs used was significantly correlated with the work/driving/social limits subscale (r = –0.72; $P = 0.004$); and health care utilization was correlated with the total QOLIE-31 score (r = –0.146; $P = 0.016$) and two of the subscales: work/driving/social limits (r = –0.182, $P = 0.002$), and medical (r = –0.136, $P = 0.020$).[40]

The minimum clinically important change was 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 QoL scales (the QOLIE-31 and QOLIE-89) and two generic health-related QoL scales (the SF-36 and the Health Utilities Index Mark 3) two times each, six months apart. Concurrent with completion of the QoL questionnaires, patients were also asked to rate changes on the following five domains over 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 QoL as per the QOLIE-89, QOLIE-31, SF-36, and Health Index Mark 3. The minimum clinically important change for the QOLIE-31 was determined to be 11.8, and for QOLIE-89, 10.1.[42]

The MIC 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 patients with partial seizures with or without secondary generalization. Three distribution-based statistics were calculated to estimate the MIC. One method, effect size, combined the change in scores with the

standard deviation of baseline scores as a measure of variability. The other methods (standard error of measurement and reliable change index) 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 MIC threshold based on effect size varied between 4.73 and 7.88. The standard error of measurement and reliable change index yielded MIC thresholds of 6.01 and 8.50, respectively. The anchor-based MIC threshold ranged between 5.19 and 5.31.[43]

Clinical Global Impression

The CGI scale consists of three components: Severity of Illness, Global Improvement, and the Efficacy Index. 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).[44] No information on the validity of CGI in patients with epilepsy was identified. A minimal clinically important difference was also not found.

Summary

The SSQ is a 24-item questionnaire developed to evaluate seizure severity as a treatment response by characterizing changes in bothersomeness and severity of specific seizure characteristics. Item scores range from 1 to 7, with higher scores indicating greater severity.[37,38] A 0.48-point change in the SSQ total score reflects a clinically meaningful change in seizure severity from the patient's perspective.[38] Derived from the longer QOLIE-89 version, the QOLIE-31 is a valid and reliable measure of QoL in patients with epilepsy.[40] It is a self-reported questionnaire comprising two factors (emotional and psychological effects, and medical and social effects), seven subscales, and 31 items. Items are measured on a four- to six-point Likert scale, with a maximum total score of 100. Higher scores indicate a better QoL. QOLIE-31 has established responsiveness and the minimal clinically important difference ranges from 4.73 points to 11.8 points.[42,43] The CGI scale consists of three components: Severity of Illness, Global Improvement, and the Efficacy Index; the first two components are rated using a seven-point ordinal scale, and the third using a four-point scale. No information on the validity of CGI in patients with epilepsy was identified.

APPENDIX 6: SUMMARY OF OPEN-LABEL EXTENSION STUDIES

1. Objective

To summarize efficacy and safety evidence from extension studies of the ESL trials included in this systematic review.

2. Findings

Three open-label, uncontrolled, extension studies (part 2 of studies 301, 302, and 303)[45-49] for the trials included in this review were identified. No data were available for the Study 304 extension study as it is still ongoing.

All patients who completed part 1 of Study 301 (including those who had received placebo during part 1) had the option to enter a one-year open-label extension (OLE) study (part 2), referred to herein as Study 301 II (Study 301 part 2). In part 2, the ESL starting dose was 800 mg once daily (with the exception of Hungarian patients who started at a 400 mg dose). After four weeks, the dose could be titrated up or down at 400 mg intervals between 400 and 1,200 mg once daily at the investigators' discretion. Of the 402 patients enrolled in part 1 of Study 301, 314 (78.1%) patients completed part 1 and were enrolled in the OLE phase. Among the 314 patients, 80 (25.5%) had been exposed to placebo in part 1 of the study. The mean (standard deviation [SD]) daily dose of ESL during the one-year duration of the OLE study was 877 mg (189 mg) (median, 800 mg).[45]

Similar to Study 301, patients who completed part 1 of Study 302 had the option to enter a one-year OLE study (Study 302 II). Dosing was the same as in Study 301 II. Of the 395 patients enrolled in part 1 of Study 302, 325 (82.3%) patients completed part 1 and were enrolled in the OLE phase. Among those 325 patients, 94 (28.9%) had been exposed to placebo in part 1 of the study. The mean (SD) daily dose of ESL during the one-year duration of the OLE study was 890 mg (182 mg) (median, 800 mg).[46]

Similar to Study 301, patients who completed part 1 of Study 303 had the option to enter a one-year OLE study (Study 303 II). Dosing was the same as in Study 301 II. Of the 253 patients enrolled in part 1 of Study 303, 194 (76.7%) patients completed part 1 and were enrolled in part 2. Among the 194 patients, 65 (33.5%) had been exposed to placebo in part 1 of the study. The mean (SD) daily dose of ESL throughout the one-year treatment was 917 mg (179 mg) (median, 800 mg).[47]

Patient Disposition

A summary of patient disposition is provided in Table 35. In Study 301 II, 23.4% of the patients who entered the OLE discontinued the study before one year of treatment, while 265 patients (84.9%) completed six months of treatment. The most frequent reason for early study termination was withdrawal of consent (39 patients, 12.5%). Two patients were excluded from the intention-to-treat (ITT) population because they had no efficacy data.[45]

In Study 302 II, 31.4% of the patients who entered the extension discontinued the study before one year of treatment, while 267 patients (82.2%) were exposed to ESL for six months. The most frequent reasons for early study discontinuation were lack of efficacy (34 patients, 10.5%), and the occurrence of unacceptable AEs (adverse events) (32 patients, 9.8%).[46]

In Study 303 II, 21.5% of the patients who entered the extension discontinued the study before one year of treatment, while 168 patients (88.0%) completed six months of treatment. The most frequent

reasons for early study discontinuation were lack of efficacy (12 patients, 6.3%), and the occurrence of unacceptable AEs (9 patients, 4.7%). Three patients were excluded from the ITT population because they lacked seizure-frequency assessments after the start of part 2.[47]

In all three studies, the efficacy assessments were based on the ITT population, defined as patients who had been administered at least one dose of ESL and had at least one seizure-frequency assessment in part 2 of the study.

