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).

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

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

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)

Treatment comparison	OR [95% Crl]	Treatment comparison	OR [95% Crl]
vs Placebo		vs Placebo	
BRV	2.21 [1.57, 3.12]	BRV	2.58 [1.82, 3.71]
ESL -	2.30 [1.66, 3.29]	ESL -	2.31 [1.65, 3.25]
GBP	2.71 [1.69, 4.49]	GBP	- 2.71 [1.70, 4.53]
LCM	2.08 [1.37, 3.21]	LCM	2.08 [1.36, 3.19]
LEV	- 3.71 [2.81, 4.94]	LEV	- 3.71 [2.81, 4.96]
LTG	1.83 [1.19, 2.81]	LTG	1.83 [1.19, 2.82]
oxc	2.72 [1.67, 4.44]	oxc	2.70 [1.69, 4.46]
PER -	1.95 [1.38, 2.81]	PER	1.96 [1.37, 2.80]
PGB -	3.23 [2.46, 4.28]	PGB -	► 3.24 [2.48, 4.24]
RTG	2.83 [1.87, 4.30]	RTG	2.83 [1.86, 4.32]
TPM -	2.52 [1.63, 4.01]	TPM	2.53 [1.61, 4.04]
ZNS	2.36 [1.67, 3.37]	ZNS	2.36 [1.67, 3.35]
vs BRV	2.00 [1.07, 0.07]	vs BRV	2.00 [1.07, 0.00]
ESL -	1.04 [0.64, 1.70]	ESL	0.89 [0.55, 1.45]
GBP	1.24 [0.67, 2.26]	GBP	1.05 [0.58, 1.93]
	0.94 [0.54, 1.64]		0.80 [0.46, 1.39]
	1.68 [1.08, 2.61]		1.44 [0.91, 2.25]
LTG	0.83 [0.47, 1.43]	LTG	
OXC		OXC	0.71 [0.40, 1.24] 1.05 [0.58, 1.93]
PER	1.24 [0.68, 2.23] 0.88 [0.54, 1.46]	PER	
PGB		PGB	
RTG	1.46 [0.95, 2.26]	RTG	1.25 [0.80, 1.95]
TPM	1.28 [0.75, 2.19] 1.15 [0.65, 2.02]	TPM	1.10 [0.63, 1.90] 0.98 [0.55, 1.72]
ZNS	1.06 [0.65, 1.76]	ZNS	0.91 [0.55, 1.49]
2110	1.00 [0.00, 1.70]	2110	0.01 [0.00, 1.40]
0.20 0.50 1.00 2.00	5.00 10.00	0.20 0.50 1.00 2.00	5.00 10.00

(a) Concomitant BRV and LEV use included

(b) Concomitant BRV and LEV use excluded

BRV brivaracetam, Crl 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)

Treatment comparison	OR [95% Crl]	Treatment comparison	OR [95% Crl]
vs Placebo BRV ESL LCM LEV LTG OXC PER PGB RTG TPM ZNS	8.37 [2.68, 35.81] 3.07 [1.30, 8.68] 3.49 [1.12, 16.40] 5.73 [3.37, 11.15] 4.29 [2.30, 8.41] 6.88 [2.58, 22.37] 3.80 [1.30, 13.43] 2.95 [1.52, 5.88] 2.98 [0.99, 11.37] 6.36 [2.51, 15.66] 1.57 [0.63, 4.11]	vs Placebo BRV ESL LCM LEV LTG OXC PER PGB RTG TPM ZNS	5.06 [1.46, 25.54] 2.41 [1.14, 5.79] 2.26 [0.83, 7.52] 4.17 [2.62, 6.87] 3.33 [1.97, 5.74] 5.88 [2.54, 15.76] 2.64 [1.06, 7.52] 2.29 [1.34, 4.06] 2.21 [0.87, 6.34] 4.85 [2.24, 10.19] 1.35 [0.60, 3.27]
vs BRV ESL LCM LEV LTG OXC PER PGB RTG TPM ZNS	0.38 [0.07, 1.58] 0.43 [0.07, 2.91] 0.69 [0.15, 2.72] 0.52 [0.11, 1.99] 0.83 [0.14, 4.13] 0.45 [0.07, 2.59] 0.35 [0.07, 1.31] 0.35 [0.06, 2.14] 0.76 [0.13, 3.34] 0.19 [0.03, 0.83]	VS BRV ESL LCM LEV LTG OXC PER PGB RTG TPM ZNS	0.47 [0.08, 2.16] 0.45 [0.07, 2.52] 0.81 [0.15, 3.10] 0.65 [0.12, 2.50] 1.16 [0.20, 5.38] 0.53 [0.08, 2.62] 0.45 [0.08, 1.75] 0.43 [0.07, 2.21] 0.94 [0.16, 3.97] 0.26 [0.05, 1.19]
0.10 0.50 1.00 2.00 5.00) Concomitant BRV and LEV	20.00	0.10 0.50 1.00 2.00 5.	00 20.00 V use excluded

