Electronic Appendix 1. Systematic Literature Review, Comprehensive Bayesian Network Meta-Analysis of 63 Trials, and Separate Fixed-Effect Meta-Analysis

Systematic Literature Review

To inform the discrete event simulation model (DESM) used in the health economic evaluation (main article "*Economic Value of Adjunctive Brivaracetam Treatment Strategy for Focal Onset Seizures in Finland*"), a systematic literature review (SLR) was carried out to identify the randomized controlled trials (RCTs) of antiepileptic drugs (AEDs) used as adjunctive therapies for focal onset seizures in adults or adolescents.

Based on the SLR, key parameters needed for the DESM were meta-analyzed in a comprehensive Bayesian network meta-analysis (BNMA) with random effects estimator (primary analysis) and in a separate secondary fixed-effects meta-analysis (FEMA) (secondary analysis examining different perampanel doses):

- At least a 50% reduction in monthly 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)
- Discontinuation due to treatment-emergent adverse events (TEAEs) during the treatment period.

The search strategy methods of SLR and BNMA as well as the included and excluded studies are described in detail in the published article by Charokopou et al. (2019). The present evaluation utilized the version of BNMA used in the Finnish and UK price and reimbursed applications (Charokopou et al. 2016, Väätäinen et al. 2017), which differs slightly from the published BNMA, which is based on an SLR updated after submitting the applications in the UK and Finland.

The relevant parts of the SLR, BNMA, and FEMA used to parameterize the DESM in the present evaluation, as well as the relevant differences between the published SLR and BNMA and data applied in the evaluation, are summarized here. The results used to inform the DESM are reported in Table 1 of the main article.

Studies Identified from the Literature and Included in the BNMA

Original database searches were performed in November 2014 (the SLR and BNMA utilized here and in Charokopou et al. 2016, Väätäinen et al. 2017), with an update conducted between September and November 2015 (SLR and BNMA reported by Charokopou et al. 2019). Searches were conducted using MEDLINE and MEDLINE In-Process, EMBASE, BIOSIS, PsycINFO, and the Cochrane Library. Recent conference proceedings of the American Epilepsy Society (2013 and 2014), International Epilepsy Congress (2011 and 2013), and American Academy of Neurology (2013, 2014, and 2015) were also searched to identify relevant abstracts. In addition, the reference lists of systematic reviews and meta-analyses included in the review were searched for relevant references (see Charokopou et al. 2019 for further details).

The original SLR and BNMA utilized in the present evaluation identified only 63 studies, whereas the published, updated SLR and BNMA (Charokopou et al. 2019) included 65 studies. The more recent BNMA included one additional lacosamide study and one additional levetiracetam study (Table S1).

Table S1 Trials included in the published BNMA, but not included here

Trial	Treatments		50% response rates	Seizure-freedom rate	Discontinuation due to adverse events
EP0008 study / NCT01710657	PBO	LCM	X	X	X
Inoue et al. (2015)	PBO	LEV	X	X	X

In addition, while Charokopou et al. (2019) report only the results examining the subgroup where concomitant use of brivaracetam and levetiracetam is excluded, the base case scenario analysis examined in the present evaluation utilizes the BNMA results from the pooled patient group, where concomitant use is included.

BNMA Results Utilized in the Present Evaluation

To inform DESM, BNMA results were converted to probabilities (reported in Table 1 of the main text).