TABLE 35: SUMMARY OF PATIENT DISPOSITION IN OPEN-LABEL EXTENSION TRIALS

Patient Disposition	Study 301 II n (%)	Study 302 II n (%)	Study 303 II n (%)
Enrolled in part 1 of the study	402	395	253
Completed part 1	330	327	197
Enrolled in part 2 (OLE)	314 (95.2)[a,b]	325 (99.4)[b]	194 (98.5)[a, b]
ITT population[c]	312 (99.4)[d]	325 (100)	191 (98.5)[d]
Discontinued prematurely[e]	73 (23.4)	102 (31.4)	41 (21.5)
• Consent withdrawal	39 (12.5)[f]	20 (6.2)[f]	8 (4.2)[f]
• Occurrence of unacceptable AE	11 (3.5)[f]	32 (9.8)[f]	9 (4.7)[f]
• Lack of efficacy	0	34 (10.5)[f]	12 (6.3)[f]
• Protocol violation	8 (2.6)[f]	0	0
• Discretion of investigator	8 (2.6)[f]	12 (3.7)[f]	1 (0.5)[f]
• Exacerbation of seizures	2 (0.6)[f]	0	0
• Pregnancy	0	1 (0.3)[f]	1 (0.5)[f]
• Patient non-compliance	0	0	4 (2.1)[f]
• Other	13 (4.2)[f]	3 (0.9)[f]	6 (3.1)[f]

AE = adverse event; ESL = eslicarbazepine acetate; ITT = intention-to-treat; n = number of patients; OLE = open-label extension.
[a] Safety analysis set.
[b] Percentage enrolled in part 2 who had completed part 1.
[c] The ITT population was defined as patients who had been administered at least one dose of ESL and had at least one seizure-frequency assessment in part 2 of the study.
[d] Percentage of the ITT population who entered part 2.
[e] Each patient could have had more than one reason for discontinuation.
[f] Percentage of the ITT population who discontinued for the reason listed.
Source: Clinical Study Reports.[45,47-49]

Efficacy Outcomes

Nearly all patients (99.4%) enrolled in the three OLE trials were administered at least one dose of ESL and had at least one seizure-frequency assessment in part 2. The occurrence of a seizure and the type of seizure were recorded by the patient (or caregiver) in an event-entry seizure diary.

Results for seizure frequency are presented in Table 36. In the three studies, the proportions of patients with a 100% reduction in seizure frequency from the part 1 baseline in the ITT population ranged from 12.0% to 13.6% during the first four weeks, from 4.6% to 8.7% during weeks 5 to 16, from 8.0% to 9.9% during weeks 17 to 28, from 8.9% to 10.5% during weeks 29 to 40, and from 10.8% to 17.8% during weeks 41 to 52 of part 2. The proportions of patients with ≥ 50% reduction in seizure frequency from the part 1 baseline in the ITT population ranged from 36.6% to 45.5% during the first four weeks, from 38.2% to 54.5% during weeks 5 to 16, from 38.5% to 52.9% during weeks 17 to 28, from 39.7% to 52.4% during weeks 29 to 40, and from 41.5% to 55.5% during weeks 41 to 52 of part 2. The median relative reduction in seizure frequency ranged from 32.1% to 47.5% during the first four weeks, from 37.6% to

56.2% during weeks 5 to 16, from 37.2% to 53.5% during weeks 17 to 28, from 38.3% to 53.7% during weeks 29 to 40, and from 39.3% to 57.5% during weeks 41 to 52 of part 2.

The change from the part 1 baseline in the QOLIE-31 overall score at the end of the study met the minimally clinically important difference only in Study 303 II. Results are presented in Table 37.

TABLE 36: EFFICACY RESULTS OF OPEN-LABEL EXTENSION TRIALS

	Study 301 II	Study 302 II	Study 303 II
Proportion of patients with 100% reduction in seizure frequency (%)[a]			
During the first 4 weeks of part 2	12.5	12.0	13.6
During weeks 5–16 of part 2	8.7	4.6	5.8
During weeks 17–28 of part 2	9.9	8.0	9.4
During weeks 29–40 of part 2	10.3	8.9	10.5
During weeks 41–52 of part 2	12.5	10.8	17.8
During part 2 overall	NR	2.5	2.6
Proportion of patients with ≥ 50% reduction in seizure frequency (%)[a]			
During the first 4 weeks of part 2	41.0	36.6	45.5
During weeks 5–16 of part 2	48.1	38.2	54.5
During weeks 17–28 of part 2	50.0	38.5	52.9
During weeks 29–40 of part 2	52.2	39.7	52.4
During weeks 41–52 of part 2	53.2	41.5	55.5
During part 2 overall	NR	37.2	52.9
Median relative reduction in seizure frequency (%)[a]			
During the first 4 weeks of part 2	39.2	32.1	47.5
During weeks 5–16 of part 2	47.6	37.6	56.2
During weeks 17–28 of part 2	49.8	37.2	53.5
During weeks 29–40 of part 2	52.1	38.3	53.7
During weeks 41–52 of part 2	56.3	39.3	57.5
During part 2 overall	NR	36.7	53.4

