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Brivaracetam (epilepsy) –

Addendum to Commission A16-08[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AED	antiepileptic drug
CSR	clinical study report
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
QOLIE 31	Quality of Life in Epilepsy Inventory-31
QOLIE-31-P	Patient-weighted Quality of Life in Epilepsy Inventory-31
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class

1 Background

On 20 June 2016, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A16-08 (Brivaracetam – Benefit assessment according to §35a Social Code Book (SGB) V [1]).

The dossier assessment on brivaracetam came to the conclusion that the indirect comparisons on brivaracetam versus lacosamide, eslicarbazepine and the joint analysis of the studies on lacosamide and eslicarbazepine submitted by the pharmaceutical company (hereinafter referred to as "the company") in the dossier were not usable [1]. On the one hand, not all studies with brivaracetam were relevant for the benefit assessment; on the other, most studies included by the company were not sufficiently similar for the indirect comparisons. In addition, the company had not conducted analyses for all relevant outcomes in the original dossier. This assessment was irrespective of the question whether the indirect comparisons presented by the company were suitable at all for a comparison with the appropriate comparator therapy (ACT) (individually optimized treatment, see dossier assessment A16-08). With its written comments [2], the company submitted new indirect comparisons, in each case with adjusted study pool. These additionally included outcomes that had been missing before (seizure frequency and specific adverse events [AEs]).

To be able to make a decision on the added benefit of brivaracetam versus lacosamide, the G-BA commissioned IQWiG with the assessment of the analyses presented by the company in the commenting procedure under consideration of the information provided in the dossier. The indirect comparison of the brivaracetam study N01254 with the lacosamide studies suitable for this indirect comparison was to be assessed.

The responsibility for the present assessment and the results of the assessment lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

2.1 Study pool

The similarity of the studies for the indirect comparison of brivaracetam (study N01254) versus lacosamide was investigated on the basis of the data presented by the company in the dossier and in the written comments. The arguments put forward by the company in the commenting procedure did not challenge the assessment justified in dossier assessment A16-08 that, of the lacosamide studies presented, only the studies EP0008 and SP755 were similar to the brivaracetam study N01254.

Hence on the brivaracetam side, the N01254 study, and on the lacosamide side, the studies EP0008 and SP755 (in each case the study arms with 400 mg lacosamide daily) were included in the present assessment. The common comparator was basic therapy + placebo.

Table 1: Study pool – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study with brivaracetam			
N01254	Yes	Yes	No
Studies with lacosamide			
EP0008	No	Yes	No
SP755	No	Yes	No

a: Study for which the company was sponsor.
RCT: randomized controlled trial; vs.: versus

Study characteristics/population

The study design and the interventions mandated according to the study protocol of the studies included are presented in Table 2 and Table 3.

Table 2: Characteristics of the studies included – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Study with brivaracetam						
N01254	RCT, double-blind, parallel	Epilepsy patients (≥ 16–70 years) ▪ with focal or generalized epilepsy ▪ patients with focal epilepsy: at least 2 partial-onset seizures per month during the 3 months before baseline, and at least 4 partial-onset seizures during the baseline period, with or without secondary generalization ▪ treatment with 1 to 3 AEDs at a stable dosage, with or without VNS, starting from at least 1 month before the baseline period	BRV 20–150 mg (N = 359) placebo (N = 121) Relevant subpopulation thereof[b]: BRV 20–150 mg (n = 323) placebo (n = 108)	▪ Baseline period: 4 weeks Treatment phase: ▪ dose-finding period: 8 weeks ▪ maintenance period: 8 weeks then either down-titration up to 3 weeks and 2 weeks dose-free period, or transition to open-label, uncontrolled extension studies	74 centres in Austria, Belgium, Czech Republic, Germany, Hong Kong, India, Italy, Norway, Russia, Sweden, Singapore, South Africa, South Korea, Taiwan, Ukraine 10/2007–12/2008	Primary: Frequency of partial-onset seizures per week during the 16-week treatment phase (dose-finding period + maintenance period) Secondary: seizure freedom, 50% responder rate, health-related quality of life, AEs

(continued)

Table 2: Characteristics of the studies included – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Studies with lacosamide						
EP0008	RCT, double-blind, parallel	Epilepsy patients (16–70 years) ▪ with partial-onset seizures with or without secondary generalization for ≥ 2 years before start of treatment despite prior therapy with at least 2 AEDs ▪ on average with at least 4 partial-onset seizures per 28 days with a seizure-free period of no longer than 21 days within 8 weeks before the baseline period ▪ treatment with at least 1, but no more than 3 AEDs at a stable dosage, with or without additional VNS, starting ≥ 4 weeks before the baseline period	LCM 200 mg (N = 183)[c] LCM 400 mg (N = 181) placebo (N = 184)	▪ Baseline period: ▪ 8 weeks ▪ treatment phase ▪ up-titration phase: 4 weeks ▪ maintenance period: ▪ 12 weeks then either down-titration for 3 weeks or 2 weeks transition to open-label, uncontrolled extension study	72 centres in China and Japan 9/2012–8/2014	Primary: change in frequency of partial-onset seizures per 28 days from baseline to maintenance period Secondary: seizure freedom, 50% responder rate, AEs

(continued)

Table 2: Characteristics of the studies included – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
SP755	RCT, double-blind, parallel	Epilepsy patients (16–70 years) ▪ with partial-onset seizures with or without secondary generalization for ≥ 2 years before start of treatment despite prior therapy with at least 2 AEDs ▪ on average with at least 4 partial-onset seizures per 28 days with a seizure-free period of no longer than 21 days within 8 weeks before the baseline period ▪ treatment with at least 1, but no more than 3 AEDs at a stable dosage, with or without additional VNS, starting ≥ 4 weeks before the baseline period	LCM 200 mg (N = 163)[c] LCM 400 mg (N = 159) placebo (N = 163)	▪ Baseline period: 8 weeks ▪ treatment phase ▪ up-titration phase: 4 weeks ▪ maintenance period: 12 weeks then either down-titration for 2 weeks or 2 weeks transition to open-label, uncontrolled extension study	75 centres in Croatia, Czech Republic, Finland, France, Germany, Hungary, Lithuania, Poland, Russia, Spain, Sweden, United Kingdom 6/2004–1/2006	Primary[d]: ▪ Europe: responder rate in partial-onset seizures of ≥ 50% from baseline to maintenance period ▪ FDA: change in seizure frequency per 28 days from baseline to maintenance period Secondary: seizure freedom, health-related quality of life, AEs

a: Primary outcomes contain information without consideration of its relevance for this benefit assessment. Secondary outcomes contain exclusively information on relevant available outcomes from the information provided by the company in the dossier.
b: Relevant subpopulation: patients with focal epilepsy, with and without secondary generalization.
c: The arm is not relevant for the assessment and is not shown in the following tables.
d: "Change or reduction of seizure frequency per 4-week period from baseline to maintenance period" was defined as primary outcome in Europe and as secondary outcome by the FDA; the outcome "responder rate in partial-onset seizures of ≥ 50% from baseline to maintenance period" was defined as primary outcome by the FDA and as secondary outcome for Europe by the FDA.

AE: adverse event; AED: antiepileptic drug; BRV: brivaracetam; FDA: Food and Drug Administration; LCM: lacosamide; N: number of randomized patients; RCT: randomized controlled trial; VNS: vagus nerve stimulation; vs.: versus

Table 3: Characteristics of the interventions – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	Intervention/comparator therapy	
Study with brivaracetam		
N01254[a]	BRV 20 to 150 mg/day, orally (in the morning and evening, divided into 2 equal doses) Treatment phase of 16 weeks: ▪ dose-finding period of 8 weeks initial dose 20 mg/day, then every 2 weeks at the investigator's discretion stepwise dose increase to initially 50 mg/day, then by another 50 mg/day to a maximum of 150 mg/day[b] ▪ Maintenance period for 8 weeks 20 mg/day, 50 mg/day, 100 mg/day, or 150 mg/day then down-titration phase from 20 mg/day: week 1-3 placebo for BRV from 50 mg/day: week 1: 20 mg/day, week 2-3: placebo for BRV from 100 mg/day: week 1: 50 mg/day, week 2: 20 mg/day, week 3: placebo for BRV from 150 mg/day: week 1: 100 mg/day, week 2: 50 mg/day, week 3: 20 mg/day and 2 weeks dose-free period or transition to open-label uncontrolled extension study	**Pretreatment and concomitant treatment** ▪ 1 to 3 AEDs in a stable dosage with or without VNS from ≥ 4 weeks (phenobarbital and primidone for at least 3 months) before baseline period: carbamazepine, clobazam, clonazepam, diazepam, ethosuximide, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, phenobarbital, phenytoin, pregabalin, primidone, tiagabine, topiramate, valproic acid, zonisamide ▪ VNS was allowed and was not counted as AED VNS had to be in place ≥ 9 months before study inclusion ▪ benzodiazepines were allowed if they were not administered for more than 1 week; otherwise they were considered as concomitant AEDs **Prohibited prior and concomitant treatment** ▪ concurrent felbamate treatment or felbamate treatment that was no longer than 18 months ago ▪ concurrent treatment with vigabatrin ▪ Agents affecting the CNS, except at a stable dosage from at least 1 month before baseline period ▪ Agents influencing the metabolism of BRV (CYP2C or CYP3A inducers/inhibitors), except at a stable dosage from at least 1 month before baseline period

