Common Drug Review
Clinical Review Report

February 2017

Drug	Brivaracetam (Brivlera)
Indication	Adjunctive therapy in the management of partial-onset seizures (POS) in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy
Reimbursement request	As per indication and in a similar manner as lacosamide, perampanel, and eslicarbazepine
Dosage form(s)	10 mg, 25 mg, 50 mg, 75 mg, and 100 mg oral tablets
NOC date	March 9, 2016
Manufacturer	UCB 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.

Through the Common Drug Review (CDR) process, CADTH undertakes reviews of drug submissions, resubmissions, and requests for advice, and provides formulary reimbursement recommendations to all Canadian publicly funded federal, provincial, and territorial drug plans, with the exception of Quebec.

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ABBREVIATIONS

AED	antiepileptic drug
CDR	CADTH Common Drug Review
CI	confidence interval
EQ-5D	EuroQol 5-Dimensions questionnaire
GS	generalized seizure
HADS	Hospital Anxiety and Depression Scale
HRQoL	health-related quality of life
ITC	indirect treatment comparison
I-GES	Investigator Global Evaluation Scale
ITT	intention to treat
LTFU	long-term follow-up
MCID	minimal clinically important difference
NMA	network meta-analysis
OR	odds ratio
P-GES	Patient Global Evaluation Scale
POS	partial-onset seizure
QOLIE-31-P	Patient-Weighted Quality of Life in Epilepsy Inventory-31
RCT	randomized controlled trial
SAE	serious adverse event
SV2A	synaptic vesicle protein 2A
TEAE	treatment-emergent adverse event
VAS	visual analogue scale
WDAE	withdrawal due to adverse event

EXECUTIVE SUMMARY

Introduction

Epilepsy is a chronic neurological disorder that manifests as a variety of seizure types and syndromes, often of unknown etiology. There are two broad categories of epileptic seizures: partial- (or focal-) onset seizures (POS) and generalized seizures (GS).[1] The goals of epilepsy treatment are to control seizures, avoid adverse events (AEs), and maintain or restore quality of life.[1] Approximately half of the patients with a new diagnosis of epilepsy will become seizure-free with the first antiepileptic drug (AED) prescribed.[1] Of those whose initial therapy is ineffective, about 10% to 20% will have a successful second drug trial.[1] The second AED is typically increased to therapeutic levels before the first drug is reduced in order to prevent seizures or status epilepticus during the switch period.[1] Combination therapy with two or more AEDs may be required for treatment-resistant or refractory epilepsy. The selection of AEDs is based on the effectiveness of the drug for the patient's seizure type, potential AEs, and interactions with medications, comorbid medical conditions, age, gender (including child-bearing plans), patient preference, and cost.[1]

Brivaracetam is the second racetam AED to be approved in Canada and compared with the first, levetiracetam, brivaracetam displays higher selectivity and affinity for synaptic vesicle protein 2A (SV2A) in the brain.[2] Although the mechanism of action of SV2A in neurotransmission is not completely known, it has been recognized as an important target for AEDs, and the anticonvulsant effect has been demonstrated in experimental studies.[3] Brivlera (brivaracetam) is available as 10 mg, 25 mg, 50 mg 75 mg and 100 mg oral tablets, 10 mg/mL oral solution, and 10 mg/mL injection.[2] The focus of the CADTH Common Drug Review (CDR) submission is on the oral tablets only.[4] The recommended starting dose for brivaracetam in adults is 50 mg twice daily (100 mg per day).[2] Based on individual patient response and tolerability, the dose may be adjusted from a minimum of 25 mg twice daily (50 mg per day) to a maximum of 100 mg twice daily (200 mg per day).[2]

Indication under review
Adjunctive therapy in the management of POS in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.
Reimbursement criteria requested by sponsor
As per indication and in a similar manner as lacosamide, perampanel and eslicarbazepine.

The objective of this review is to perform a systematic review of the beneficial and harmful effects of brivaracetam at doses between 25 mg and 100 mg twice daily for adjunctive therapy in the management of POS in adult patients with epilepsy 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 trials met the selection criteria for this systematic review. Study 1252 (N = 399), Study 1253 (N = 400), Study 1254 (N = 480), and Study 1358 (N = 768) all investigated the efficacy, safety and tolerability of brivaracetam given as adjunctive therapy (i.e., added on to a background regimen of one to three AEDs) in patients 16

years of age and older for the treatment of uncontrolled POS. The trials investigated different doses of brivaracetam (5 mg/day to 200 mg/day); however, only results for the Health Canada–approved doses (50 mg/day to 200 mg/day) are reported in this review. Patients were randomized to brivaracetam or placebo, while remaining on a baseline-fixed AED background regimen. The duration of double-blind treatment was 12 weeks in studies 1252, 1253, and 1358, and 16 weeks (i.e., eight-week dose-finding period plus eight-week maintenance period) in Study 1254. The primary efficacy outcome for all trials was the change from baseline in POS frequency per week (Studies 1252, 1253, and 1254) or per 28 days (Study 1358). With the exception of Study 1254, which was a flexible-dose study, patients were randomized to the full doses of brivaracetam used in the trials without any up-titration. Pooled results of the ongoing, open-label, long-term follow-up extension phases of the included trials are summarized in Appendix 6: Summary of Other Studies.

Key limitations of the available evidence are the lack of active comparator trials comparing brivaracetam with other clinically relevant comparator AEDs (e.g., perampanel, lacosamide, and eslicarbazepine), the lack of validation and minimal clinically important differences (MCIDs) in patients with epilepsy for the measured outcomes, and the short duration of the treatment for an intervention intended for chronic use.

Efficacy

Key efficacy outcomes identified in the review protocol were seizure-free status, health-related quality of life (HRQoL), and change in seizure frequency. Other efficacy outcomes were responder rates (i.e., ≥ 50% reduction in seizure frequency), patient or clinician global impression of change, reduction in use of concomitant AEDs, patient adherence to treatment, and health care resource utilization. The included trials did not include any outcomes pertaining to reduced use of concomitant AEDs.

In all four included trials, the proportion of patients who were seizure-free was small, ranging from 0% to 5.2% with brivaracetam compared with 0% to 0.8% with placebo. The brivaracetam results were statistically significantly different from placebo only in Study 1358; however, in that study, a larger proportion of patients who were treated with brivaracetam 100 mg/day (5.2%) than were treated with the 200 mg/day dose (4.0%) achieved this outcome. This trial was the only trial to evaluate the highest recommended dose of brivaracetam (200 mg/day) along with the 100 mg/day dose, which suggests that possibly higher doses are required to achieve seizure freedom. Nonetheless, the small proportion of patients who achieved this outcome is not unexpected, as complete freedom from seizures is unlikely in refractory patients, such as those enrolled in the included trials (i.e., who had uncontrolled epilepsy despite use of one to three AEDs).

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[redacted]

The primary efficacy outcome across all trials was the reduction in POS frequency from baseline, measured either per week (Studies 1252, 1253, and 1254) or per 28 days (Study 1358). At baseline, the median POS frequency per week in studies 1252, 1253, and 1254 (or per 28 days in Study 1358) was similar among all treatment groups, ranging from 1.80 to 2.85 (or 9.3 to 10.0 per 28 days in Study 1358). At the end of treatment, the median POS frequency per week for brivaracetam ranged from 1.26 to 1.74 (or 6.8 to 6.9 per 28 days in Study 1358) compared with 1.75 to 2.15 per week (or 9.2 per 28 days in Study 1358) for placebo. The treatment difference in per-week POS frequency was statistically significant for brivaracetam 100 mg/day in Study 1252 and 50 mg/day in Study 1253, and per 28 days for both the 100 mg/day and 200 mg/day doses in Study 1358. The median per cent reduction in POS frequency over the treatment period ranged from 26.83% to 37.2% with brivaracetam, and 17.03% to 18.93% with placebo. The median per cent reduction achieved with brivaracetam over placebo ranged from 9.07% to 19.35% for brivaracetam, and the results were statistically significant for brivaracetam 100 mg/day (–19.35%) in Study 1252, 50 mg/day (–15.69%) in Study 1253, and for both the 100 mg/day (–15.8%) and 200 mg/day doses (–18.1%) in Study 1358. Although statistically significantly different from placebo, the magnitude of the POS frequency reduction with brivaracetam suggests it did not demonstrate a clinically important reduction.

A patient was defined as a responder if they were able to achieve at least a 50% reduction in POS frequency from baseline to end of treatment. A 50% reduction in POS was considered clinically meaningful, according to the clinical expert consulted for this review. The 50% responder rates ranged from 27.3% to 38.9% with brivaracetam compared with 16.7% to 21.6% with placebo. According to the Health Canada reviewer's report,[5] a 15% difference compared with placebo in the 50% responder rate is typically considered "acceptable," so the difference in the brivaracetam and placebo values would suggest the results are clinically meaningful. The odds ratio (OR) for the comparison of brivaracetam versus placebo was statistically significant for brivaracetam 100 mg/day in Study 1252 (OR = 2.13; 95% confidence interval [CI], 1.11 to 4.10); brivaracetam 50 mg/day in Study 1253 (OR = 2.51; 95% CI, 1.27 to 4.96); the combined brivaracetam doses in Study 1254 (OR = 2.18; 95% CI, 1.24 to 3.81); and both brivaracetam doses of 100 mg/day (OR = 2.39; 95% CI, 1.6 to 3.6) and 200 mg/day (OR = 2.19; 95% CI, 1.5 to 3.3) in Study 1358.

An important clinical question is whether or not patients previously or concurrently treated with levetiracetam could benefit from brivaracetam, given the presumed similarity in mechanism of action. In the included trials, approximately 22% to 55% of patients had used levetiracetam prior to study entry and, with the exception of Study 1358, approximately 20% of patients received concomitant levetiracetam during the trials. The median per cent reduction in POS frequency by the stratification factor of concomitant levetiracetam use over the treatment period was investigated for studies 1252, 1253, and 1254. In patients with concomitant levetiracetam use at study entry, the median per cent reduction in POS frequency over the treatment period ranged from 3.16% to15.93% with brivaracetam compared with 14.18% to 22.11% with placebo. None of the comparisons of the median per cent reduction with brivaracetam over placebo were statistically significant. In patients with no concomitant levetiracetam use at study entry, the median per cent reduction in POS frequency over the treatment period ranged from 31.51% to 38.31% with brivaracetam compared with 15.70% to 19.19% with placebo. All comparisons of the median per cent reduction with brivaracetam over placebo were

statistically significant. Pre-specified subgroup analyses of the per cent reduction in POS frequency per 28-day period by levetiracetam status were conducted in Study 1358. For patients who never used levetiracetam, the 28-day POS frequency was reduced by 29.5% (brivaracetam 100 mg/day) and 27.1% (brivaracetam 200 mg/day). For patients with prior levetiracetam use, the per cent reduction over placebo was 15.8% (brivaracetam 100 mg/day) and 19.4% (brivaracetam 200 mg/day). No pre-specified statistical comparisons between groups were conducted in Study 1358. Taken together, these results suggest the addition of brivaracetam to levetiracetam does not appear to provide additional treatment benefits; however, these findings require confirmation in further appropriately designed clinical trials.

[redacted]. Across all the trials, patient compliance with treatment was high: more than 92% of patients in the brivaracetam groups and 93% of patients in the placebo groups had between 80% to 120% compliance. Discontinuation rates were low, ranging from 5.1% to 11.4% in individual treatment groups, although a consideration is the relatively short duration of the trials. Health care resource utilization (e.g., additional medical procedures, health care provider visits, emergency room visits, and hospitalizations) was an exploratory outcome in the trials; thus, no statistical comparisons were made between treatment groups. Overall, use of health care resources appeared to be low and similar between brivaracetam and placebo in all the trials.

In the absence of head-to-head comparisons, it is difficult to evaluate the relative efficacy and safety/tolerability of brivaracetam compared with other clinically relevant AEDs. In lieu of the lack of direct evidence comparing brivaracetam with other relevant AEDs, the manufacturer conducted an indirect treatment comparison (ITC) of brivaracetam compared with eslicarbazepine, lacosamide, perampanel, and retigabine/ezogabine, the latter of which is not available in Canada.[6] In addition, one other ITC of brivaracetam and levetiracetam was identified in the medical literature.[7] Both ITCs are summarized and critically appraised in Appendix 7: Summary of Indirect Treatment Comparisons. The manufacturer's ITC included the efficacy outcomes of 50% response rate and seizure-freedom rate, and the harms outcomes of serious adverse events (SAEs), discontinuation rates due to treatment-emergent adverse events (TEAEs) or for any reason, and rates of selected TEAEs (i.e., dizziness, fatigue, nausea, and somnolence). For the efficacy outcomes, when compared with placebo, all AEDs had an increased probability of response and there was no statistically significant difference in response among the comparator AED treatments to brivaracetam. For the harms outcomes, in general, the AEDs had an increased risk of TEAEs and discontinuations (with the exception of SAEs) compared with placebo; however, there were no statistically significant differences between the other AEDs and brivaracetam. In the ITC identified in the literature which compared brivaracetam and levetiracetam,[7] the efficacy outcomes of 50% responder rate and seizure freedom, and the harms outcomes of TEAEs and adverse withdrawal effects were investigated. A comparison of three dose levels was performed: high (levetiracetam 3,000 mg/day versus brivaracetam 200 mg/day and 150 mg/day), middle (levetiracetam 2,000 mg/day versus brivaracetam 100 mg/day), and low (levetiracetam 1,000 mg/day and 500 mg/day

versus brivaracetam 50 mg/day, 25 mg/day, 20 mg/day, and 5 mg/day). For the efficacy outcomes, there was no statistical difference between levetiracetam and brivaracetam at all dose levels. In addition, there were no differences between levetiracetam and brivaracetam for AEs with the exception of dizziness, which occurred at a statistically significantly higher rate at the high-dose level with brivaracetam, but not at the middle- or low-dose levels.

Harms

Harms outcomes identified in the review protocol were mortality, TEAEs, SAEs, withdrawals due to adverse events (WDAEs), and notable AEs (e.g., central nervous system [CNS]-related, psychiatric, hematologic, hepatotoxicity, and weight gain).

There were five deaths reported in groups receiving either the Health Canada–approved brivaracetam dose or placebo during the treatment periods of the four included trials. Of these, only one death, which was due to brain hypoxia in the brivaracetam 50 mg/day group of Study 1253, was considered to be possibly related to the study drug.

Across the four trials, approximately 63% to 75% of patients in the brivaracetam groups compared with 53% to 65% of patients in the placebo groups experienced at least one TEAE. Overall, the most frequently reported TEAEs were somnolence, dizziness, fatigue, and headache. Somnolence occurred more frequently in the brivaracetam groups (6.1% to 19.4%) compared with the placebo groups (4.1% to 7.7%). Similarly, dizziness (5.0% to 15.8%) and fatigue (4.0% to 11.6%) occurred more frequently with brivaracetam compared with placebo (5.0% to 9.2% and 2.0% to 4.1%, respectively). Headache was reported in a similar proportion of brivaracetam (6.7% to 18.2%) and placebo (8.4% to 19.8%) patients. The majority of TEAEs were mild to moderate in intensity. In a pooled analysis of long-term safety data for brivaracetam reported in Appendix 6: Summary of Other Studies, more than 84% of patients experienced at least one TEAE.[8] The most frequent TEAEs were consistent with those reported in the treatment phases of the trials, which included headache, dizziness, somnolence, and fatigue.

The incidence of SAEs and WDAEs across the trials was low and similar across treatment groups. The proportion of patients with at least one SAE ranged from 2.0% to 5.3% among the brivaracetam groups compared with 0% to 7.4% among the placebo groups of the included trials. The proportion of patients with WDAEs ranged from 5.0% to 8.3% in the brivaracetam groups compared with 2.0% to 5.0% in the placebo groups of the included trials. The most common reason for SAEs or WDAEs in both the brivaracetam and placebo treatment groups was convulsion.

[redacted] The CNS-related effects of brivaracetam (i.e., neurologic and psychiatric) are clearly identified in the Warnings and Precautions section of the Brivlera Product Monograph.[2]

There did not appear to be any substantial change in weight from baseline to the end of the treatment period in either the brivaracetam or placebo groups of any of the trials. In the brivaracetam groups, the

mean weight change varied from no change to a loss of 0.6 kg compared with a loss of 0.2 kg to a gain of 0.2 kg in the placebo groups.

Other Considerations

The Canadian Drug Expert Committee (CDEC) has reviewed and made recommendations for three AEDs that have Health Canada–approved indications for use as adjunctive therapy in patients with uncontrolled POS that are similar to the indication for brivaracetam: lacosamide (Vimpat) was approved in April 2011,[9] eslicarbazepine (Aptiom) was approved in April 2015,[10] and perampanel (Fycompa) was approved for POS in October 2013[11] and for primary generalized tonic-clonic seizures in May 2016.[12] For each of these AEDs used as adjunctive therapy in the treatment of POS in patients with epilepsy who are uncontrolled with conventional therapy, CDEC has recommended that the AED be reimbursed with clinical criteria and conditions. In general, the clinical criteria are that a patient must be currently receiving two or more AEDs, and less costly AEDs are either ineffective or not clinically appropriate. The condition is that the patient be under the care of a physician experienced in the treatment of epilepsy.

Place in Therapy

The clinical expert involved in the review stated there is an unmet treatment need in the management of patients with POS who are not satisfactorily controlled with conventional therapy. According to the clinical expert, patients with "resistant" or "refractory" epilepsy are variably defined but, in essence, the terms are applied to those continue to experience seizures despite adequate trials of standard AEDs. There are no standardized guidelines for the treatment of epilepsy but, in practice, an "adequate" trial of AED usually means several months of phenytoin, carbamazepine, or valproic acid, either alone or in combination. Many physicians treating patients with epilepsy would now add levetiracetam and lamotrigine to the list of "standard" AEDs. In the total population of people with epilepsy, about 20% to 30% prove to be resistant or refractory to these standard AEDs[13] and, among these patients, roughly one-half would have resistant or refractory POS. Thus, a substantial proportion of patients with epilepsy would require add-on therapy to manage their POS.

Brivaracetam joins a group of newer AEDs, any or several of which might be tried in a given patient with resistant or refractory POS. In general, the data presented in this review indicate that brivaracetam produces a statistically significant short-term reduction in POS frequency compared with placebo. The effect is modest, however, falling short of the 20% seizure-frequency reduction commonly used as a measure to define a clinically meaningful effect. On the other hand, the fraction of patients experiencing at least a 50% reduction in seizure frequency, another commonly used measure of a clinically meaningful effect, was increased with brivaracetam compared with placebo. The efficacy of brivaracetam as an add-on AED appears to be roughly similar to alternative new AEDs used as adjunctive therapy, but there are no direct comparison data available. There is some evidence that any benefit offered by add-on brivaracetam may not be found in patients concurrently taking levetiracetam. Given that levetiracetam is increasingly considered a "standard" AED, this may limit the population for whom brivaracetam might be considered as an add-on therapy. The main adverse effects of brivaracetam compared with placebo seem to be dizziness and somnolence. The studies reviewed did not show a positive or negative impact of brivaracetam on quality-of-life measures, but these adverse effects may become important when the drug is used in clinical practice. Therefore, while it is another therapeutic option for the management of patients who continue to experience seizures despite background treatment (i.e., refractory POS), the added value of brivaracetam compared with alternative adjunct AEDs is unclear.

Conclusions

In four phase 3 RCTs of 12- to 16-week treatment duration, brivaracetam 50 mg/day to 200 mg/day generally demonstrated statistically significant greater reductions in POS frequency from baseline compared with placebo in patients aged 16 years and older with uncontrolled POS, despite concomitant treatment with one to three AEDs. A small proportion of patients treated with brivaracetam 100 mg/day and 200 mg/day achieved statistically significant seizure freedom when compared with placebo. The included trials suggest brivaracetam has no additional benefit for patients who are being concurrently treated with levetiracetam. The benefit of brivaracetam in patients who have previously been treated with levetiracetam is uncertain and requires confirmation in appropriately designed clinical trials. There were minimal changes in HRQoL in all treatment groups. There were five deaths during the treatment periods, of which only one was considered possibly related to brivaracetam. Overall, the frequency of SAEs and WDAEs was low and similar between treatment groups. More than half of all patients in the trials experienced TEAEs, of which the most common were somnolence, dizziness, and fatigue, which occurred more frequently with brivaracetam, and headache, which were experienced in similar proportion by brivaracetam- and placebo-treated patients. [redacted] An important limitation is the lack of evidence directly comparing brivaracetam with another clinically relevant AEDs used as adjunctive therapy in patients with uncontrolled POS. An ITC submitted by the manufacturer suggested similar efficacy and safety/tolerability of brivaracetam as compared with eslicarbazepine, perampanel, and lacosamide.

TABLE 1: SUMMARY OF RESULTS (ITT OR ITT POS POPULATION)

Outcome	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 96)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
Seizure-Free (All Type 1, 2, and 3 Seizures)										
Seizure-free, n (%)	0	4 (4.0)	0	4 (4.0)	0	5 (1.5)	0	13 (5.2)	10 (4.0)	2 (0.8)
P value (BRV vs. PL)	NA	0.121	-	0.122	-	0.337	-	0.003	0.019	-
[redacted]										
[redacted]										
Per Cent Reduction in Partial (Type 1) Seizure Frequency from Baseline to End of Treatment										
Per cent reduction (median)	26.83	32.45	17.03	30.47	17.75	26.92	18.93	37.2	35.6	17.6
Treatment comparison vs. PL: median difference vs. PL *P* value	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	15.8 < 0.001	18.1 < 0.001	-
50% Responder Rate in Partial (Type 1) Seizure Frequency from Baseline to End of Treatment										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	[redacted] (27.3)	[redacted] (36.0)	[redacted] (20.0)	33 (32.7)	16 (16.7)	[redacted] (30.3)	[redacted] (16.7)	[redacted] (38.9)	[redacted] (37.8)	[redacted] (21.6)
OR (BRV vs. PL): 95% CI *P* value	[redacted] 0.372	[redacted] 0.023	-	[redacted] 0.008	-	[redacted] 0.006	-	2.39 1.6 to 3.6 < 0.001	2.19 1.5 to 3.3 < 0.001	-
Number of deaths, n (%)[a]	0	0	1 (1.0)	1 (1.0)	0	1 (0.3)	0	0	2(0.8)	0
Patients with ≥ 1 TEAE, n (%)	62 (62.6)	63 (63.0)	53 (53.0)	76 (75.2)	69 (70.4)	237 (66.0)	79 (65.3)	173 (68.4)	167 (66.8)	155 (59.4)
Patients with ≥ 1 SAE, n (%)	4 (4.0)	2 (2.0)	6 (6.0)	4 (4.0)	0	19 (5.3)	9 (7.4)	8 (3.2)	8 (3.2)	9 (3.4)

Outcome	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 96)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
Patients with ≥ 1 WDAE, n (%)	5 (5.1)	5 (5.0)	4 (4.0)	6 (5.9)	2 (2.0)	22 (6.1)	6 (5.0)	21 (8.3)	17 (6.8)	10 (3.8)
Notable TEAEs (≥ 1 TEAE in SOC), n (%)										
[redacted]										

BL = baseline; BRV = brivaracetam; ITT = intention to treat; NA (cannot be calculated); OR = odds ratio; PL = placebo; POS = partial-onset seizure; SAE = serious adverse event; SOC = system organ class; SUDEP = sudden unexplained death in epilepsy; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to an adverse event.

[a] Causes of death: Study 1252: n = 1 in PL group due to sepsis considered unlikely related to study drug; Study 1253: n = 2; 1 death each in the BRV 20 mg/day and 50 mg/day groups. In the BRV 50 mg/day group, cause was due to brain hypoxia considered possibly related to study drug; Study 1254: n = 1 in BRV group due to drowning considered unlikely related to study drug. Study 1358: n = 2 deaths in BRV 200 mg/day group. One death was due to SUDEP and the other due to unknown cause(s), both deaths were considered not related to study drug.

[b] Mean weight change from BL to last value in the treatment period.

Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

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- (or focal-) onset seizures (POS) and generalized seizures (GS).[1] POS involve only a portion of the brain, typically one lobe of one hemisphere, while GS involve large parts of both hemispheres of the brain.[1] Simple POS are not associated with loss of consciousness, while consciousness is affected in complex POS and GS.[1]

The estimated prevalence of epilepsy is 400 per 100,000 Canadians, based on data from the 2010–2011 Canadian Community Health Survey.[18] Each day in Canada, an average of 42 people, or approximately 15,500 people annually, are diagnosed with epilepsy.[19] Of these, 44% are diagnosed before the age of 5, 55% before age 10, 75% to 85% before age 18, and 1.3% over the age of 60 years.[19]

The impact of epilepsy can affect all aspects of life, as seizures vary widely in terms of frequency, severity and duration. Patients with uncontrolled epilepsy are often placed in dangerous situations: seizures may occur while riding a bus, shopping, or crossing a street. In addition, patients with uncontrolled epilepsy are not permitted by law to operate motor vehicles. It follows that patients with epilepsy may face stigma and discrimination and have difficulty obtaining and retaining employment. If they are housebound, they could be dealing with loss of independence, and be socially isolated and have difficulties maintaining relationships.

1.2 Standards of Therapy

The goals of epilepsy treatment are to control seizures, avoid adverse events (AEs), and maintain or restore quality of life.[1] Approximately half of the patients with a new diagnosis of epilepsy will become seizure-free with the first antiepileptic drug (AED) prescribed.[1] Of those whose initial therapy is ineffective, about 10% to 20% will have a successful second drug trial (i.e., the second AED is typically increased to therapeutic levels before the first drug is reduced in order to prevent seizures or status epilepticus during the switch period).[1] Combination therapy with two or more AEDs may be required for some patients whose epilepsy is treatment-resistant. The selection of AEDs is usually based on various factors. These include the effectiveness of the drug for the patient's seizure type, potential AEs and interactions with medications, comorbid medical conditions, age, gender (including child-bearing plans), patient preference, and cost.[1] Non-pharmacological treatments for refractory epilepsy include vagal nerve stimulation or surgical resection.[1,20] For select patients (primarily children), dietary therapies may also be used.