NR = not reported.
[a] ITT population.
Source: Clinical Study Reports.[47-49]

TABLE 37: BASELINE AND MEAN CHANGE FROM BASELINE AT WEEK 56 IN QOLIE-31, OLE TRIALS

	Study 301 II	Study 302 II	Study 303 II
Baseline, n	NR	255	154
Mean (SD)	54.8	55.4 (15.4)	56.2 (16.2)
Median (min, max)	NR	55.5 (14.7, 89.3)	55.9 (19.1, 93.7)
n at last assessment	NR	255	154
Change from part 1 baseline at last assessment	3.8	2.1 (13.5)	6.7 (14.9)
Median (min, max)	NR	1.0 (–34.1, 48.2)	8.4 (–36.1, 42.0)
P value for change from baseline	< 0.0001	0.0146	< 0.0001

max = maximum; min = minimum; NR = not reported; OLE = open-label extension; QOLIE-31 = 31-item Quality of Life in Epilepsy Inventory; SD = standard deviation.
Source: Clinical Study Reports.[47-49]

Harms Outcomes

Mortality

One patient died in Study 301 II due to drowning, but the death was considered by the investigator as unrelated to study treatment. Three patients died in Study 302 II, two of drowning, and one due to severe coronary atherosclerosis. Two patients died in Study 303 II, one patient experienced tumour relapse and died as a result of the event, the other died during a seizure. The latter was considered possibly related to ESL treatment.

Treatment-Emergent Adverse Events

The percentages of total patients experiencing at least one treatment-emergent adverse event (TEAE) were similar in Study 301 II and Study 303 II (51% versus 58%, respectively) and higher in Study 302 II (83%). As shown in Table 38, the most frequently reported TEAEs in studies 301 II and 302 II were dizziness (10.2% and 26.5%, respectively) and headache (10.2% and 15.7%, respectively), while the most frequently reported TEAEs in Study 303 II were dizziness (17.0%) and somnolence (9.8%). Other AEs that occurred in one or more of the studies included: vomiting, nausea, convulsion, diplopia, fatigue, upper respiratory tract infection, nasopharyngitis, and contusion.

TABLE 38: SUMMARY OF TREATMENT-EMERGENT ADVERSE EVENTS, OPEN-LABEL EXTENSION TRIALS

	Study 301 II (N = 314)	Study 302 II (N = 325)	Study 303 II (N = 194)
Any TEAE	160 (51.0)	270 (83.1)	112 (57.7)
Most common TEAEs (> 5%), n (%)			
Headache	32 (10.2)	51 (15.7)	17 (8.8)
Dizziness	32 (10.2)	86 (26.5)	33 (17.0)
Diplopia	17 (5.4)	28 (8.6)	
Nasopharyngitis	16 (5.1)	20 (6.2)	2 (1.0)
Somnolence		39 (12.0)	19 (9.8)
Diastolic blood pressure decreased		28 (8.6)	
Coordination abnormal		28 (8.6)	
Vomiting		22 (6.8)	11 (5.7)
Nausea		21 (6.5)	
Diarrhea		18 (5.5)	
Back pain		17 (5.2)	
Blurred vision		17 (5.2)	
Any serious TEAE	19 (6.1)	28 (8.6)	11 (5.7)
TEAE leading to study discontinuation	11 (3.5)	37 (11.4)	9 (4.6)
TEAE leading to death	1 (< 1)	3 (0.9)	2 (1.0)

TEAE = treatment-emergent adverse event.
Source: Clinical Study Reports.[47-49]

Serious Adverse Events

The total percentage of patients experiencing treatment-emergent serious adverse events (SAEs) was 6.1%, 8.6%, and 5.7% in studies 301 II, 302 II, and 303 II, respectively.

In Study 301 II, the SAEs that affected more than one patient were grand mal convulsion (three patients) and drug toxicity (two patients). In Study 302 II, SAEs that affected more than one patient were convulsion (three patients) and somnolence, status epilepticus, psychotic disorder, and drowning (two patients each). The only SAE that affected more than one patient in Study 303 II was multiple injuries (two patients).

Discontinuations Due to Adverse Events

The total percentage of patients who discontinued from study due to TEAEs was 3.5%, 11.4%, and 4.6% in studies 301 II, 302 II, and 303 II, respectively.

The only TEAE that led to discontinuation and occurred in more than one patient in Study 301 II was dizziness (two patients). The TEAEs that led to discontinuation and occurred in more than one patient in Study 301 II were abnormal coordination, convulsion, diplopia, dizziness, irritability, nausea, somnolence, and vomiting. In Study 303 II, none of the TEAEs that led to discontinuation occurred in more than one patient.

Limitations

Like most extension studies, the lack of a control group in the ESL OLE studies prevents estimation of the treatment effect attributable to ESL. Another limitation of all extension studies is that only those patients in the original randomized controlled trials who found study treatment to be tolerable and efficacious are likely to enrol in the extension study, which would limit the generalizability of the results. Perhaps more importantly, over time, the cohort increasingly represents patients who have the highest likelihood of benefit and lowest likelihood for experiencing adverse events because such patients self-select to continue in the study. Hence the efficacy of ESL is likely overestimated, particularly in the latter time points. However, the completion rates in the ESL OLE studies were actually quite high (69% to 78%); hence, the effects of self-selection are less of a concern.