(continued)

Table 3: Characteristics of the interventions – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	Intervention/comparator therapy	
Studies with lacosamide		
EP0008[a]	LCM 400 mg/day, orally (in the morning and evening, divided into 2 equal doses) Treatment phase of 16 weeks: ▪ up-titration phase[c] week 1: 100 mg/day week 2: 200 mg/day week 3: 300 mg/day week 4: 400 mg/day ▪ maintenance period[d] for 12 weeks twice 200 mg/day then down-titration phase week 1-3: 200 mg/day or 2 weeks transition to open-label uncontrolled extension study	**Pretreatment and concomitant treatment** ▪ AED: at least 1, but no more than 3 per day (orally) at a stable dosage from ≥ 4 weeks before baseline period and for the total study period with or without additional VNS. VNS was not counted as AED and had to be in place ≥ 6 months before study inclusion ▪ Anxiolytic and hypnotic drugs were allowed in a stable and low dosage **Rescue medication** Benzodiazepines were allowed once each during the titration phase and the maintenance period (3 doses in a 24-hour period), except during the 8-week baseline period. During the down-titration phase, the investigator decided on the administration. **Prohibited prior and concomitant treatment** (4 weeks before screening and during the entire study period) ▪ non-oral AEDs (except benzodiazepines as rescue medication), felbamate, and vigabatrin (from 6 weeks before screening) ▪ antischizophrenic drugs ▪ psychostimulants ▪ monoamine oxidase (MAO) inhibitors ▪ barbiturates (except the ones as concomitant anti-cramping agents) ▪ anaesthetics (except short-term treatment for surgery) ▪ potassium bromide ▪ sodium bromide ▪ calcium bromide ▪ bemegride ▪ pregabalin ▪ herbal drugs approved for epilepsy ▪ ketogenic diet ▪ brain surgery (within 2 years before screening, except VNS implantation)

(continued)

Table 3: Characteristics of the interventions – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	Intervention/comparator therapy	
SP755[a]	LCM 400 mg/day, orally (in the morning and evening, divided into 2 equal doses) Treatment phase of 16 weeks: ▪ up-titration phase[c] week 1: 100 mg/day week 2: 200 mg/day week 3: 300 mg/day week 4: 400 mg/day ▪ maintenance period[d] for 12 weeks twice 200 mg/day then down-titration phase week 1: 200 mg/day week 2: placebo for LCM or 2 weeks transition to open-label uncontrolled extension study	**Pretreatment and concomitant treatment** ▪ AEDs: at least 1, but no more than 3 AEDs per day (orally) at a stable dosage, with or without VNS, starting ≥ 4 weeks before the baseline period VNS had to be in place ≥ 6 months before study inclusion ▪ Anxiolytic and hypnotic drugs were allowed in a stable and low dosage ▪ amphetamines and sedating antihistamines at a stable dosage were allowed **Rescue medication** ▪ Benzodiazepines were allowed once each during the titration phase and the maintenance period (3 doses in a 24-hour period), except during the 8-week baseline period. During the down-titration phase, the investigator decided on the administration. **Prohibited prior and concomitant treatment** (4 weeks before the start of the study and during the entire study period) ▪ neuroleptic drugs ▪ monoamine oxidase (MAO) inhibitors ▪ barbiturates (except as anticonvulsant medication) ▪ anaesthetics

a: The common comparator placebo is not shown in the table.
b: Back-titration during the dose-finding period by one step in the titration scheme was allowed; the reduced dose was continued.
c: Back-titration at the end of the titration phase by one step (100 mg/day) was allowed; the reduced dose was continued in the subsequent maintenance period.
d: Further dose reduction during the maintenance period was not allowed; in this case, the patients had to leave the study.
AED: antiepileptic drug; BRV: brivaracetam; CNS: central nervous system; CYP2C: cytochrome P450 2C; CYP3A: cytochrome P450 3A; LCM: lacosamide; RCT: randomized controlled trial; VNS: vagus nerve stimulation; vs.: versus

Study N01254

The N01254 study was a randomized, double-blind, placebo-controlled study for the approval of brivaracetam. The study had 2 treatment arms: brivaracetam in an individual dosage of 20 mg/day to 150 mg/day and placebo. Brivaracetam and placebo were administered in addition to ongoing stable basic therapy of 1 to 3 antiepileptic drugs (AEDs). The study was conducted in Western Europe, Eastern Europe, and Asia.

Patients with localization-related or generalized epilepsy who were between 16 and 70 years of age were included. The population of patients with localization-related epilepsy was relevant for the present benefit assessment. This comprised 431 of the 480 patients included (90%). The patients were required to have had at least 2 partial-onset seizures per month during the 3 months before the start of the study, and at least 4 partial-onset seizures, each

with or without secondary generalization of the seizures, in the 4 weeks before the baseline period.

At the end of a 4-week baseline period, the patients were randomly assigned in a ratio of 3:1 to the 2 treatment arms, 323 patients to the brivaracetam arm and 108 patients to the placebo arm. Stratification factors were type of epilepsy (localization-related/generalized), region, and concomitant levetiracetam treatment at the start of the study. The proportion of patients with levetiracetam as basic therapy was limited to 20%.

After randomization, the starting dose of 20 mg/day in the brivaracetam arm was gradually and individually increased in an 8-week titration phase. Then the achieved dose was to remain stable for another 8 weeks (maintenance period). The starting dose of 20 mg/day was not relevant for the present assessment because the approved starting dose is 50 mg/day according to the approval [3]. The end of the study was followed by a down-titration phase or transition to an open-label, one-arm extension study.

The primary outcome of the study was the frequency of partial-onset seizures per week during the 16-week treatment phase (titration + maintenance). Further patient-relevant outcomes were seizure freedom, 50% responder rate, health-related quality of life (recorded with the Patient-weighted Quality of Life in Epilepsy Inventory-31; QOLIE-31-P), and AEs.

Study EP0008

The EP0008 study was a randomized, double-blind, placebo-controlled study conducted in China and Japan. The study had 3 treatment arms: lacosamide in dosages of 200 mg/day to 400 mg/day and placebo. Lacosamide and placebo were administered in addition to ongoing stable basic therapy of 1 to 3 AEDs.

Patients with partial-onset epileptic seizures with or without secondary generalization who were between 16 and 70 years of age were included. The patients had to have partial-onset seizures for at least 2 years despite treatment with at least 2 AEDs, with an average of 4 seizures per month with seizure-free periods of no longer than 21 days.

A total of 548 patients were enrolled in the study. At the end of an 8-week baseline period, the patients were randomly assigned in a ratio of 1:1:1, stratified by country (China/Japan), to the 3 treatment arms, 181 patients to the relevant lacosamide arm with 400 mg/day and 184 patients to the placebo arm.

After randomization, in a 4-week titration phase, the dose in the lacosamide arm was gradually increased to the mandated dose of 400 mg/day. If needed, the dose could be reduced by 100 mg at the end of the titration phase. Then the achieved dose was to remain stable for another 12 weeks (maintenance period). The end of the study was followed by a down-titration phase or transition to an open-label, one-arm extension study.

The primary outcome of the study was the change in the frequency of partial-onset seizures per 28 days from the baseline period to the maintenance period. Further patient-relevant outcomes were seizure freedom, 50% responder rate, and AEs.

Study SP755

The SP755 study was a randomized, double-blind, placebo-controlled study conducted in Europe and Australia. The study had 3 treatment arms: lacosamide in dosages of 200 mg/day to 400 mg/day and placebo. Lacosamide and placebo were administered in addition to ongoing stable basic therapy of 1 to 3 AEDs.

Patients with partial-onset epileptic seizures with or without secondary generalization who were between 16 and 70 years of age were included. The patients had to have partial-onset seizures for at least 2 years despite treatment with at least 2 AEDs, with an average of 4 seizures per month with seizure-free periods of no longer than 21 days.