There are various AEDs approved for use in Canada with indications for use as adjunctive therapy in the management of POS. According to input received from patients, effective anti-seizure medications are life-saving and can assist patients to enjoy a fulfilled life; however, existing therapies are not effective for some patients and the associated AEs can be debilitating and detrimental to the patient's well-being. Feedback from patients is that novel treatment options are required for those who have failed to achieve complete seizure elimination or who cannot tolerate the AEs of existing AEDs.

1.3 Drug

Brivaracetam is the second racetam AED to be approved in Canada. It is indicated for adjunctive therapy in the management of POS in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.[2] Compared with levetiracetam, brivaracetam displays higher selectivity and affinity for synaptic vesicle protein 2A (SV2A) in the brain.[2] Although the mechanism of action of SV2A in neurotransmission is not completely known, it has been recognized as an important target for AEDs, and the anticonvulsant effect has been demonstrated in experimental studies.[3]

The recommended starting dose of brivaracetam in adults is 50 mg twice daily (100 mg per day).[2] Based on individual patient response and tolerability, the dose may be lowered to 25 mg twice daily (50 mg per day), or up-titrated to 100 mg twice daily (200 mg per day). The maximum recommended daily dose is 200 mg, administered in two equal amounts of 100 mg. Brivlera (brivaracetam) is available as 10 mg, 25 mg, 50 mg, 75 mg, and 100 mg oral tablets, 10 mg/mL oral solution, and 10 mg/mL injection.[2] The focus of the CADTH Common Drug Review (CDR) submission is for the oral tablets only.[4] Of note, brivaracetam can be initiated with either intravenous or oral administration and when switching between oral and intravenous administration; in all cases, the total daily dose and frequency of administration should be maintained.[2] As with all AEDs, withdrawal of brivaracetam should be done gradually due to the risk of increased seizure frequency and, possibly, status epilepticus.[2] When discontinuing brivaracetam, the dose should be tapered gradually by 50 mg/day on a weekly basis and, after one week of treatment at 50 mg/day, a final week of treatment at 20 mg/day is recommended.[2]

Indication under review
Adjunctive therapy in the management of POS in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.
Reimbursement criteria requested by sponsor
As per indication and in a similar manner as lacosamide, perampanel and eslicarbazepine.

The AED comparators for brivaracetam with similar Health Canada–approved indications are eslicarbazepine (Aptiom), perampanel (Fycompa), and lacosamide (Vimpat), which were approved by Health Canada in July 2014, April 2013, and September 2010, respectively. All three AEDs are indicated as adjunctive therapy in the management of POS in adult patients with epilepsy who are not controlled with conventional treatments. In addition, all three AEDs were recommended for reimbursement with criteria by CDEC, as detailed in Section 4.3.[9-12] A comparison of the key characteristics of brivaracetam, eslicarbazepine, perampanel, and lacosamide is provided in Table 2.

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

	Brivaracetam	Eslicarbazepine	Lacosamide	Perampanel
Trade name	**Brivlera**	**Aptiom**	**Vimpat**	**Fycompa**
Mechanism of Action	Binds to SV2A protein in the brain but precise MOA not fully elucidated	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 adult patients with epilepsy who are not satisfactorily controlled with conventional therapy	Adjunctive therapy in the treatment of POS in patients[c] 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	Adjunctive therapy in the management of POS in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy
Route of Administration	• Tablets: 10 mg, 25 mg, 50 mg, 75 mg and 100 mg • Oral solution: 10 mg/mL • Injection: 10 mg/mL[b]	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 at 50 mg b.i.d. (100 mg per day) and, based on response and tolerability, adjust dose between 25 mg b.i.d. (50 mg per day) and 100 mg b.i.d. (200 mg per day). The maximum recommended dose is 200 mg per day administered in two equal intakes.	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 200 mg b.i.d. The maximum recommended dose is 400 mg daily.	**In the presence of EIAEDs:**[d] 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	Hematologic abnormalities, neurologic reactions, psychiatric and behavioural disorders	Hyponatremia and skin reactions	Cardiac rhythm and conduction abnormalities	Serious psychiatric and behavioural reactions

AMPA = ionotropic α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, b.i.d. = twice daily; EIAED = enzyme-inducing antiepileptic drug; MOA = mechanism of action; POS = partial-onset seizures; q.d. = once daily; SV2A = synaptic vesicle protein 2A.

[a] Health Canada–approved indications.

[b] Only the tablets are the focus of the CADTH Common Drug Review submission.

[c] According to the Aptiom Product Monograph, although the indication does not specify adult patients, it does state that, "the efficacy and safety of Aptiom in pediatric patients has not been studied. Aptiom is not indicated for use in this population."[21]

2. OBJECTIVES AND METHODS

2.1 Objectives

To perform a systematic review of the beneficial and harmful effects of brivaracetam at doses between 25 mg and 100 mg twice daily for adjunctive therapy in the management of POS in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.

2.2 Methods

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

TABLE 3: INCLUSION CRITERIA FOR THE SYSTEMATIC REVIEW

Patient Population	Adult patients (≥ 18 years) with epilepsy and POS who are not satisfactorily controlled with conventional therapy **Subgroups:** Age (e.g., ≥ 18 yrs to < 65 yrs, ≥ 65 yrs), seizure type (e.g., simple POS, complex POS, secondarily GS), background AED use (e.g., number of AEDs, enzyme inducers vs. non-inducers, etc.)
Intervention	Brivaracetam 25 mg to 100 mg twice daily, in combination with at least 1 AED
Comparators	AEDs available in Canada (used alone or in combination): • carbamazepine • clobazam • eslicarbazepine • ethosuximide • gabapentin • lacosamide • lamotrigine • levetiracetam • oxcarbazepine • perampanel • phenobarbital • phenytoin • primidone • topiramate • valproic acid/divalproex • vigabatrin • placebo (in combination with at least 1 AED)
Outcomes	**Key Efficacy Outcomes** • Seizure-free status (i.e., proportion of patients who are seizure-free) • Health-related quality of life[a] • Change in seizure frequency[a] **Other Efficacy Outcomes** • Responder rates (i.e., proportion of patients with ≥ 50% or ≥ 75% reduction in seizure frequency) • Patient or clinician global impression of change • Reduction in use of concomitant AEDs • Patient adherence to treatment • Health care resource utilization **Harms Outcomes** • Mortality (SUDEP), AEs, SAEs, WDAEs, AEs of special interest (e.g., CNS-related, psychiatric, hematologic, hepatotoxicity, weight gain)
Study Design	Published and unpublished phase 3 DB RCTs

AE = adverse event; AED = antiepileptic drug; CNS = central nervous system; DB = double blind; GS = generalized seizure; POS = partial-onset seizures; RCT = randomized controlled trial; SAE = serious adverse event; SUDEP = sudden unexplained death in epilepsy; vs. = versus; WDAE = withdrawal due to adverse event; yrs = years.
[a] Identified as important to patients in the Patient Input Summary.

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 through Ovid; Embase (1974–), through Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were Brivlera (brivaracetam).

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

The initial search was completed on May 17, 2016. Regular alerts were established to update the search until the meeting of CDEC on September 21, 2016. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (www.cadth.ca/grey-matters): Health Technology Assessment Agencies, Health Economics, Clinical Practice Guidelines, Drug and Device Regulatory Approvals, Advisories and Warnings, Drug Class Reviews, Databases (free), 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 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. There were no excluded studies as per Appendix 3.

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. As per Appendix 3, there were no excluded studies.

FIGURE 1: FLOW DIAGRAM FOR INCLUSION AND EXCLUSION OF STUDIES

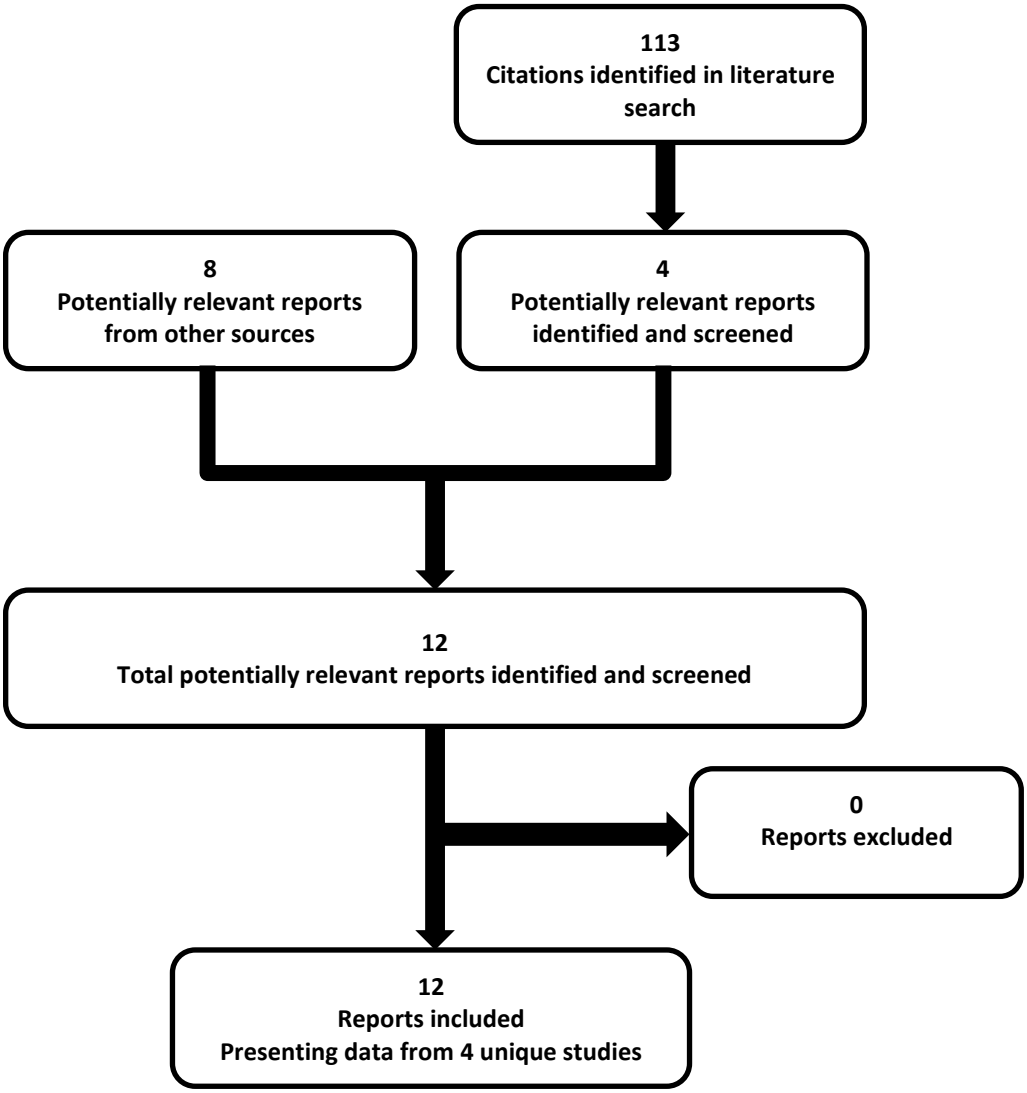


TABLE 4: DETAILS OF INCLUDED STUDIES

		Study 1252	Study 1253	Study 1254	Study 1358
DESIGNS AND POPULATIONS	**Study Design**	double-blind, parallel-group, placebo-controlled, multi-centre, phase 3 randomized controlled trial			
	Locations	Europe and India	North America, South America, Australia	Europe, Asia, South Africa, India, Norway	North America, Europe, Latin America, Asia
	Randomized (N)[a]	399	400	480	768
	Inclusion Criteria	Patients (≥ 16 to ≤ 70 years) with focal epilepsy (SG or not) as per ILAE (type 1), history of POS, ≥ 2 POS/mo in previous 3 months, ≥ 8 POS in 8-wk BL period, uncontrolled despite 1 to 2 concomitant AEDs		Patients (≥ 16 to ≤ 70 years) with localization-related epilepsy or generalized epilepsy as per ILAE, uncontrolled despite 1 to 3 concomitant AEDs	Patients (≥ 16 to ≤ 80 years) with focal epilepsy/epileptic syndrome as per ILAE, EEG evidence of focal epilepsy, ≥ 8 type 1 POS in 8-wk BL period with ≥ 2 type 1 seizures during each 4-wk interval of BL, 2 POS (SG or not) in 3 months prior to visit 1, uncontrolled despite 1 to 2 concomitant AEDs
	Exclusion Criteria	History or presence of cluster seizures (too frequent or indistinct to be reliably counted) or occurring as type 1A non-motor or status epilepticus			Seizure type 1A non-motor as only seizure type, current treatment with LEV or taken LEV within 90 days of visit 1, cluster or flurries seizures, status epilepticus
DRUGS	**Intervention**	BRV: 20 mg/day, 50 mg/day, or 100 mg/day in two divided doses PO	BRV: 5 mg/day, 20 mg/day, or 50 mg/day in two divided doses PO	BRV: 20 mg/day up-titrated to 50 mg/day, 100 mg/day or 150 mg/day in two divided doses PO	BRV: 100 mg/day or 200 mg/day in two divided doses PO
	Comparator(s)	PL: matched PL in two divided doses PO			
DURATION	**Phase**				
	Run-in	8-week BL period		4-week BL period	8-week BL period
	Double-blind	12-week treatment period		8-week treatment period + 8-week maintenance period	12-week treatment period
	Follow-up	LTFU study or 2-week down-titration period and 2-week study drug-free period	LTFU study or 1-week down-titration period and 2-week study drug-free period	3-week down-titration period and 2-week study drug-free period	LTFU study upon completion of treatment period

		Study 1252	Study 1253	Study 1254	Study 1358
Outcomes	**Primary End Point**	Frequency of POS (type 1) per week during the treatment period		Safety and tolerability	POS (type 1) frequency per 28 days during treatment period[b]
	Other End Points	Responder rate (≥ 50%) and other measures of reduction in seizure frequency, [redacted]		Frequency of POS (type 1) per week during the treatment period and other measures of reduction in seizure frequency, responder rate (≥ 50%), [redacted]	Per cent reduction in POS (type 1) frequency from BL to 12-week treatment period and other measures of reduction in seizure frequency, [redacted]
Notes	**Publications**	Ryvlin et al., 2014[22]	Biton et al., 2014[23]	Kwan et al., 2014[24]	Klein et al., 2015[25]

AED = antiepileptic drug; BL = baseline; BRV = brivaracetam; EEG = electroencephalogram; EQ-5D = EuroQol 5-Dimensions Questionnaire; HADS = Hamilton Anxiety and Depression Scale; I-GES = Investigator Global Evaluation Scale; ILAE = International League Against Epilepsy; LEV = levetiracetam; LTFU = long-term follow-up; P-GES = Patient Global Evaluation Scale; PL = placebo; PO = orally; POS = partial-onset seizures; QoL = quality of life; QOLIE-31-P = Quality of Life in Epilepsy Inventory Form 31; SG = secondarily generalized.

Note: Four additional reports were included (manufacturer's submission,[4] Health Canada Reviewer's Report,[5] United States Food and Drug Administration medical review.[26] and statistical review[27]).

[a] Only data from the treatment groups of Health Canada–approved doses for BRV are reported in the Clinical Review.

[b] In Study 1358, the primary efficacy outcome for the United States was the per cent reduction in POS (type 1) frequency over PL based on analysis of covariance; for Europe the primary efficacy outcome was 50% responder rate based on per cent reduction in POS (type 1) frequency from BL to 12-week treatment period.

Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

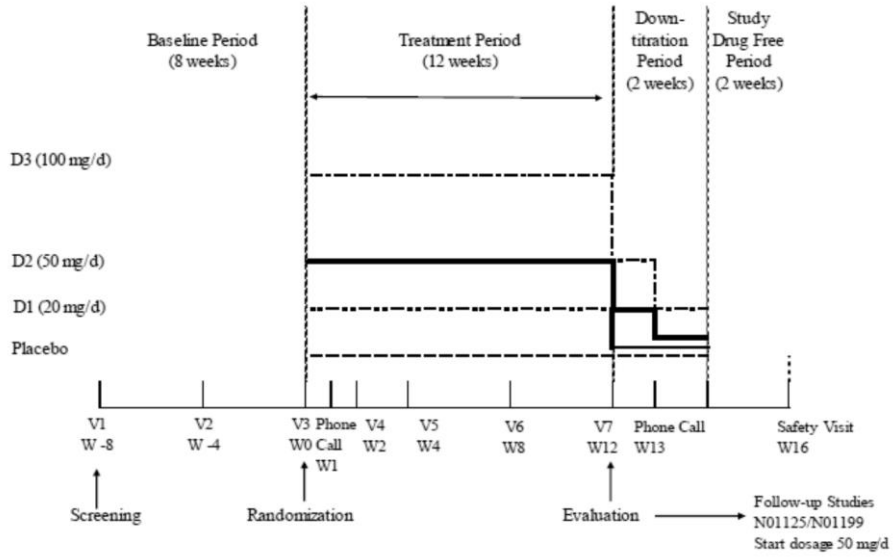
3.2 Included Studies

3.2.1 Description of Studies

Four multi-centre, double-blind, placebo-controlled, parallel-group phase 3 randomized controlled trials (RCTs) were included in the systematic review: Study 1252 (N = 399),[14,22] Study 1253 (N = 400),[15,23] Study 1254 (N = 480),[16,24] and Study 1358 (N = 768).[17,25] All trials investigated the efficacy, safety and tolerability of brivaracetam given as adjunctive therapy (i.e., added on to a background regimen of one to three AEDs) in patients aged 16 years and older for the treatment of uncontrolled POS. Studies 1252 and 1253 were identical in design, with the exception of the brivaracetam doses evaluated (figures 2 and 3). Study 1358 was also of similar design, but included patients up to 80 years of age, whereas all the other trials included only patients up to age 70 (Figure 5). Study 1358 also investigated the highest recommended dosage of brivaracetam (200 mg/day) and excluded patients who had been exposed to levetiracetam within the past 90 days. With the exception of Study 1254, patients were randomized to the full dose of brivaracetam without any up-titration phase. Study 1254 was a flexible-dose trial that included both a dose-finding (up-titration) phase and a maintenance phase during the treatment period (Figure 4). All four trials were published in the peer-reviewed medical literature.[22-25]

Study 1252 was a 24-week, therapeutic confirmatory RCT (Figure 2). Patients were enrolled and entered an eight-week baseline period, at the end of which 399 patients were randomized in a 1:1:1:1 fashion to one of four treatment groups (brivaracetam 20 mg/day, 50 mg/day, 100 mg/day, or matching placebo) Randomization was stratified by geographical region and by use of concomitant levetiracetam at study entry.

FIGURE 2: DESIGN OF STUDY 1252

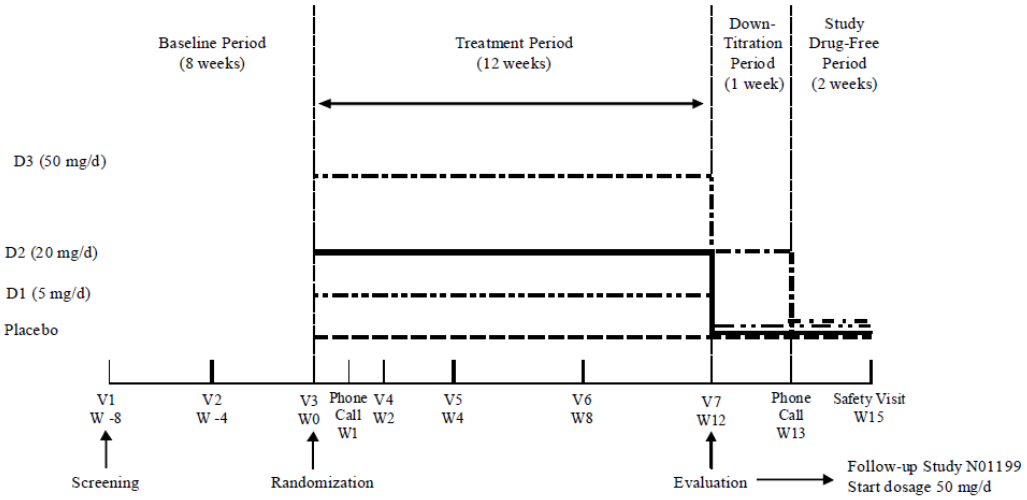


D = dose; V = visit; W = week.
Source: Study 1252 Clinical Study Report.[14]

Study 1253 was a 23-week RCT that was identical in design to Study 1252, with the exception of the brivaracetam doses studied (Figure 3). Enrolled patients entered an eight-week baseline period, at the end of which 400 patients were randomized in a 1:1:1:1 fashion to one of four treatment groups

(brivaracetam 5mg/day, 20 mg/day, 50 mg/day, or matching placebo). Randomization was also stratified by geographical region and by use of concomitant levetiracetam at study entry.

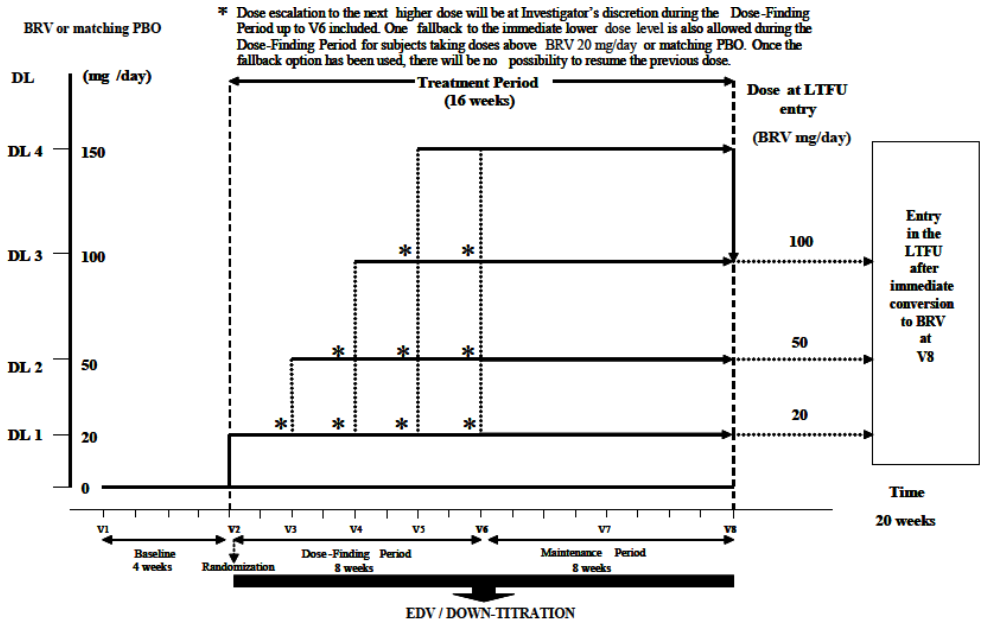
FIGURE 3: DESIGN OF STUDY 1253



D = dose; V = visit; W = week.
Source: Study 1253 Clinical Study Report.[15]

Study 1254 was a 19-week, flexible-dose study conducted to determine the safety and tolerability of brivaracetam in patients with localization-related or generalized epilepsy (Figure 4). A secondary objective was to confirm the efficacy of brivaracetam in reducing POS, and data from the POS population are reported in this review. Patients entered a four-week baseline period after which they were centrally randomized 3:1 to either brivaracetam 20 mg/day or matching placebo. Randomization was stratified by type of epilepsy, geographic region, and concomitant levetiracetam use at study entry. Following the baseline period, patients entered an eight-week dose-finding phase during which brivaracetam was initiated at 20 mg/day and up-titrated in a stepwise manner to either brivaracetam 50 mg/day, 100 mg/day or 150 mg/day based on the investigator's assessment of efficacy and tolerability, or matching placebo. Patients then entered an eight-week maintenance period at the last dose reached in the dose-finding period.

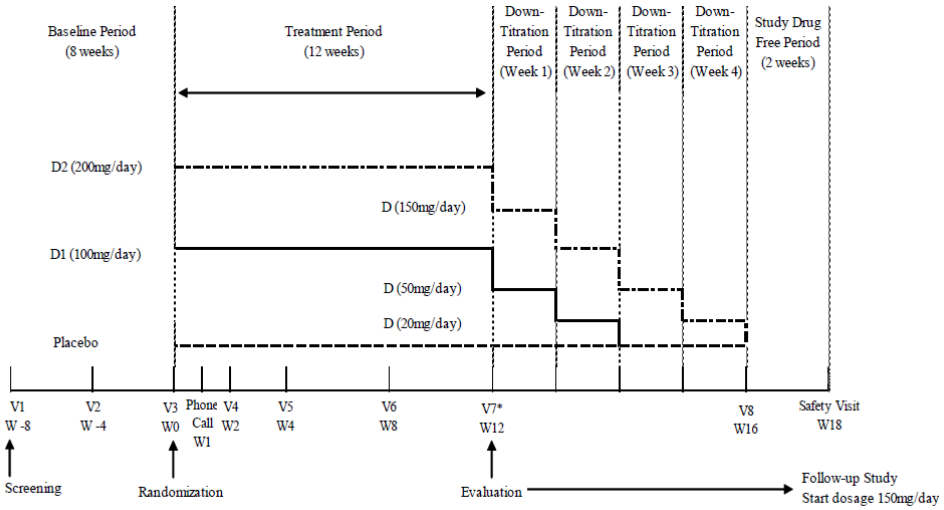
FIGURE 4: DESIGN OF STUDY 1254



BRV = brivaracetam; DL = dose level; EDV = early discontinuation visit; LTFU = long-term follow-up; PBO = placebo; V = visit.
Source: Study 1254 Clinical Study Report.[16]

Study 1358 was a 26-week trial that evaluated two active doses of brivaracetam (100 mg/day or 200 mg/day). Upon entry, patients completed an eight-week baseline period, after which they were centrally randomized 1:1:1 to either a brivaracetam dose or matching placebo. Randomization was stratified by country, levetiracetam use status, and number of AEDs previously used but discontinued prior to study entry. This was followed by a 12-week treatment period as illustrated in Figure 5. Study 1358 differed from the other trials in that patients exposed to levetiracetam for 90 days or more before the first study visit were excluded from entering the study.