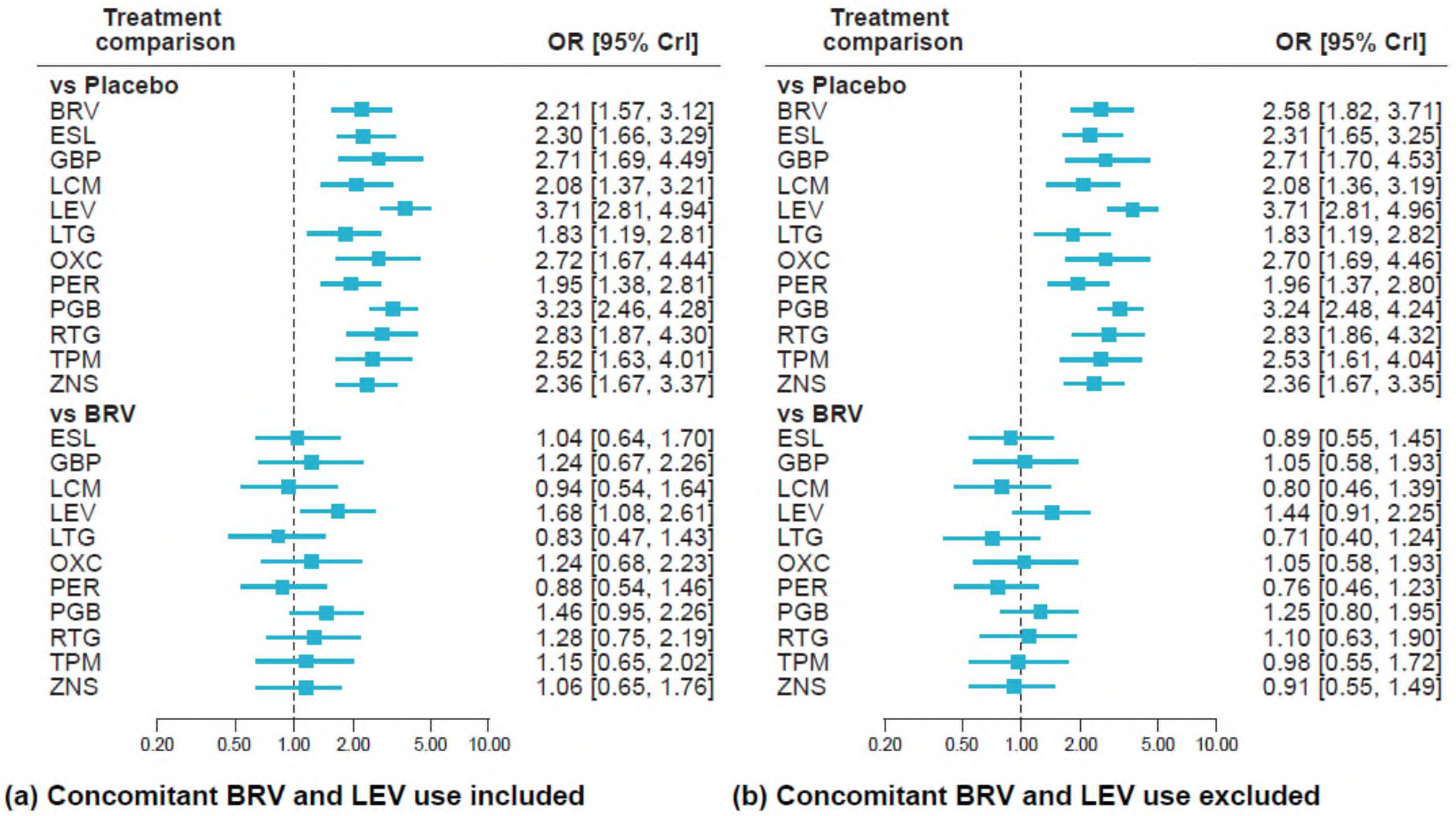
Below, the key results of the BNMA are reported in terms of odds ratios to allow comparison between the published BNMA results and the BNMA results utilized in the present evaluation (Table S2 and Figs S1–S3). Relevant tables in Charokopou et al. 2019 can be referred to for easier comparison.