A total of 485 patients were enrolled in the study. At the end of an 8-week baseline period, the patients were randomly assigned in a ratio of 1:1:1, stratified by country, to the 3 treatment arms, 159 patients to the relevant lacosamide arm with 400 mg/day and 163 patients to the placebo arm.

After randomization, in a 4-week titration phase, the dose in the lacosamide arm was gradually increased to the mandated dose of 400 mg/day. If needed, the dose could be reduced by 100 mg at the end of the titration phase. Then the achieved dose was to remain stable for another 12 weeks (maintenance period). The end of the study was followed by a down-titration phase or transition to an open-label, one-arm extension study.

The primary outcome of the study for the US approval was the change in frequency of partial-onset seizures per 28 days from the baseline period to the maintenance period, and for the European approval, the 50% responder rate from the baseline period to the maintenance period. Further patient-relevant outcomes were seizure freedom, health-related quality of life (recorded with the Quality of Life in Epilepsy Inventory-31; QOLIE-31), and AEs.

Patient characteristics

Table 4 shows the demographic characteristics of the relevant patient populations in the relevant treatment arms of each of the included studies. Table 5 shows the disease-specific patient characteristics. Table 6 shows the basic therapies of the study populations.

Table 4: Characteristics of the study populations (demography) – brivaracetam vs. lacosamide

Study Group	N	Age [years] mean (SD)	Sex [F/M] %	Ethnicity [Caucasian/black/ Asian/other] %[a]	Treatment discon-tinuation[b] n (%)	Study discon-tinuation[c] n (%)
Study with brivaracetam						
N01254[d]						
BRV 20-150 mg	323	36 (12)	49/51	58/0/42/0	33 (10.2)	33 (10.2)
Placebo	108	37 (12)	44/56	57/0/42/1[e]	10 (9.3)	10 (9.3)
Studies with lacosamide						
EP0008[f]						
LCM 400 mg	181	32 (12)	42/58	0/0/100/0	30 (16.8)[g]	31 (17.3)
Placebo	184	32 (12)	45/55	0/0/100/0	15 (8.2)[g]	17 (9.3)
SP755[f]						
LCM 400 mg	159	38 (13)	57/43	99/0/1/0	35 (22.2)[g]	36 (22.8)
Placebo	163	39 (11)	43/57	99/0/1/0	16 (10.1)[g]	18 (11.3)

a: Sum > 100% possible in the individual study arms due to rounding.
b: The number of treatment discontinuations includes patients in the treatment phase, which includes the up-titration and the maintenance period.
c: The number of study discontinuations includes the patients in the total treatment phase and, if applicable, down-titration and conversion phase (transition).
d: Data refer to the patient number for the ITT study population.
e: "Other" summarizes native Americans, inhabitants of Alaska, Hawaiians or others, Pacific islanders, and mixed-race patients.
f: Data refer to the patient numbers for the FAS population.
g: Institute's calculation.

AED: antiepileptic drug; BRV: brivaracetam; F: female; FAS: full analysis set; ITT: intention to treat; LCM: lacosamide; M: male; n: number of patients with event; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 5: Characteristics of the study populations (disease characteristics) – brivaracetam vs. lacosamide

Study Group	N	Age at disease onset [years] mean (SD)	Duration of disease at randomization [years] mean (SD) Median [min; max]	Number of partial-onset seizures per 4 weeks at baseline median [mix; max]
Study with brivaracetam				
N01254[a]				
BRV 20-150 mg	323	14.7 (10.3)	21.8 (12.5) 20.0 [0.9; 60.3] [Q1; Q3]: [13.0; 30.42]	8.8 [1.6; 714.4][b] *1 week: 2.2 [0.4; 178.6]*
Placebo	108	14.6 (11.3)	22.1 (11.7) 21.67 [1.8; 63.0] [Q1; Q3]: [15.00; 27.00]	9.2 [3.2; 479.6][b] *1 week: 2.3 [0.8; 119.9]*
Studies with lacosamide				
EP0008[c]				
LCM 400 mg	181	ND	17.9 (11.7) 15.45 [0.4; 56.4]	10.0 [2.6; 221.0]
Placebo	184	ND	16.8 (11.5) 14.34 [1.2; 59.0]	10.5 [3.6; 707.6]
SP755[c]				
LCM 400 mg	159	ND	22.8 (13.2) 22.3 [1.8; 61.9]	10.3 [3.1; 2415.8]
Placebo	163	ND	21.3 (12.3) 20.2 [2.2; 50.8]	9.9 [3.6; 220.0]

a: Data refer to the patient number for the ITT study population.
b: Institute's calculation, multiplied by factor 4.
c: Data refer to the patient numbers for the FAS population.
AED: antiepileptic drug; BRV: brivaracetam; FAS: full analysis set; ITT: intention to treat; LCM: lacosamide; max: maximum; min: minimum; n: number of patients with event; N: number of randomized patients; ND: no data; Q: quartile; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 6: Basic therapies in the total populations of the studies (% of all patients, ≥ 3%) – brivaracetam vs. lacosamide

Study with brivaracetam		Studies with lacosamide			
N01254[a] N = 431 (ITT)		EP0008[a] N = 544 (FAS)		SP755[b] N = 477 (FAS)	
Drug	**n (%)**	**Drug**	**n (%)**	**Drug**	**n (%)**
CBZ	208 (48.3)	CBZ	259 (47.6)	CBZ	227 (47.6)
VPA	136 (31.6)	VPA[c]	250 (46.0)	LTG	146 (30.6)
LTG	111 (25.8)	LEV	130 (23.9)	TPM	135 (28.3)
TPM	110 (25.5)	LTG	117 (21.5)	LEV	94 (19.7)
LEV	84 (19.5)	OXC	86 (15.8)	VPA[c]	81 (17.0)
OXC	58 (13.5)	TPM	83 (15.3)	OXC	75 (15.7)
PHT	48 (11.1)	CZP	61 (11.2)	CZP	53 (11.1)
CLB	52 (12.1)	PHT[d]	55 (10.1)	PHT[d]	39 (8.2)
CZP	40 (9.3)	PB	49 (9.0)	CLB	35 (7.3)
PB	35 (8.1)	CLB	23 (4.2)	GBP	32 (6.7)
PGB	29 (6.7)			PB	18 (3.8)
ZNS	26 (6.0)			Methyl PB	18 (3.8)
Diazepam	21 (4.9)			PRM	17 (3.6)

a: Basic therapies of the treatment phase (titration + maintenance).
b: Basic therapies of the treatment phase (titration + maintenance) and down-titration or transition to open-label extension study.
c: Institute's calculation: sodium valproate + valproic acid + magnesium valproate + valpromide.
d: Institute's calculation: phenytoin + phenytoin sodium.
CBZ: carbamazepine; CLB: clobazam; CZP: clonazepam; FAS: full analysis set; GBP: gabapentin; ITT: intention to treat; LEV: levetiracetam; LTG: lamotrigine; OXC: oxcarbazepine; PB: phenobarbital; PGB: pregabalin; PHT: phenytoin; PRM: primidone; TPM: topiramate; VPA: valproate; ZNS: zonisamide

The patient characteristics were balanced within the studies. Also between the studies, the patient characteristics were largely comparable. There were differences regarding ethnicity: The EP0008 study was conducted only in Asians, the SP755 study only in Caucasians, and the N12054 study in both ethnicities. Regarding the basic therapies, there were certain differences between the studies. Valproic acid was used to a smaller proportion in the SP755 study than in both other studies; topiramate, in contrast, was used to a smaller proportion in the EP0008 study. Carbamazepine was the most commonly used drug in all 3 studies, however; levetiracetam was used in about 20% of the patients in all 3 studies.

2.2 Certainty of results

No study of direct comparison was available for the comparison of brivaracetam with lacosamide. The available adjusted indirect comparison with partly heterogeneous results had a low certainty of results.