FIGURE 5: DESIGN OF STUDY 1358



D = dose; V = visit; W = week.
Source: Study 1358 Clinical Study Report.[17]

Following the treatment periods of studies 1252, 1253, and 1358, patients had the option of continuing in long-term follow-up (LTFU) studies or undergoing a down-titration phase of one to two weeks and a study drug-free period of two weeks. Pooled data from the LTFU studies have been published and the findings are summarized in Appendix 6: Summary of Other Studies. In Study 1254, patients did not enter a LTFU study; instead, they underwent a three-week down-titration period followed by a two-week study drug-free period. Only results from the treatment groups of the trials that correspond with the Health Canada–approved doses for brivaracetam (i.e., 50 mg to 200 mg daily in two divided doses) are reported in this review.

3.2.2 Populations

a) Inclusion and Exclusion Criteria

All four included trials enrolled patients 16 years of age and older with localization-related or focal epilepsy according to the International League Against Epilepsy classification of epileptic seizures (i.e., type 1 seizures). Studies 1252, 1253, and 1254 enrolled only patients up to age 70, whereas Study 1358 enrolled patients up to age 80. All trials required that patients have electroencephalogram evidence of focal epilepsy within the past five years. Patients were required to have uncontrolled POS, whether or not secondarily generalized, while being treated with one to three AEDs. Patients were considered uncontrolled if they experienced ≥ 2 focal seizures/month for three months prior to screening and ≥ 4 (Study 1254) or ≥ 8 (Studies 1252, 1253, and 1358) focal seizures during the four- or eight-week baseline period. Vagal nerve stimulation was allowed, but was not counted as a concomitant AED.
Key exclusion criteria were the history or presence of only type 1A non-motor seizures or cluster seizures (i.e., occurring too frequently or indistinctly separated to be reliably counted) or status epilepticus. Patients were excluded if their medication (e.g., drugs with central nervous system effects or drugs such as cytochrome P450 2C or CYP3A potent inducers/inhibitors that could have influenced the metabolism of brivaracetam, unless the dose of the concomitant drug was stable) or disease histories or clinical conditions (e.g., cerebrovascular accident, brain disorder, brain tumour, impaired hematologic, renal or hepatic function) that could have potentially affected the trial outcomes.

b) Baseline Characteristics

Patient populations were similar across the four trials and baseline characteristics appear to be well balanced between the treatment groups in individual trials, as detailed in Table 5. There was fairly equal representation of male and female patients in all treatment groups across the trials. The mean age of included patients ranged from 36 to 39 years of age and the majority of included patients were Caucasian (approximately 70%), with the exception of Study 1254 where only approximately 57% of patients were Caucasian, followed by approximately 42% Asian patients.

The duration of epilepsy in enrolled patients ranged from 20 to 26 years across the trials. The age of onset of epilepsy was in the teenage years, ranging from 15 to 17 years in studies 1252 and 1358, and 12 to 14 years in studies 1253 and 1254. Across all the trials, enrolled patients had epilepsy for more than half their lives. As per the inclusion criteria, all patients had POS, with the majority of patients having complex partial seizures (type 1B) and partial seizures that secondarily generalize (type 1C). The proportion of patients with GS (i.e., approximately 1.5% to 8%), was low and similar between treatment groups in the trials. Although the exclusion criteria stated that patients with cluster seizures should be excluded, in Study 1358, approximately 3% to 6% of patients in the individual treatment groups had cluster seizures at baseline.

The history of use of previous AEDs (i.e., up to five years prior to baseline) by the number of AEDs used is presented in Table 6. The most common AEDs used (i.e., taken by at least 5% of patients) prior to

study entry are summarized by generic drug name and treatment group in Table 7. The majority of patients in all trials (i.e., approximately 70% or more) had historically used two or more AEDs. In studies 1252, 1253, and 1254, approximately 10% to 19% of patients had historically tried five or more AEDs, whereas in Study 1358, approximately 47% of patients had used five or more AEDs. The most common AEDs that had been used were levetiracetam (21.8% to 54.8%), carbamazepine (19.4% to 51.0%), valproic acid (18.0% to 51.0%), topiramate (17.3% to 43.4%), and lamotrigine (13.9% to 43.4%). Of note, prior clobazam use was only reported in Study 1358, where between 16.2% and 18.1% of patients in the treatment groups had previous use.

All patients were taking at least one concomitant AED at baseline (Table 10). The most frequently used concomitant AEDs were carbamazepine (37.1% to 48.5%), lamotrigine (20.0% to 29.6%), valproic acid (15.3% to 31.9%), oxcarbazepine (9.9% to 22.0%), and topiramate (3.0% to 22.2%). Of note, concomitant levetiracetam was used by 18.0% to 20.4% of patients in studies 1252, 1253, and 1254 (i.e., use of levetiracetam was an exclusion criterion in Study 1358). The frequency of use of these AEDs was generally similar across treatment groups in the individual trials — with the possible exception of more frequent topiramate use in the placebo groups, as compared with the brivaracetam groups — of studies 1252, 1253, and 1358 (Table 10).

TABLE 5: SUMMARY OF BASELINE CHARACTERISTICS

Characteristic[a]	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 98)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
Gender, n (%)										
Male	54 (54.5)	58 (58.0)	54 (54.0)	51 (50.5)	43 (43.9)	164 (50.8)	60 (55.6)	102 (40.3)	133 (53.2)	133 (51.0)
Age (yrs)										
Mean (SD)	38.9 (13.6)	38.0 (13.1)	36.4 (13.0)	38.9 (12.3)	37.5 (12.6)	36.4 (11.5)	36.6 (11.9)	39.1 (13.4)	39.8 (12.8)	39.8 (12.5)
Min–Max	18.2–71.1	17.6–70.8	16.2–68.9	16.6–69.9	16.5–66.5	16.5–70.4	16.1–67.2	16–80	16–73	16–77
Race, n (%)										
Caucasian	76 (76.8)	76 (76.0)	77 (77.0)	77 (76.2)	66 (67.3)	186 (57.6)	62 (57.4)	182 (71.9)	182 (72.8)	189 (72.4)
Asian	23 (23.2)	24 (24.0)	23 (23.0)	3 (3.0)	1 (1.0)	137 (42.4)	45 (41.7)	32 (12.6)	29 (11.6)	32 (12.3)
Weight (kg)	71.1 (14.4)	72.0 (18.1)	70.1 (17.3)	75.0 (20.1)	77.0 (21.4)	69.9 (15.7)	68.9 (14.8)	74.1 (16.8)	75.4 (19.0)	76.1 (20.0)
BMI (kg/m^2)	25.1 (4.2)	25.2 (5.3)	24.8 (5.2)	27.1 (6.4)	28.0 (6.9)	24.8 (4.8)	24.5 (4.7)	26.7 (5.7)	26.4 (6.0)	26.7 (5.7)
Epilepsy duration (yrs)	22.3 (13.0)	22.1 (12.8)	20.4 (12.3)	26.2 (12.0)	24.3 (12.2)	21.8 (12.5)	22.1 (11.7)	22.2 (13.3)	23.4 (14.6)	22.7 (13.3)
Age at onset of first seizure (yrs)	16.5 (13.5)	15.9 (12.6)	16.0 (12.9)	12.7 (11.5)	13.3 (12.1)	14.7 (10.3)	14.6 (11.3)	17.4 (13.9)	16.8 (13.5)	17.5 (13.4)
[redacted]										
[redacted]										

BMI = body mass index; BRV = brivaracetam; PL = placebo; SD = standard deviation; SG = secondarily generalized; yrs = years.

[a] Mean (SD) unless otherwise indicated.

[b] Seizure type was not mutually exclusive (i.e., one patient could have had more than one type of seizure).

Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 6: HISTORY[a] OF NUMBER OF PREVIOUS ANTIEPILEPTIC DRUGS AT STUDY ENTRY (ITT POPULATION OR ITT POS POPULATION)

Number of Previous AEDs, n (%)	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 98)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
0 to 1	30 (30.3)	33 (33.0)	33 (33.0)	37 (36.6)	35 (35.7)	127 (35.4)	43 (35.5)	53 (21.0)	45 (18.1)	46 (17.8)
2 to 4	54 (54.5)	50 (50.0)	48 (48.0)	45 (44.6)	50 (51.0)	194 (54.0)	62 (51.2)	80 (31.7)	85 (34.1)	92 (35.5)
≥ 5	15 (15.2)	17 (17.0)	19 (19.0)	19 (18.8)	13 (13.3)	38 (10.6)	16 (13.2)	119 (47.2)	119 (47.8)	121 (46.7)

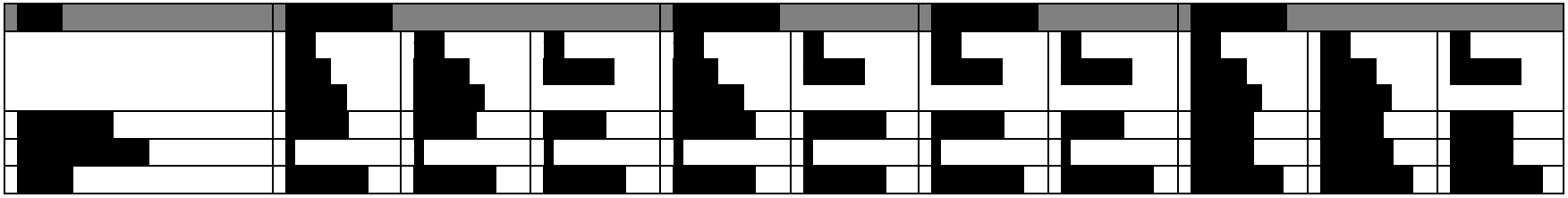
AED = antiepileptic drug; BRV = brivaracetam; ITT = intention to treat; PL = placebo; POS = partial-onset seizure.
[a] History includes AED use up to 5 years prior to baseline.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 7: HISTORY[a] OF PREVIOUS ANTIEPILEPTIC DRUG USE AT STUDY ENTRY (BY AT LEAST 5% OF OVERALL PATIENTS)[a] (ITT POPULATION OR ITT POS POPULATION)

Number of Patients With a History of at Least 1 AED, n (%)	Study 1252			Study 1253		Study 1254		Study 1358[b]		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 98)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
Patients with history of ≥ 1 AED, n (%)	83 (83.8)	82 (82.0)	86 (86.0)	83 (82.2)	80 (81.6)	260 (80.5)	89 (82.4)	235 (93.3)	235 (94.4)	237 (91.5)
Carbamazepine	36 (36.4)	34 (34.0)	29 (29.0)	24 (23.8)	22 (22.4)	78 (24.1)	21 (19.4)	116 (46.0)	121 (48.6)	132 (51.0)
[redacted]										
Lacosamide	NR	NR	NR	7 (6.9)	2 (2.0)	5 (1.5)	3 (2.8)	50 (19.8)	52 (20.9)	41 (15.8)
Lamotrigine	19 (19.2)	16 (16.0)	21 (21.0)	19 (18.8)	17 (17.3)	62 (19.2)	15 (13.9)	91 (36.1)	94 (37.8)	90 (34.7)
Levetiracetam	28 (28.3)	23 (23.0)	27 (27.0)	22 (21.8)	22 (22.4)	71 (22.0)	28 (25.9)	136 (54.0)	134 (53.8)	142 (54.8)
Oxcarbazepine	17 (17.2)	20 (20.0)	14 (14.0)	17 (16.8)	12 (12.2)	27 (8.4)	10 (9.3)	75 (29.8)	55 (22.1)	68 (26.3)
[redacted]										
Phenytoin	9 (9.1)	9 (9.0)	19 (19.0)	25 (24.8)	24 (24.5)	35 (10.8)	11 (10.2)	98 (38.9)	100 (40.2)	91 (35.1)
[redacted]										
Topiramate	31 (31.3)	28 (28.0)	24 (24.0)	22 (21.8)	17 (17.3)	76 (23.5)	29 (26.9)	97 (38.5)	108 (43.4)	99 (38.2)
Valproic acid	24 (24.2)	18 (18.0)	28 (28.0)	25 (24.8)	25 (25.5)	82 (25.4)	27 (25.0)	117 (46.4)	127 (51.0)	133 (51.0)
[redacted]										

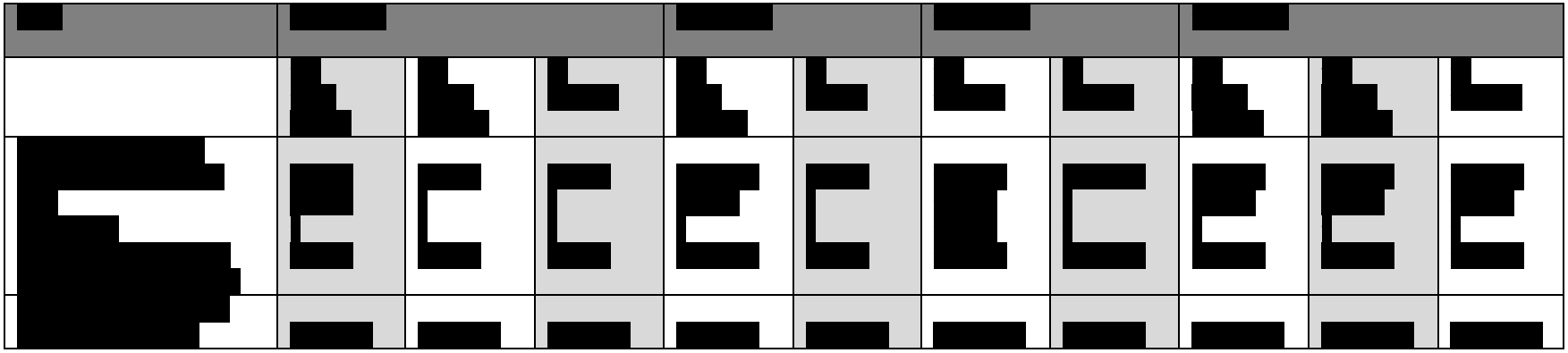
AED = antiepileptic drug; BRV = brivaracetam; ITT = intention to treat; NR = not reported; PL = placebo; POS = partial-onset seizure.
[a] History includes AED use up to five years prior to baseline.
[b] For Study 1358 the summary is in at least 10% of all patients.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 8: HISTORY OF VAGAL NERVE STIMULATION AT STUDY ENTRY (ITT POPULATION OR ITT POS POPULATION)



ITT = intention to treat; POS = partial-onset seizure; VNS = vagal nerve stimulation.
[a] Studies 1252, 1253, and 1254 did not collect information on the status of VNS (i.e., active or not active). For these studies, patients with medical history indicating prior VNS implantation are assumed to be active VNS unless they also had medical history of VNS removal, in which case they are included in the no-VNS group. According to the manufacturer, the data are based on data from the Clinical Study Reports as well as pooled data from the long-term follow-up studies, which provided additional information regarding prior VNS surgery.
Source: UCB Canada response to request for additional information.[28]

TABLE 9: HISTORY OF SURGICAL PROCEDURES AT STUDY ENTRY (ITT POPULATION OR ITT POS POPULATION)



ITT = intention to treat; POS = partial-onset seizure.
Source: UCB Canada response to request for additional information.[29]

TABLE 10: SUMMARY OF CONCOMITANT ANTIEPILEPTIC DRUG USE DURING BASELINE (BY AT LEAST 3% OF OVERALL PATIENTS)[a] (ITT POPULATION OR ITT POS POPULATION)

Number of Patients With a History of at Least 1 AED, n (%)	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 98)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
Patients with ≥ 1 AED, n (%)	99 (100)	100 (100)	100 (100)	101 (100)	97 (99.0)	323 (100)	108 (100)	252 (100.0)	249 (100.0)	259 (100.0)
Carbamazepine	48 (48.5)	40 (40.0)	42 (42.0)	38 (37.6)	44 (44.9)	156 (48.3)	52 (48.1)	94 (37.3)	93 (37.3)	96 (37.1)
[redacted]										
Lacosamide	NR	NR	NR	NR	NR	NR	NR	34 (13.5)	38 (15.3)	36 (13.9)
Lamotrigine	25 (25.3)	20 (20.0)	22 (22.0)	25 (24.8)	29 (29.6)	80 (24.8)	31 (28.7)	69 (27.4)	61 (24.5)	67 (25.9)
Levetiracetam	20 (20.2)	20 (20.0)	18 (18.0)	19 (18.8)	19 (19.4)	61 (18.9)	22 (20.4)	NR	NR	NR
Oxcarbazepine	15 (15.2)	22 (22.0)	22 (22.0)	10 (9.9)	10 (10.2)	43 (13.3)	14 (13.0)	38 (15.1)	50 (20.1)	32 (12.4)
[redacted]										
Phenytoin			10 (10.0)	19 (18.8)						
Topiramate						86 (26.6)	24 (22.2)	38 (15.1)	28 (11.2)	48 (18.5)
Valproic acid	28 (28.3)	28 (28.0)	17 (17.0)	19 (18.8)	15 (15.3)	103 (31.9)	33 (30.6)	58 (23.0)	48 (19.3)	60 (23.2)
[redacted]										

AED = antiepileptic drug; BRV = brivaracetam; ITT = intention to treat; NR = not reported; PL = placebo; POS = partial-onset seizure.

[a] For Study 1358, the summary includes concomitant AED use by at least 5% of all patients.

Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

3.2.3 Interventions

In all four trials, the intervention was brivaracetam oral tablets (i.e., 5 mg/day to 200 mg/day in two divided doses depending upon the individual trial). As previously stated, only results pertaining to the Health Canada–approved doses for brivaracetam are reported in this review (i.e., 50 mg/day to 200 mg/day). In studies 1252, 1253, and 1358, patients were randomized to the full dose of brivaracetam or matching placebo without an up-titration phase. In Study 1254, during the dose-finding period, patients started on brivaracetam 20 mg/day or matching placebo and then had the dose escalated to the next level (brivaracetam 50 mg/day, 100 mg/day, or 150 mg/day or matching placebo), based on the investigator's assessment of efficacy and tolerability. At the end of the dose-finding period, patients were maintained on the final dose during the maintenance period. In studies 1252, 1253, and 1254, during the treatment period, the dose could be reduced using a fallback option as follows: brivaracetam 150 mg/day to 100 mg/day, brivaracetam 100 mg/day to 50 mg/day, brivaracetam 50 mg/day to 20 mg/day, brivaracetam 20 mg/day to 5 mg/day or placebo, brivaracetam 5 mg/day to placebo, or from placebo to placebo. The fallback option could be exercised only once and, once it had occurred, the dose was kept stable for the rest of the treatment period. The comparator in all four trials was matched oral placebo tablets.

Patients were permitted to be on at least one, but not more than two (Studies 1252, 1253, and 1358) or three (Study 1254), concomitant AEDs. Provided patients were at a stable dose for at least one month (or three months for phenobarbital or primidone) prior to the first visit, and kept stable during the entire study period, the following concomitant AEDs were allowed during the study: carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproic acid, and zonisamide. Prohibited AEDs included felbamate (unless used continuously for more than 18 months before the first visit) and vigabatrin.

Benzodiazepines were considered concomitant AEDs if taken more than once a week, for any indication. Vagal nerve stimulation was allowed if it had been implanted at least nine months prior to entering the study, and if was stable for one month prior to the first study visit and was kept stable during the entire study period.

3.2.4 Outcomes

The primary efficacy outcome was POS (type 1) frequency per week (Studies 1252 and 1253) or per 28 days (Study 1358). In Study 1254, the primary outcome was safety and tolerability; however, the key secondary outcome (or primary efficacy outcome) was the POS (type 1) frequency per week. Other measures of seizure reduction were the seizure-freedom rate (i.e., the proportion of patients who were free of all types of seizures [type 1, 2, and 3]), 50% responder rate (i.e., the proportion of patients with ≥ 50% reduction in POS frequency per week), and the per cent reduction or categorized per cent reduction in POS (type 1) frequency over the treatment period. A 50% reduction in POS frequency was considered to be clinically meaningful, according to the clinical expert consulted for this review. To record seizure frequency, patients filled in a daily record card that was returned at each study visit. The investigator assessed the seizures according to the International League Against Epilepsy codes and recorded the seizure types and frequency on the case report form.

For Study 1358, the primary efficacy outcome for the United States was the per cent reduction in POS (type 1) frequency over placebo based on analysis of covariance. The primary efficacy outcome for the European Union was the 50% responder rate based on per cent reduction in POS (type 1) frequency

from baseline to the end of the 12-week treatment period. [redacted][17]

[redacted] As detailed in Appendix 5: Validity of Outcome Measures, the Patient-Weighted Quality of Life in Epilepsy Inventory-31 (QOLIE-31-P) is an adaptation of the original QOLIE-31 instrument.[30] Scoring requires the conversion of raw data to a scale of 0 to 100 for each sub-scale, with higher scores reflecting higher health-related quality of life (HRQoL), and lower scores reflecting worse HRQoL. The maximum total score is 100 per sub-scale and total score.[30] No information on the validity and minimal clinically important difference (MCID) of the QOLIE-31-P in patients with epilepsy was identified. The MCID of the original QOLIE-31 instrument using various methodologies is reported to range from 4.73 to 11.8.[31,32]

The EuroQol 5-Dimensions Questionnaire (EQ-5D) is a generic HRQoL instrument that has been applied to a wide range of health conditions and treatments.[33,34] [redacted] The EQ-5D visual analogue scale (VAS) comprises a 20 cm scale with end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state." Respondents rate their own health on that day using the EQ-VAS. Thus, lower scores indicate poorer health and higher scores, better health. As per Appendix 5, the validity and MCID of the EQ-5D have not been formally assessed in patients with epilepsy.

[redacted] The Hospital Anxiety and Depression Scale (HADS) is an instrument that assesses the presence and severity of anxiety and depressed mood. It consists of 14 items that are scored on a four-point severity scale ranging from 0 to 3. A score per dimension (anxiety, depression) can range from 0 to 21, with higher scores indicating higher depression/anxiety. A score of 0 to 7 for either the anxiety or depression sub-scale is suggested as being in the normal range, a score of 8 to 10 suggests the presence of the respective state, and a score of 11 or higher indicates the probable presence of the mood disorder.[35] The HADS depression sub-scale was validated and found to be a reliable instrument to screen for depressive disorders in patients with epilepsy.[36] No MCID has been identified for the HADS in epilepsy patients.

[redacted] The Patient Global Evaluation Scale (P-GES) and Investigator Global Evaluation Scale (I-GES) both use a seven-point scale, with the start of the study as the reference time point. The patient completes the P-GES by answering the following question: "Overall, has there been a change in your seizures since the start of the study drug?" The investigator completes the I-GES by responding to the following: "Assess the overall change in the severity of patient's illness, compared to the start of study drug." Numerical values are assigned to each response as follows: 1 = marked worsening, 2 = moderate worsening, 3 = slight worsening, 4 = no change, 5 = slight improvement, 6 = moderate improvement, and 7 = marked improvement. As per Appendix 5, no information on the validity and the MCID of the P-GES and I-GES in patients with epilepsy was identified.

[redacted]

Safety variables included AEs, laboratory tests (e.g., blood chemistry, hematology, urinalysis, etc.), electrocardiogram, vital signs, body weight, physical examination, neurological examination, mental status, and psychiatric status.

3.2.5 Statistical Analysis

In all four included trials, sample size considerations were based on the primary efficacy variable. For studies 1252 and 1253, an estimate of the standard deviation for seizure frequency, based on data from phase 2 trials, was [redacted]. With a power of 90% and a two-sided level of significance of 5%, 87 patients per group were required to detect a treatment difference of –0.223 in log-transformed seizure frequency per week between brivaracetam and placebo. The treatment difference of –0.223 in log-transformed seizure frequency corresponds to a 20% reduction over placebo. Since the various doses of brivaracetam were tested hierarchically at the 5% level of significance, power was lost for lower doses. To compensate for this loss in power, 100 patients per group were included in the trials.

In Study 1254, with a significance level of 5%, a two-sided test with 376 patients randomized in a 3:1 (brivaracetam:placebo) ratio yielded 80% power to detect a difference of –0.174 on the natural log-transformed scale, with an assumed standard deviation of 0.50. Using an approximate formula, this corresponds to a per cent reduction from placebo of 16%. Since up to 20% of patients had generalized epilepsy, in order to secure 376 patients suffering from localization-related (POS) epilepsy, the number of 376 patients had to be adjusted by 1.25. Therefore, the total number of patients that needed to be randomized was 470.

In Study 1358, the sample size was based on the 50% responder rate outcomes, since this yielded the larger sample size across primary outcomes (i.e., the primary outcomes for the United States and European Union differed). Therefore, based on a 50% responder outcome, 231 analyzable patients per treatment group provided 90% power to detect a 15% difference between brivaracetam and placebo at the 0.025 significance level, assuming responder rates of 35% and 20%, respectively. The actual power for the United States' outcome was 94% based on this sample size. To account for patients who may not have qualified for the primary analysis, 240 patients were randomized in each group, for a total of 720 patients across all three treatment groups.

For all studies, summary statistics were provided for all efficacy, safety, and baseline/demographic variables. Summary statistics consisted of frequency tables for categorical variables. For continuous variables, descriptive statistics (e.g., number of available observations, mean, median, standard deviation, minimum, maximum) were tabulated.