Table S2 Goodness of fit for each model (compare with Table 3 in Charokopou et al. 2019)

Model	Goodness-of-fit (total residual deviance), mean	Number of data points in the model
Pooled analysis including concomitant levetiracetam use		
50% response rate	115.1	117
Seizure-freedom rate	91.1	93
Discontinuation due to TEAEs	119.2	117
Subgroup analyses excluding concomitant levetiracetam use		
50% response rate	114.2	117
Seizure-freedom rate	86.3	85
Discontinuation due to TEAEs	116.2	111

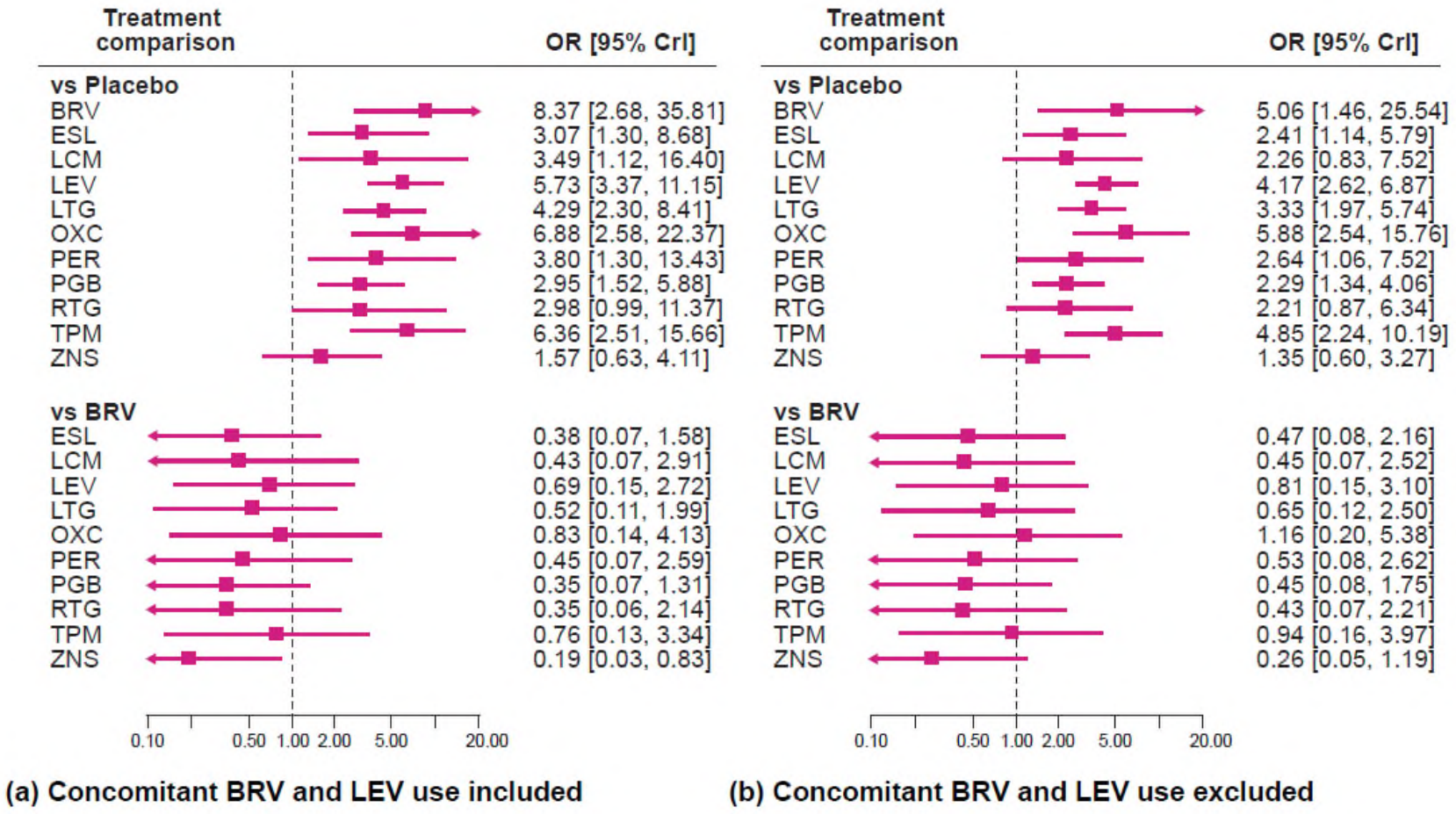
TEAE treatment-emergent adverse event

Fig. S1 Forest plots showing relative efficacy of all interventions vs placebo and brivaracetam for ≥50% responder rate (compare with Fig. 4A and Table 4 in Charokopou et al. 2019)