2.3 Results

The following patient-relevant outcomes were considered in the assessment:

- Mortality
  - all-cause mortality
- Morbidity
  - seizure frequency
  - 50% responder rate
  - seizure freedom (supplementary information)
- Health-related quality of life
  - health-related quality of life (QOLIE-31)
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to AEs
  - if applicable, further specific AEs

The results of the included studies were only comparable to a limited extent. The reason for this was the different duration of the individual study periods (titration and maintenance period). In both lacosamide studies, the study periods lasted the same amount of time (titration phase: 4 weeks, maintenance period: 12 weeks). The titration phase of the brivaracetam study lasted 8 weeks, hence twice as long as the one of the lacosamide studies; the maintenance period of the brivaracetam study, in contrast, lasted 8 weeks and hence was 4 weeks shorter than the maintenance period of the lacosamide studies. In outcomes that are not standardized for time, such as 50% responder rate, seizure freedom, and AEs, the total treatment period was therefore considered to ensure the best possible comparability of the studies. In seizure frequency, however, the results of the maintenance period were used. On the one hand, this was standardized for time; on the other, the maintenance period constituted the more meaningful reference parameter with regard to content for a comparison with baseline.[3]

[3] When standardizing for time, all events that occurred in the maintenance period are counted and standardized for a period of time (e.g. in the lacosamide studies: number of events in 4 weeks = number of events in 12 weeks/3). This standardization is based on the assumption that the seizure rates do not change substantially during the maintenance period. For the present benefit assessment, the results of the individual studies supported this standardization because the seizure rates in the individual periods of the maintenance period did not differ to an important degree. Irrespective of the present benefit assessment, it would generally be meaningful for the joint analysis of different studies to conduct analyses comprising a fixed period of time (e.g. the last 4 weeks of the maintenance period), which would therefore be usable without assumption of similarity of the maintenance period.

Table 7 to Table 10 summarize the results on the indirect comparison of brivaracetam versus lacosamide with the common comparator placebo (each plus basic therapy). Where necessary, the data provided by the company were supplemented with the Institute's calculations.

Table 7: Results on morbidity (50% responder rate, seizure freedom) – RCT, indirect comparison: brivaracetam vs. lacosamide

Outcome category **Outcome** **Comparison** **Study**	**Brivaracetam or lacosamide** **N**	**Patients with event n (%)**	**Placebo** **N**	**Patients with event n (%)**	**Group difference** **RR [95% CI]; p-value**
Morbidity					
50% responder rate[a]					
Study with brivaracetam					
N01254[b]	323	98 (30.3)	108	18 (16.7)	1.82 [1.16; 2.86]; 0.008[c]
Studies with lacosamide 400 mg					
EP0008[d]	179	82 (45.8)	183	28 (15.3)	2.99 [2.06; 4.36]; < 0.001[c]
SP755[d]	158	61 (38.6)	159	33 (20.8)	1.86 [1.30; 2.67]; < 0.001[c]
Total					Heterogeneity: I^2 = 68.8%, p = 0.073
Adjusted indirect comparison[e]:					
brivaracetam vs. lacosamide 400 mg					
N01254 and EP0008:					0.61 [0.34; 1.10]; 0.098
N01254 and SP755:					0.98 [0.55; 1.75]; 0.942
Seizure freedom					
Study with brivaracetam					
N01254[b]					
Maintenance (8 W)	323	21 (6.5)	108	0 (0)	14.47 [0.88; 236.81]; 0.061
Treatment[a] (16 W)	323	5 (1.5)	108	0 (0)	3.70 [0.21; 66.38]; 0.221[c]
Studies with lacosamide 400 mg					
EP0008[d]					
Maintenance (12 W)	179	8 (5.4)	183	0 (0)	17.38 [1.01; 298.85]; 0.049
Treatment[a] (16 W)			No data available		
SP755[d]					
Maintenance (12 W)	158	3 (1.9)	159	3 (1.9)	1.01 [0.21; 4.91]; 0.994
Treatment[a] (16 W)			No data available		
Total maintenance					Heterogeneity: I^2 = 71.3%, p = 0.062

a: Data of the treatment phase (titration + maintenance).
b: Data refer to the patient number for the ITT study population.
c: Institute's calculation of RR, 95% CI (asymptotic) and p-value (unconditional exact test; CSZ method according to [4]).
d: Data refer to the patient numbers for the FAS population.
e: Institute's calculation, adjusted indirect comparison according to Bucher [5].

CI: confidence interval; CSZ: convexity, symmetry, z score; FAS: full analysis set; ITT: intention to treat; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; vs.: versus; W: weeks

Table 8: Results on morbidity (seizure frequency) – RCT, indirect comparison: brivaracetam vs. lacosamide

Outcome category Outcome Study	Brivaracetam or lacosamide			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study LS means[b] (SE)	N[a]	Baseline values mean (SD)	Change at end of study LS means[b] (SE)	MD [95% CI]; p-value
Morbidity							
Seizure frequency[c]							
Study with brivaracetam							
N01254[d]	323	1.38 (0.73)	per 1 week: 1.171 (0.035) per 28 days: 4.68 (2.52[e])[f]	108	1.37 (0.74)	per 1 week: 1.201 (0.053) per 28 days: 4.8 (2.2[e])[f]	-0.03 [-0.15; 0.09]; ND Analysis 1 [f]: -0.12 [-0.62; 0.38]; ND Analysis 2[g]: -0.12 [-0.27; 0.03]; ND
Studies with lacosamide 400 mg							
EP0008	179	20.70 (28.06)	per 28 days: 2.016 (ND)	183	26.71 (57.90)	per 28 days: 2.520 (ND)	-0.50 [-0.64; -0.37]; ND
SP755	158	42.0 (203.39)	per 28 days: 2.255 (ND)	159	21.8 (31.18)	per 28 days: 2.418 (ND)	-0.16 [-0.32; -0.01]; ND
Total							Heterogeneity: I^2 = 90.3%, p = 0.001
Adjusted indirect comparison[h]:							
brivaracetam vs. lacosamide 400 mg							
Analysis 1 [f]:							
N01254 and EP0008:							0.39 [-0.13; 0.90]; 0.146
N01254 and SP755:							0.04 [-0.48; 0.57]; 0.872
Analysis 2[g]:							
N01254 and EP0008:							0.39 [0.18; 0.59]; < 0.001
N01254 and SP755:							0.04 [-0.17; 0.26]; 0.695

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Analysis of the FAS population; log-transformed seizure frequency, ANCOVA.
c: Data of the maintenance period: N01245: 8 weeks, EP0008 and SP755: 12 weeks each.
d: Data refer to the patient number for the ITT study population.
e: SD.
f: Analysis 1: multiplication of LS mean and SE of the treatment groups by 4, Institute's calculation.
g: Analysis 2: multiplication of mean value by 4, SE estimated with mean SE (= 0.075) of the effect estimates of the lacosamide studies EP0008 (0.07) and SP755 (0.08); Institute's calculation.
h: Institute's calculation, adjusted indirect comparison according to Bucher [5].
ANCOVA: analysis of covariance; CI: confidence interval; FAS: full analysis set; ITT: intention to treat; LS: least square; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; vs.: versus

Table 9: Results (health-related quality of life) – RCT, indirect comparison: brivaracetam vs. lacosamide

Outcome category Outcome Study	Brivaracetam or lacosamide			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SD)	SMD [95% CI]; p-value
Health-related quality of life							
QOLIE-31 total score							
Study with brivaracetam							
N01254[c]	284	55.9 (15)	4.2 (13.7)	98	54.4 (13.8)	3 (12.6)	0.09 [-0.14; 0.32]; 0.447
Study with lacosamide 400 mg							
SP755	146	54.3 (14.6)	2.5 (13.3)	152	57.5 (15.5)	1.7 (11.3)	0.06 [-0.16; 0.29]; 0.576
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							-0.02 [-0.35; 0.30]; ND
QOLIE-31 cognitive functioning							
Study with brivaracetam							
N01254[c]	290	57.6 (23)	5.5 (18.6)	99	56.1 (23.1)	2.3 (19.9)	0.17 [-0.06; 0.40]; 0.148
Study with lacosamide 400 mg							
SP755	146	54.2 (21.2)	3.1 (16.6)	152	57.9 (22)	1.6 (16.5)	0.09 [-0.14; 0.32]; 0.436
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							-0.08 [-0.40; 0.24]; ND
QOLIE-31 emotional well-being							
Study with brivaracetam							
N01254[c]	287	60.3 (17.9)	2.8 (18.1)	99	58.7 (18)	2 (19.3)	0.04 [-0.19; 0.27]; 0.710
Study with lacosamide 400 mg							
SP755	146	58 (16.4)	1.7 (16)	152	61.8 (16.4)	2 (14)	-0.02 [-0.25; 0.21]; 0.863
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							-0.06 [-0.39; 0.26]; ND

(continued)