The primary efficacy variable (i.e., POS [type 1] frequency per week or per 28 days) was analyzed according to an analysis of covariance model, including treatment and stratification data (i.e., country/region and concomitant levetiracetam use) as factors, and the log-transformed baseline seizure frequency per week or per 28 days as covariate. In Study 1358, an additional stratification factor was the number of AEDs previously used (≤ 2 or > 2) and discontinued prior to study entry. The primary efficacy variable was log-transformed prior to analysis, as prior data (including results from phase 2 studies) showed this transformation was appropriate to approximate normally distributed data.

In studies 1252, 1253, and 1254, brivaracetam dose groups were tested at the 5% significance level compared with placebo, according to a predefined hierarchical sequentially rejective testing procedure. The highest brivaracetam dose was tested versus placebo and, if the comparison was not statistically significant, the procedure stopped and no groups were declared different from placebo. If the comparison was statistically significant, then that brivaracetam dose group was considered different from placebo and the procedure continued with the next-lower brivaracetam dose and so on. The procedure controlled the overall type 1 error rate at 0.05.

In Study 1358, statistical testing was based on the comparison of each brivaracetam group with placebo, with control of the overall type 1 error rate based on the Hochberg procedure. The Hochberg procedure does not require a pre-specified order of testing for brivaracetam dose groups versus placebo. In a setting with a comparison of two active treatment groups to placebo, the Hochberg procedure was applied by first testing the brivaracetam group with the larger *P* value with testing at the 0.05 level. If statistical significance was achieved at this step, then the study was positive and both brivaracetam dose groups were declared statistically different from placebo. If the largest *P* value was not significant at the 0.05 level, then the Hochberg procedure steps to the smaller *P* value with testing at the 0.025 level. If statistical significance was achieved at this step, then the study was positive and the brivaracetam dose group associated with the smaller *P* value was declared statistically different from placebo. If the smaller *P* value was not significant at the 0.025 level, then neither brivaracetam dose group was statistically different from placebo, and the study was not positive.

[redacted]

For the comparison of POS responder rate for each brivaracetam dose and placebo, a logistic-regression model was used, including treatment as a factor and the log-transformed baseline seizure frequency per week as a covariate. An estimate of the treatment odds ratio (OR) and 95% confidence interval (CI) was derived from this model. The per cent reduction from baseline for POS frequency was analyzed by applying the Wilcoxon-Mann-Whitney test to compare brivaracetam dose and placebo. The categorized response in POS frequency per week for brivaracetam compared with placebo was tested using the Cochran-Mantel-Haenszel test. Patients who had no (zero) baseline seizure frequency per week were categorized in the "under –25%" category. Seizure freedom rates for each brivaracetam dose were compared with placebo using the Fisher's exact test. [redacted]

a) Analysis Populations

The analysis populations included the following.

Intention-to-Treat Population

This was defined as all randomized patients who received at least one dose of study medication. The primary efficacy analysis and all secondary efficacy analyses were performed on the ITT population and patients were analyzed according to the randomized treatment.

In Study 1253, a modified ITT population was used that excluded four randomized patients (i.e., three patients from a clinical site [site 404] with serious and persistent non-compliance issues, and one patient identified as an outlier due to seizure frequency [> 100 per day] and uncertainty regarding seizure type). The primary and secondary efficacy analyses in Study 1253 were carried out using the mITT population.

In Study 1254, two ITT populations were identified due to the mixed patient population: the localization-related epilepsy (POS) ITT population and the generalized epilepsy ITT population. The primary analysis and all secondary analyses were performed on the ITT POS population.

Per-protocol Population

This was a subset of the ITT populations consisting of patients who had no major protocol deviations affecting the primary efficacy variable, as confirmed during a pre-analysis review meeting prior to the unblinding of the data. A primary efficacy analysis of the per-protocol population was also planned if more than 10% of the ITT population was totally or partially excluded from the per-protocol population.

Safety Population
This comprised the same set of patients as the ITT population.

3.3 Patient Disposition

Across the four studies, discontinuations ranged from 5.1% to 11.4% in individual treatment groups as detailed in Table 11. Overall, the primary reason for discontinuation was AEs, which ranged from 2.0% to 8.3% in individual treatment groups. Details of screening failures are provided in this section by individual study. The main reasons for screening failures in all four studies were ineligibility and withdrawal of consent (not related to AEs) for personal reasons.

3.3.1 Study 1252

A total of 486 patients were screened, and of these, 87 (17.9%) were screening failures. One patient randomized to brivaracetam 50 mg/day was dispensed the drug, but died prior to consuming any study drug and thus was excluded from the ITT population. Across treatment groups, 82.8% to 88.0% of patients completed the study and entered the LTFU, whereas 4.0% to 6.1% completed the study but did not enter the LTFU; rather, they completed the down-titration period and safety follow-up.

3.3.2 Study 1253

A total of 509 patients were screened and, of these, 109 (21.4%) were screening failures. Four patients were excluded from the ITT population. One patient (in the brivaracetam 5 mg/day group) was excluded for failing to take the study drug and three patients randomized to brivaracetam 5 mg/day, placebo and brivaracetam 50 mg/day, respectively, were randomized in error and were not dispensed the study drug. Across treatment groups, 87.8% to 90.1% of patients completed the study and entered the LTFU, whereas 2.0% to 7.1% completed the study but did not enter the LTFU; rather, they completed the down-titration period and safety follow-up.

3.3.3 Study 1254

A total of 543 patients were screened and of these, 63 (11.6%) were screening failures. No patients were excluded from the ITT population. Across treatment groups, 86.1% to 91.7% of patients completed the study and entered the LTFU, whereas 2.5% to 3.9% completed the study but did not enter the LTFU; rather, they completed the down-titration period and safety follow-up. The disposition of patients with POS was similar to the overall population.

3.3.4 Study 1358

A total of 1,045 patients were screened and of these, 277 (26.5%) were screening failures. No patients were excluded from the ITT population. Across treatment groups, 86.2% to 90.1% of patients completed the study and entered the LTFU, whereas 2.0% to 3.4% completed the study but did not enter the LTFU; rather, they completed the down-titration period and safety follow-up.

3.4 Exposure to Study Treatments

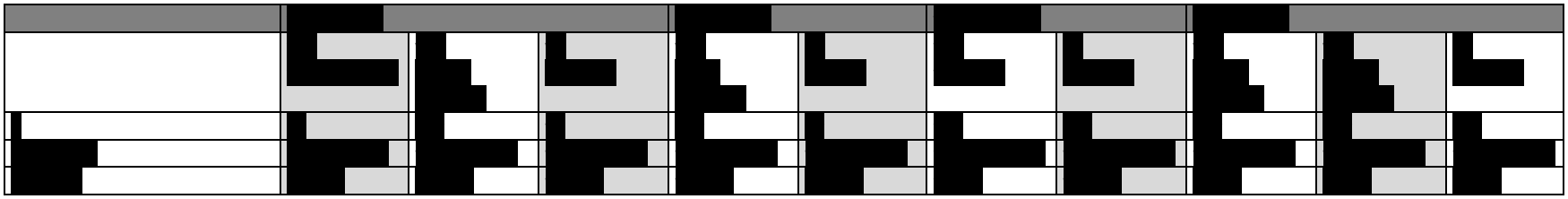
[redacted]

TABLE 11: PATIENT DISPOSITION

	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg	BRV 100 mg	PL	BRV 50 mg	PL	BRV	PL	BRV 100 mg	BRV 200 mg	PL
Screened, N[a]	486			509		543		1045		
Randomized, n (%)	100	100	100	102	99	359	121	254	251	263
ITT population, N	99	100	100	101	98	359	121	252	249	259
Completed and LTFU, n (%)	82 (82.8)	88 (88.0)	88 (88.0)	91 (90.1)	86 (87.8)	309 (86.1)	111 (91.7)	219 (86.2)	220 (87.6)	237 (90.1)
Completed and no LTFU, n (%)	6 (6.1)	6 (6.0)	4 (4.0)	2 (2.0)	7 (7.1)	14 (3.9)	3 (2.5)	6 (2.4)	5 (2.0)	9 (3.4)
Discontinued, n (%)	11 (11.1)	6 (6.0)	8 (8.0)	8 (7.9)	5 (5.1)	36 (10.0)	10 (8.3)	29 (11.4)	26 (10.4)	17 (6.5)
AE	6 (6.1)	5 (5.0)	4 (4.0)	6 (5.9)	2 (2.0)	23 (6.4)	7 (5.8)	21 (8.3)	17 (6.8)	10 (3.8)
Lack of efficacy	0	0	0	0	1 (1.0)	5 (1.4)	1 (0.8)	1 (0.4)	0	1 (0.4)
Lost to follow-up	1 (1.0)	0	2 (2.0)	1 (1.0)	0	2 (0.6)	0	1 (0.4)	3 (1.2)	0
Withdrawal for personal reasons	1 (1.0)	0	2(2.0)	1 (1.0)	0	4 (1.1)	1 (0.8)	2 (0.8)	4 (1.6)	2 (0.8)
Other	3 (3.0)	1 (1.0)	0	0	2 (2.0)	2 (0.6)	1 (0.8)	4 (1.6)	2 (0.8)	4 (1.5)
Safety population, N	99	100	100	101	98	359	121	253	250	261
PP population, n (%)	86 (86.9)	90 (90.0)	85 (85.0)	91 (90.1)	87 (88.8)	318 (88.6)	113 (93.4)	232 (91.3)	237 (94.4)	245 (93.2)

AE = adverse event; AED = antiepileptic drug; BRV = brivaracetam; ITT = intention to treat; LTFU = long-term follow-up; PL = placebo; PP = per protocol.
[a] Number of screened patients includes patients randomized to other treatment groups of non-approved doses not included in this report.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 12: OVERALL DURATION OF EXPOSURE[a] TO STUDY DRUG (DAYS) (SAFETY POPULATION)



[a] Defined as the number of days between the first intake of BRV and the last intake of BRV during the relevant period. Unscheduled gaps are counted in the duration.

Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

3.5 Critical Appraisal

3.5.1 Internal Validity

All four included trials were prospective, multi-centre, double-blind, randomized, placebo-controlled trials that demonstrated a number of methodological strengths. Treatment was assigned via an Interactive Voice Response System using a central randomization method with stratification as detailed in Section 3.2.1. Allocation concealment methods were appropriate, and matched placebo tablets were used to ensure blinding during the treatment phases. Baseline demographic and disease characteristics were generally well balanced across treatment groups, with no significant baseline imbalances expected to have affected the study outcomes. Discontinuation rates were low in all trials and similar between treatment groups; however, a consideration is that the duration of treatment was only 12 to 16 weeks.

The primary efficacy outcome in all the trials was the reduction in POS frequency; to record seizure frequency, patients filled in a daily record card that was returned at each study visit. Although this is a standard method of reporting seizure frequency related outcomes in clinical trials of AEDs, self-reporting is subject to individual variability in reporting accuracy and completion.

[redacted]

Although the analysis populations in studies 1252, 1254, and 1358 were identified as being ITT populations, due to the definition used (i.e., all randomized patients who received at least one dose of study medication), the study populations are technically a modified ITT population due to the requirement to have had at least one dose of study medication. Nonetheless, the number of randomized patients and patients included in the ITT populations does not differ by more than 2% in any of the trials, so it is unlikely this would have had any effect on treatment outcomes.

With the exception of the three selected scores of the QOLIE-31-P in studies 1252, 1253, and 1254, all secondary outcomes were tested without adjustment for multiplicity. Due to the potential risk of type 1 error, the results of the secondary outcomes should be interpreted with caution.

3.5.2 External Validity

According to the clinical expert consulted for this review, the baseline demographic and disease characteristics of the patients enrolled in the four trials are representative of patients with refractory epilepsy encountered in clinical practice in Canada. Although the pattern of prior AED use was also what would be expected in Canada generally, it was noted that no reported use of clobazam by patients in studies 1252, 1253, and 1254 is not in line with what would be expected in Canada. [redacted]

As detailed in Table 6, across the treatment groups, from 10.6% to 47.8% of patients had tried five or more AEDs in the past five years prior to entry into the included trials. Due to the large number of prior AEDs tried by these patients, it is likely their epilepsy was more refractory and therefore more difficult to treat than would be found in a less treatment-experienced patient population. This may have an impact on the generalizability of the trial results to patients who have not had as extensive background use of other AEDs and whose epilepsy may not be considered as refractory to treatment.

The included trials enrolled mainly Caucasian patients, followed by Asian patients, which may affect the generalizability of the trial results to a more heterogeneous population with mixed ethnicity, such as the Canadian population. In addition, the results of the trials would not be generalizable to a pediatric or older geriatric population, as these patients were not represented in the trials.

All four trials included stratification based on levetiracetam use (i.e., studies 1252, 1253, and 1254 stratified on concomitant levetiracetam use; Study 1358 stratified based on prior levetiracetam use as the use of levetiracetam ≤ 90 days prior to study entry was an exclusion criterion). This approach has direct clinical relevance because, due to the presumed similar mechanism of action of brivaracetam and levetiracetam (i.e., binding to the SV2A protein), it is important to determine whether or not patients who had previously been uncontrolled on levetiracetam, or a combination of AEDs including levetiracetam, would benefit from brivaracetam. In the included trials, there was a large proportion of patients who used levetiracetam prior to study entry, with the main reason for discontinuation of levetiracetam being due to lack of efficacy. In addition, in studies 1252, 1253, and 1254, approximately 20% of patients (regardless of treatment) used concomitant levetiracetam during baseline. An analysis of the per cent reduction in POS frequency by concomitant levetiracetam use in these studies showed that for patients who received concomitant levetiracetam, the differences between brivaracetam and placebo were not statistically significant, whereas in patients who did not receive concomitant levetiracetam, the differences between brivaracetam and placebo were statistically significant for all comparisons. Study 1358 also included pre-specified subgroup analyses by levetiracetam status; however, no statistical comparisons between subgroups were conducted.

Studies 1252, 1253, and 1358 did not include an up-titration phase, as patients were randomized directly to the full, fixed dose of brivaracetam or matching placebo. Patients remained on the full dose unless they had to exercise the dosing fallback option. In contrast, Study 1254 had a flexible dosing design. This may have complicated the efficacy assessment, because patients who responded well to treatment may have remained on lower brivaracetam doses, whereas in the fixed-dose trials, patients could have been on brivaracetam doses that were higher than required. Study 1254 also had baseline period of only four weeks, whereas the other trials had eight-week baseline periods. It is possible that the shorter baseline period may have led to increased variability in responses, although the treatment period (comprising both the dose-finding and maintenance phases), was longer than the other trials (i.e., 16 weeks versus 12 weeks). There is also a possibility that in Study 1254, due to up-titration relying on the investigator's assessment of efficacy and tolerability, patients on placebo might have been identifiable due to their need for up-titration, thus potentially compromising the blinding in the study.

All four trials were placebo-controlled, as no active-controlled trials of brivaracetam in patients with uncontrolled POS epilepsy were identified. The use of placebo as a comparator in this refractory patient population does not reflect clinical practice. Such patients would most likely be considered for adjunctive therapy with newer AEDs such as perampanel, lacosamide, or eslicarbazepine. An active comparator trial against one or more of these drugs would have permitted an assessment of the relative benefit-risk profile of brivaracetam compared with another AED currently listed for the treatment of

refractory epilepsy in the same target patient population. Of note, the manufacturer did conduct a network meta-analysis of brivaracetam with third-generation AEDs used as adjunctive therapy in patients with refractory POS, including perampanel, lacosamide, and eslicarbazepine. This is summarized in Appendix 7: Summary of Indirect Treatment Comparisons.

The choice of the primary efficacy outcome (i.e., reduction in POS frequency from baseline per week or per 28 days) was clinically relevant, as were the majority of secondary outcomes related to reduction in seizure frequency or HRQoL. Interpretation of the results, however, was limited by the lack of validation of many of the outcomes in patients with epilepsy, as well as the limited identification of MCIDs for the outcomes. The outcomes of the EQ-5D and health care resource utilization parameters could have provided useful information; however, [redacted]

While the duration of the treatment phases (12 to 16 weeks) in the included trials was sufficient to show early efficacy of brivaracetam, it is inadequate to characterize long-term efficacy and safety. The clinical expert advised this is not unique among trials of AEDs, as the treatment phase in most AED trials is short, even though these therapies are intended for chronic use. Pooled long-term follow-up data from patients who entered the LTFU phases of the included trials are summarized in Appendix 6.

3.6 Efficacy

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

3.6.1 Seizure-Free Status

In all four included trials, seizure-free status was included as a secondary outcome (Table 14). Over the treatment periods, the proportion of patients who were seizure-free was small in all trials, ranging from 0% to 5.2% among the brivaracetam groups compared with 0% to 0.8% among the placebo groups. In Study 1358, a larger proportion of patients treated with brivaracetam 100 mg/day (5.2%) and brivaracetam 200 mg/day (4.0%) were seizure-free compared with placebo-treated patients (0.8%). The differences were statistically significant for both brivaracetam doses relative to placebo. Differences in the proportion of seizure-free patients treated with brivaracetam 50 mg/day to 150 mg/day in the other trials were not statistically significantly different from placebo.

3.6.2 Health-Related Quality of Life

[redacted]

[redacted]

[redacted]

3.6.3 Change in Seizure Frequency

The results for the change from baseline to end of treatment in the POS frequency per week in studies 1252, 1253, and 1254, and per 28 days in Study 1358, are provided in Table 17 and Table 18. At baseline, the median POS frequency per week was similar between all treatment groups, ranging from 1.80 to 2.85 (or 9.3 to 10.0 per 28 days in Study 1358). At the end of treatment, the median POS frequency per week ranged from 1.26 to 1.74 for brivaracetam (or 6.8 to 6.9 per 28 days in Study 1358), compared with 1.75 to 2.15 per week (or 9.2 per 28 days in Study 1358) for placebo. The treatment difference in POS frequency per week was statistically significant for brivaracetam 100 mg/day in Study 1252 and for brivaracetam 50 mg/day in Study 1253, and per 28 days for both brivaracetam 100 mg/day and 200 mg/day in Study 1358.

The median per cent reduction in POS frequency over the treatment period ranged from 26.83% to 37.2% with brivaracetam and 17.03% to 18.93% with placebo (Table 20). The median per cent reduction with brivaracetam over placebo ranged from 9.07% to 19.35% for brivaracetam, and the results were statistically significant for brivaracetam 100 mg/day (–19.35%) in Study 1252, brivaracetam 50 mg/day (–15.69%) in Study 1253, and for both brivaracetam 100 mg/day (–15.8%) and 200 mg/day (–18.1%) in Study 1358. There did not appear to be a dose response demonstrated for brivaracetam.

The median per cent reduction in POS frequency by the stratification factor of concomitant levetiracetam use over the treatment period was investigated for studies 1252, 1253, and 1254 (Table 21). In patients with concomitant levetiracetam use at study entry, the median per cent reduction in POS frequency over the treatment period ranged from 3.16% to 15.93% with brivaracetam compared with 14.18% to 22.11% with placebo. None of the comparisons of the median per cent reduction with brivaracetam over placebo were statistically significant. In patients with no concomitant levetiracetam at study entry, the median per cent reduction in POS frequency over the treatment period ranged from 31.51% to 38.31% with brivaracetam compared with 15.70% to 19.19% with placebo. All comparisons of the median per cent reduction with brivaracetam over placebo were statistically significant.

Pre-specified subgroup analyses of the per cent reduction over placebo in POS frequency per 28 days by levetiracetam status and by number of previous AEDs (≤ 2 or > 2) was conducted in Study 1358. For patients who never used levetiracetam, the per cent reduction in 28-day POS frequency over placebo was 29.5% with brivaracetam 100 mg/day, and 27.1% with brivaracetam 200 mg/day. For patients with prior levetiracetam use, the per cent reduction with brivaracetam over placebo was 15.8% with

brivaracetam 100 mg/day, and 19.4% with brivaracetam 200 mg/day. The per cent reduction with brivaracetam over placebo in the 28-day–adjusted POS frequency for patients who used ≤ 2 previous AEDs was 27.1% with brivaracetam 100 mg/day, and 27.3% with brivaracetam 200 mg/day. In comparison, for patients who used > 2 previous AEDs, the per cent reduction over placebo was 20.2% with brivaracetam 100 mg/day, and 21.7% with brivaracetam 200 mg/day. Only descriptive statistics were reported and no statistical comparisons were made between either of the subgroups.

The results of the categorized response in POS seizure frequency over the treatment period are provided in Table 22. Patients who had no (zero) baseline seizure frequency per week were categorized in the "under –25%" category. For all studies, the category with the largest proportion of patients across treatment groups was the –25% to 25% group, which included from 28.6% to 33.3% of patients in the brivaracetam groups compared with 40.5% to 44.8% of placebo patients. Overall, the proportion of patients who achieved 75% or better response ranged from 10.1% to 19.9% in the brivaracetam groups compared with 2.8% to 8.0% in the placebo groups. When the proportions of patients in each category were compared across treatment groups, the differences were statistically significant for all comparisons of brivaracetam versus placebo in all the trials, with the exception of the brivaracetam 50 mg/day group in Study 1252.

3.6.4 Other Efficacy Outcomes

a) Responder Rates

Across the trials, the 50% responder rates ranged from 27.3% to 38.9% with brivaracetam compared with 16.7% to 21.6% with placebo (Table 19). The OR for the comparison of brivaracetam versus placebo was statistically significant for brivaracetam 100 mg/day in Study 1252 (OR = 2.13; 95% CI, 1.11 to 4.10), brivaracetam 50 mg/day (OR = 2.51; 95% CI, 1.27 to 4.96) in Study 1253, the combined brivaracetam doses (OR = 2.18; 95% CI, 1.24 to 3.81) in Study 1254 and both brivaracetam doses of 100 mg/day (OR = 2.39; 95% CI, 1.6 to 3.6) and 200 mg/day (OR = 2.19; 95% CI, 1.5 to 3.3) in Study 1358.

In Study 1358, pre-specified subgroup analyses of the 50% responder outcomes were conducted by levetiracetam status and by number of previous AEDs (≤ 2 or > 2). [redacted]

b) Patient or Clinician Global Impression of Change

[redacted]

[redacted]

c) Patient Adherence to Treatment

Across all the trials, patient compliance with treatment was high. Over 92% of patients in the brivaracetam groups and 93% of patients in the placebo groups had between 80% to 120% compliance with the study drug (Table 26). As per Table 11, discontinuation rates were low, ranging from 5.1% to 11.4% in individual treatment groups across the included trials.

d) Health Care Resource Utilization

[redacted]. The corresponding proportions of placebo-treated patients were 3.7% to 6.5% and 1.0% to 7.3%.

No data for the reduction in use of concomitant AEDs was reported for the included trials.

3.7 Harms

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

3.7.1 Adverse Events

Across the four included trials, approximately 63% to 75% of patients in the brivaracetam groups compared with 53% to 65% of patients in the placebo groups experienced at least one treatment-emergent adverse event (TEAE) as detailed in Table 13. Overall, the most frequently reported TEAEs were somnolence, dizziness, fatigue and headache. Somnolence occurred more frequently in the brivaracetam groups (6.1% to 19.4%) compared with the placebo groups (4.1% to 7.7%). Similarly, dizziness (5.0% to 15.8%) and fatigue (4.0% to 11.6%) occurred more frequently with brivaracetam compared with placebo (5.0% to 9.2% and 2.0% to 4.1%, respectively). Headache was reported in a similar proportion of brivaracetam (6.7% to 18.2%) and placebo (8.4% to 19.8%) patients. The majority of TEAEs were mild to moderate in intensity.

3.7.2 Serious Adverse Events

The incidence of serious adverse events (SAEs) across the four trials was low and similar across treatment groups (Table 13). The proportion of patients with at least one SAE ranged from 2.0% to 5.3% among the brivaracetam groups compared with 0% to 7.4% among the placebo groups of the included trials. [redacted]

3.7.3 Withdrawals Due to Adverse Events

Withdrawals due to adverse events (WDAEs) were also low and similar across treatment groups (Table 13). The proportion of patients with WDAEs ranged from 5.0% to 8.3% in the brivaracetam groups compared 2.0% to 5.0% in the placebo groups of the included trials. The most common reason for WDAEs in both the brivaracetam and placebo treatment groups was convulsion, which occurred in 0.4% to 2.0% of patients in the brivaracetam groups and 0.4% to 1.0% of patients in the placebo groups.

3.7.4 Mortality

There were five deaths reported in the recommended brivaracetam dose or placebo groups during the treatment periods of the four included trials. Of these, only one death was considered to be possibly related to the study drug; it was due to brain hypoxia in the brivaracetam 50 mg/day group of Study 1253. The other causes of death (i.e., sepsis in one patient receiving placebo in Study 1252, drowning of one patient in Study 1254, and two deaths due to sudden unexplained death in epilepsy and unknown cause, respectively, in Study 1358) were unlikely or not considered to be related to the study drug.