3. Summary

Three open-label, uncontrolled, extension studies (part 2 of studies 301, 302, and 303)[45-49] of the three pivotal trials included in this review (part 1 of studies 301, 302, and 303, respectively)[1,3,4,18-20] were identified. The results in part 2 of the three studies were consistent with the therapeutic efficacy profile of ESL observed in part 1. The proportions of patients with 100% reduction in seizure frequency during weeks 41 to 52 were 12.5%, 10.8%, and 17.8% in studies 301 II, 302 II, and 303 II, respectively. The proportion of patients experiencing a ≥ 50% reduction in seizure frequency during weeks 41 to 52 were 53.2%, 41.5%, and 55.5% in studies 301 II, 302 II, and 303 II, respectively. A clinically important improvement in the QOLIE-31 overall score at the end of the study compared with baseline was observed only in Study 303 II. Eighty-three per cent of patients experienced at least one TEAE in Study 302 II, while 51% and 58% experienced at least one TEAE in studies 301 II and 303 II, respectively. The most frequently reported TEAEs in studies 301 II and 302 II were dizziness (10.2% versus 26.5%) and headache (10.2% versus 15.7%), while in Study 303 II they were dizziness (17.0%) and somnolence (9.8%). Treatment-emergent serious adverse events occurred in 6.1%, 8.6%, and 5.7% of patients in studies 301 II, 302 II, and 303 II, respectively, and 3.5%, 11.4%, and 4.6% of patients discontinued due to AEs from studies 301 II, 302 II, and 303 II, respectively. The safety profile was similar overall to that observed in the double-blind randomized controlled trials. Due to the lack of a comparator group, and due to patients self-selecting to enter and continue in extension studies, the results should be interpreted with caution.

APPENDIX 7: SUMMARY AND CRITICAL APPRAISAL OF THE MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS

1. Objective

The manufacturer conducted a network meta-analysis (NMA) comparing the efficacy and tolerability of eslicarbazepine acetate (ESL) once daily with third-generation AEDs as adjunctive therapy in patients with refractory partial-onset seizures (POS) who are not satisfactorily controlled with conventional therapy. This NMA was an update of a systematic review and NMA published by Khan et al.[50] This brief provides a summary and critical appraisal of the methods and main findings of the NMA.

2. Summary of Network Meta-analysis

As all of the ESL randomized controlled trials (RCTs) were designed to compare this drug with only placebo, an NMA was performed by the manufacturer to estimate the comparative efficacy and tolerability of ESL, lacosamide (LCS), and perampanel (PER) on the following outcomes: ≥ 50% reduction in seizure frequency (response); discontinuation of treatment; any treatment-emergent adverse events (TEAEs); TEAEs leading to discontinuations; and serious adverse events (SAE).

Methods

a) Eligibility Criteria

The NMA was based on three of the four RCTs of ESL (studies 301, 302, 304) included in the CADTH Common Drug Review systematic review; the six RCTs identified by Khan et al.; and a systematic review based on a literature search from March 2013 (the literature search cut-off date for the Khan systematic review) to June 16, 2014. Study 303[20] was included in the NMA conducted by Khan et al. but excluded from the manufacturer's analysis due to non-compliance with GCP guidelines. Also, unlike the review by Khan et al., unpublished data derived from the Integrated Summary of Efficacy (ISE) and the Integrated Summary of Safety were included in the manufacturer's NMA for studies 301 and 302. The inclusion criteria for the systematic review consisted of the following: double-blind RCTs in adult patients 12 years of age or older with refractory POS; and at least one of the RCT groups had to have received adjunctive therapy with ESL, LCS, or PER.

b) Network Meta-analysis

Bayesian NMA models were used to analyze the outcomes of interest. In the base-case analysis, the data included in the NMA were combined across all doses for each of the AEDs to give a single estimate of effect for ESL, PER, and LCS. A sensitivity analysis was conducted in which the data were disaggregated and analyzed separately by dose for each comparator; another sensitivity analysis was conducted using published data for ESL studies 301 and 302.

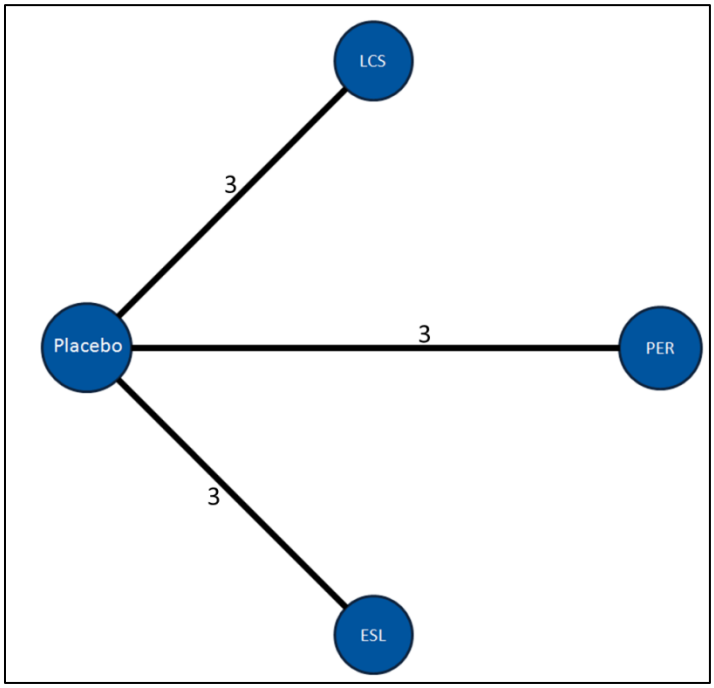
Analysis was conducted on the odds ratio (OR). For each outcome, the NMA was fitted using both a fixed and a random effects (RE) model. Heterogeneity between the included studies was assessed based on the baseline characteristics of included patients and study design characteristics. To validate the choice of the a priori model, the deviance information criterion (DIC) was used to compare the fixed and random effects models. The model with the lowest DIC value for the same data among a series of competing models was selected. Inconsistency was assessed by comparing the consistency and inconsistency models.