Table 9: Results (health-related quality of life) – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Outcome category Outcome Study	Brivaracetam or lacosamide			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SD)	SMD [95% CI]; p-value
QOLIE-31 daily activities/social functioning							
Study with brivaracetam							
N01254[c]	290	58.1 (21.8)	2.7 (23.5)	99	54.5 (21.2)	5.6 (21.9)	-0.13 [-0.35; 0.10]; 0.282
Study with lacosamide 400 mg							
SP755	146	54.5 (24.3)	1.1 (21.5)	152	56.9 (23.2)	1.3 (20)	-0.01 [-0.24; 0.22]; 0.934
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							0.12 [-0.21; 0.44]; ND
QOLIE-31 energy/fatigue							
Study with brivaracetam							
N01254[c]	286	50.1 (19.7)	3.3 (19.1)	99	49.2 (17.3)	3 (18)	0.02 [-0.21; 0.24]; 0.892
Study with lacosamide 400 mg							
SP755	146	51.7 (17)	2.4 (16.9)	152	56.3 (18.8)	0.4 (16.2)	0.12 [-0.11; 0.35]; 0.299
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							0.10 [-0.22; 0.43]; ND
QOLIE-31: worry about seizure							
Study with brivaracetam							
N01254[c]	291	43.1 (25.7)	10.3 (22)	99	47.1 (28)	4.7 (23.2)	0.25 [0.02; 0.48]; 0.032
Study with lacosamide 400 mg							
SP755	146	48.4 (24.9)	6.4 (22.4)	152	50.6 (28.1)	3.4 (19.3)	0.14 [-0.08; 0.37]; 0.217
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							-0.11 [-0.43; 0.22]; ND

(continued)

Table 9: Results (health-related quality of life) – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Outcome category Outcome Study	Brivaracetam or lacosamide			Placebo			Group difference
	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SD)	N[a]	Baseline values mean (SD)	Change at end of study mean[b] (SD)	SMD [95% CI]; p-value
QOLIE-31: medication effects							
Study with brivaracetam							
N01254[c]	290	59.2 (25.5)	-0.2 (25.8)	99	58.3 (24.8)	2.8 (27.2)	-0.11 [-0.34; 0.11]; 0.326
Study with lacosamide 400 mg							
SP755	146	55.9 (28.7)	-1 (24.5)	152	54.7 (29)	3.3 (26.6)	-0.17 [-0.40; 0.06]; 0.149
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							-0.05 [-0.38; 0.27]; ND
QOLIE-31: overall health-related quality of life							
Study with brivaracetam							
N01254[c]	291	55 (17)	4.1 (19.2)	98	55.6 (17.8)	-0.5 (17.4)	0.24 [0.02; 0.47]; 0.037
Study with lacosamide 400 mg							
SP755	146	55.7 (16.3)	3.3 (17.6)	153	58.9 (15.9)	2.3 (16.8)	0.06 [-0.17; 0.28]; 0.616
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							-0.19 [-0.51; 0.14]; ND
QOLIE-31 health status							
Study with brivaracetam							
N01254[c]	289	53.7 (21.2)	6.2 (22)	99	52.8 (18.5)	3.7 (18.8)	0.12 [-0.11; 0.35]; 0.313
Study with lacosamide 400 mg							
SP755	146	51.5 (19.1)	3.9 (19)	153	56.7 (19.7)	2.6 (17.8)	0.07 [-0.16; 0.30]; 0.543
Adjusted indirect comparison[d]:							
brivaracetam vs. lacosamide 400 mg							-0.05 [-0.37; 0.27]; ND

a: Number of patients considered in the analysis for the calculation of the effect estimate; the values at the start of the study may be based on other patient numbers.
b: Related to the change from the start of the study until the last study visit of the maintenance period for patients with sufficiently completed questionnaire.
c: Study population with stratification factor: partial-onset seizures.
d: Adjusted indirect comparison according to Bucher [5].

CI: confidence interval; SMD: standardized mean difference (Hedges' g); N: number of analysed patients; ND: no data; QOLIE: Quality of Life in Epilepsy Inventory; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Table 10: Results on all-cause mortality, side effects – RCT, indirect comparison: brivaracetam vs. lacosamide

Outcome category Outcome Comparison Study	Brivaracetam or lacosamide N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
All-cause mortality					
Mortality					
Study with brivaracetam					
N01254[a]	323	1 (0.3)	108	0 (0)	1.01 [0.04; 24.52]; ND
Studies with lacosamide 400 mg					
EP0008	180	0 (0)	184	0 (0)	NC
SP755	159	0 (0)	163	0 (0)	NC
Total					
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					NC
Side effects[c]					
AEs (supplementary information)					
Study with brivaracetam					
N01254[a]	323	211 (65.3)	108	69 (63.9)	–
Studies with lacosamide 400 mg					
EP0008	180	143 (79.4)	184	128 (69.6)	–
SP755	159	109 (68.6)	163	87 (53.4)	–
Total					
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					
SAEs					
Study with brivaracetam					
N01254[a]	323	15 (4.6)	108	9 (8.3)	0.56 [0.25; 1.24]; 0.151
Studies with lacosamide 400 mg					
EP0008	180	9 (5.0)	184	3 (1.6)	3.07 [0.84; 11.14]; 0.089
SP755	159	15 (9.4)	163	6 (3.7)	2.56 [1.02; 6.44]; 0.045
Total					2.72 [1.29; 5.76]; ND
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					0.20 [0.07; 0.61]; ND

(continued)

Table 10: Results on all-cause mortality, side effects – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Outcome category Outcome Comparison Study	Brivaracetam or lacosamide N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Discontinuation due to AEs					
Study with brivaracetam					
N01254[a]	323	21 (6.5)	108	6 (5.6)	1.17 [0.49; 2.82]; 0.726
Studies with lacosamide 400 mg					
EP0008	180	28 (15.6)	184	12 (6.5)	2.39 [1.25; 4.54]; 0.008
SP755	159	24 (15.1)	163	8 (4.9)	3.08 [1.42; 6.64]; 0.004
Total					2.65 [1.62; 4.34]; ND
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					0.44 [0.16; 1.21]; ND
Fatigue (PT)					
Study with brivaracetam					
N01254[a]	323	27 (8.4)	108	4 (3.7)	2.26 [0.81; 6.30]; 0.120
Studies with lacosamide 400 mg					
EP0008	180	0 (0)	184	0 (0)	NC
SP755	159	10 (6.3)	163	6 (3.7)	1.71 [0.64; 4.59]; 0.288
Total					1.71 [0.64; 4.59]; 0.288
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					1.32 [0.32; 5.49]; ND
Dizziness (PT)					
Study with brivaracetam					
N01254[a]	323	28 (8.7)	108	7 (6.5)	1.34 [0.60; 2.97]; 0.476
Studies with lacosamide 400 mg					
EP0008	180	64 (35.6)	184	17 (9.2)	3.85 [2.35; 6.31]; < 0.001
SP755	159	25 (15.7)	163	8 (4.9)	3.20 [1.49; 6.89]; 0.003
Total					3.65 [2.41; 5.52]; ND
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					0.37 [0.15; 0.90]; ND

(continued)

Table 10: Results on all-cause mortality, side effects – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Outcome category Outcome Comparison Study	Brivaracetam or lacosamide N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
General disorders and administration site conditions (SOC)[d]					
Study with brivaracetam					
N01254[a]	323	61 (18.9[e])	108	15 (13.9[e])	1.36 [0.81; 2.29]; ND
Studies with lacosamide 400 mg					
EP0008	180	13 (7.2)	184	12 (6.5)	1.11 [0.52; 2.36]; ND
SP755	159	22 (13.8)	163	12 (7.4)	1.88 [0.96; 3.67]; ND
Total					1.49 [0.89; 2.49]; ND
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					0.91 [0.44; 1.90]; ND
Eye disorders (SOC)[f]					
Study with brivaracetam					
N01254[a]	323	19 (5.9[e])	108	8 (7.4[e])	0.79 [0.36; 1.76]; ND
Studies with lacosamide 400 mg					
EP0008	180	25 (13.9)	184	7 (3.8)	3.65 [1.62; 8.23]; ND
SP755	159	23 (14.5)	163	7 (4.3)	3.37 [1.49; 7.63]; ND
Total					3.51 [1.97; 6.24]; ND
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					0.23 [0.08; 0.61]; ND
Respiratory, thoracic and mediastinal disorders (SOC)[g]					
Study with brivaracetam					
N01254[a]	323	6 (1.9[e])	108	8 (7.4[e])	0.25 [0.09; 0.71]; ND
Studies with lacosamide 400 mg					
EP0008	180	12 (6.7)	184	9 (4.9)	1.36 [0.59; 3.16]; ND
SP755	159	9 (5.7)	163	7 (4.3)	1.32 [0.50; 3.45]; ND
Total					1.34 [0.71; 2.53]; ND
Adjusted indirect comparison[b]: brivaracetam vs. lacosamide 400 mg					0.19 [0.06; 0.63]; ND

(continued)