BRV brivaracetam, Crl 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)

Treatment comparison	OR [95% Crl]	Treatment comparison	OR [95% Crl]
vs Placebo BRV	1.62 [0.97, 2.82]	vs Placebo BRV	1.84 [0.88, 4.06]
ESL	2.70 [1.72, 4.33]	ESL	2.58 [1.68, 4.02]
GBP	2.39 [1.08, 5.33]	GBP	2.01 [1.03, 4.34]
LCM	3.16 [1.82, 6.01]	LCM	3.01 [1.76, 5.43]
LEV	2.02 [1.32, 3.13]	LEV	1.89 1.26, 2.81
LTG	2.17 [1.42, 3.30]	LTG	2.00 [1.35, 3.00]
OXC	5.10 [2.90, 8.93]	OXC	4.93 2.89, 8.47
PER	2.25 [1.32, 4.08]	PER	2.10 1.25, 3.64
PGB —	2.80 [1.96, 4.14]	PGB —	2.62 1.85, 3.72
RTG -	2.93 [1.85, 4.75]	RTG -	2.83 [1.83, 4.46]
TPM	2.72 [1.58, 4.74]	TPM	2.40 [1.46, 4.06]
ZNS	2.44 [1.45, 4.30]	ZNS	2.26 [1.37, 3.88]
vs BRV		vs BRV	
ESL	1.66 [0.82, 3.35]	ESL	1.40 [0.57, 3.34]
GBP	1.48 [0.57, 3.82]	GBP 🔶	- 1.10 [0.38, 3.19]
LCM	1.95 [0.90, 4.47]	LCM	1.63 [0.64, 4.24]
LEV	1.25 [0.62, 2.43]	LEV 🔶	1.01 [0.42, 2.40]
LTG	1.33 [0.66, 2.64]	LTG 🔶	1.08 [0.45, 2.55]
OXC	3.14 [1.44, 6.56]	OXC	2.66 [1.04, 6.74]
PER	- 1.40 [0.64, 3.06]	PER 🗕	1.13 [0.44, 2.81]
PGB	1.73 [0.91, 3.32]	PGB	- 1.42 [0.61, 3.28]
RTG -	1.81 [0.89, 3.67]	RTG	1.53 [0.63, 3.65]
TPM	1.68 [0.76, 3.64]	TPM	- 1.30 [0.51, 3.25]
ZNS	1.52 [0.70, 3.19]	ZNS	1.22 [0.49, 3.04]
		T 1 T	
0.50 1.00 2.00	5.00 10.00	0.50 1.00 2.00	5.00 10.00



(b) Concomitant BRV and LEV use excluded

BRV brivaracetam, Crl 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.

Study	Drug	Examined doses	Titration (weeks)	Maintenance (weeks)	50% response	Seizure freedom	
Van Paesschen et al. (2013)	BRV	50, 150 mg	3	7	x	x	х
Ryvlin et al. (2014)	BRV	20, 50, 100 mg	0	12	x	х	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	х	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	х	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). ^aDose-finding period titrated at 2-week intervals from 20 mg/day; some patients used a therapeutic dose for up to 14 weeks