For fixed and random effects NMAs, a flat normal prior distribution with a mean of 0 and variance of 10,000 was assumed for the log OR of treatment k relative to the baseline treatment. For random effects analysis, a uniform prior distribution with a range of 0 to 2 was used for the between-study variance. WinBUGS version 1.4 was used for the analyses.

c) Study and Patient Characteristics

Nine RCTs were included in the meta-analysis (Figure 2). All studies were double-blind, randomized, placebo-controlled trials. The studies evaluated the following interventions: PER 2 mg, 4 mg, 8 mg, or 12 mg (n = 3 studies), LCS 200 mg, 400 mg, or 600 mg (n = 3 studies), and ESL 400 mg, 800 mg, or 1,200 mg (n = 3 studies). Unpublished data for ESL from studies 301, 302, and 304 were used in the base-case analysis of the NMA. The included studies randomized 386 to 706 patients per treatment group.

FIGURE 2: NETWORK OF INCLUDED RCTS, MANUFACTURER-SUBMITTED NETWORK META-ANALYSIS



ESL = eslicarbazepine acetate; LCS = lacosamide; PER = perampanel.

Overall, the included RCTs were of similar study design. The definition of treatment response (≥ 50% reduction in seizure frequency from baseline to the end of the maintenance phase) was consistent across all included RCTs. There were differences in terms of the duration of the baseline evaluation, titration, maintenance, and follow-up periods. The duration of the baseline period ranged from six to eight weeks. The titration period was two, four, and six weeks for ESL, LCS, and PER, respectively. The duration of the maintenance period ranged from 12 to 13 weeks. Also, there were differences in the eligible age for inclusion; some studies included patients who were 12 years of age or older (all PER RCTs), others included patients who were 16 years of age or older (two LCS RCTs, and one ESL RCT), while the rest included only adults.

The enrolled patients consisted of a mixture of adolescents and adults aged 12 years and older with POS. The mean average age ranged between 33.4 to 41.3 years. The percentage of female patients was similar across trials, approximately 50%. Pre-randomization median seizure frequency ranged between

8.0 and 16.5 per 28 days. The percentage of patients using one, two, and three concomitant AEDs was 7% to 39%, 44% to 76%, and 0% to 41%, respectively. Mean duration of epilepsy ranged from 17 to 25 years.

Risk of bias was assessed using the Cochrane Collaboration guidelines.[51] The RCTs were of comparable methodological quality. All studies were double-blinded and the sequence generations were random, and the risk of performance bias and detection bias was low across studies. The risk of reporting bias was considered to be moderate in several studies in which limited data were reported regarding specific AEs.

Results

a) Treatment Response

The NMA base-case results for treatment response (≥ 50% reduction in seizure frequency from baseline to the end of the maintenance phase) are presented in Table 39. Only the results of the RE model (with a vague prior) were reported, both because the DICs were very similar across all of the models tested and to take into consideration potential heterogeneity across the included RCTs. The inconsistency results for the models indicated the data were not skewed.

The estimated ORs and the 95% credible intervals for all treatments analyzed were significantly greater than 1 when compared with placebo, indicating that ESL, LCS, and PER had an increased probability of response compared with placebo. No statistically significant difference in treatment response was observed when treatments were compared against each other, although the 95% credible intervals for comparisons of ESL with other drugs were wide, indicating a high degree of uncertainty regarding relative efficacy.

TABLE 39: RESULTS FROM THE NETWORK META-ANALYSIS FOR TREATMENT RESPONSE (AT LEAST 50% REDUCTION IN SEIZURE FREQUENCY FROM BASELINE)

Interventions	Odds Ratios Relative to Placebo for Response (95% CrI)	Odds Ratios of Active Comparators Versus ESL for Response (95% CrI)
LCS (200, 400, or 600 mg)	2.15 (1.48 to 3.21)	1.09 (0.63 to 1.89)
PER (2, 4, 8, or 12 mg)	2.00 (1.38 to 2.94)	1.01 (0.59 to 1.73)
ESL (400, 800, or 1,200 mg)	1.98 (1.35 to 2.95)	

CrI = credible interval; ESL = eslicarbazepine acetate; LCS = lacosamide; PER = perampanel.

In the sensitivity analysis by dose for each of the comparators, lower doses for each AED were less efficacious than the higher doses. There were no statistically significant differences in treatment response between the three AEDs when comparing them at low, middle, or high doses.