Table 10: Results on all-cause mortality, side effects – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Outcome category Outcome Comparison Study	Brivaracetam or lacosamide N	 Patients with event n (%)	Placebo N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Gastrointestinal disorders (SOC)[h]					
Study with brivaracetam					
N01254[a]	323	64 (19.8[e])	108	24 (22.2[e])	0.89 [0.59; 1.35]; ND
Studies with lacosamide 400 mg					
EP0008	180	42 (23.3)	184	31 (16.8)	1.38 [0.91; 2.10][e]; ND
SP755	159	26 (16.4)	163	15 (9.2)	1.78 [0.98; 3.23]; ND
Total					1.50 [1.07; 2.11]; 0.019[e]
Adjusted indirect comparison[b]:					
brivaracetam vs. lacosamide 400 mg					0.59 [0.35; 1.02]; 0.057[e]
Psychiatric disorders (SOC)[i]					
Study with brivaracetam					
N01254[a]	323	28 (8.7[e])	108	12 (11.1[e])	0.78 [0.41; 1.48]; ND
Studies with lacosamide 400 mg					
EP0008	180	14 (7.8)	184	8 (4.3)	1.79 [0.77; 4.16]; ND
SP755	159	11 (6.9)	163	10 (6.1)	1.13 [0.49; 2.58]; ND
Total					1.41 [0.78; 2.55]; ND
Adjusted indirect comparison[b]:					
brivaracetam vs. lacosamide 400 mg					0.55 [0.23; 1.32]; ND

a: Data refer to the patient number for the ITT study population with stratification factor: partial-onset seizures; MedDRA classification of AEs.
b: Adjusted indirect comparison according to Bucher [5].
c: Data of the treatment phase (titration + maintenance).
d: General disorders and administration site conditions are mainly caused by the following events (PT): fatigue, fever.
e: Institute's calculation.
f: Eye disorders are mainly caused by the following events (PT): double vision and blurred vision.
g: Respiratory, thoracic and mediastinal disorders are mainly caused by the following events (PT): cough, oropharyngeal pain.
h: Gastrointestinal disorders are mainly caused by the following events (PT): nausea, diarrhoea, and vomiting.
i: Psychiatric disorders cannot be mainly allocated to any PT.

AE: adverse event; CI: confidence interval; ITT: intention to treat; n: number of patients with event; N: number of analysed patients; NC: not calculable; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Mortality

All-cause mortality

There was no difference between brivaracetam and lacosamide for the outcome "all-cause mortality". Only one patient had died in the N01254 study.

Morbidity

Three outcomes (seizure frequency, 50% responder rate, seizure freedom), each of which constitute different operationalizations of the same data collection, were used for the assessment of morbidity. Hereinafter, the results on these 3 operationalizations are therefore first described individually and then interpreted jointly.

Seizure frequency

Approach to adjust the standardizing for time

In all studies, the seizure frequency was operationalized as number of events per period of time. In the framework of the statistical analysis, the seizure frequency first underwent logarithmic transformation and was then analysed using an analysis of covariance (ANCOVA) adjusted for baseline value and further relevant factors. The reported analyses of seizure frequency in the studies were partly based on time periods of different duration (study N01254: 7 days; studies EP0008, SP755: 28 days). For a joint analysis of the studies in the framework of a direct or indirect comparison, analyses regarding a uniform period of time in all studies were required. With its written comments, the company therefore adjusted the data by multiplying the logarithmically transformed ANCOVA results of the N01254 study by a factor 4. This approach was inadequate, however, because multiplication by 4 has to be conducted before the logarithmic transformation in order to obtain correct estimations. To estimate the effect of the erroneous estimation of variance, the Institute therefore conducted its own analysis (analysis 2), in which the variance of the lacosamide studies was assumed for the N01254 study.

Results

No statistically significant result to the advantage or disadvantage of brivaracetam versus placebo was shown in the N01254 study. In contrast, a statistically significant result in favour of lacosamide versus placebo was shown in both lacosamide studies with the effect being notably larger in the EP0008 study than in the SP755 study. Since both studies with lacosamide produced heterogeneous results, the indirect comparison of brivaracetam versus lacosamide was conducted separately for both lacosamide studies.

The analysis according to the company's approach (analysis 1, multiplication of least square means and standard error [SE] of the treatment groups by 4) in both adjusted indirect comparisons showed no statistically significant effect to the advantage or disadvantage of brivaracetam. As described above, this analysis was not usable because of erroneous estimation of variance.

The analysis with assumed variance (analysis 2, multiplication of the mean value by 4, SE estimated with the mean SE of the effect estimates of the lacosamide studies) in the comparison of the studies N01254 and SP755 also showed no statistically significant effect to the advantage or disadvantage of brivaracetam versus lacosamide. The comparison of the studies N01254 and EP0008, in contrast, showed a statistically significant effect to the disadvantage of brivaracetam versus lacosamide.

50% responder rate

All 3 studies showed a statistically significant result to the advantage of brivaracetam or lacosamide versus placebo for the outcome "50% responder rate" with the effect being notably larger in the lacosamide study EP0008 than in the 2 other studies. Since both studies with lacosamide, EP0008 and SP755, produced heterogeneous results for the outcome "50% responder rate", the indirect comparison of brivaracetam versus lacosamide was conducted separately for both lacosamide studies.

Both indirect comparisons showed no statistically significant effect to the advantage or disadvantage of brivaracetam versus lacosamide for the outcome "50% responder rate".

Seizure freedom

The results on seizure freedom could only be interpreted to a limited extent because of the different observation periods: Whereas data for the total treatment phase were available for the N01254 study, only data on the maintenance period were available for the lacosamide studies. No indirect comparison was therefore conducted between the studies. However, no hint of an important difference between brivaracetam and lacosamide resulted from the available data, with heterogeneity between both lacosamide being shown also regarding the outcome "seizure freedom".

Interpretation of the results on morbidity

Heterogeneity between both lacosamide studies was shown in all 3 outcomes on morbidity, and the effect was larger in the EP0008 study than in the SP755 study. The comparison with the EP0008 study showed a disadvantage of brivaracetam regarding seizure frequency. Correspondingly, a marked numerical difference to the disadvantage of brivaracetam was shown in the 50% responder rate, but the difference was not statistically significant. The comparison with the SP755 study showed no marked difference between brivaracetam and lacosamide.

This heterogeneity cannot be clearly explained. In contrast to the SP755 study, the EP0008 study was only conducted in Asian patients. The influence of the ethnicity on efficacy is questionable, however, because the brivaracetam study N01254 was conducted both in Caucasians and in Asians without ethnicity constituting an effect modifier. The differences in basic therapy described above could also be responsible for the heterogeneity, with deviations from the brivaracetam study being shown for both lacosamide studies for individual drugs.

In summary, the joint consideration of the data on morbidity produced no evidence of a disadvantage of brivaracetam versus lacosamide, but raised doubts about brivaracetam having at least the same efficacy as lacosamide.

Health-related quality of life

Health-related quality of life was recorded with the QOLIE-31-P in the N01254 study, and with the previous version QOLIE-31 in the SP755 study. The differences between both versions did not come into effect in the analysis because the QOLIE-31-P was analysed in the N01254 study in the same way as the QOLIE-31.

No statistically significant effects were shown in the individual studies or in the indirect comparison for the total score of the QOLIE-31 or for the individual scales. Overall, neither an advantage nor a disadvantage of brivaracetam versus lacosamide resulted from this.

Side effects

Serious adverse events

In the N01254 study, fewer SAEs occurred under brivaracetam than under placebo (each in combination with basic therapy). In contrast, the meta-analysis of the lacosamide studies showed that SAEs were more frequent under lacosamide than under placebo (each in combination with basic therapy).

The indirect comparison showed a statistically significant effect in favour of brivaracetam versus lacosamide.

Discontinuation due to adverse events

In the N01254 study, discontinuations due to AEs did not occur more frequently under brivaracetam than under placebo (each in combination with basic therapy). In contrast, the meta-analysis of the lacosamide studies showed that discontinuations due to AEs were more frequent under lacosamide than under placebo (each in combination with basic therapy).

The indirect comparison showed no statistically significant effect to the advantage or disadvantage of brivaracetam versus lacosamide for the outcome “discontinuation due to AEs”.

Specific adverse events

The brivaracetam study showed no statistically significant result to the advantage or disadvantage of brivaracetam for the specific AEs considered. In contrast, the meta-analysis of the lacosamide studies showed a statistically significant result to the disadvantage of lacosamide for individual AEs.

The indirect comparison showed a statistically significant effect in favour of brivaracetam versus lacosamide for the AE “dizziness” and for the System Organ Class (SOC) “eye disorders” (mainly caused by the AEs “double vision” and “blurred vision”) and the SOC

"respiratory, thoracic and mediastinal disorders" (mainly caused by the AEs "cough" and "oropharyngeal pain").