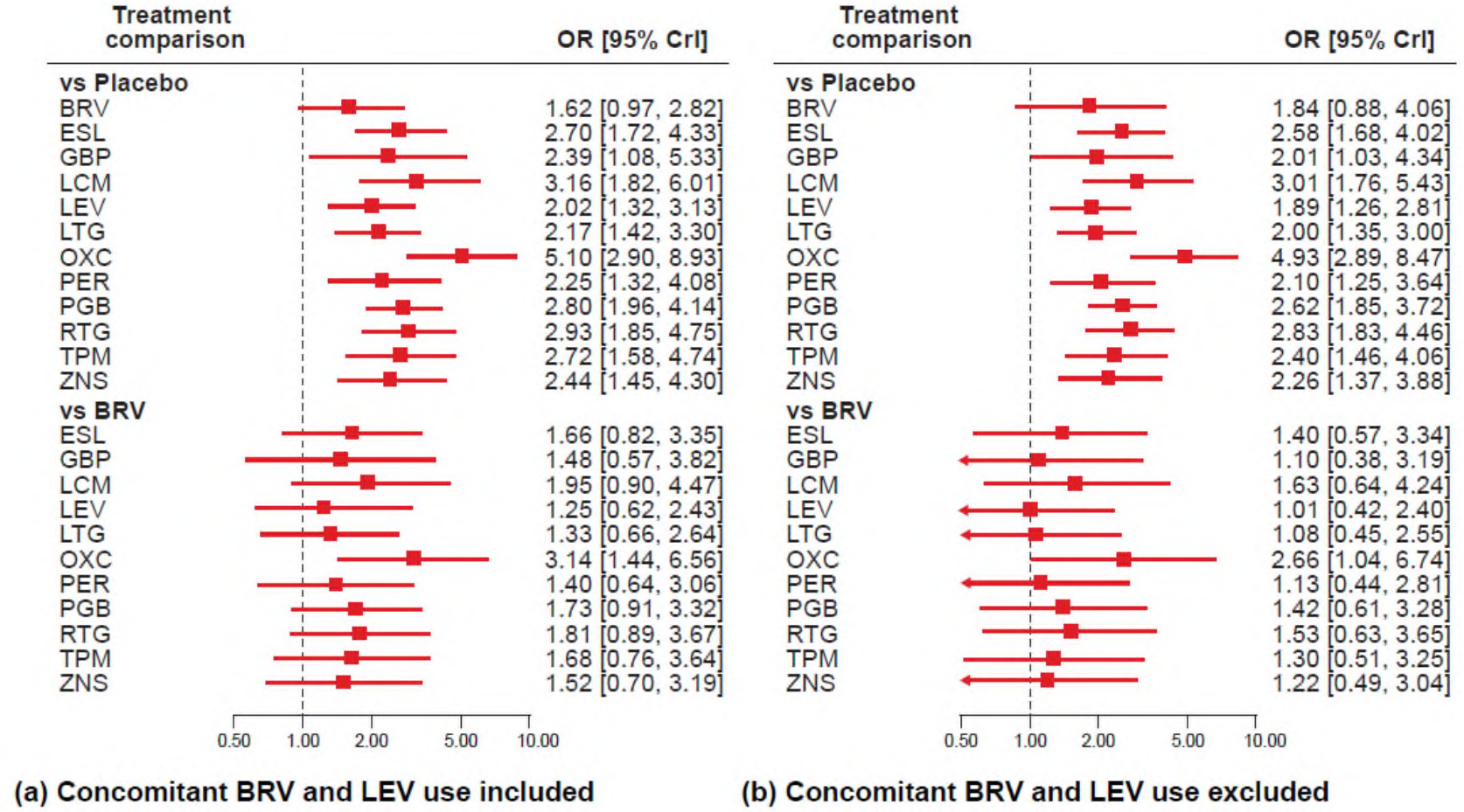
BRV brivaracetam, *CrI* credible interval, *ESL* eslicarbazepine, *GBP* gabapentin, *LCM* lacosamide, *LTG* lamotrigine, *LEV* levetiracetam, *OR* odds ratio, *OXC* oxcarbazepine, *PER* perampanel, *PHT* phenytoin, *PGB* pregabalin, *RTG* retigabine, *TPM* topiramate, *ZNS* zonisamide