In the sensitivity analysis that pooled data across all doses for each of the comparators and used the published data for the ESL studies 301 and 302, as opposed to the ISE, the findings were similar to those in the base-case analysis.

b) Discontinuation

The NMA base-case results for discontinuation for any reason are presented in Table 40. Only the results of the RE model (with a vague prior) were reported, both because the DICs were very similar across all of the models tested and to take into consideration potential heterogeneity across the included RCTs. The inconsistency results for the models indicated the data were not skewed.

The estimated ORs and the 95% CrI for ESL and LCS were significantly greater than 1, showing that in comparison with placebo, ESL and LCS had an increased probability of discontinuation. A similar trend was seen for PER; however, the estimated OR was not statistically significant. No statistically significant difference in the odds of discontinuation was observed when treatments were compared against each other, although the 95% credible intervals for comparisons of ESL with other drugs were wide, indicating a high degree of uncertainty.

TABLE 40: RESULTS FROM THE NETWORK META-ANALYSIS FOR DISCONTINUATION DUE TO ANY REASON

Interventions	Odds Ratios Relative to Placebo for Discontinuation (95% CrI)	Odds Ratios of Active Comparators Versus ESL for Discontinuation (95% CrI)
LCS (200, 400, or 600 mg)	2.22 (1.16 to 4.35)	1.19 (0.45 to 3.03)
PER (2, 4, 8, or 12 mg)	1.59 (0.83 to 3.13)	0.85 (0.33 to 2.1)
ESL (400, 800, or 1,200 mg)	1.85 (1.0 to 3.7)	

CrI = credible interval; ESL = eslicarbazepine acetate; LCS = lacosamide; PER = perampanel.

In the sensitivity analysis by dose for each of the comparators, patients treated with lower doses of each AED had a lower discontinuation rate compared with patients treated with the higher doses. There were no statistically significant differences in treatment discontinuation between the three AEDs when comparing them at low, middle, or high doses.

In the sensitivity analysis that pooled the data across all doses for each of the comparators and used the published data for ESL studies 301 and 302, as opposed to the ISE, the findings were similar to the findings of the base-case analysis.

c) Any Treatment-Emergent Adverse Events

The NMA base-case results for patients experiencing any TEAE post-randomization are presented in Table 41. Only the results of the RE model (with a vague prior) were reported, both because the DICs were very similar across all of the models tested and to take into consideration potential heterogeneity across the included RCTs. The inconsistency results for the models indicated the data were not skewed.

The estimated ORs for all treatments analyzed were greater than 1 when compared with placebo; however, the 95% CrI included 1, indicating there was no statistically significant difference between the three active treatments and placebo. Also, no statistically significant difference in the odds of experiencing a TEAE was observed when treatments were compared against each other, although the 95% credible intervals for comparisons of ESL with other drugs were wide, indicating a high degree of uncertainty.

TABLE 41: RESULTS FROM THE NETWORK META-ANALYSIS FOR ANY TREATMENT-EMERGENT ADVERSE EVENTS

Interventions	Odds Ratios Relative to Placebo for any TEAE (95% CrI)	Odds Ratios of Active Comparators Versus ESL for any TEAE (95% CrI)
LCS (200 mg, 400 mg, or 600 mg)	2.27 (0.42 to 12.5)	1.15 (0.11 to 12.5)
PER (2 mg, 4 mg, 8 mg, or 12 mg)	2.0 (0.78 to 5.56)	1.02 (0.15 to 7.14)
ESL (400 mg, 800 mg, or 1,200 mg)	1.96 (0.38 to 10.0)	

CrI = credible interval; ESL = eslicarbazepine acetate; LCS = lacosamide; PER = perampanel; TEAE = treatment-emergent adverse event.

In the sensitivity analysis by dose for each of the comparators, fewer patients treated with lower doses of each AED experienced a TEAE compared with patients treated with higher doses. There were no statistically significant differences in the percentage of patients reporting a TEAE between the three AEDs when comparing them at low, middle, or high doses.

In the sensitivity analysis that pooled the data across all doses for each of the comparators and used the published data for ESL studies 301 and 302, as opposed to the ISE, no statistically significant difference in percentage of patients reporting TEAEs was observed when treatments were compared against each other; however, there were statistically significantly more TEAEs in patients treated with ESL and PER than placebo.

d) Adverse Events Leading to Discontinuation

The NMA base-case results for TEAEs leading to discontinuation are presented in Table 42. Only the results of the RE model (with a vague prior) were reported, both because the DICs were very similar across all of the models tested and to take into consideration potential heterogeneity across the included RCTs. The inconsistency results for the models indicated the data were not skewed.

The estimated ORs for PER and LCS were significantly greater than one, indicating that ESL and LCS had an increased risk of TEAEs that led to discontinuation compared with placebo. A similar trend was seen for ESL, but the estimated OR was not statistically significant. No statistically significant difference in TEAEs that led to discontinuation was observed when treatments were compared against each other, although the 95% credible intervals for comparisons of ESL with other drugs were wide, indicating a high degree of uncertainty.

TABLE 42: RESULTS FROM THE NETWORK META-ANALYSIS FOR ADVERSE EVENTS LEADING TO DISCONTINUATION

Interventions	Odds Ratios Relative to Placebo for TEAE Leading to Discontinuation (95% CrI)	Odds Ratios of Active Comparators Versus ESL for TEAE Leading to Discontinuation (95% CrI)
LCS (200, 400 or 600 mg)	3.85 (1.72 to 9.09)	1.2 (0.27 to 5.88)
PER (2, 4, 8, or 12 mg)	2.33 (1.03 to 5.56)	0.73 (0.16 to 3.37)
ESL (400, 800 or 1,200 mg)	3.23 (0.88 to 11.11)	

CrI = credible interval; ESL = eslicarbazepine acetate; LCS = lacosamide; PER = perampanel; TEAE = treatment-emergent adverse event.