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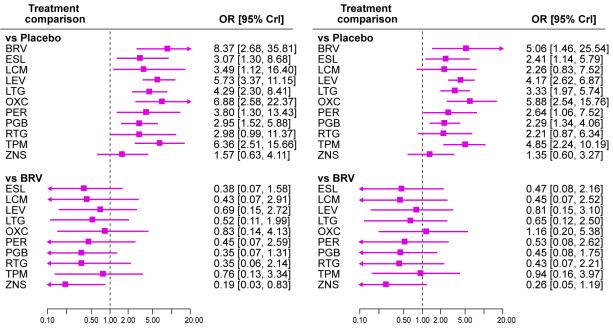
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Fig. S1 50% response

Treatme comparis		OR [95% Crl]	Treatme comparis		OR [95% Crl]
vs Placebo BRV ESL GBP LCM LEV LTG OXC PER		2.21 [1.57, 3.12] 2.30 [1.66, 3.29] 2.71 [1.69, 4.49] 2.08 [1.37, 3.21] 3.71 [2.81, 4.94] 1.83 [1.19, 2.81] 2.72 [1.67, 4.44] 1.95 [1.38, 2.81]	vs Placebo BRV ESL GBP LCM LEV LTG OXC PER		2.58 [1.82, 3.71] 2.31 [1.65, 3.25] 2.71 [1.70, 4.53] 2.08 [1.36, 3.19] 3.71 [2.81, 4.96] 1.83 [1.19, 2.82] 2.70 [1.69, 4.46] 1.96 [1.37, 2.80]
PGB RTG TPM ZNS vs BRV	ŧ	3.23 [2.46, 4.28] 2.83 [1.87, 4.30] 2.52 [1.63, 4.01] 2.36 [1.67, 3.37]	PGB RTG TPM ZNS vs BRV	ŧ	3.24 [2.48, 4.24] 2.83 [1.86, 4.32] 2.53 [1.61, 4.04] 2.36 [1.67, 3.35]
ESL GBP LCM LEV LTG OXC PER PGB RTG TPM ZNS		$\begin{array}{c} 1.04 \left[0.64, 1.70 \right] \\ 1.24 \left[0.67, 2.26 \right] \\ 0.94 \left[0.54, 1.64 \right] \\ 1.68 \left[1.08, 2.61 \right] \\ 0.83 \left[0.47, 1.43 \right] \\ 1.24 \left[0.68, 2.23 \right] \\ 0.88 \left[0.54, 1.46 \right] \\ 1.46 \left[0.95, 2.26 \right] \\ 1.28 \left[0.75, 2.19 \right] \\ 1.15 \left[0.65, 2.02 \right] \\ 1.06 \left[0.65, 1.76 \right] \end{array}$	ESL GBP LCM LEV LTG OXC PER PGB RTG TPM ZNS		$\begin{array}{c} 0.89 & [0.55, \ 1.45] \\ 1.05 & [0.58, \ 1.93] \\ 0.80 & [0.46, \ 1.39] \\ 1.44 & [0.91, \ 2.25] \\ 0.71 & [0.40, \ 1.24] \\ 1.05 & [0.58, \ 1.93] \\ 0.76 & [0.46, \ 1.23] \\ 1.25 & [0.80, \ 1.95] \\ 1.10 & [0.63, \ 1.90] \\ 0.98 & [0.55, \ 1.72] \\ 0.91 & [0.55, \ 1.49] \end{array}$
0.20	0.50 1.00 2.00 5.00 1	0.00	0.20	0.50 1.00 2.00 5.00 10.	00

(a) Concomitant BRV and LEV use included

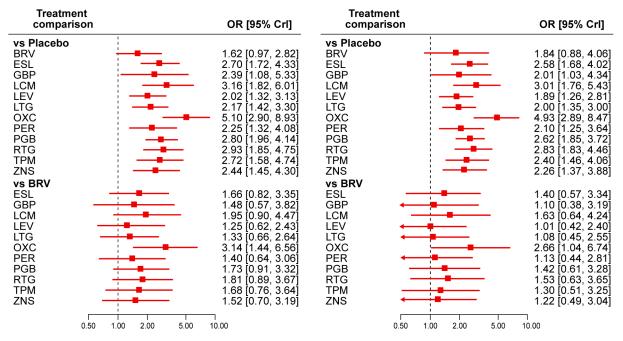
(b) Concomitant BRV and LEV use excluded



(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