Fig. S2 Forest plots showing relative efficacy of all interventions vs placebo and brivaracetam for seizure freedom (compare with Fig. 4B and Table 4 in Charokopou et al. 2019)



BRV brivaracetam, *CrI* credible interval, *ESL* eslicarbazepine, *LCM* lacosamide, *LTG* lamotrigine, *LEV* levetiracetam, *OR* odds ratio, *OXC* oxcarbazepine, *PER* perampanel, *PGB* pregabalin, *RTG* retigabine, *TPM* topiramate, *ZNS* zonisamide

Fig. S3 Forest plots showing relative safety of all interventions vs placebo and brivaracetam for discontinuation rates due to TEAEs (compare with Fig. 5A and Table 4 in Charokopou et al. 2019)



BRV brivaracetam, *CrI* credible interval, *ESL* eslicarbazepine, *GBP* gabapentin, *LCM* lacosamide, *LTG* lamotrigine, *LEV* levetiracetam, *OR* odds ratio, *OXC* oxcarbazepine, *PER* perampanel, *PGB* pregabalin, *RTG* retigabine, *TPM* topiramate, *ZNS* zonisamide

FEMA Examining Brivaracetam and Perampanel

Perampanel dosages were analyzed on the intent-to-treat (ITT) population data of 10 trials available for analysis (Table S3) based on the SLR. First, the results of placebo-controlled RCTs examining brivaracetam and perampanel were pooled in separate FEMA. Then, meta-analyses of brivaracetam and perampanel placebo-controlled trials were carried out using Mantel-Haenszel methodology, without zero-cell correction for the studies with zero events in either arm. This method was chosen to address very small base rates observed in seizure freedom – a well-known challenge in binary meta-analyses. To estimate average outcome probabilities, placebo rates were pooled from all brivaracetam and perampanel clinical trials. FEMA was conducted using inverse variance weighting and logit transformation for proportions.

Heterogeneity among the trials was assessed using the standard T^2 and I^2 statistics, as well as χ^2 test for heterogeneity. All statistical analyses were conducted using *R* statistical software, version 3.3.1, together with meta-analyses and generation of forest plots using package "*meta"*, version 4.5-0.

Table S3 Placebo-controlled brivaracetam and perampanel trials included in the FEMA

Study	Drug	Examined doses	Titration (weeks)	Maintenance (weeks)	50% response	Seizure freedom	Adverse events
Van Paesschen et al. (2013)	BRV	50, 150 mg	3	7	x	x	x
Ryvlin et al. (2014)	BRV	20, 50, 100 mg	0	12	x	x	x
Biton et al. (2014)	BRV	5, 20, 50 mg	0	12	x	x	x
Kwan et al. (2014)	BRV	Mixed dose, ad. 150 mg	8[a]	8	x	x	x
Klein et al. (2015)	BRV	100, 200 mg	0	12	x	x	x
Krauss et al. (2008)	PER	Mixed dose, ad. 4 mg	8	4	x	-	x
Squillacote et al. (2011)	PER	Mixed dose, ad. 12 mg	12	4	x	-	x
French et al. (2012)	PER	8, 12 mg	6	13	x	x	x
Krauss et al. (2012)	PER	2, 4, 8 mg	6	13	x	x	x
French et al. (2013)	PER	8, 12 mg	6	13	x	x	x

ad. up to the specified dose, *BRV* brivaracetam, *PER* perampanel. Assessment only includes the arms examining licensed drug doses (BRV 50–200 mg, PER 2–12 mg). [a]Dose-finding period titrated at 2-week intervals from 20 mg/day; some patients used a therapeutic dose for up to 14 weeks

REFERENCES

Biton V, Berkovic SF, Abou-Khalil B, Sperling MR, Johnson ME, Lu S. Brivaracetam as adjunctive treatment for uncontrolled partial epilepsy in adults: a phase III randomized, double-blind, placebo-controlled trial. Epilepsia. 2014;55:57–66.