In the sensitivity analysis by dose for each of the comparators, fewer patients treated with lower doses of each AED reported TEAEs leading to discontinuation compared with patients treated with higher doses. There were no statistically significant differences in the percentage of patients reporting TEAEs leading to discontinuation between the three AEDs when comparing them at low, middle, or high doses.

In the sensitivity analysis that pooled the data across all doses for each of the comparators and used the published data for ESL studies 301 and 302, as opposed to the ISE, no statistically significant difference in percentage of patients reporting TEAEs was observed when treatments were compared against each other; however, there were statistically significantly more TEAEs leading to discontinuation in patients treated with ESL, LCS, and PER than placebo.

e) Serious Adverse Events

The NMA base-case results for SAEs are presented in Table 43. Only the results of the RE model (with a vague prior) were reported, both because the DICs were very similar across all of the models tested and to take into consideration potential heterogeneity across the included RCTs. The inconsistency results for the models indicated the data were not skewed.

The estimated 95% credible intervals of the ORs for all treatments analyzed included one, indicating no statistically significant difference between any treatment and placebo. No statistically significant difference in the odds of experiencing an SAE was observed when treatments were compared against each other, although the 95% credible intervals for comparisons of ESL with other drugs were wide, indicating a high degree of uncertainty.

TABLE 43: RESULTS FROM THE NETWORK META-ANALYSIS FOR SERIOUS ADVERSE EVENTS

Interventions	Odds Ratios Relative to Placebo for SAEs (95% CrI)	Odds Ratios of Active Comparators Versus ESL for SAEs (95% CrI)
LCS (200, 400, or 600 mg)	1.85 (0.75 to 4.76)	1.06 (0.19 to 5.56)
PER (2, 4, 8, or 12 mg)	1.19 (0.51 to 2.94)	0.68 (0.13 to 3.56)
ESL (400, 800, or 1,200 mg)	1.72 (0.43 to 7.14)	

CrI = credible interval; ESL = eslicarbazepine acetate; LCS = lacosamide; PER = perampanel; SAE = serious adverse event.

In the sensitivity analysis by dose for each of the comparators, fewer patients treated with lower doses of each AED reported SAEs compared with patients treated with higher doses. There were no statistically significant differences in the percentage of patients reporting SAEs between the three AEDs when comparing them at low, middle, or high doses.

In the sensitivity analysis that pooled the data across all doses for each of the comparators and used the published data for ESL studies 301 and 302, as opposed to the ISE, no statistically significant difference in percentage of patients reporting SAEs was observed when treatments were compared against each other.

3. Critical Appraisal of Network Meta-analysis

The manufacturer-submitted NMA was appraised according to recommendations provided by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on Indirect Treatment Comparisons.[52] Details and commentary for each of the relevant items identified by ISPOR are provided in Table 44.

Strengths

The NMA appears to satisfy many of the ISPOR criteria. It was based on an updated systematic review to identify all relevant studies.

Risk of bias was assessed using the Cochrane Collaboration guidelines.[51] The RCTs were of comparable methodological quality. All studies were double-blinded and the sequence generations were random; the risk of performance bias and detection bias was low across studies. Patient characteristics in the individual studies were well reported.

The analysis was conducted using an appropriate and well-reported methodology (i.e., Bayesian NMA models created with WinBUGS 1.4). The outcome measures assessed in the NMA were appropriate. As well, model diagnostic statistics such as DIC were used to assess model fit, and a number of sensitivity analyses were performed to verify the robustness of the base-case models.

Limitations

As with all NMA, a statistically non-significant difference between treatments does not necessarily imply the treatments are equivalent or non-inferior. In the case of the indirect estimates for ESL versus other drugs, the 95% credible intervals were very wide despite the fact that point estimates centred on parity. Hence, the results are somewhat inconclusive regarding the relative efficacy and safety of ESL compared with other drugs. However, this issue is not unique to the current analysis, as a similar degree of imprecision was seen in the NMA by Khan et al.[50]

This NMA did not compare ESL versus all possible comparators. As per the opinion of the clinical expert, ESL could replace any of the AEDs that are used in clinical practice as adjunctive therapy in patients with refractory epilepsy. For example, lamotrigine, topiramate, gabapentin, and levetiracetam are all indicated in Canada for patients as adjunctive therapy.[53-56] However, the choice of perampanel and lacosamide as the main comparators is appropriate in that these are the two most recent entrants to the AED market for the treatment of refractory epilepsy, and both have been recommended by the CADTH Common Drug Review (CDR) for listing.

There was some heterogeneity across studies. For example, PER RCTs allowed patients aged 12 years and older to be included, while patients aged 16 years or older were eligible for inclusion in the LCS and ESL RCTs. In addition, the number of patients on three AEDs at baseline was lowest in the ESL RCTs and highest in the PER RCTs; seizure frequency at baseline ranged from 8.0 to 16.5 across the included RCTs, and mean duration of epilepsy ranged from 17 to 25 years. Also, not all outcomes could be evaluated in the NMA because not all outcomes were consistently reported across trials, particularly for safety outcomes. The analysis did not account for those sources of heterogeneity, such as through meta-regression or sensitivity analyses.