3.7.5 Notable Harms

[redacted]

TABLE 13: HARMS DURING TREATMENT PERIOD (SAFETY POPULATION)

	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 98)	BRV (N = 359)	PL (N = 121)	BRV 100 mg (N = 253)	BRV 200 mg (N = 250)	PL (N = 261)
Number of deaths, n (%)[a]	0	0	1 (1.0)	1 (1.0)	0	1 (0.3)	0	0	2(0.8)	0
Patients with ≥ 1 TEAE, n (%)	62 (62.6)	63 (63.0)	53 (53.0)	76 (75.2)	69 (70.4)	237 (66.0)	79 (65.3)	173 (68.4)	167 (66.8)	155 (59.4)
Most common TEAEs (≥ 5% in any treatment group), n (%)										
Back pain	NR	NR	NR	NR	NR	11 (3.1)	8 (6.6)	[redacted]	[redacted]	[redacted]
Convulsion	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	18 (5.0)	4 (3.3)	[redacted]	[redacted]	[redacted]
Diarrhea	0	1 (1.0)	1 (1.0)	6 (5.9)	2 (2.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Dizziness	7 (7.1)	5 (5.0)	5 (5.0)	16 (15.8)	9 (9.2)	31 (8.6)	7 (5.8)	26 (10.3)	36 (14.4)	13 (5.0)
Fatigue	4 (4.0)	8 (8.0)	2 (2.0)	10 (9.9)	2 (2.0)	28 (7.8)	5 (4.1)	19 (7.5)	29 (11.6)	10 (3.8)
Headache	18 (18.2)	9 (9.0)	9 (9.0)	13 (12.9)	14 (14.3)	51 (14.2)	24 (19.8)	17 (6.7)	20 (8.0)	22 (8.4)
Influenza	NR	NR	NR	4 (4.0)	1 (1.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Insomnia	[redacted]	[redacted]	[redacted]	7 (6.9)	2 (2.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Irritability	5 (5.1)	1 (1.0)	0	5 (5.0)	2 (2.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Nasopharyngitis	1 (1.0)	2 (2.0)	1 (1.0)	5 (5.0)	1 (1.0)	14 (3.9)	8 (6.6)	10 (4.0)	9 (3.6)	12 (4.6)
Nausea	1 (1.0)	6 (6.0)	4 (4.0)	6 (5.9)	3 (3.1)	20 (5.6)	10 (8.3)	9 (3.6)	9 (3.6)	5 (1.9)
Somnolence	6 (6.1)	8 (8.0)	6 (6.0)	17 (16.8)	7 (7.1)	40 (11.1)	5 (4.1)	49 (19.4)	42 (16.8)	20 (7.7)
URTI	NR	NR	NR	0	4 (4.1)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UTI	NR	NR	NR	1 (1.0)	2 (2.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vertigo	2 (2.0)	8 (8.0)	3 (3.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vomiting	[redacted]	[redacted]	[redacted]	5 (5.0)	1 (1.0)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Patients with ≥ 1 SAE, n (%)	4 (4.0)	2 (2.0)	6 (6.0)	4 (4.0)	0	19 (5.3)	9 (7.4)	8 (3.2)	8 (3.2)	9 (3.4)
Patients with ≥ 1 WDAE, n (%)	5 (5.1)	5 (5.0)	4 (4.0)	6 (5.9)	2 (2.0)	22 (6.1)	6 (5.0)	21 (8.3)	17 (6.8)	10 (3.8)
[redacted]										
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 98)	BRV (N = 359)	PL (N = 121)	BRV 100 mg (N = 253)	BRV 200 mg (N = 250)	PL (N = 261)
[redacted]										
[redacted]										
[redacted]										

BRV = brivaracetam; NR = not reported; PL = placebo; SAE = serious adverse event; SUDEP = sudden unexplained death in epilepsy; TEAE = treatment-emergent adverse event; URTI = upper respiratory tract infection; UTI = urinary tract infection; WDAE = withdrawal due to adverse event.

[a] Causes of death: Study 1252: n = 1 in PL group due to sepsis considered unlikely related to study drug; Study 1253: n = 2; 1 death each in BRV 20 mg/day and 50 mg/day groups. In the BRV 50 mg/day group, cause was due to brain hypoxia considered possibly related to study drug; Study 1254: n = 1 in BRV group due to drowning considered unlikely related to study drug. Study 1358: n = 2 deaths in BRV 200 mg/day group. One death was due to SUDEP and the other due to unknown cause(s), both of which were considered not related to study drug.

[redacted]

Note: An individual patient may have experienced > 1 TEAE, SAE or WDAE. For Study 1254, results are reported for the treatment period (dose-finding and maintenance periods).
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

4. DISCUSSION

4.1 Summary of Available Evidence

Four multi-centre, double-blind, parallel-group, randomized, placebo-controlled, phase 3 trials met the selection criteria for this systematic review. Study 1252 (N = 399), Study 1253 (N = 400), Study 1254 (N = 480), and Study 1358 (N = 768) all investigated the efficacy, safety, and tolerability of brivaracetam given as adjunctive therapy (i.e., added on to a background regimen of one to three AEDs) for the treatment of uncontrolled POS in patients 16 years of age and older. The trials investigated different doses of brivaracetam (5 mg/day to 200 mg/day); however, only results for the Health Canada–approved doses of brivaracetam (50 mg/day to 200 mg/day) are reported in this review. Patients were randomized to brivaracetam or placebo, while remaining on a baseline-fixed AED background regimen. The duration of double-blind treatment was 12 weeks in studies 1252, 1253, and 1358 and 16 weeks (i.e., dose-finding plus maintenance periods) in Study 1254. The primary efficacy outcome for all trials was the change from baseline in POS frequency per week (studies 1252, 1253, and 1254) or per 28 days (Study 1358). With the exception of Study 1254, which was a flexible-dose study, patients were randomized to the full dose of brivaracetam without any up-titration. Pooled results of the ongoing, open-label, LTFU extension phases of the included trials are summarized in Appendix 6: Summary of Other Studies.

Key limitations of the available evidence are the lack of active comparator trials comparing brivaracetam with other clinically relevant comparator AEDs (e.g., perampanel, lacosamide, eslicarbazepine), the lack of validation and MCIDs in patients with epilepsy for the measured outcomes, and the short duration of the treatment for an intervention intended for chronic use.

4.2 Interpretation of Results

4.2.1 Efficacy

The ultimate goal of AED treatment is to achieve seizure-free status with minimal or no AEs. Seizure-free status (seizure types 1, 2, and 3) was evaluated in each of the four included trials; however, in each trial, only a small proportion of patients achieved this outcome and the differences between brivaracetam and placebo were statistically significant only in Study 1358. This trial was the only trial to evaluate the highest recommended dose of brivaracetam (200 mg/day) along with brivaracetam 100 mg/day, which suggests that possibly higher brivaracetam doses are required to achieve this outcome. The results, however, do not support a dose-response relationship for brivaracetam, as 5.2% of patients receiving 100 mg/day compared with 4.0% of patients receiving 200 mg/day achieved seizure freedom. The small proportion of patients who achieved this outcome is not unexpected, as complete freedom from seizures is unlikely in a refractory (i.e., uncontrolled epilepsy despite use of one to three AEDs) patient population such as was enrolled in the included trials.

Seizure freedom was assessed in the pooled analysis of long-term brivaracetam use that is summarized in Appendix 6: Summary of Other Studies. The proportion of patients who were seizure-free remained small over time (3.3% at 60 months). In addition, seizure freedom was an efficacy outcome that was included in both the indirect treatment comparisons (ITCs) that are summarized and critically appraised in Appendix 7: Summary of Indirect Treatment Comparisons. When brivaracetam was compared with eslicarbazepine, lacosamide, perampanel, or levetiracetam, there did not appear to be any statistical differences in seizure-freedom rates between the AEDs.

The primary efficacy outcome across all trials was the reduction in POS frequency from baseline, measured either per week (studies 1252, 1253, and 1254) or per 28 days (Study 1358). Overall, doses of brivaracetam 100 mg/day and 200 mg/day consistently achieved statistically significant reductions in POS frequency compared with placebo, measured as either the median number of POS or the per cent reduction in POS frequency. The magnitude of POS reduction over placebo with brivaracetam ranged from 9.07% to 19.35%, which suggests that although differences compared with placebo were statistically significant, brivaracetam did not demonstrate a clinically important reduction in POS frequency. In addition, there does not appear to be a large dose-response difference between brivaracetam 100 mg/day and 200 mg/day. The lack of dose response has been observed in previous studies of brivaracetam and, at present, it appears there is no clear explanation for the diversity in the dose-response effect.[25] Furthermore, the efficacy of the brivaracetam 50 mg/day dose is also unclear, as in Study 1253 for most outcomes, brivaracetam 50 mg/day achieved statistical significance compared with placebo; however, in Study 1252, this dose consistently failed to reach statistical significance compared with placebo.

Seizure reduction was also measured by the 50% response rate; patients were defined as responders if they were able to achieve at least a 50% reduction in POS (type 1) seizure frequency from baseline to end of treatment. A 50% reduction from baseline in POS was considered to be clinically meaningful, according to the clinical expert consulted for this review. The 50% responder rates ranged from 27.3% to 38.9% with brivaracetam compared with 16.7% to 21.6% with placebo. According to the Health Canada reviewer's report,[5] a 15% difference compared with placebo in the 50% responder rate is typically considered acceptable. As a result, the difference in the brivaracetam and placebo values would suggest the results are clinically meaningful. In the included trials, the mean difference between brivaracetam and placebo in the proportion of patients who were considered to be 50% responders was not reported; rather, ORs and 95% CIs were calculated. The ORs favouring brivaracetam versus placebo were statistically significant for brivaracetam 100 mg/day in Study 1252, brivaracetam 50 mg/day in Study 1253, the combined brivaracetam doses in Study 1254, and both brivaracetam 100 mg/day and 200 mg/day in Study 1358.

An important clinical question is whether or not patients previously or concurrently treated with levetiracetam could benefit from brivaracetam, given the presumed similarity in mechanism of action. In the included trials, approximately 22% to 55% of patients had used levetiracetam prior to study entry, and, with the exception of Study 1358, approximately 20% of patients received concomitant levetiracetam during the trials. In all trials, patients were stratified by either concomitant or previous levetiracetam use, which allowed for various pre-specified analyses by levetiracetam status to be conducted. In studies 1252, 1253, and 1254, an analysis of the per cent reduction in POS frequency by concomitant levetiracetam use showed that for patients who received concomitant levetiracetam, the differences between brivaracetam and placebo were not statistically significant, whereas in patients who did not receive concomitant levetiracetam, the differences between brivaracetam and placebo were statistically significant for all comparisons. In Study 1358, the per cent reduction in POS frequency by levetiracetam status showed that in patients who never used levetiracetam, the POS frequency was reduced by about 27% to 30%, whereas in patients who had used levetiracetam in the past, the per cent reduction was in the order of 16% to 19%. No pre-specified statistical comparisons between groups were conducted in Study 1358, although the results of a post-hoc analysis showed the per cent reduction in the 28-day–adjusted POS frequency over placebo was statistically significant in patients who received prior levetiracetam and patients who were levetiracetam-naive.[25] Taken together, these results suggest the addition of brivaracetam to levetiracetam does not appear to provide additional

treatment benefits; however, these findings require confirmation in further appropriately designed clinical trials.

Based on the patient input received, it was acknowledged that no anti-seizure medication is expected to be beneficial for everyone, but it is hoped that a new AED would improve patients' HRQoL and that it would have fewer AEs when compared with other drug treatments. [redacted] The original QOLIE-31 instrument; however, has been validated in this patient population and the MCID (using various methodologies) is reported to range from 4.73 to 11.8.[31,32] [redacted]. In the LTFU studies of brivaracetam, HRQoL continued to be assessed using the QOLIE-31-P.[8] The results; however, are inconclusive, as although patients appeared to exhibit early improvement in HRQoL, because of the changing composition of patients in the LTFU as new patients entered, discontinuation of patients over time, and increased variability of later exposure cohorts, it is difficult to interpret the long-term impact of brivaracetam on HRQoL.

[redacted]

[redacted]

In the absence of direct comparisons, it is difficult to evaluate the relative efficacy and safety/tolerability of brivaracetam compared with other clinically relevant AEDs such as perampanel, lacosamide, and eslicarbazepine. In lieu of the lack of direct evidence comparing brivaracetam with other relevant AEDs, the manufacturer conducted an ITC of brivaracetam compared with other available adjunctive therapies

(i.e., eslicarbazepine, lacosamide, perampanel, and retigabine/ezogabine, the latter of which is not available in Canada).[6] In addition, one other ITC of brivaracetam and levetiracetam was identified in the medical literature.[7] Both ITCs are summarized and critically appraised in Appendix 7: Summary of Indirect Treatment Comparisons. The manufacturer performed a Bayesian network meta-analysis for the efficacy outcomes of 50% response rates and seizure-freedom rates and the harms outcomes of SAEs, discontinuation rates due to TEAEs or for any reason, and rates of selected AEs (i.e., dizziness, fatigue, nausea, and somnolence). For the efficacy outcomes, it was found that when compared with placebo, all AEDs had an increased probability of response and that there was no statistically significant difference in response among the AED treatments compared with brivaracetam. For the harms outcomes, in general, it appeared the AEDs had an increased risk of AEs and discontinuations (with the exception of SAEs) compared with placebo, and there were no statistically significant differences between brivaracetam and the other AEDs. Eslicarbazepine was found to have a statistically significant increased risk of nausea compared with brivaracetam, whereas perampanel had a statistically significant lower risk of nausea compared with brivaracetam. In sensitivity analyses that excluded patients receiving concomitant levetiracetam in the brivaracetam trials, results were consistent with the overall findings of the ITC. In the ITC identified in the literature by Zhang et al.,[7] the Bucher method was used to conduct an ITC of brivaracetam and levetiracetam in patients with refractory focal seizures. Efficacy outcomes included 50% responder rate and seizure-freedom rate, and harms outcomes included AEs and adverse withdrawal effects. A comparison of three dose levels was performed: high (levetiracetam 3,000 mg/day versus brivaracetam 200 mg/day and 150 mg/day), middle (levetiracetam 2,000 mg/day versus brivaracetam100 mg/day), and low (levetiracetam 1,000 mg/day and 500 mg/day versus brivaracetam 50 mg/day, 25 mg/day, 20 mg/day, and 5 mg/day). For the efficacy outcomes, there was no statistical difference between levetiracetam and brivaracetam at all dose levels. In addition, there were no differences between levetiracetam and brivaracetam for AEs, with the exception of dizziness, which occurred at a statistically significantly higher rate at the high-dose level with brivaracetam, but not at the middle- or low-dose levels.

4.2.2 Harms

There were five deaths during the treatment periods of the four included trials. Of these, only one death was considered to be possibly related to study drug (i.e., brain hypoxia in the brivaracetam 50 mg/day group of Study 1253). More than half of the patients in both the brivaracetam and placebo groups of the trials experienced at least one TEAE. When considering the incidence of TEAEs, consideration must be given to the fact that patients were on concomitant background AED regimens, which could have contributed to the safety and tolerability profile of brivaracetam. Despite this, brivaracetam appeared to be relatively well tolerated and most TEAEs were mild to moderate in severity. The frequency of SAEs and WDAEs was low and similar between treatment groups, with the most common reason for each being convulsion. Overall, the most frequently reported TEAEs were somnolence, dizziness, fatigue, and headache. Of these, somnolence, dizziness, and fatigue occurred more frequently in the brivaracetam groups of the trials, whereas headache occurred in a similar proportion of brivaracetam- and placebo-treated patients.

In the pooled analysis of long-term safety data reported in Appendix 6: Summary of Other Studies, it was reported that more than 84% of patients experienced at least one TEAE. The most frequent TEAEs were consistent with those reported in the treatment phases of the trials and included headache, dizziness, somnolence, and fatigue. Similarly, the main reason for SAEs and WDAEs, which also remained relatively low, was convulsion. Overall, the long-term data suggests that the safety profile during the long-term period appeared to be similar to that observed during the treatment phases. Nonetheless, caution is required for the interpretation of all outcomes given the high degree of uncertainty resulting from the

key limitations of the uncontrolled, non-randomized, open-label, pooled data from the extension phase with a highly selected patient population.

[redacted]

[redacted]

4.3 Other Considerations

CDEC has reviewed and issued recommendations for three AEDs that have Health Canada–approved indications that are similar to the indication for brivaracetam: lacosamide (Vimpat), approved for POS in April 2011;[9] eslicarbazepine (Aptiom), approved in April 2015;[10] and perampanel (Fycompa), approved for POS in October 2013[11] and for primary generalized tonic-clonic seizures in May 2016.[12] For each of these AEDs used as adjunctive therapy in the treatment of POS in patients with epilepsy that is not satisfactorily controlled with conventional therapy, CDEC has recommended they be listed for reimbursement with clinical criteria. For Fycompa[11] and Aptiom,[10] CDEC recommended that the following clinical criteria and conditions must be met:

- clinical criteria:
  - patient is currently receiving two or more AEDs
  - patient for whom less costly AEDs are ineffective or not clinically appropriate.
- conditions:
  - patient is under the care of a physician experienced in the treatment of epilepsy.

For Aptiom,[10] an additional condition was that the daily cost of treatment should not exceed the daily cost of alternative adjunctive therapies.

For Vimpat,[9] the reimbursement criteria are as follows:

- patient is under the care of a physician experienced in the treatment of epilepsy
- patient is currently receiving two or more AEDs
- patient for whom all other AEDs are ineffective or not appropriate.

4.4 Potential Place in Therapy[1]

The clinical expert involved in the review stated there is an unmet treatment need in the management of patients with POS whose epilepsy is not satisfactorily controlled with conventional therapy. According to the clinical expert, patients with "resistant" or "refractory" epilepsy are variably defined but, in essence, the terms are applied to those in whom seizures continue despite adequate trials of standard AEDs. There are no standardized guidelines for the treatment of epilepsy but, in practice, an "adequate" trial of AED usually means several months of phenytoin, carbamazepine, or valproic acid, either alone or in combination. Many physicians treating patients with epilepsy would now add levetiracetam and lamotrigine to the list of "standard" AEDs. In the total population of people with epilepsy, about 20% to 30% prove to be resistant or refractory to these standard AEDs[13] and, among these patients, roughly one-half would have resistant or refractory POS. Thus, a substantial proportion of patients with epilepsy would require add-on therapy to manage their POS.

Brivaracetam joins a group of newer AEDs, any or several of which might be tried in a given patient with resistant or refractory POS. In general, the data presented in this review indicate that brivaracetam produces a statistically significant short-term reduction in POS frequency compared with placebo. The effect is modest, however, falling short of the 20% seizure frequency reduction commonly used as a measure to define a clinically meaningful effect. On the other hand, the fraction of patients experiencing at least a 50% reduction in seizure frequency, another commonly used measure of a clinically meaningful effect, was increased with brivaracetam compared with placebo. The efficacy of brivaracetam as an add-on AED appears to be roughly similar to new, alternative AEDs used as adjunctive therapy, but there are no direct comparison data available. There is some evidence that any benefit offered by add-on brivaracetam may not be found in patients concurrently taking levetiracetam. Given that levetiracetam is increasingly considered a "standard" AED, this may limit the population for whom brivaracetam might be considered as an add-on therapy. The main adverse effects of brivaracetam compared with placebo seem to be dizziness and somnolence. The studies reviewed did not show a positive or negative impact of brivaracetam on quality-of-life measures, but these adverse effects may become important when the drug is used in clinical practice. Therefore, while it is another therapeutic option for the management of patients who continue to experience seizures despite background treatment (i.e., refractory POS), the added value of brivaracetam over alternative adjunct AEDs is not clear.

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

5. CONCLUSIONS

In four phase 3 RCTs of 12- to 16-week treatment duration, brivaracetam 50 mg/day to 200 mg/day generally demonstrated statistically significant greater reductions in POS frequency from baseline compared with placebo in patients aged 16 years and over with uncontrolled POS, despite concomitant treatment with one to three AEDs. A small proportion of patients treated with brivaracetam 100 mg/day and 200 mg/day achieved statistically significant seizure freedom when compared with placebo. The included trials suggest there is no additional benefit of brivaracetam in patients who are concurrently treated with levetiracetam. The benefit of brivaracetam in patients who have previously received levetiracetam is uncertain and requires confirmation in appropriately designed clinical trials. There were minimal changes in HRQoL in all treatment groups. There were five deaths during the treatment periods, of which only one was considered possibly related to brivaracetam. Overall, the frequency of SAEs and WDAEs was low and similar between treatment groups. More than half of all patients in the trials experienced TEAEs, of which the most common were somnolence, dizziness, and fatigue, which occurred more frequently with brivaracetam, and headache, which occurred in a similar proportion of brivaracetam- and placebo-treated patients. [redacted]. An important limitation is the lack of evidence directly comparing brivaracetam with another clinically relevant AED indicated for use as adjunctive therapy in patients with uncontrolled POS. An ITC submitted by the manufacturer suggested similar efficacy and safety/tolerability of brivaracetam compared with eslicarbazepine, perampanel, and lacosamide.

APPENDIX 1: PATIENT INPUT SUMMARY

This section was prepared by CADTH staff. No patient input was received from any group. The Patient Input Summary presented here was adapted from the patient input received for the CDR review of perampanel (Fycompa) as adjunctive therapy in the management of primary generalized tonic-clonic seizures in adult patients with epilepsy who are not satisfactorily controlled with conventional therapy.

1. Brief Description of Patient Group(s) Supplying Input
Two patient groups submitted input.

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

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

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

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

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

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

3. Current Therapy–Related Information

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

4. Expectations About the Drug Being Reviewed

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

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

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

APPENDIX 2: LITERATURE SEARCH STRATEGY

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present MEDLINE Daily and MEDLINE 1946 to present MEDLINE In-Process & Other Non-Indexed Citations **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	May 17, 2016
Alerts:	Weekly search updates until (September 21, 2016 CDEC meeting)
Study Types:	No search filters were applied
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
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.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	
#	**Searches**
1	357336-20-0.rn,nm.
2	(Brivlera* or brivaracetam* or Briviact* or UCB 34714 or UCB34714 or U863JGG2IA or "2-(2-oxo-4-propylpyrrolidin-1-yl)butanamide").ti,ab,ot,hw,rn,nm,kf.
3	or/1-2
4	3 use pmez
5	*brivaracetam/
6	(Brivlera* or brivaracetam* or Briviact* or UCB 34714 or UCB34714 or U863JGG2IA or "2-(2-oxo-4-propylpyrrolidin-1-yl)butanamide").ti,ab,kw.
7	or/5-6
8	7 use oemezd
9	4 or 8
10	9 not conference abstract.pt.
11	remove duplicates from 10

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

Grey Literature

Dates for Search:	May 2016
Keywords:	Brivlera, brivaracetam, seizure, epilepsy
Limits:	No date or language limits used

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

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

APPENDIX 3: EXCLUDED STUDIES

There were no excluded studies.

APPENDIX 4: DETAILED OUTCOME DATA

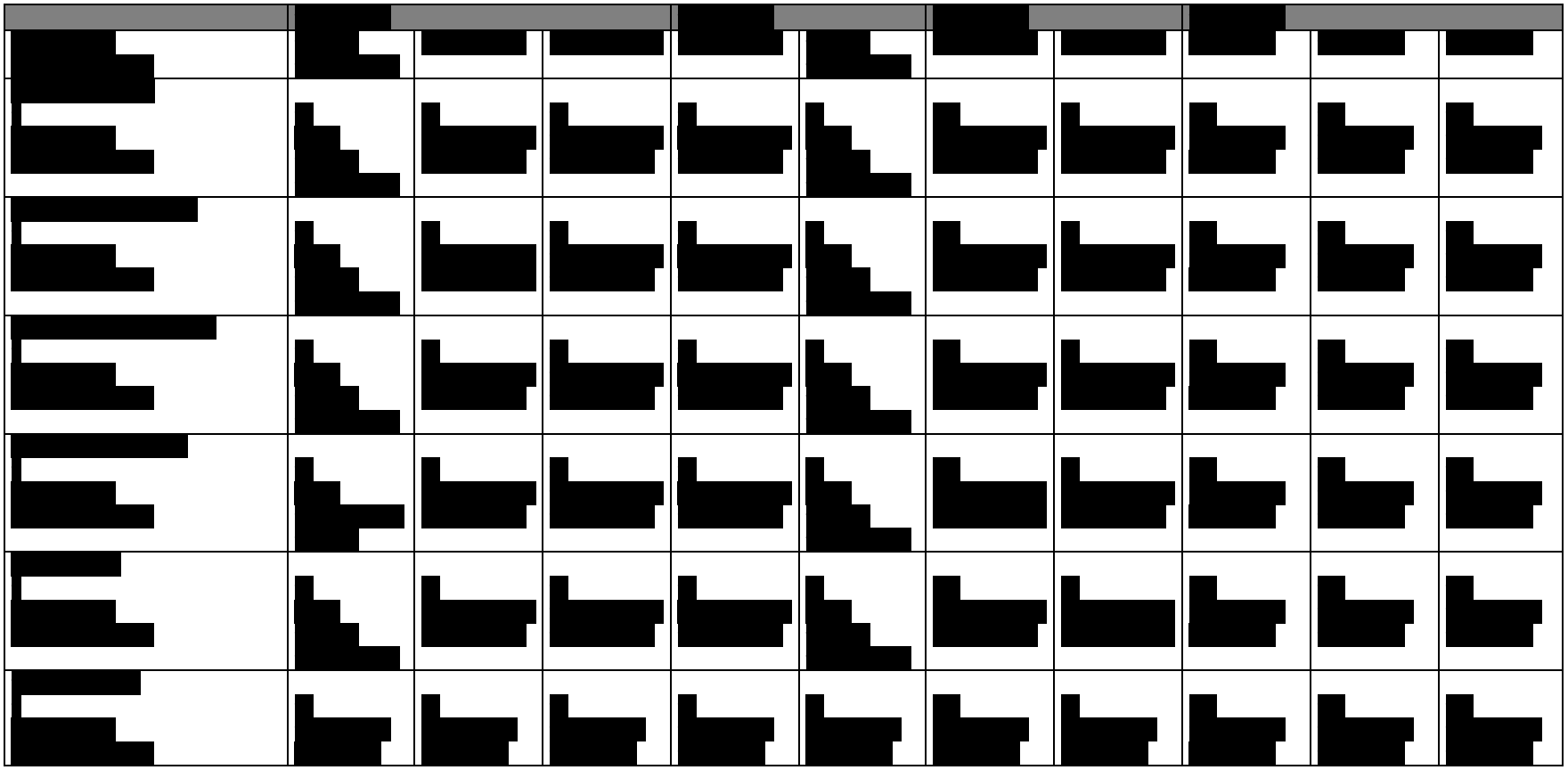
TABLE 14: SEIZURE FREEDOM IN ALL SEIZURES (TYPE 1, 2, AND 3) OVER TREATMENT PERIOD (INTENTION-TO-TREAT POPULATION)