Charokopou M, Sander J, Saha R, et al. Cost-effectiveness of brivaracetam versus other antiepileptic drugs used as adjunctive treatment for focal seizures in the UK: a discrete event simulation model. Value Health 2016;19:A365.

Charokopou M, Harvey R, Srivastava K, Brandt C, Borghs S. Relative performance of brivaracetam as adjunctive treatment of focal seizures in adults: a network meta-analysis. Curr Med Res Opin. 2019;35:1345–54.

NCT01710657. A trial to evaluate the efficacy and safety of adjunctive therapy with lacosamide in adults with partial-onset seizures [updated 2017 Aug 25; cited 2017 Nov 10]. Available at: https://clinicaltrials.gov/ct2/show/study/NCT01710657?term=NCT01710657&rank=1#locn

French JA, Krauss GL, Biton V, et al. Adjunctive perampanel for refractory partial-onset seizures: randomized phase III study 304. Neurology. 2012;79:589–96.

French JA, Krauss GL, Steinhoff BJ, et al. Evaluation of adjunctive perampanel in patients with refractory partial-onset seizures: results of randomized global phase III study 305. Epilepsia. 2013;54:117–25.

Inoue Y, Yagi K, Ikeda A, et al. Efficacy and tolerability of levetiracetam as adjunctive therapy in Japanese patients with uncontrolled partial-onset seizures. Psychiatry Clin Neurosci. 2015;69:640–8.

Klein P, Schiemann J, Sperling MR, et al. A randomized, double-blind, placebo-controlled, multicenter, parallel-group study to evaluate the efficacy and safety of adjunctive brivaracetam in adult patients with uncontrolled partial-onset seizures. Epilepsia. 2015;56:1890–8.

Krauss G, Yang J, Biton V, et al. Determination of maximum tolerated dose (MTD), safety, efficacy, and pharmaco-kinetics (PK) of perampanel, a selective AMPA receptor antagonist, as adjunctive therapy in subjects with refractory partial seizures. Epilepsia. 2008;49:1–498. Abst 1.106.

Krauss GL, Serratosa JM, Villanueva V, et al. Randomized phase III study 306: adjunctive perampanel for refractory partial-onset seizures. Neurology. 2012;78:1408–15.

Kwan P, Trinka E, Van Paesschen W, et al. Adjunctive brivaracetam for uncontrolled focal and generalized epilepsies: results of a phase III, double-blind, randomized, placebo-controlled, flexible-dose trial. Epilepsia. 2014;55:38–46.

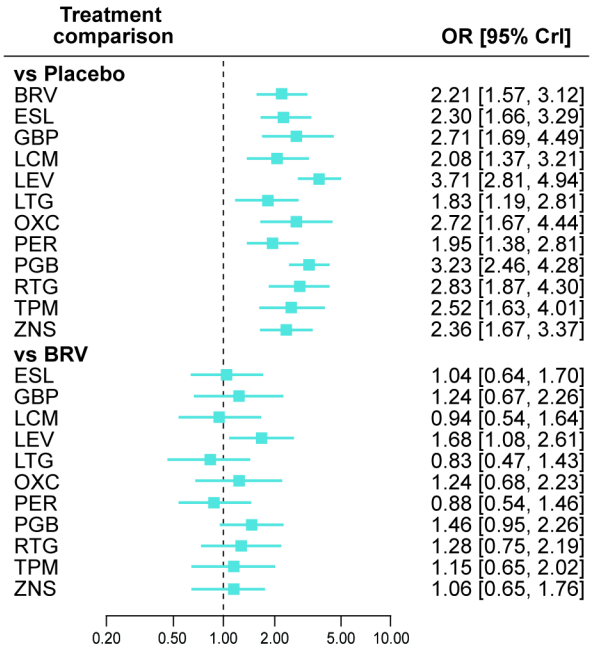
Ryvlin P, Werhahn KJ, Blaszczyk B, Johnson ME, Lu S. Adjunctive brivaracetam in adults with uncontrolled focal epilepsy: results from a double-blind, randomized, placebo-controlled trial. Epilepsia. 2014;55:47–56.