Methods used to assess consistency were not fully explained in the methods section of the NMA report.

Some AED doses included in the NMA were not consistent with approved doses in Canada, although this is not expected to have any significant effect on the generalizability of results.

In the base-case analyses for TEAEs, TEAEs leading to discontinuation, and SAEs, data from the ESL RCTs (301, 302, and 304) were pooled together before including them in the NMA. This resulted in wide credible intervals, indicating there was no significant difference between placebo and the three AEDs, or between the three AEDs when they were compared against each other. In the sensitivity analyses that used the published data for ESL studies 301 and 302, data were not pooled. These analyses resulted in a smaller credible interval and, in some instances, the differences between the three AEDs and placebo were statistically significant. Hence, the sensitivity analysis results may provide the more conservative interpretation of relative rates of adverse events between the three AEDs and placebo, although the finding of no significant differences between AEDs is consistent across both analyses.

RCT 303 was excluded from this NMA due to non-compliance with GCP guidelines. However, in a response to the draft clinical review report, the manufacturer stated that a sensitivity analysis that Study 303 was and the results did not substantially differ from the base case.[57]

There were no analyses on outcomes of interest identified in the protocol for the CDR review, such as seizure freedom; in addition, there were no analyses on subgroups of interest (e.g., age, seizure type, and background AED use).

4. Summary

In the absence of head-to-head trial data for ESL versus other AEDs, the manufacturer conducted a Bayesian NMA to compare ESL with LCS and PER. Overall, the systematic review and NMA showed that ESL, LCS, and PER were more effective than placebo in terms of 50% response rate, but with higher risks for discontinuation and AEs leading to discontinuation. There were no significant differences in efficacy, discontinuation, TEAEs, TEAEs leading to discontinuation, or SAEs between any of the comparators; however, these results do not allow for a conclusion of equivalence or non-inferiority across drugs. In sensitivity analyses by dose (high, medium, low), higher doses of each AED were associated with greater discontinuation, higher reporting of TEAEs, TEAEs leading to discontinuation, and SAEs. Although the NMA demonstrated sufficient methodological rigour for a number of criteria, there were some limitations, such as incorporation of doses not approved for use in Canada.

TABLE 44: APPRAISAL OF NETWORK META-ANALYSIS USING ISPOR CRITERIA

ISPOR Checklist Item		Details and Comments
1.	Are the rationale for the study and the objectives stated clearly?	• A clear rationale for the review and a clear research question that pertained to the NMA were clearly stated.
2.	Does the methods section include the following? • Eligibility criteria • Information sources • Search strategy • Study selection process • Data extraction • Validity of individual studies	• The eligibility criteria for individual RCTs were clearly stated and seem appropriate. • Several databases were searched, including PubMed and the Cochrane Central Register of Controlled Trials. • The search strategy was well reported. • The inclusion/exclusion process and data extraction methods used were clearly reported. • The risk of bias was assessed using the Cochrane Collaboration guidelines. This tool assesses sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting.
3.	Are the outcome measures described?	• Outcomes assessed in the network meta-analysis were clearly described. • There was no analysis on seizure freedom, which is the primary outcome assessed in this CDR review.
4.	Is there a description of the methods for analysis/synthesis of evidence? • Description of analyses methods/models • Handling of potential bias/inconsistency • Analysis framework	• A description and justification of the statistical model used was provided. • The NMA fitted both fixed effects models and random effects models and used the DIC in order to test the goodness of fit of each model. • A Bayesian approach was used, but non-informative priors were chosen so that observed data were not driven by the prior chosen but completely driven by the data, which is analogous to a frequentist approach. • The models were conducted without covariate adjustment. Also, due to the absence of head-to-head trials, it was not possible to compare the direct evidence with the indirect evidence. Hence, the NMA did not handle potential bias/inconsistency. • Odds ratios were used to present the findings.
5.	Are sensitivity analyses presented?	• Sensitivity analyses were performed by utilizing data by individual dose for each of the comparators used, and using the published data for ESL studies 301 and 302.

ISPOR Checklist Item		Details and Comments
		• The inclusion of results from Study 303 was not explored in any of the analyses. • No analyses for subgroups of interest were undertaken.
6.	Do the results include a summary of the studies included in the network of evidence? • Individual study data? • Network of studies?	• The identification and selection of full-text studies for the NMA were well reported. • A table with study and patient characteristics was provided. • A figure showing the network of studies was provided. • A table with raw data by study and treatment as used in the NMA was available.
7.	Does the study describe an assessment of model fit?	• Both fixed and random effects models were considered; model selection was based on the DIC model–fit measure, with some interpretation as to which model to use in each analysis.
8.	Are the results of the evidence synthesis presented clearly?	• The results of the analysis were clearly reported for each outcome measure, including point estimates and 95% credible intervals.
9.	Sensitivity/scenario analyses	• Results of the sensitivity analyses were presented in the report.
10.	Does the discussion include the following? • Description/summary of main findings • Internal validity of analysis External validity • Implications of results for target audience	• A description/summary of main findings was presented in the conclusion section. • The internal validity of analysis was discussed. • No discussion was made regarding the generalizability of findings.

CDR = CADTH Common Drug Review; DIC = deviance information criterion; ESL = eslicarbazepine acetate; ISPOR = International Society for Pharmacoeconomics and Outcomes Research; NMA = network meta-analysis; RCT = randomized controlled trial.

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