	Study 1252			Study 1253		Study 1254		Study 1358		
All n (%) Unless Otherwise Noted	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 96)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
n	99	100	100	101	96	323	108	252	249	259
Seizure-free	0	4 (4.0)	0	4 (4.0)	0	5 (1.5)	0	13 (5.2)	10 (4.0)	2 (0.8)
[redacted]										
[redacted]										
Treatment comparison vs. PL *P* value[b]	NA	0.121	–	0.122	–	0.337	–	0.003	0.019	–

BRV = brivaracetam; NA (cannot be calculated); PL = placebo; vs. = versus.
[a] A patient who had no seizures during the treatment period but did not complete it.
[b] *P* value from Fisher's exact test for comparison of BRV vs. PL.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

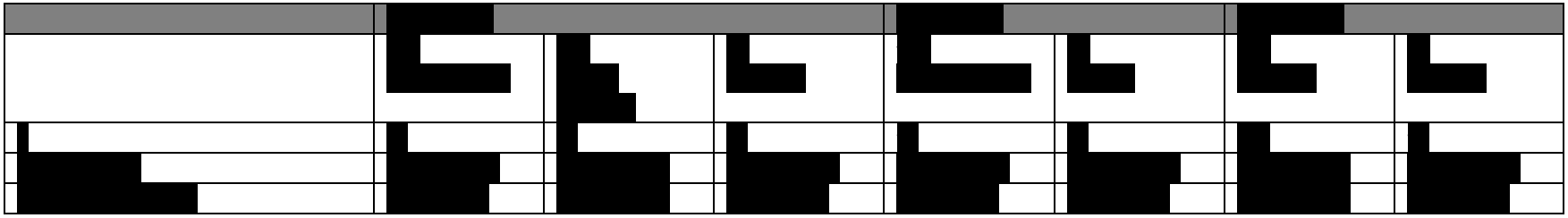
TABLE 15: CHANGE[a] FROM BASELINE TO END OF TREATMENT PERIOD FOR QOLIE-31-P TOTAL SCORE, SUB-SCALE SCORES AND HEALTH STATUS ITEM (INTENTION-TO-TREAT POPULATION)

[redacted]										



QOLIE-31-P = Patient-Weighted Quality of Life in Epilepsy Inventory-31.
[a] Descriptive statistics only.
Note: Scores range from 0 to 100, with a positive change indicating improvement in functioning/health status. Only patients who are not mentally impaired were to complete the QOLIE-31-P. Only patients having values at baseline at the considered visit are included.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 16: CHANGE FROM BASELINE IN EQ-5D VISUAL ANALOGUE SCALE FOR LAST VALUE IN TREATMENT PERIOD[a] (INTENTION-TO-TREAT POPULATION)



EQ-5D = EuroQol 5-Dimensions Questionnaire; POS = partial-onset seizure; VAS = visual analogue scale.
[a] For Study 1254, the treatment period is (dose-finding plus maintenance periods) and results are presented for the POS population.
[b] EQ-5D was an exploratory variable and only descriptive statistics for the VAS were reported.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] and Study 1254 Clinical Study Report.[16]

TABLE 17: PARTIAL (TYPE 1) SEIZURE FREQUENCY PER WEEK (INTENTION-TO-TREAT POPULATION)

`	Study 1252			Study 1253		Study 1254	
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 96)	BRV (N = 323)	PL (N = 108)
BL (median number per week)	1.80	2.02	2.07	2.85	2.63	2.21	2.29
Treatment (median number per week)[a]	1.49	1.26	1.75	1.70	2.15	1.74	1.86
[redacted]							
[redacted]							
Treatment comparison vs. PL:							
per cent reduction over PL	6.5	11.7		12.8		7.3	
95% CI	–5.2 to 16.9	0.7 to 21.4		1.7 to 22.6		–2.2 to 15.9	
P value	0.261	0.037		0.025		0.125	

ANCOVA = analysis of covariance; BL = baseline; BRV = brivaracetam; CI = confidence interval; PL = placebo.
[a] For Study 1254, the treatment period is dose-finding plus maintenance periods.
[b] ANCOVA on log-transformed partial seizure frequency per week over treatment period, with log-transformed BL seizure frequency per week as covariate, including terms for treatment and stratification factors.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] and Study 1254 Clinical Study Report.[16]

TABLE 18: PARTIAL (TYPE 1) SEIZURE FREQUENCY PER 28 DAYS IN STUDY 1358 (INTENTION-TO-TREAT POPULATION)

	Study 1358		
	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
BL (median number per 28 days)	9.5	9.3	10.0
[redacted]	[redacted]	[redacted]	[redacted]
Treatment comparison vs. PL:			
per cent reduction over PL	22.8	23.2	
95% CI	13.3 to 31.2	13.8 to 31.6	
P value	< 0.001	< 0.001	

AED = antiepileptic drug; ANCOVA = analysis of covariance; BL = baseline; BRV = brivaracetam; CI = confidence interval; LEV = levetiracetam; PL = placebo; POS = partial-onset seizure; vs. = versus.
Note: Parametric effect estimates and treatment group comparisons were based on an ANCOVA with log-transformed (log[x + 1]) treatment period and 28-day–adjusted POS frequency as the outcome and an effect for treatment, an effect for pooled country, and an effect for the four combinations of stratification levels for number of previous AEDs and LEV status, and log-transformed baseline POS frequency as a continuous covariate.
Source: Study 1358 Clinical Study Report.[17]

TABLE 19: FIFTY PER CENT (50%) RESPONDER RATE IN PARTIAL (TYPE 1) SEIZURE FREQUENCY FROM BASELINE TO END OF TREATMENT[a] (INTENTION-TO-TREAT POPULATION)

	Study 1252			Study 1253		Study 1254		Study 1358		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 96)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Responders, n (%)	(27.3)	(36.0)	(20.0)	33 (32.7)	16 (16.7)	(30.3)	(16.7)	(38.9)	(37.8)	(21.6)
OR (BRV vs. PL):[b]	[redacted]	[redacted]		[redacted]		[redacted]		[redacted]	[redacted]	
95% CI										
P value	0.372	0.023		0.008		0.006		< 0.001	< 0.001	

BRV = brivaracetam; CI = confidence interval; OR = odds ratio; PL = placebo; vs. = versus.
[a] For Study 1254, the treatment period is (dose-finding plus maintenance periods).
[b] OR, CI (two-sided), and *P* value on per cent responders based on a logistic-regression model including treatment as a factor and log-transformed partial seizure frequency per week as covariate.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 20: PER CENT REDUCTION IN PARTIAL (TYPE 1) SEIZURE FREQUENCY OVER THE TREATMENT PERIOD[a] (INTENTION-TO-TREAT POPULATION)

	Study 1252			Study 1253		Study 1254		Study 1358c		
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 96)	BRV (N = 323)	PL (N = 108)	BRV 100 mg (N = 252)	BRV 200 mg (N = 249)	PL (N = 259)
Per cent reduction (median)	26.83	32.45	17.03	30.47	17.75	26.92	18.93	37.2	35.6	17.6
Treatment comparison vs. PL: Median difference vs. PL[b] 95% CI *P* value	[redacted] 0.092	[redacted] 0.004		[redacted] 0.003		[redacted] 0.070		–15.8 –7.6 to –24.2 < 0.001	–18.1 –10.4 to –26.4 < 0.001	

ANCOVA = analysis of covariance; BRV = brivaracetam; CI = confidence interval; PL = placebo; POS = partial-onset seizure; vs. = versus.
[a] For Study 1254, the treatment period is dose-finding plus maintenance periods.
[b] Testing was performed in a stepwise manner starting with 50 mg/day then 100 mg/day using ANCOVA with log-transformed baseline POS frequency per week as covariate and including terms for treatment and stratification factors.
[c] Seizure frequency is per 28 days for Study 1358.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 21: PER CENT REDUCTION IN PARTIAL (TYPE 1) SEIZURE FREQUENCY BY CONCOMITANT LEVETIRACETAM USE[a] (INTENTION-TO-TREAT POPULATION)

	Study 1252			Study 1253		Study 1254	
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 96)	BRV (N = 323)	PL (N = 108)
Concomitant Levetiracetam at Study Entry							
n	20	20	18	19	19	61	22
Per cent reduction (median)	3.16	4.71	17.22	14.39	22.11	15.93	14.18
Treatment comparison vs. PL: Median difference vs. PL[b] 95% CI *P* value	[redacted]	[redacted]		[redacted]		[redacted]	
No Concomitant Levetiracetam at Study Entry							
n	79	80	82	82	76	262	86
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]							

	Study 1252			Study 1253		Study 1254	
	BRV 50 mg (N = 99)	BRV 100 mg (N = 100)	PL (N = 100)	BRV 50 mg (N = 101)	PL (N = 96)	BRV (N = 323)	PL (N = 108)
[redacted] [redacted]	[redacted]	[redacted]		[redacted]		[redacted]	

BRV = brivaracetam; CI = confidence interval; PL = placebo; POS = partial-onset seizure; vs. = versus.

[a] For Study 1254, the treatment period is dose-finding plus maintenance periods, and results are reported in the ITT POS population.

[b] Median difference, CI (two-sided), and *P* value for the treatment effect on per cent reduction from baseline. CI from the Hodges-Lehmann method and *P* value from Wilcoxon-Mann-Whitney test.

Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

Table 22: Categorized Response in Partial (Type 1) Seizure Frequency Over the Treatment Period[a] (Intention-to-Treat Population)

	[redacted]			[redacted]		[redacted]		[redacted]		
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

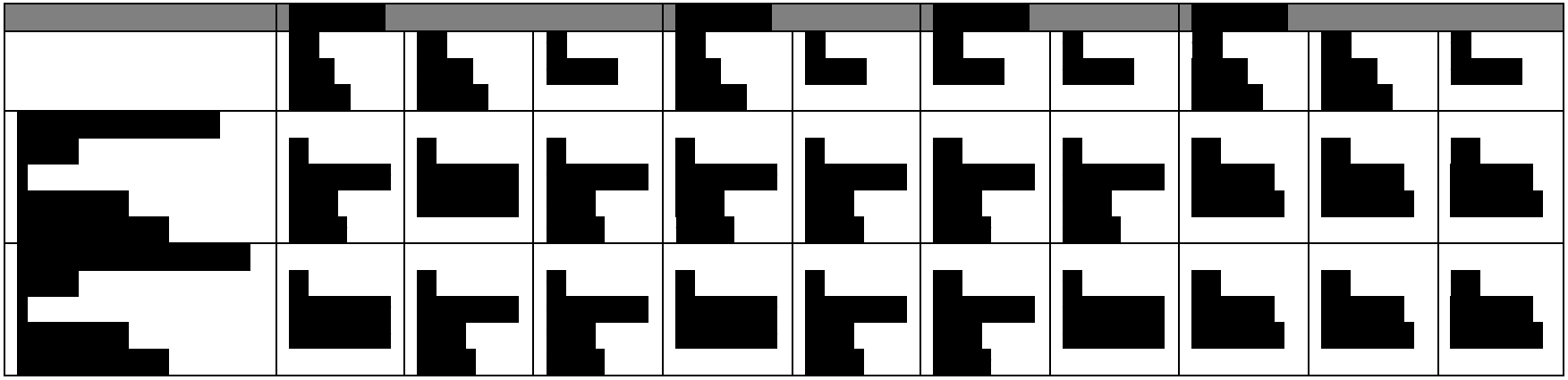
ITT = intention to treat; POS = partial-onset seizures.

[a] For Study 1254, the treatment period is dose-finding plus maintenance periods, and results are reported in the ITT POS population.

[b] *P* value is from Cochran-Mantel-Haenszel test based on modified ridit scores (row mean scores differ).

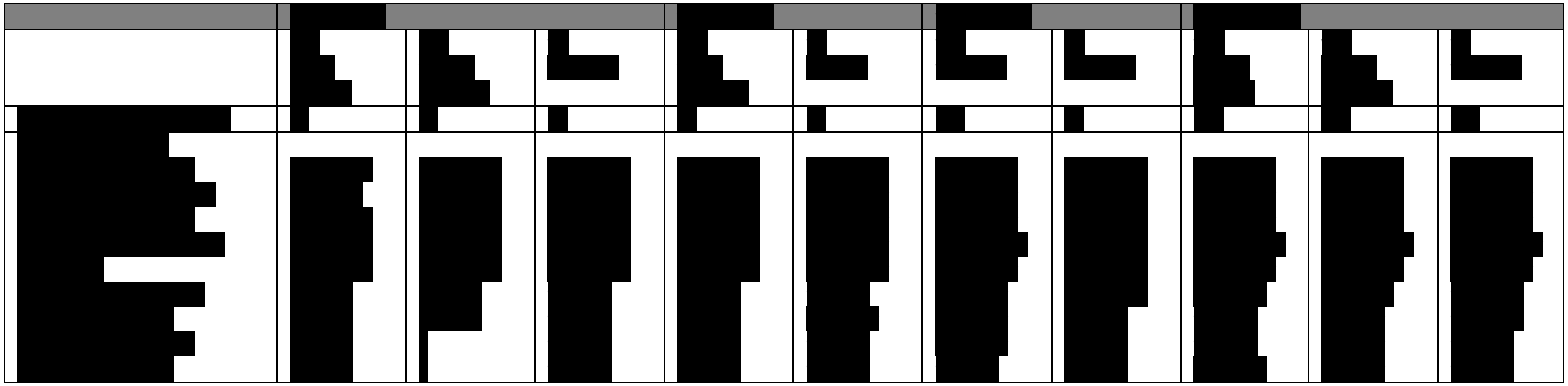
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

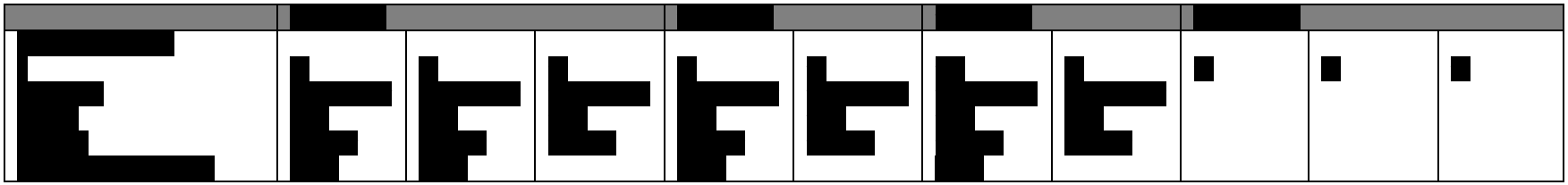
TABLE 23: CHANGE[a] FROM BASELINE TO END OF TREATMENT PERIOD IN HADS SUB-SCALE SCORES (INTENTION-TO-TREAT POPULATION)



HADS = Hospital Anxiety and Depression Scale; ITT = intention-to-treat.
[a] Descriptive statistics only.
Note: Anxiety and depression scores range from 0 to 21, with a positive change indicating higher anxiety or depression. Only patients who were not mentally impaired completed the HADS.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 24: DISTRIBUTION OF PATIENTS BY PATIENT GLOBAL EVALUATION SCALE AT LAST VISIT OR EARLY DISCONTINUATION (INTENTION-TO-TREAT POPULATION)

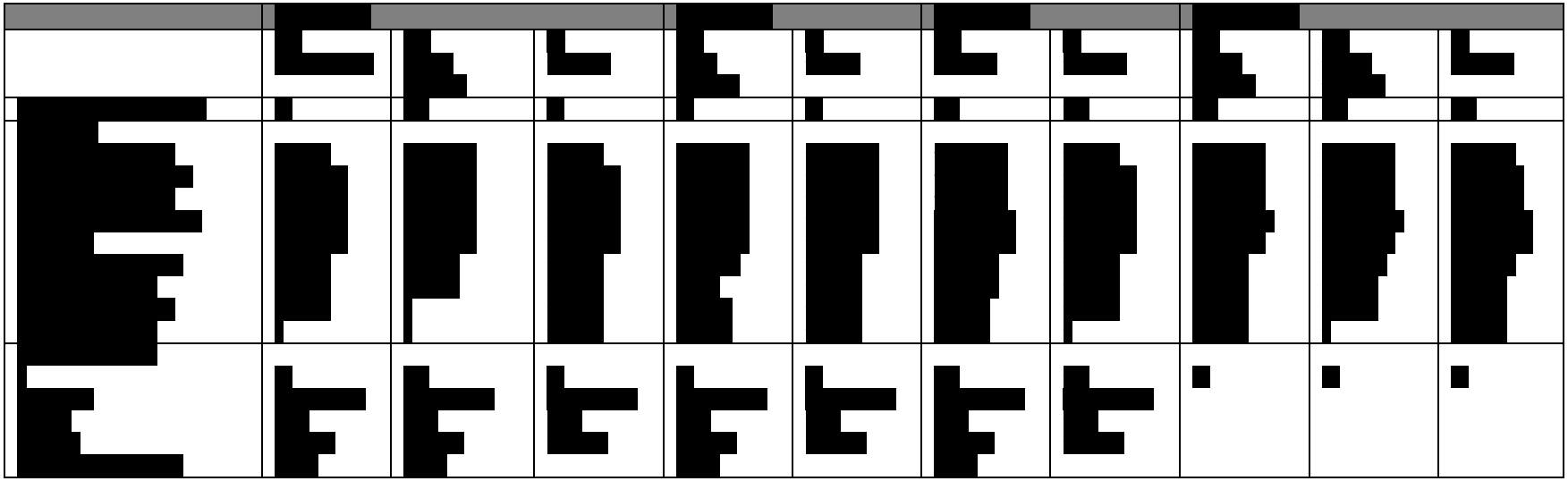




BRV = brivaracetam; PL = placebo.

Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 25: DISTRIBUTION OF PATIENTS BY INVESTIGATOR GLOBAL EVALUATION SCALE AT LAST VISIT OR EARLY DISCONTINUATION (INTENTION-TO-TREAT POPULATION)



BRV = brivaracetam; PL = placebo; vs. = versus.

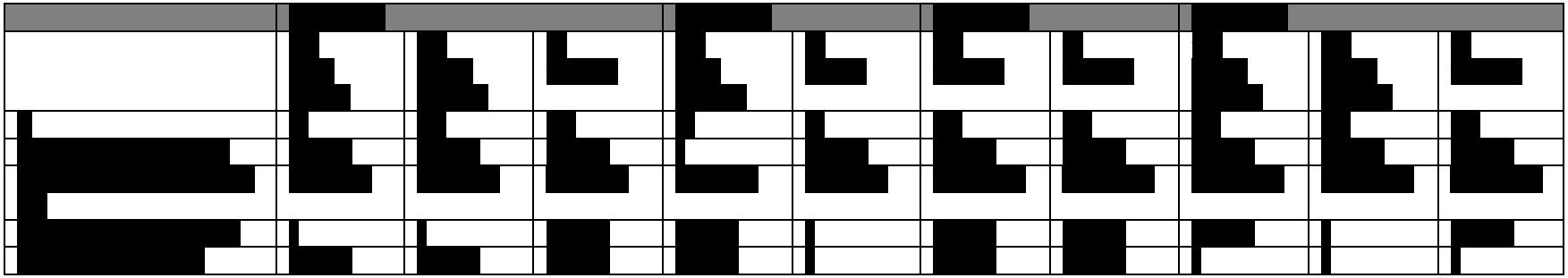
[a] Evaluable patients are patients who completed the Global Evaluation Scale at last treatment period (visit 7 or early discontinuation visit).

[b] Treatment comparisons vs. PL were conducted based on a Cochran-Mantel-Haenszel test for the comparison of row mean scores, and both BRV 100 mg and BRV 200 mg vs. PL were $P < 0.001$.

[c] Treatment comparisons vs. PL were based on a stratified Wilcoxon test.

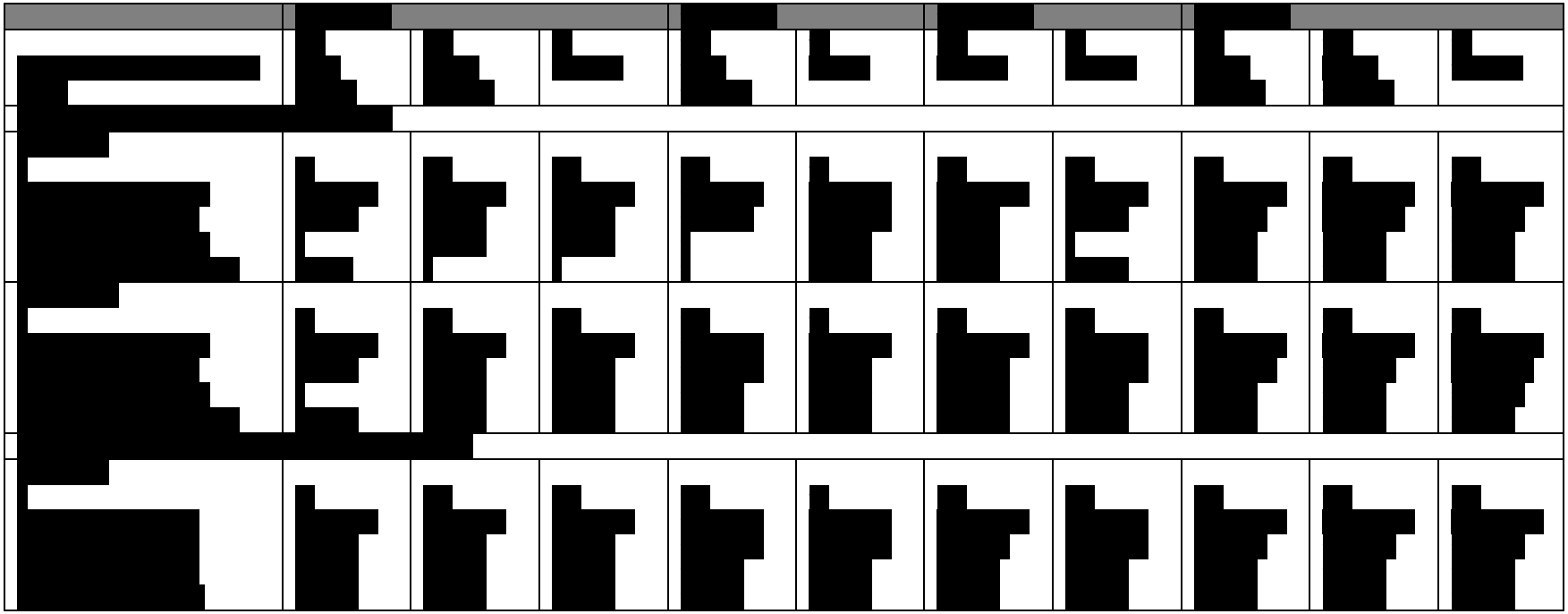
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

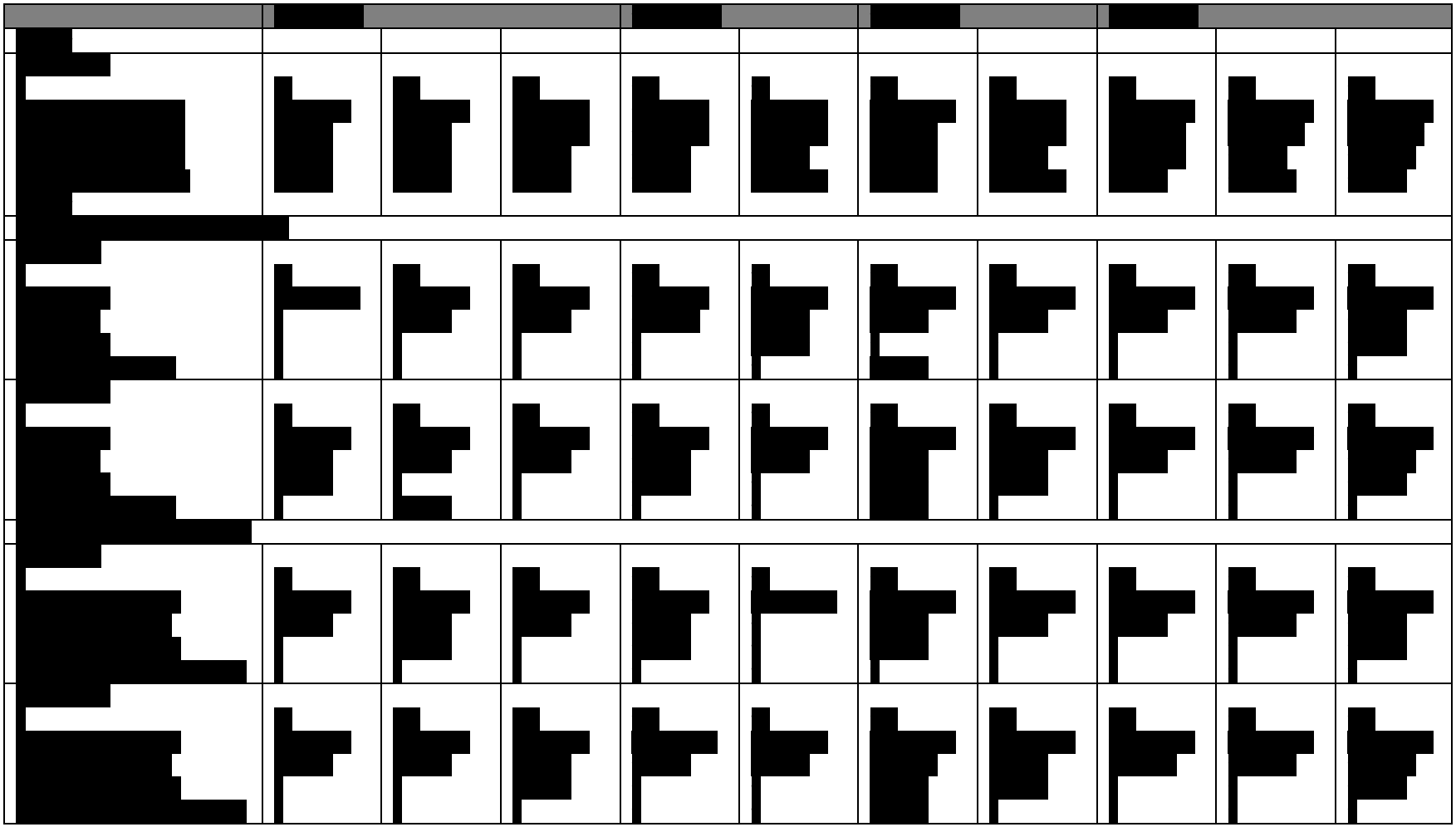
TABLE 26: TREATMENT COMPLIANCE[a] OVER TREATMENT PERIOD (INTENTION-TO-TREAT POPULATION)



BRV = brivaracetam; PL = placebo.
[a] Compliance is calculated based on the number of tablets dispensed and returned.
Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

TABLE 27: SUMMARY OF CONCOMITANT HEALTH CARE RESOURCE UTILIZATION BY ANALYSIS PERIOD[a] (INTENTION-TO-TREAT POPULATION)





ITT = intention to treat; POS = partial-onset seizure.