Squillacote D, Krauss G, Vaiciene-Magistris N, Kumar D. A phase II study evaluating the safety, tolerability and efficacy of perampanel, a selective AMPA receptor antagonist, in patients with refractory partial seizures. Epilepsy Curr. 2011;11:Abst 1.280.

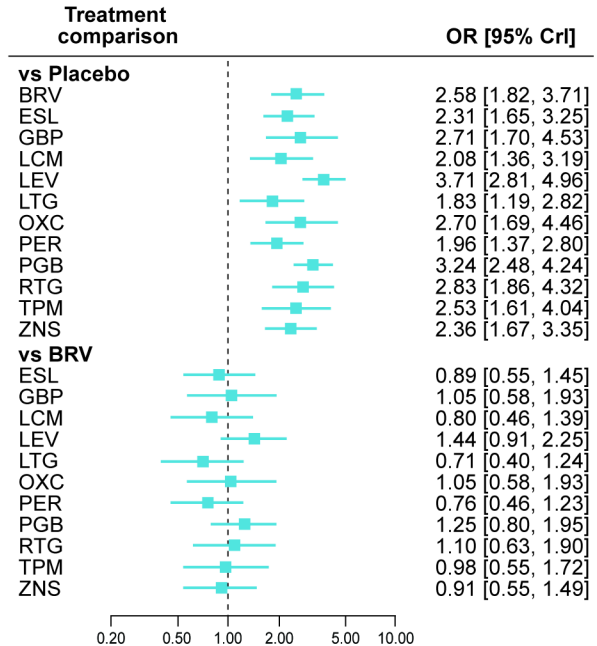
Van Paesschen W, Hirsch E, Johnson M, Falter U, von Rosenstiel P. Efficacy and tolerability of adjunctive brivaracetam in adults with uncontrolled partial-onset seizures: a phase IIb, randomized, controlled trial. Epilepsia. 2013;54:89–97.

Väätäinen S, Soini E, Peltola J, Charokopou M, Taiha M, Kälviäinen R. Cost-effectiveness of brivaracetam as adjunctive therapy for partial-onset epilepsy in the Finnish setting. Value Health 2017;20:A722.