Deviating from the company's analyses, no statistically significant effect to the advantage of brivaracetam was shown for the SOC "gastrointestinal disorders". Discrepant data of the company in comparison with the clinical study report (CSR) were available for the lacosamide arm of the EP0008 study (44 patients with event in the analyses subsequently submitted by the company versus 42 patients with event in the CSR).

2.4 Positive and negative effects

The following Table 11 shows an overview of the effects resulting from the indirect comparison of brivaracetam and lacosamide.

Table 11: Positive and negative effects for brivaracetam in the indirect comparison with lacosamide

Positive effects	**Negative effects**
Serious/severe side effects ▪ SAEs Non-serious/non-severe side effects ▪ specific AEs (dizziness, eye disorders, respiratory, thoracic and mediastinal disorders)	-
The available data on morbidity put into question that brivaracetam has at least the same efficacy as lacosamide.	
AE: adverse event; SAE: serious adverse event	

In the overall consideration, there is an advantage of brivaracetam based solely on few outcomes on side effects (SAEs and different specific AEs). However, the available data on morbidity put into question that brivaracetam has at least the same efficacy as lacosamide.

In the overall consideration, no advantage of brivaracetam versus lacosamide resulted from the indirect comparison presented by the company.

This conclusion is irrespective of the question whether the indirect comparison with lacosamide presented by the company was suitable at all for a comparison with the ACT.

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Appendix A – Results on side effects

Table 12: Study N01254, common AEs (in the SOC and in the PT ≥ 2% in at least one study arm) – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**BRV 20-150 mg** **N = 323[b]**	**Placebo** **N = 108[b]**
N01254		
Overall rate of AEs[c]	211 (65.3)	69 (63.9)
NERVOUS SYSTEM DISORDERS	114 (35.3)	33 (30.6)
Dizziness	28 (8.7)	7 (6.5)
Somnolence	36 (11.1)	5 (4.6)
Headache	44 (13.6)	20 (18.5)
Convulsion	16 (5.0)	3 (2.8)
GASTROINTESTINAL DISORDERS	64 (19.8)	24 (22.2)
Nausea	18 (5.6)	9 (8.3)
Diarrhoea	13 (4.0)	5 (4.6)
Vomiting	9 (2.8)	4 (3.7)
Abdominal pain upper	8 (2.5)	4 (3.7)
Dyspepsia	5 (1.5)	4 (3.7)
INFECTIONS AND INFESTATIONS	46 (14.2)	22 (20.4)
Nasopharyngitis	12 (3.7)	8 (7.4)
Upper respiratory tract infection	3 (0.9)	4 (3.7)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	54 (16.7)	13 (12.0)
Fatigue	27 (8.4)	4 (3.7)
Asthenia	7 (2.2)	3 (2.8)
Pyrexia	9 (2.8)	4 (3.7)
PSYCHIATRIC DISORDERS	40 (12.4)	13 (12.0)
Irritability[d]	7 (2.2)	0 (0)
Insomnia	5 (1.5)	3 (2.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	24 (7.4)	12 (11.1)
Back pain	8 (2.5)	7 (6.5)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	26 (8.0)	10 (9.3)
Contusion	7 (2.2)	1 (0.9)
Face injury	0 (0)	3 (2.8)
Head injury	1 (0.3)	4 (3.7)
METABOLISM AND NUTRITION DISORDERS	28 (8.7)	4 (3.7)
Anorexia	7 (2.2)	0 (0)

(continued)

Table 12: Study N01254, common AEs (in the SOC and in the PT ≥ 2% in at least one study arm) – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**BRV 20-150 mg** **N = 323[b]**	**Placebo** **N = 108[b]**
N01254		
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	6 (1.9)	8 (7.4)
Cough	1 (0.3)	3 (2.8)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	19 (5.9)	6 (5.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	18 (5.6)	5 (4.6)
EYE DISORDERS	14 (4.3)	6 (5.6)
RENAL AND URINARY DISORDERS	13 (4.0)	6 (5.6)
Red blood cells urine positive[d]	4 (1.2)	4 (3.7)
EAR AND LABYRINTH DISORDERS	11 (3.4)	5 (4.6)
Vertigo	7 (2.2)	3 (2.8)

a: MedDRA version 9.0; contains several modifications by the company.
b: Data refer to the patient number for the ITT study population with stratification factor partial-onset seizures.
c: Recorded for the total treatment phase (titration phase + maintenance period).
d: The SOC differs from the primary SOC allocated by MedDRA.
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 13: Study N01254, SAEs – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**BRV 20-150 mg** **N = 359[b]**	**Placebo** **N = 121[b]**
N01254		
Overall rate of SAEs[c]	19 (5.3)	9 (7.4)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	3 (0.8)	4 (3.3)
Drug toxicity	1 (0.3)	0 (0)
Ankle fracture	0 (0)	1 (0.8)
Burns second degree	1 (0.3)	0 (0)
Face injury	0 (0)	1 (0.8)
Fall	0 (0)	1 (0.8)
Head injury	0 (0)	1 (0.8)
Skin laceration	1 (0.3)	0 (0)
Spinal fracture	0 (0)	1 (0.8)
NERVOUS SYSTEM DISORDERS	9 (2.5)	2 (1.7)
Headache	1 (0.3)	0 (0)
Tremor	0 (0)	1 (0.8)
Dizziness	1 (0.3)	0 (0)
Postictal state	1 (0.3)	0 (0)
Convulsion	7 (1.9)	1 (0.8)
INFECTIONS AND INFESTATIONS	0 (0)	2 (1.7)
Hepatitis B	0 (0)	1 (0.8)
Pyelonephritis acute	0 (0)	1 (0.8)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (0.8)	0 (0)
Chest pain	1 (0.3)	0 (0)
Drowning	1 (0.3)	0 (0)
Fatigue	1 (0.3)	0 (0)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	2 (0.6)	0 (0)
Pregnancy	2 (0.6)	0 (0)
PSYCHIATRIC DISORDERS	1 (0.3)	1 (0.8)
Depression	1 (0.3)	1 (0.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.3)	0 (0)
Neutropenia	1 (0.3)	0 (0)
EAR AND LABYRINTH DISORDERS	1 (0.3)	0 (0)
Vertigo	1 (0.3)	0 (0)
CARDIAC DISORDERS	1 (0.3)	0 (0)
Myocardial ischaemia	1 (0.3)	0 (0)

(continued)

Table 13: Study N01254, SAEs – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**BRV 20-150 mg** **N = 359[b]**	**Placebo** **N = 121[b]**
N01254		
METABOLISM AND NUTRITION DISORDERS	1 (0.3)	0 (0)
Diabetes mellitus inadequate control	1 (0.3)	0 (0)
GASTROINTESTINAL DISORDERS	1 (0.3)	0 (0)
Abdominal pain	1 (0.3)	0 (0)

a: MedDRA version 9.0; contains several modifications by the company.
b: Number of patients of the total population. No results for SAEs according to SOC/PT are available for the study population with stratification factor "partial-onset seizures", BRV 20-150 mg (N = 323) vs. placebo (N = 108); the overall rate is: 15 (4.6) vs. 9 (8.3)
c: Recorded for the total treatment phase (titration phase + maintenance period).
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 14: Study N01254, discontinuation due to AEs – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**BRV 20-150 mg** **N = 359[b]**	**Placebo** **N = 121[b]**
N01254		
Overall rate of discontinuations due to AEs[c]	22 (6.1)	6 (5.0)
NERVOUS SYSTEM DISORDERS	9 (2.5)	2 (1.7)
Convulsion	4 (1.1)	1 (0.8)
Headache	0 (0)	1 (0.8)
Dizziness	2 (0.6)	0 (0)
Somnolence	2 (0.6)	0 (0)
Balance disorder	1 (0.3)	0 (0)
Coordination abnormal	1 (0.3)	0 (0)
PSYCHIATRIC DISORDERS	7 (1.9)	2 (1.7)
Stress	1 (0.3)	0 (0)
Memory impairment[d]	1 (0.3)	0 (0)
Irritability[d]	2 (0.6)	0 (0)
Depression	2 (0.6)	1 (0.8)
Dysphoria	0 (0)	1 (0.8)
Suicidal ideation	1 (0.3)	0 (0)
Sleep disorder	1 (0.3)	0 (0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (0.8)	2 (1.7)
Asthenia	0 (0)	1 (0.8)
Drowning	1 (0.3)	0 (0)
Fatigue	2 (0.6)	1 (0.8)
Malaise	1 (0.3)	0 (0)
INFECTIONS AND INFESTATIONS	0 (0)	1 (0.8)
Hepatitis B	0 (0)	1 (0.8)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.3)	1 (0.8)
Thrombocytopenia	0 (0)	1 (0.8)
Neutropenia	1 (0.3)	0 (0)
EYE DISORDERS	2 (0.6)	0 (0)
Vision blurred	2 (0.6)	0 (0)
EAR AND LABYRINTH DISORDERS	2 (0.6)	0 (0)
Vertigo	2 (0.6)	0 (0)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	2 (0.6)	0 (0)
Erythema multiforme	1 (0.3)	0 (0)
Urticaria	1 (0.3)	0 (0)