[a] For Study 1254, the treatment period is treatment plus maintenance periods, and results are presented for the ITT POS population. For Study 1358, results are reported in the safety population.

Note: Cost parameters were an exploratory variable and only descriptive statistics were reported in the included trials (i.e., n, %).

Source: Study 1252 Clinical Study Report,[14] Study 1253 Clinical Study Report,[15] Study 1254 Clinical Study Report,[16] and Study 1358 Clinical Study Report.[17]

APPENDIX 5: VALIDITY OF OUTCOME MEASURES

Aim

To summarize the validity of the following outcome measures:

- Patient-Weighted Quality of Life in Epilepsy Inventory-31 (QOLIE-31-P)
- Hospital Anxiety and Depression Scale (HADS)
- Patient Global Evaluation Scale (P-GES)
- Investigator Global Evaluation Scale (I-GES)
- EuroQoL-5 Dimensions questionnaire (EQ-5D).

Findings

Instrument	Type	Evidence of Validity	MCID	References
QOLIE-31-P	The QOLIE-31 is a valid and reliable measure of QoL in patients with epilepsy derived from the longer version QOLIE-89.[30] It is a self-reported questionnaire comprising two factors (emotional and psychological effects, and medical and social effects), seven sub-scales, 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. A variant of the original QOLIE-31, the QOLIE-31-P has an extra item added to each of the seven sub-scales which asks the patient to grade their overall distress with respect to the sub-scale in question. No information on the validity of the QOLIE-31-P in patients with epilepsy was identified. An MCID was also not found. No information was found suggesting that the validity and MCID identified for the QOLIE-31 are transferable to the QOLIE-31-P.	No	Unspecified	Cramer, 1998[30] Devinsky, 1995[37] Wiebe, 2002[32] Borghs, 2012[31] Cramer, 2003[38]
HADS	The HADS consists of seven multiple-choice items assessing depressive symptoms (HADS depression sub-scale) and seven multiple-choice items assessing anxiety symptoms (HADS anxiety sub-scale). The items are presented in the form of a 4-point Likert scale, resulting in a final score ranging from 0 to 21 for each of the sub-scales, with higher scores indicating higher depression/anxiety. The HADS depression sub-scale is a valid and reliable measure of depressive symptoms in patients with epilepsy.	Yes, for depression; not validated for anxiety	Unspecified	Zigmond, 1983[39] Snaith, 2003[35] Wiglusz, 2016[36] de Oliveira, 2014[40]
P-GES	A global assessment of the disease evolution that is performed by patients using a 7-point scale.	No	Unspecified	

Instrument	Type	Evidence of Validity	MCID	References
I-GES	A global assessment of the disease evolution that is performed by investigators using a 7-point scale.	No	Unspecified	
EQ-5D	The EQ-5D is a general, non–disease-specific health-related quality-of-life questionnaire.	Yes	Epilepsy: unknown General use: 0.033 to 0.074 for index score	Sinnott 2007[41]

EQ-5D = EuroQol 5-Dimensions Questionnaire; HADS = Hospital Anxiety and Depression Scale; I-GES = Investigator Global Evaluation Scale; MCID = minimal clinically important difference; P-GES = Patient Global Evaluation Scale; QoL = quality of life; QOLIE-31-P = Patient-Weighted Quality of Life in Epilepsy Inventory-31; QOLIE-89 = Quality of Life in Epilepsy Inventory-89.

Patient-Weighted Quality of Life in Epilepsy Inventory-31

The QOLIE-31-P is an epilepsy-specific health-related quality of life (HRQoL) scale[30] derived from the longer QOLIE-89, which was developed and validated in 1995.[37] The QOLIE-89 is an epilepsy-focused scale comprising 17 sub-scales, including the entire generic HRQoL measure, the 36-Item Short Form Health Survey (SF-36). Four dimensions of health scores (epilepsy-targeted, mental health, physical health, and cognitive distress) plus an overall QOLIE-89 score are obtained from the QOLIE-89.

The QOLIE-31 was developed by an expert panel (QOLIE Development Group) in 1998. The group selected the most relevant HRQoL sub-scales of the QOLIE-89 based on empirical evidence of the most commonly reported issues by patients with epilepsy.[30] This selection resulted in seven sub-scales (seizure worry, overall quality of life, emotional well-being, energy/fatigue, medication effects, work/driving/social limits, and cognitive functioning) and one overall item, creating the 31-item questionnaire rated on a four- to six-point Likert scale, the QOLIE-31, version 1.1. Scoring of the QOLIE-31 requires the conversion of raw data to a scale of 0 to 100 for each sub-scale, with higher scores reflecting higher quality of life. The total score is calculated as a weighted mean of the sub-scale scores. The sub-scales showed an adequate range of variability; where all of the seven sub-scales showed the absolute maximum of 100, and five of the seven sub-scales showed the lowest absolute minimum of 100, with mean scores for the seven sub-scales ranging from 55 to 67. The maximum total score is 100 per sub-scale and total score.[30]

Internal consistency reliability coefficients (Cronbach's alpha) demonstrated adequate-to-high internal consistency within each sub-scale, ranging from alpha = 0.77 (social functioning) to alpha = 0.85 (cognitive functioning).[30] Intra-rater reliability was demonstrated for all of the sub-scales; Pearson correlation coefficients between test and re-test data (with re-test date from one to 21 days after the initial date) ranged from a correlation coefficient (r) of 0.64 (medication effects) to r = 0.85 (cognitive functioning), demonstrating adequate-to-high intra-rater reliability.[30] These assessment were based on answers from 304 adults with epilepsy who were functioning at a relatively normal level who could read and comprehend the questions.

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 Affairs 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.[30] As expected, the correlations between the systemic toxicity scores and the QOLIE-31 sub-scales were low (range r = 0.00 to r = 0.006). Six of the scales were statistically significantly correlated with neurotoxicity with $P < 0.0001$ (r = 0.24 to 0.36) and one scale (seizure/worry) was significant ($P < 0.03$; r = 0.12); however, these are considered small-to-moderate correlations. The number of antiepileptic drugs used was statistically significantly correlated with the work/driving/social limits sub-scale (r = –0.72; $P = 0.004$) which is considered a large correlation; and health care utilization was correlated with total QOLIE score (r = –0.146; $P = 0.016$) and two of the sub-scales (work/driving/social limits [r = –0.182; $P = 0.002$] and medical [r = –0.136; $P = 0.020$]); these are considered small correlations.[30]

The minimal clinically important difference (MCID) has also been established for the QOLIE-31 in a study of 136 consecutive adult patients with refractory focal epilepsy with or without secondary generalization who were being evaluated for epilepsy surgery. Patients completed two epilepsy-specific quality of life scales (the QOLIE-31 and QOLIE-89), and two HRQoL scales (the SF-36 and the Health Utilities Index Mark 3 [HUI3]), two times each, six months apart. Concurrent with completion of the quality-of-life scales, patients were also asked to rate changes on the following five domains 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 quality of life as per the QOLIE-89, QOLIE-31, SF-36 and HUI3. The MCID for QOLIE-31 was determined to be 11.8, and for QOLIE-89, 10.1.[32]

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

The QOLIE-31-P is a variant of the original QOLIE-31. In the QOLIE-31-P, an extra item was added to each of the seven sub-scales asking patients to grade their overall distress with respect to the sub-scale in question. An additional item was also added asking patients to rank the importance of each sub-scale topic for a total of 39 items and eight sub-scales.[38] The newly added items related to distress were rated using a 5-point scale (not at all, somewhat, moderately, a lot, and very much), in which the ratings were converted to a scale of 0 to 100, with higher scores reflecting higher distress and lower scores, lower distress.[38] No information on the validity of the QOLIE-31-P in patients with epilepsy was identified. A MCID was also not found.

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

Hospital Anxiety and Depression Scale

The HADS is a self-administered scale to assess the presence and severity of anxiety and depression.[35,39] HADS consists of 14 items that are scored on a four-point severity scale ranging from 0 to 3, with higher scores indicating greater severity.[35,39] There are two dimensions (anxiety and depression), with seven of the items related to the anxiety dimension and seven related to the depression dimension. A score per dimension ranges from 0 to 21, with higher scores indicating higher depression/anxiety.[35,39] The scale authors recommended that a score of 0 to 7 for either the anxiety or depression sub-scale could be regarded as being in the normal range, a score of 8 to 10 suggests the presence of the respective state, and a score of 11 or higher indicates the probable presence of the mood disorder.[35]

The HADS depression sub-scale was validated and was found to be a reliable psychometric instrument in terms of screening for depressive disorders in patients with epilepsy.[36] In another study that assessed and compared several screening instruments for depression and suicidality in people with epilepsy, it was found the HADS depression sub-scale is a brief, efficient screening instrument to identify depression in people with epilepsy.[40] In addition, the HADS depression sub-scale demonstrated a sensitivity of 85.7% and a specificity of 68% in the screening for people with moderate/severe suicide risk.[40] No MCID for the HADS depression sub-scale in patients with epilepsy was identified. No information on the validity and the MCID for the HADS anxiety sub-scale in patients with epilepsy was identified.

Patient Global Evaluation Scale

The P-GES is a global assessment of the disease evolution that is performed using a seven-point scale. Patients complete the scale by answering the following question: "Overall, has there been a change in your seizures since the start of the study medication?" Answers range from 1 for marked worsening to 7 for marked improvement.[14-17] The validity and MCID of the P-GES have not been assessed in patients with epilepsy. No information on the validity and the MCID of P-GES in patients with epilepsy was identified.

Investigator Global Evaluation Scale

The I-GES is a global assessment of the disease evolution that is performed using a seven-point scale. Investigators complete the scale by answering the following statement: "Assess the overall change in the severity of patient's illness, compared with the start of study medication," with answers ranging from 1 for marked worsening to 7 for marked improvement.[14-17] No information on the validity and the MCID of I-GES in patients with epilepsy was identified.

EuroQol 5-Dimensions Questionnaire

The EQ-5D[33,34] is a generic quality-of-life instrument that has been applied to a wide range of health conditions and treatments including epilepsy. The first of two parts of the three-level EQ-5D (EQ-5D-3L) is a descriptive system that classifies respondents (aged ≥ 12 years) on the following five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. For the EQ-5D-3L, each dimension has three possible response options (1, 2, or 3) representing "no problems," "some problems," and "extreme problems," respectively, resulting in 243 distinct health states. Respondents are asked to choose the response option that reflects their own health state for each of the five dimensions.

A scoring function can be used to assign a value (EQ-5D index score) to self-reported health states from a set of population-based preference weights.[33,34] The EQ-5D index score is generated by applying a multi-attribute utility function to the descriptive system. Different utility functions are available that reflect the preferences of specific populations (e.g., United States or United Kingdom). The lowest possible overall score (corresponding to severe problems on all five attributes) varies depending on the utility function that is applied to the descriptive system (e.g., −0.59 for the United Kingdom algorithm and −0.109 for the United States algorithm). Scores less than 0 represent health states that are valued by society as being worse than dead, while scores of 0 and 1.00 are assigned to the health states "dead" and "perfect health," respectively.

The second part of the EQ-5D is a 20 cm visual analogue scale (EQ-VAS) that has end points labelled 0 and 100, with respective anchors of "worst imaginable health state" and "best imaginable health state," respectively. Respondents are asked to rate their own health by drawing a line from an anchor box to the point on the EQ-VAS that best represents their own health on that day. Hence, the EQ-5D-3L produces three types of data for each respondent:

1. a profile indicating the extent of problems on each of the five dimensions represented by a five-digit descriptor, such as 11121, 33211, etc.
2. a population preference-weighted health index score based on the descriptive system
3. a self-reported assessment of health status based on the EQ-VAS.

The clinically important difference (CID) for the EQ-5D-3L index score ranges from 0.033 to 0.074.[41] The CIDs were derived from patients with a variety of chronic and acute conditions, including rheumatoid arthritis, osteoarthritis, irritable bowel syndrome, and acute myocardial infarction.[42,43] The validity and MCID of the EQ-5D-3L have not been formally assessed in patients with epilepsy.

3. Summary

The QOLIE-31-P consists of eight sub-scales and 39 items rated on a four- to six-point Likert scale. No information on the validity of the QOLIE-31-P in patients with epilepsy was identified. The HADS consists of seven multiple-choice items assessing depressive symptoms (HADS depression sub-scale) and seven multiple-choice items assessing anxiety symptoms (HADS anxiety sub-scale). There is evidence for the validity and reliability of the HADS depression sub-scale in identifying depression in patients with epilepsy. No information on the validity of the HADS anxiety sub-scale in patients with epilepsy was identified. The P-GES and I-GES are a global assessment of the disease evolution that are performed using a seven-point scale with answers ranging from 1 for marked worsening to 7 for marked improvement. No information on the validity and the MCID of the P-GES and I-GES in patients with epilepsy was identified. A CID for EQ-5D-3L index or VAS scores in patients with epilepsy was not identified. The CID for the EQ-5D-3L index score in general use ranges from 0.033 to 0.074.

APPENDIX 6: SUMMARY OF OTHER STUDIES

Objective

To summarize efficacy and safety evidence from pooled long-term data reported by Toledo et al.,[8] and to summarize study N01395 which reported non-psychotic behavioural adverse events (BAEs) in patients receiving levetiracetam who switched to brivaracetam by Yates et al.[44]

Summary of Pooled Long-Term Data

Toledo et al.[8] reported seizure outcome data, safety, and tolerability for adjunctive brivaracetam 50 mg/day to 200 mg/day from phase 2b and phase 3 trials, and long-term follow-up (LTFU) studies in patients with partial-onset seizures (POS). Patients who took part in the phase 2b and phase 3 double-blind, randomized, placebo-controlled trials of adjunctive brivaracetam were ≥ 16 years old, had epilepsy diagnosis according to the International League Against Epilepsy classification, and had POS uncontrolled on one to three AEDs. Two studies (n = 60) also recruited patients with primary generalized seizures; these studies were included in the safety analyses. Patients had the opportunity to join open-label LTFU studies if the investigator believed that a reasonable benefit could be expected from long-term brivaracetam administration; the recommended initial dose in the LTFU studies was 50 mg day, and a flexible dosing regimen (≤ 200 mg/day) was permitted.

The efficacy population comprised patients with focal epilepsy from two phase 2 studies (N01114 and N01193) and the four phase 3 studies included in this review (N01252, N01253, N01254, N01358) who received brivaracetam in the LTFU studies N01125, N01199, and N01379. Pooled summaries of seizure outcome data were based on data collected during the LTFU studies. Baseline POS frequency was derived from the baseline period (which ranged from 4 weeks to 12 weeks) of the core studies. A total of 1,836 patients were included in the efficacy analysis.

The safety population comprised patients with focal or generalized epilepsy who received brivaracetam in studies that were included in the efficacy analysis, as well as the patients included in N01395, N01372, and NCT01405508 (patients from study N01258 were included if they had received brivaracetam in the LTFU study N01379).

Of the 2,186 patients who received brivaracetam, 2,051 (93.86%) completed their core studies and continued in the LTFU studies and were included in the safety population. Patients were recruited from North America (427; 19.5%), Europe (1,055; 49.3%), Latin America (271; 12.4%), and Asia Pacific and other countries (433; 19.8%).

In both efficacy and safety populations, patients had a mean age of 37 years, with an approximately equal proportion of male and female patients, and the majority of patients (71%) were Caucasian. At entry to the core studies, the most common concomitant AEDs were carbamazepine, lamotrigine, and valproate.

Efficacy Outcomes

The percentage of patients with at least 50% reduction in POS frequency from baseline increased from 43.5% at one to three months (1,836 patients were included in this analysis), to 71.0% at 58 to 60 months; however, only 541 patients were included in this analysis.

The percentage of patients who were seizure-free for the first 6, 12, 18, 24, 36, 48, and 60 months of treatment with brivaracetam were 4.9%, 4.2%, 3.5%, 3.0%, 3.0%, 2.9%, and 3.3%, respectively. The percentage of patients who were seizure-free during treatment for any 6-, 12-, 18-, 24-, 36-, 48-, and 60-month period were 16.9%, 10.4%, 7.2%, 5.5%, 3.5%, 2.4%, and 1.4%, respectively. Among patients who had received treatment with brivaracetam for at least 60 months (n = 518 patients), 32.4%, 22.4%, 13.7%, and 3.3% of patients were seizure-free for any 6-, 12-, 24-, or 60-month period, respectively, during this treatment period.

Harms Outcomes

Of the 2,186 patients included in the safety population, 1,848 (84.5%) reported at least one treatment-emergent adverse event (TEAE). For brivaracetam doses of 50 mg, 100 mg, and 150 mg, the most frequently reported TEAE was headache (21.9 to 24.8%), while dizziness (15.4%) was the most frequent TEAE in the 200 mg dose group. For patients who received brivaracetam doses of 50 mg, 100 mg, and 150 mg, TEAEs reported by > 10% were headache, dizziness, somnolence, nasopharyngitis, fatigue, and convulsion; while for patients in the 200 mg dose group, TEAEs reported by > 10% were headache, dizziness, somnolence, and fatigue (Table 28).

A total of 264 patients (12.1%) had a TEAE that resulted in discontinuation of brivaracetam (Table 28). The most frequently reported TEAEs leading to discontinuation were convulsion (1.4%), pregnancy (0.9%), somnolence (0.7%), depression (0.6%), dizziness (0.6%), fatigue (0.5%), suicidal ideation (0.5%), and suicide attempt (0.5%).

Serious TEAEs were reported in 401 out of 2,186 patients (18.3%) (Table 28). Overall, the most common serious adverse events (SAEs) were convulsion (2.6%), status epilepticus (0.9%), pneumonia (0.5%), epilepsy (0.6%), suicidal ideation (0.5%), suicide attempt (0.5%), and fall (0.5%). There were a total of 28 (1.3%) deaths reported in patients in the safety population (brivaracetam doses of 50 mg/day to 200 mg/day). Cause of death reported in at least one patient included cancer (n = 6), drowning (n = 4), sudden unexpected death in epilepsy (n = 4), myocardial infarction (n = 3), accident (n = 2), and suicide (n = 2). Four (14.3%) of the 28 deaths were considered by the investigator to be possibly related to treatment with brivaracetam.

TABLE 28: SUMMARY OF TEAES AND MOST COMMONLY REPORTED TEAES FOR BRIVARACETAM DOSE GROUPS 50 MG TO 200 MG PER DAY IN THE SAFETY POPULATION

	BRV 50 mg (N = 319)	BRV 100 mg (N = 544)	BRV 150 mg (N = 869)	BRV 200 mg (N = 454)	BRV Overall (N = 2,186)
Number of deaths, n (%)[a]	7 (2.2)	10 (1.8)	9 (1.0)	2 (0.4)	28 (1.3)
Patients with ≥ 1 TEAE, n (%)	277 (86.8)	469 (86.2)	750 (86.3)	352 (77.5)	1,848 (84.5)
Most common TEAEs (≥ 5% the overall BRV group), n (%)					
Headache	79 (24.8)	119 (21.9)	196 (22.6)	63 (13.9)	457 (20.9)
Dizziness	63 (19.7)	90 (16.5)	159 (18.3)	70 (15.4)	382 (17.5)
Somnolence	53 (16.6)	98 (18.0)	120 (13.8)	62 (13.7)	333 (15.2)
Nasopharyngitis	32 (10.0)	79 (14.5)	143 (16.5)	34 (7.5)	288 (13.2)
Fatigue	37 (11.6)	58 (10.7)	101 (11.6)	51 (11.2)	274 (11.3)
Convulsion	47 (14.7)	56 (10.3)	102 (11.7)	26 (5.7)	231 (10.6)
Influenza	35 (11.0)	45 (8.3)	75 (8.6)	15 (3.3)	170 (7.8)
Nausea	35 (11.0)	40 (7.4)	70 (8.1)	23 (5.1)	168 (7.7)

	BRV 50 mg (N = 319)	BRV 100 mg (N = 544)	BRV 150 mg (N = 869)	BRV 200 mg (N = 454)	BRV Overall (N = 2,186)
Diarrhea	27 (8.5)	42 (7.7)	76 (8.7)	21 (4.6)	166 (7.6)
Depression	36 (11.3)	38 (7.0)	61 (7.0)	21 (4.6)	156 (7.1)
Urinary tract infection	24 (7.5)	37 (6.8)	63 (7.2)	31 (6.8)	155 (7.1)
Back pain	26 (8.2)	31 (5.7)	66 (7.6)	19 (4.2)	142 (6.5)
Upper respiratory tract infection	16 (5.0)	37 (6.8)	67 (7.7)	22 (4.8)	142 (6.5)
Insomnia	22 (6.9)	39 (7.2)	56 (6.4)	18 (4.0)	135 (6.2)
Vomiting	17 (5.3)	39 (7.2)	65 (7.5)	13 (2.9)	134 (6.1)
Irritability	21 (6.6)	29 (5.3)	46 (5.3)	18 (4.0)	114 (5.2)
Patients with ≥ 1 SAE, n (%)	66 (20.7)	106 (19.5)	168 (19.3)	61 (13.4)	401 (18.3)
Patients with ≥ 1 WDAE, n (%)	70 (21.9)	79 (14.5)	73 (8.4)	42 (9.3)	264 (12.1)

BRV = brivaracetam; SAE = serious treatment-emergent adverse event; TEAE = treatment-emergent adverse event; WDAE = withdrawal due to adverse event.

Limitations

There are many important limitations related to this pooled data, the main ones being that pooling of open-label, non-randomized studies with no control group prevents estimation of the treatment effect attributable to brivaracetam. Another limitation is that patients were enrolled in the extension studies if the investigator believed that a reasonable benefit could be expected from long-term brivaracetam administration, 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. Efficacy results for the percentage of patients with at least 50% reduction in POS frequency from baseline were reported. However, it should be noted that data on patients diminished with time; therefore, there were fewer patients exposed to brivaracetam at later time points (where only 541 out of 1,836 patients were included in the analysis of 58 to 60 months). There is potential for an overestimation of the efficacy and underestimation of the adverse events results due to the fact that the patients who discontinued may not have been doing well on brivaracetam, leaving only those able to tolerate and, subsequently, do well long term. Finally, there are limitations associated with the analysis of pooling data from different studies, as there would be differences between study populations in terms of their demographics and baseline characteristics, and differences related to the studies' geographic locations.

Summary

The safety and tolerability of brivaracetam was reported based on TEAEs and SAEs, with no new safety signals identified in comparison with the four phase 3 studies included in this review (N01252, N01253, N01254, N01358). However, while the data suggests no new safety concerns and that the reduction in POS frequency was maintained with longer-term treatment, caution is required for the interpretation of all outcomes given the high degree of uncertainty resulting from the key limitations of this uncontrolled, non-randomized, open-label study using pooled data from an extension phase with a highly select patient population.

Summary of Study N01395

Study N01395 was a phase 3b, open-label, single-group, prospective, multi-centre trial. Patients were enrolled from the United States, France, Germany, and Spain. The study comprised a screening period of no longer than one week and a retrospective baseline period during levetiracetam treatment where

BAEs were recorded for up to 16 weeks and seizure counts were recorded for 4 weeks before switching to brivaracetam, and a treatment period of 12 weeks with brivaracetam. On day 1 of the treatment period, the last dose of levetiracetam was taken in the morning, while in the evening, patients received the first dose of brivaracetam 100 mg twice daily (200 mg/day) without titration. If necessary, dose adjustments within the range of 50 mg/day to 200 mg/day were allowed.

Patients included in the study were at least 16 years old, with well-characterized POS or primary generalized epilepsy. Patients receiving levetiracetam at a recommended therapeutic dose (1 g to 3 g per day) were eligible to participate if the investigator expected they would have benefited or were benefiting from levetiracetam, but discontinuation of levetiracetam was warranted within 16 weeks of initiation because of BAEs. Patients must have been receiving two to three AEDs, including levetiracetam, at a dosage that had been stable for ≥ 4 weeks (≥ 12 weeks for primidone, phenytoin, and phenobarbital) prior to screening. Key exclusion criteria for the study included a history or presence of psychogenic non-epileptic seizures, or status epilepticus during the year preceding the study, or experience of cluster or flurry seizures. Patients receiving levetiracetam at a dose 1 g to 3 g per day for at least 16 weeks were not eligible for inclusion in the study.

Study N01395 enrolled 29 patients. Of the 29 patients enrolled, 26 (89.7%) patients completed the study. During the treatment period, 24.1% patients required a dose adjustment. The mean age was 35.8 years (range: 19 to 55 years); 51.7% were male, and 82.8% were Caucasian. The primary BAEs that led to discontinuation of levetiracetam treatment in more than one patient were: irritability, aggression, anxiety, anger, agitation, depression, fatigue, mood swings, and insomnia.

Efficacy Outcomes
Seizure freedom during the treatment period was observed in seven patients (24.1%).

The median number of POS during the treatment period increased by 0.6 seizures per 28 days relative to the median number of POS at baseline during levetiracetam treatment.