Fig. S1 50% response

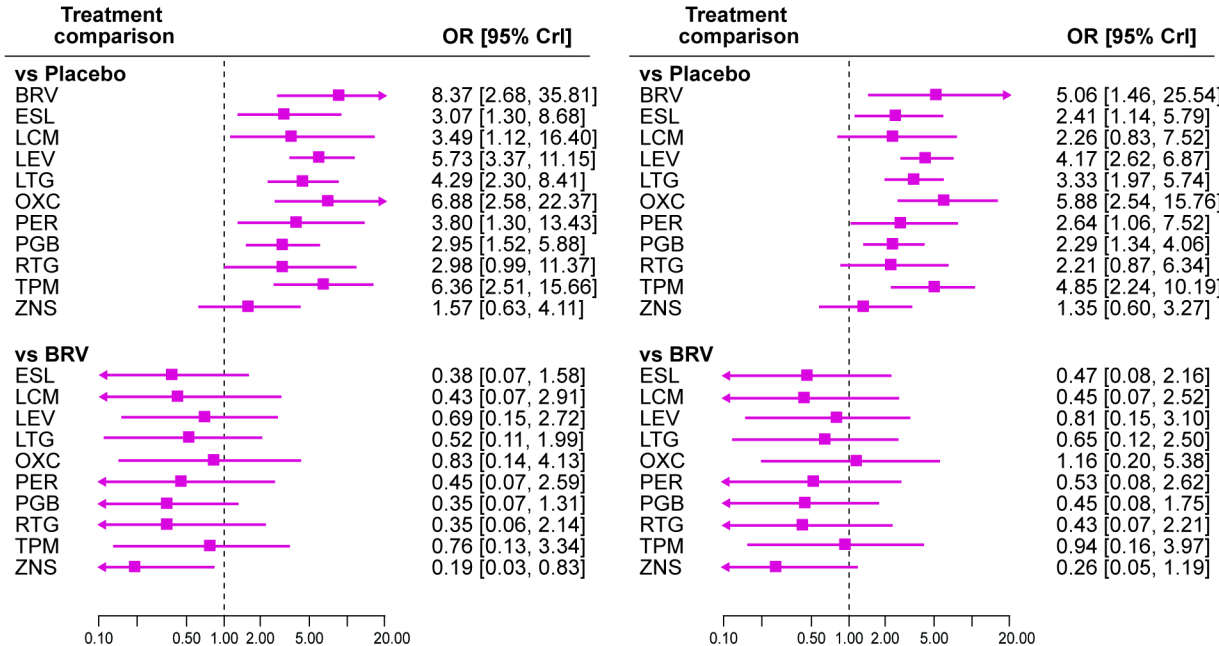


(a) Concomitant BRV and LEV use included



(b) Concomitant BRV and LEV use excluded

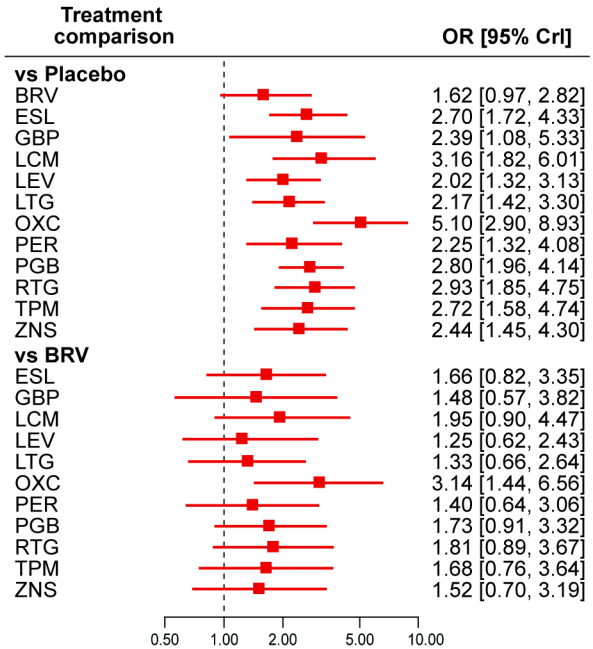
Fig. S2 Seizure freedom



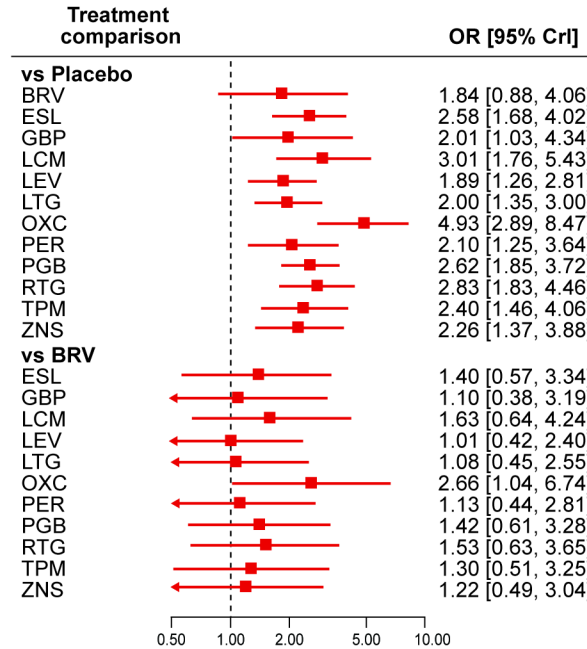
(a) Concomitant BRV and LEV use included

(b) Concomitant BRV and LEV use excluded

Fig. S3 Discontinuation due to AEs



(a) Concomitant BRV and LEV use included



(b) Concomitant BRV and LEV use excluded