Administration of brivaracetam resulted in improved QOLIE-31-P total score, with a mean (standard deviation) increase of 12.1 (11.4) from baseline to the end of the treatment period. The mean (standard deviation) improvement in all QOLIE-31-P sub-scale scores from baseline to the end of the treatment period were as follows: emotional well-being, 14.0 (17.4); cognitive functioning, 10.4 (19.0); medication effects, 27.6 (25.5); energy/fatigue, 10.6 (13.7); overall quality of life, 13.8 (13.3); seizure worry, 12.1 (26.0); social functioning, 10.3 (23.3); and health status, 6.5 (16.5).

Only 26 patients were included in the P-GES and I-GES. For the P-GES, 20 out of 26 patients (76.9%) reported an improvement, and 1 patient (3.8%) reported worsening. For the I-GES, 24 out of 26 investigators (92.3%) reported improvement, and 1 investigator (3.8%) reported worsening.

Harms Outcomes
Twenty-seven patients (93.1%) out of the 29 who switched from levetiracetam to brivaracetam had a clinically meaningful reduction in BAEs, as determined by the investigator, at the end of the treatment period.

TEAEs were reported in 23 patients (79.3%); the most frequently reported TEAEs were headache (17.2%); fatigue (10.3%); and back pain (10.3%); and depression, dizziness, insomnia, nasopharyngitis, and tremor (6.9% for each TEAE). Two patients (6.9%) discontinued the study drug due to TEAE. One

patient discontinued treatment due to lack of efficacy. No death was reported during the study period. One patient (3.4%) experienced an SAE (suicidal ideation and suicide attempt) that was not considered related to the study drug as the patient had a history of altered moods and morbid thoughts that had been attributed to levetiracetam treatment.

Limitations

There are many important limitations related to this study, the main ones being that it was an open-label, non-randomized study, with no control group. In addition, the study had a small sample size and it was an exploratory study with no sample-size calculation and all analyses were descriptive. Also, the study had a short duration. Given that patients and investigators knew what treatment they were receiving; this would bias the results of patient- and investigator-reported outcomes, such as health-related quality of life, P-GES, and I-GES, as well as adverse events. The other limitation is no placebo control. It is particularly problematic for the interpretation of patient-reported outcomes and subjective outcomes, where it is uncertain what the gain in health-related quality of life would be above and beyond the effect of placebo.

Summary

Results from this study suggest that patients who experience BAEs necessitating the discontinuation of levetiracetam treatment might benefit from a switch to brivaracetam. During treatment with brivaracetam, POS frequency was slightly higher (0.6 seizures per 28 days) than the retrospective baseline. However, results should be interpreted with caution owing to the small sample size, lack of comparator, short treatment period, and open-label design.

APPENDIX 7: SUMMARY OF INDIRECT TREATMENT COMPARISONS

Introduction

Background

The included clinical trials in this review did not provide direct evidence about the comparative efficacy and safety of brivaracetam relative to other specified adjunctive antiepileptic drugs (AEDs). The objective of this section is to summarize and critically appraise published and unpublished indirect evidence available for assessment of comparative efficacy and harms of brivaracetam versus other adjunctive AEDs. This summary will inform the pharmacoeconomic evaluation.

Methods

One indirect treatment comparison (ITC) submitted by the manufacturer was reviewed in this section.[6] Although an information specialist conducted an independent literature search for a published ITC that compared brivaracetam with other AEDs, we were able to identify one additional published indirect evidence study.[7]

Description of Indirect Treatment Comparisons Identified

Table 29 presents the population, interventions, comparisons, outcomes, and study design (PICOS) criteria for each ITC identified.

TABLE 29: PICOS CRITERIA FOR STUDY INCLUSION

	Manufacturer-Submitted ITC[6]	Zhang et al.[7]
Population	Adults with partial-onset seizures	Patients with refractory focal seizure
Interventions	As adjunctive therapies: • brivaracetam: 50 mg/day to 200 mg/day • eslicarbazepine acetate 400 mg/day to 1,200 mg/day • lacosamide: 200 mg/day to 400 mg/day • perampanel: 2 mg/day to 12 mg/day • retigabine/ezogabine: 600 mg/day to 1,200 mg/day	As adjunctive therapies: • brivaracetam: 5 mg/day 20 mg/day 25 mg/day 50 mg/day 100 mg/day 150 mg/day 200 mg/day • levetiracetam: 500 mg/day 1,000 mg/day 2,000 mg/day 3,000 mg/day
Comparisons	Placebo or any of the previously mentioned interventions	Placebo

	Manufacturer-Submitted ITC[6]	Zhang et al.[7]
Outcomes	• 50% response rate • Seizure-freedom rate • Serious adverse event rate • Rate of dizziness as an adverse event • Rate of fatigue as an adverse event • Rate of nausea as an adverse event • Rate of somnolence as an adverse event • Discontinuation rate due to TEAEs • Discontinuation rate due to any reason	• 50% response rate • Seizure-freedom rate • AEs • Adverse withdrawal effects
Study Design	RCTs	RCTs
Other	All languages	Only articles published in English with the full text available were included

AE = adverse event; ITC = indirect treatment comparison; PICOS = population, intervention, comparator, outcomes, study design; RCT = randomized controlled trial; TEAE = treatment-emergent adverse event.

Review and Appraisal of Indirect Treatment Comparisons

Review of the Manufacturer-Submitted Indirect Treatment Comparison

Objectives and Rationale for Indirect Treatment Comparison A

The objective of the ITC was to evaluate the efficacy, safety, and tolerability of brivaracetam compared with the latest approved antiepileptic drugs (eslicarbazepine, lacosamide, perampanel, and retigabine/ezogabine). The manufacturer used this information to support the submitted pharmacoeconomic evaluation of brivaracetam.

Methods for Indirect Treatment Comparison A

Study Eligibility and Selection Process

A systematic review was performed to identify randomized controlled trials (RCTs) in comparators of adjunctive therapy of partial-onset seizures (POS) in adults. Databases were searched during a period from November 13, 2014 to November 17, 2014, however, methods used for the literatures search were not provided. Specific treatments included in this review were brivaracetam, eslicarbazepine, lacosamide, perampanel, and retigabine/ezogabine. Inclusion criteria required that the RCTs enroll adult patients with POS. Outcomes of interest were 50% response rate, seizure-freedom rate, serious adverse event rate, rate of dizziness as an adverse event, rate of fatigue as an adverse event, rate of nausea as an adverse event, rate of somnolence as an adverse event, discontinuation rate due to treatment-emergent adverse events, and discontinuation rate due to any reason. Network meta-analyses (NMAs), using the Bayesian framework, were performed for each outcome.

Data Extraction

In total, 21 trials were identified that included one of the comparators of interest (brivaracetam, eslicarbazepine, lacosamide, perampanel, and retigabine/ezogabine) and met the inclusion criteria. Patient characteristics across trials for each comparator are summarized in Table 30. Patients included in all the studies were epileptic patients with POS, with or without secondary generalized seizure. All patients in these trials were adults ≥ 18 years of age. Three of the trials that used the perampanel regimen had patients ≥ 12 years of age. [redacted] All 21 studies included had AEDs as the add-on or adjunctive therapy.

Comparators

In all the 21 studies that had AEDs as the add-on or adjunctive therapy, the comparator group was placebo. [redacted]

Outcomes

Separate ITCs have been conducted for 11 outcomes, detailed as the following:

- 50% response rate (i.e., at least a 50% reduction in monthly type 1 seizure frequency from baseline to the treatment period); calculated using available data for all patients, including patients not completing the assessment period
- seizure-freedom rate during the treatment period; calculated for assessment period completers and defined as the percentage of patients who were free of all seizures (100% reduction)
- 50% response rate (i.e., at least a 50% reduction in monthly type 1 seizure frequency from baseline to the treatment period or maintenance period [where treatment period is not reported])
- seizure-freedom rate during the treatment period or maintenance period (where treatment period is not reported)
- serious adverse event rate during the treatment period
- rate of dizziness as an adverse event during the treatment period
- rate of fatigue as an adverse event during the treatment period
- rate of nausea as an adverse event during the treatment period
- rate of somnolence as an adverse event during the treatment period
- discontinuation rate due to treatment-emergent adverse events during the treatment period
- discontinuation rate due to any reason during the treatment period.

Comparative efficacy was measured using odds ratios.

[redacted]. However, the clinical expert consulted for this review indicated the most meaningful outcome is that measured during the longer treatment period, and results using the treatment period or maintenance period (which was considered secondary by the manufacturer) is preferred; hence, the clinical reviewer included such results only in this summary and appraisal.

TABLE 30: PATIENTS CHARACTERISTICS IN THE INCLUDED STUDIES

Treatment	Total Number of Studies	Mean Age (Years) (Mean [Range])	% Male (Mean [Range])	Epilepsy Duration (Years) (Mean [Range])	Median Seizure Frequency (Mean [Range])	Mean Seizure Frequency (Mean [Range])	Baseline Period (Weeks) (Mean [Range])	Titration Period (Weeks) (Mean [Range])	Maintenance Period (Weeks) (Mean [Range])	Treatment Period (Weeks) (Mean [Range])
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Brivaracetam	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Eslicarbazepine acetate	[redacted]	38.0 (36.4 to 39.5)	48.4 (42.5 to 50.3)	21.8 (18.0 to 23.3)	8.2 (7.3 to 8.7)	14.6 (11.4 to 17.8)	8.0 (8.0 to 8.0)	1.7 (0.7 to 2.0)	12.3 (12.0 to 13.3)	14.0 (14.0 to 14.0)
Lacosamide	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Source: Manufacturer's submission.[6]

TABLE 31: STUDY CHARACTERISTICS

TRIAL (NS = 21)	Treatments		Outcomes								
			Efficacy		Safety					Tolerability	
			50% Response Rate	Seizure-Freedom Rate	Serious AEs	Dizziness	Nausea	Somnolence	Fatigue	Discontinuation Due to AEs	Discontinuation Due to Any Reason
[redacted]											

AE = adverse event; NS = number of studies.

[redacted]

Source: Manufacturer's submission.[6]

Quality Assessment of Included Studies

The authors did not describe how the study quality was assessed or if any assessment was undertaken.

Evidence Network

[redacted]

FIGURE 6: NETWORK OF EVIDENCE FOR 50% RESPONSE RATE

[redacted]

Indirect Treatment Comparison Methods

[redacted]

[redacted]

Results

[redacted]

[redacted]

[redacted]

TABLE 32: RESULTS FROM THE NETWORK META-ANALYSIS OF 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 Brivaracetam for Response (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval.

[redacted]

[redacted]

[redacted]

[redacted]

TABLE 33: RESULTS FROM THE NETWORK META-ANALYSIS OF SEIZURE-FREEDOM RATE DURING THE TREATMENT PERIOD OR MAINTENANCE PERIOD (WHERE TREATMENT PERIOD IS NOT REPORTED)

Interventions	Odds Ratios Relative to Placebo for Seizure Freedom (95% CrI)	Odds Ratios of Active Comparators Versus Brivaracetam for Seizure Freedom (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval.

[redacted]

TABLE 34: RESULTS FROM THE NETWORK META-ANALYSIS OF DISCONTINUATIONS DUE TO TREATMENT-EMERGENT ADVERSE EVENTS DURING THE TREATMENT PERIOD

Interventions	Odds Ratios Relative to Placebo for Discontinuation Due to TEAE (95% CrI)	Odds Ratios of Active Comparators Versus Brivaracetam for Discontinuation Due to TEAE (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval; TEAE = treatment-emergent adverse event.

[redacted]

[redacted]

[redacted]

TABLE 35: RESULTS FROM THE NETWORK META-ANALYSIS OF DISCONTINUATIONS DUE TO ANY REASON DURING THE TREATMENT PERIOD

Interventions	Odds Ratios Relative to Placebo for Discontinuation Due to Any Reason (95% CrI)	Odds Ratios of Active Comparators Versus Brivaracetam for Discontinuation Due to Any Reason (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval.

[redacted]

[redacted]

[redacted]

TABLE 36: RESULTS FROM THE NETWORK META-ANALYSIS OF SERIOUS ADVERSE EVENT RATE DURING THE TREATMENT PERIOD

Interventions	Odds Ratios Relative to Placebo for SAEs (95% CrI)	Odds Ratios of Active Comparators Versus Brivaracetam for SAEs (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval; SAE = serious adverse event.

[redacted]

TABLE 37: RESULTS FROM THE NETWORK META-ANALYSIS OF DIZZINESS AS AN ADVERSE EVENT DURING THE TREATMENT PERIOD

Interventions	Odds Ratios Relative to Placebo for Dizziness (95% CrI)	Odds Ratios of Active Comparators Versus Brivaracetam for Dizziness (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval.

[redacted]

TABLE 38: RESULTS FROM THE NETWORK META-ANALYSIS OF FATIGUE AS AN ADVERSE EVENT DURING THE TREATMENT PERIOD

Interventions	Odds Ratios Relative to Placebo for Fatigue (95% CrI)	Odds Ratios of Active Comparators Versus Brivaracetam for Fatigue (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval.

[redacted]

CrI for

[redacted]

TABLE 39: RESULTS FROM THE NETWORK META-ANALYSIS OF NAUSEA AS AN ADVERSE EVENT DURING THE TREATMENT PERIOD

Interventions	Odds Ratios Relative to Placebo for Nausea (95% CrI)	Odds Ratios of Active Comparators Versus Brivaracetam for Nausea (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval.

Somnolence as an Adverse Event During the Treatment Period

[redacted]

[redacted]

TABLE 40: RESULTS FROM THE NETWORK META-ANALYSIS OF SOMNOLENCE AS AN ADVERSE EVENT DURING THE TREATMENT PERIOD

Interventions	Odds Ratios Relative to Placebo for Somnolence (95% CrI)	Odds Ratios of Active Comparators Versus Brivaracetam for Somnolence (95% CrI)
Eslicarbazepine	[redacted]	[redacted]
Lacosamide	[redacted]	[redacted]
Perampanel	[redacted]	[redacted]
Retigabine	[redacted]	[redacted]
Brivaracetam	[redacted]	

CrI = credible interval.

Critical Appraisal

The literature search is [redacted]. Since then, there may have been new trials published and these would have been excluded from the analysis, potentially impacting the conclusions of the NMA.

Methods used for the literature search, study selection, and data extraction, as well as quality assessment of included trials were provided as part of a systematic review report sent to CDR by the manufacturer at the time it provided comments on the draft review.

[redacted]; consistency testing is useful to validate the ITC results by comparing them with the available direct evidence.

[redacted]

[redacted]

As with all NMA, a statistically non-significant difference between treatments does not necessarily imply that the treatments are equivalent or non-inferior.

In addition, this NMA did not compare brivaracetam versus all possible comparators. As per the opinion of the clinical expert, brivaracetam could replace any of the AEDs that are used in clinical practice as adjunctive therapy in patients with refractory epilepsy such as levetiracetam, clobazam, and lamotrigine. However, the choice of eslicarbazepine, perampanel, and lacosamide as the main comparators is appropriate in that these are the most recent entrants to the AED market for the treatment of refractory epilepsy, and have been recommended for reimbursement by CDR.

Combination of all doses of AEDs in the NMA is a limitation, since this approach does not account for potential dose-response relationships. Furthermore, there is the possibility of bias in the analysis if the amount of evidence available for low, medium, and high doses differed across drugs. As well, the generalizability of combined-dose results to clinical practice may be questionable, since they do not directly relate to any specific dose.

It is noteworthy that a similar NMA (direct comparisons only) by Lattanzi et al.[45] published in 2016 included one additional study of brivaracetam by French et al.,[46] which was not included in the manufacturer-submitted NMA.

The ITC included a regimen (retigabine/ezogabine) that is not currently available in Canada. Lastly, there were no analyses on subgroups of interest (e.g., age, seizure type, and background AED use).

Additional Evidence

One article that compared the efficacy and safety of brivaracetam relative to levetiracetam for the treatment of adults with refractory focal seizures was identified from the literature by Zhang et al.[7]

Methods

The Bucher method was used to conduct the ITCs, and these ITCs were made through placebo groups, which were the common comparators. If the *P* value for ITC of the two treatments was less than 0.05, then the two treatments were considered significantly different. All statistical analyses were performed using Review Manager 5.3 and CADTH ITC software. The Cochran-Mantel-Haenszel test, risk ratio, and 95% confidence interval were used to compare discrete variables. The intention-to-treat populations were used in the analyses of the data. Outcome measures assessed were 50% responder rate (defined as the percentage of patients with at least a 50% reduction in focal-onset seizure frequency from baseline), seizure-free rate (the percentage of patients completing the treatment period without experiencing seizures of any type), adverse events, and adverse withdrawal effects. A comparison of three dose levels was performed: high (levetiracetam 3,000 mg/day versus 200 mg/day, and brivaracetam 150 mg/day), middle (levetiracetam 2,000 mg/day versus brivaracetam 100 mg/day), and low (levetiracetam 1,000 mg/day and 500 mg/day versus brivaracetam 50 mg/day, 25 mg/day, 20 mg/day, and 5 mg/day). The 50% responder rates, seizure-free rates, adverse events, and adverse withdrawal effects of levetiracetam and brivaracetam were first compared against placebo in patients with refractory focal seizures. Then, an ITC for levetiracetam against brivaracetam in patients with refractory focal seizures was performed using CADTH ITC software.

Three electronic databases (MEDLINE, EMBASE, and The Cochrane Library) were searched to identify studies to be included in the analyses. References of all identified publications and ClinicalTrials.gov were also searched in order to identify any additional studies. The cut-off day for the literature search was November 6, 2015. Randomized, double-blind, and placebo-controlled trials, which reported the detailed adverse effects of levetiracetam and brivaracetam in patients with refractory focal seizures and which are published in English with the full text available, were included.

The bias and quality of the published RCTs were assessed using the tool for assessing risk of bias in the Cochrane handbook. Two authors independently searched and screened the titles, abstracts, and full-text articles; in addition, they independently extracted relevant information from each eligible study using the same extraction form. Clinical heterogeneity was assessed by comparing the distribution of important patient factors between studies (age, epilepsy type, duration of epilepsy, and baseline seizure frequency) and trial factors (study design and type of control group). Statistical heterogeneity was assessed by using the I^2 statistic. If I^2 was less than 50%, the heterogeneity was acceptable and the data were analyzed with the fixed-effects model. If I^2 was more than 50% but less than 75%, the heterogeneity was considered unacceptable and the data were analyzed with the random-effects model. If the I^2 value was 75% or more, an a priori decision not to carry out a meta-analysis was made.

Results

Thirteen trials that met the inclusion criteria were identified, of which eight studies in levetiracetam and five studies in brivaracetam compared the study drug with placebo. The eight studies in levetiracetam and five studies in brivaracetam included a total of 1,765 patients and 1,919 patients, respectively. For each included RCT, the baseline characteristics were well balanced in all treatment groups. All of the included RCTs were of high quality. The I^2 values were 50% or more, but not more than 75% for the statistical heterogeneity of efficacy, adverse events, and withdrawal.

Efficacy

Results of the ITC for the 50% responders and seizure-free patients are presented in Table 41. The ITC of levetiracetam versus brivaracetam in patients with refractory focal seizures shows there were no statistical differences at any dose level. However, most risk ratios at three dose levels were higher than 1.00 for the 50% response proportions.

TABLE 41: INDIRECT TREATMENT COMPARISON OF EFFICACY OF LEVETIRACETAM VERSUS BRIVARACETAM

Efficacy and Dose Levels	Levetiracetam Versus Brivaracetam	
	Risk Ratio	95% CI
50% Responders		
High[a]	1.40	0.85 to 2.30
Middle[b]	1.77	0.74 to 4.21
Low[c]	1.14	0.64 to 2.04
Overall	1.34	0.98 to 1.85
Seizure-Free Patients		
High[a]	1.28	0.28 to 5.94
Middle[b]	0.62	0.07 to 5.65
Low[c]	1.00	0.24 to 4.21
Overall	1.01	0.41 to 2.49

BRV = brivaracetam; CI = confidence interval; LEV = levetiracetam; vs. = versus.
[a] High-dose level: LEV 3,000 mg vs. BRV 200 mg and 150 mg.
[b] Middle-dose level: LEV 2,000 mg vs. BRV 100 mg.
[c] Low-dose level: LEV 1,000 mg and 500 mg vs. BRV 50 mg, 25 mg, 20 mg, and 5 mg.

Adverse Events

Results of the ITCs for adverse events are presented in Table 42. The ITC of levetiracetam and brivaracetam in patients with refractory focal seizures showed that only dizziness (risk ratio 0.38; 95% confidence interval, 0.18 to 0.83; *P* = 0.03), showed statistically significant differences at the high-dose level. There were no statistically significant differences in other adverse events at the middle- and low-dose levels.

TABLE 42: INDIRECT TREATMENT COMPARISON OF ADVERSE EVENTS FOR LEVETIRACETAM VERSUS BRIVARACETAM

AEs and Dose Levels	Levetiracetam Versus Brivaracetam	
	Risk Ratio	95% CI
WDAEs		
High[a]	0.94	0.40 to 2.25
Middle[b]	1.51	0.55 to 4.12
Low[c]	1.17	0.52 to 2.64
Overall	1.15	0.70 to 1.89
SAEs		
High[a]	0.57	0.20 to 1.64
Middle[b]	1.85	0.58 to 5.96
Low[c]	1.01	0.45 to 2.29
Overall	1.01	0.57 to 1.79
At least one TEAEs		
High[a]	0.95	0.83 to 1.10
Middle[b]	0.86	0.74 to 1.01
Low[c]	0.94	0.82 to 1.09
Overall	0.92	0.84 to 1.00
Headache		
High[a]	0.41	0.12 to 1.37
Middle[b]	1.06	0.30 to 3.71
Low[c]	0.68	0.33 to 1.39
Overall	0.67	0.40 to 1.12
Dizziness		
High[a]	0.38	0.18 to 0.83
Middle[b]	0.95	0.38 to 2.37
Low[c]	1.35	0.70 to 2.59
Overall	0.85	0.56 to 1.31
Somnolence		
High[a]	0.65	0.36 to 1.18
Middle[b]	1.14	0.58 to 2.25
Low[c]	1.07	0.62 to 1.87
Overall	0.9	0.64 to 1.26
Asthenia		
High[a]	0.87	0.21 to 3.70
Middle[b]	0.71	0.25 to 2.01
Low[c]	0.63	0.26 to 1.53
Overall	0.67	0.40 to 1.10

AE = adverse event; BRV = brivaracetam; CI = confidence interval; LEV = levetiracetam; SAE = serious adverse event; TEAE = treatment-emergent adverse event; vs. = versus; WDAE = withdrawal due to adverse events.

[a] High-dose level: 3,000 mg LEV vs. 200 mg and 150 mg BRV.

[b] Middle-dose level: 2,000 mg LEV vs. 100 mg BRV.

[c] Low-dose level: 1,000 and 500 mg LEV vs. 50 mg, 25 mg, 20 mg, and 5 mg BRV.

Discussion

The Zhang et al.[7] ITC appears to have been conducted with reasonable rigour based on information in the publication; however, the ITCs were based on the Bucher method. The Bucher method, which uses a frequentist approach, only compares two treatments against each other whenever there is a common comparator, while the NMA submitted by the manufacturer compared all treatments against each other using a Bayesian approach. The ITC undertaken by Zhang et al.[7] compared brivaracetam with levetiracetam, while the manufacturer compared brivaracetam with three other adjunct AEDs but did not include levetiracetam in the list of comparators in the submitted ITC.

The manufacturer-submitted ITC generally showed no large and consistent differences between AEDs in efficacy and tolerability outcomes.

The ITC of efficacy between levetiracetam and brivaracetam by Zhang et al.[7] showed no statistical differences at any dose level, which indicates there is insufficient evidence to determine if the efficacy between the two groups at the three dose levels was different. Of note, many of the compared doses for both brivaracetam and levetiracetam are not approved by Health Canada. The ITC of adverse events showed statistical differences for dizziness, which might indicate that brivaracetam had a higher incidence of dizziness compared with levetiracetam. Several potentially confounding factors may have contributed to the findings, where the inclusion criteria of populations in the two treatments had different numbers of resistant AEDs at baseline. In addition, some of the brivaracetam studies had patients who are on concomitant levetiracetam.

Conclusion

In the absence of head-to-head trial data for brivaracetam versus other AEDs, the manufacturer conducted a Bayesian NMA to compare brivaracetam with eslicarbazepine, lacosamide, perampanel, and retigabine/ezogabine. Overall, the ITC showed that brivaracetam, eslicarbazepine, lacosamide, perampanel, and retigabine/ezogabine were more effective than placebo in terms of 50% response rate. It also showed that brivaracetam, eslicarbazepine, and perampanel were more effective than placebo in terms of seizure-freedom rate, but with higher odds for discontinuation (due to any reason and discontinuation due to adverse events), and higher rates of dizziness, fatigue, nausea, and somnolence. There were no significant differences in efficacy; discontinuation due to any reason; or discontinuation due to TEAEs, SAEs, dizziness, fatigue, and somnolence between any of the drugs compared with brivaracetam; however, these results do not allow for a conclusion of equivalence or non-inferiority across drugs. Eslicarbazepine had a statistically significantly increased risk of nausea compared with brivaracetam, while perampanel had a statistically significantly lower risk of nausea compared with brivaracetam. Although the NMA demonstrated sufficient methodological rigour on some criteria, there were some important limitations. These included the lack of subgroup analyses on the population in the indication for brivaracetam (i.e., those aged ≥ 18 years) as well as the choice of comparators (i.e., incorporation of AEDs not approved for use in Canada, as well as exclusion of comparators used in Canadian clinical practice for patients with refractory epilepsy).

The ITC of brivaracetam relative to levetiracetam by Zhang et al.[7] showed no statistical differences at any dose level with respect to efficacy and adverse events, except levetiracetam at high doses may be associated with a lower probability of dizziness, compared with brivaracetam at high doses, for patients with refractory focal seizures.

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