(continued)

Table 14: Study N01254, discontinuation due to AEs – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**BRV 20-150 mg** **N = 359[b]**	**Placebo** **N = 121[b]**
N01254		
METABOLISM AND NUTRITION DISORDERS	1 (0.3)	0 (0)
Anorexia	1 (0.3)	0 (0)
CARDIAC DISORDERS	1 (0.3)	0 (0)
Myocardial ischaemia	1 (0.3)	0 (0)
GASTROINTESTINAL DISORDERS	1 (0.3)	0 (0)
Pancreatitis chronic	1 (0.3)	0 (0)

a: MedDRA version 9.0; contains several modifications by the company.
b: Number of patients of the total population. No results for discontinuations due to AEs according to SOC/PT are available for the study population with stratification factor "partial-onset seizures", BRV 20-150 mg (N = 323) vs. placebo (N = 108); the overall rate is: 21 (6.5) vs. 6 (5.6).
c: Recorded for the total treatment phase (titration phase + maintenance period).
d: The SOC differs from the primary SOC allocated by MedDRA.
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 15: Study EP0008, common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 180**	**Placebo** **N = 184**
EP0008		
Overall rate of AEs[b]	143 (79.4)	128 (69.6)
NERVOUS SYSTEM DISORDERS	92 (51.1)	38 (20.7)
Dizziness	64 (35.6)	17 (9.2)
Somnolence	19 (10.6)	7 (3.8)
Headache	19 (10.6)	11 (6.0)
INFECTIONS AND INFESTATIONS	54 (30.0)	51 (27.7)
Nasopharyngitis	27 (15.0)	23 (12.5)
Upper respiratory tract infection	16 (8.9)	22 (12.0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	13 (7.2)	12 (6.5)
GASTROINTESTINAL DISORDERS	42 (23.3)	31 (16.8)
Nausea	10 (5.6)	5 (2.7)
Diarrhoea	8 (4.4)	3 (1.6)
Vomiting	14 (7.8)	3 (1.6)
Abdominal pain upper	6 (3.3)	4 (2.2)
Hepatobiliary disorders	7 (3.9)	3 (1.6)
Investigations	23 (12.8)	20 (10.9)
White blood cell count decreased	9 (5.0)	1 (0.5)
Metabolism and nutrition disorders	6 (3.3)	7 (3.8)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	9 (5.0)	5 (2.7)
PSYCHIATRIC DISORDERS	14 (7.8)	8 (4.3)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	14 (7.8)	13 (7.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	12 (6.7)	8 (4.3)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	12 (6.7)	9 (4.9)
EYE DISORDERS	25 (13.9)	7 (3.8)
Diplopia	13 (7.2)	1 (0.5)
Vision blurred	8 (4.4)	1 (0.5)
Cardiac disorders	7 (3.9)	2 (1.1)
Vascular disorders	7 (3.9)	0 (0)

a: MedDRA version 16.1.
b: Recorded for the total treatment phase (titration phase + maintenance period).
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 16: Study EP0008, SAEs – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 180**	**Placebo** **N = 184**
EP0008		
Overall rate of SAEs[b]	9 (5.0)	3 (1.6)
Injury, poisoning and procedural complications	3 (1.7)	0 (0)
Comminuted fracture	1 (0.6)	0 (0)
Hand fracture	1 (0.6)	0 (0)
Subdural haematoma	1 (0.6)	0 (0)
Nervous system disorders	2 (1.1)	2 (1.1)
Dizziness	1 (0.6)	0 (0)
Grand mal convulsion	1 (0.6)	0 (0)
Status epilepticus	0 (0)	2 (1.1)
Psychiatric disorders	1 (0.6)	0 (0)
Epileptic psychosis	1 (0.6)	0 (0)
Suicide attempt	0 (0)	0 (0)
Gastrointestinal disorders	1 (0.6)	0 (0)
Upper gastrointestinal haemorrhage	1 (0.6)	0 (0)
Hepatobiliary disorders	1 (0.6)	0 (0)
Drug-induced liver injury	1 (0.6)	0 (0)
Infections and infestations	1 (0.6)	1 (0.5)
Bronchitis	1 (0.6)	0 (0)
Pneumonia	1 (0.6)	1 (0.5)
Metabolism and nutrition disorders	1 (0.6)	0 (0)
Diabetes mellitus	1 (0.6)	0 (0)
Surgical and medical procedures	1 (0.6)	0 (0)
Abortion induced	1 (0.6)	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	0 (0)
Breast cancer	0 (0)	0 (0)

a: MedDRA version 16.1.
b: Recorded for the total treatment phase (titration phase + maintenance period).
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 17: Study EP0008, discontinuation due to AEs – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 180**	**Placebo** **N = 184**
EP0008		
Overall rate of discontinuations due to AEs[b]	28 (15.6)	12 (6.5)
Nervous system disorders	18 (10.0)	3 (1.6)
Dizziness	16 (8.9)	1 (0.5)
Headache	2 (1.1)	1 (0.5)
Somnolence	3 (1.7)	0 (0)
Dysarthria	1 (0.6)	0 (0)
Dyskinesia	1 (0.6)	0 (0)
Epilepsy	1 (0.6)	0 (0)
Memory impairment	0 (0)	0 (0)
Syncope	1 (0.6)	0 (0)
Convulsion	0 (0)	1 (0.5)
Eye disorders	8 (4.4)	1 (0.5)
Diplopia	5 (2.8)	0 (0)
Vision blurred	2 (1.1)	0 (0)
Visual impairment	1 (0.6)	0 (0)
Eyelid oedema	0 (0)	1 (0.5)
Gastrointestinal disorders	5 (2.8)	3 (1.6)
Nausea	3 (1.7)	2 (1.1)
Vomiting	2 (1.1)	1 (0.5)
Abdominal pain upper	1 (0.6)	0 (0)
Diarrhoea	0 (0)	0 (0)
Psychiatric disorders	3 (1.7)	2 (1.1)
Agitation	1 (0.6)	0 (0)
Anxiety disorder	1 (0.6)	0 (0)
Dysphoria	0 (0)	0 (0)
Epileptic psychosis	1 (0.6)	0 (0)
Suicide attempt	0 (0)	0 (0)
Bradyphrenia	0 (0)	1 (0.5)
Nervousness	0 (0)	1 (0.5)
General disorders and administration site conditions	0 (0)	3 (1.6)
Chest discomfort	0 (0)	1 (0.5)
Feeling jittery	0 (0)	1 (0.5)
Malaise	0 (0)	1 (0.5)

(continued)

Table 17: Study EP0008, discontinuation due to AEs – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	Patients with event n (%)	
SOC[a] PT[a]	LCM 400 mg N = 180	Placebo N = 184
EP0008		
Cardiac disorders	0 (0)	2 (1.1)
Palpitations	0 (0)	1 (0.5)
Ventricular extrasystoles	0 (0)	1 (0.5)
Investigations	2 (1.1)	2 (1.1)
Aspartate aminotransferase increased	2 (1.1)	1 (0.5)
Alanine aminotransferase increased	1 (0.6)	1 (0.5)
Gamma-glutamyltransferase increased	1 (0.6)	1 (0.5)
Transaminases increased	1 (0.6)	0 (0)
Hepatobiliary disorders	2 (1.1)	0 (0)
Drug-induced liver injury	1 (0.6)	0 (0)
Hepatic function abnormal	1 (0.6)	0 (0)
Skin and subcutaneous tissue disorders	2 (1.1)	0 (0)
Dermatitis allergic	1 (0.6)	0 (0)
Rash	1 (0.6)	0 (0)
Injury, poisoning and procedural complications	1 (0.6)	0 (0)
Contusion	1 (0.6)	0 (0)
Fibula fracture	0 (0)	0 (0)
Vascular disorders	1 (0.6)	0 (0)
Pallor	1 (0.6)	0 (0)
Congenital, familial and genetic disorders	0 (0)	1 (0.5)
Cerebral palsy	0 (0)	1 (0.5)
Ear and labyrinth disorders	0 (0)	0 (0)
Vertigo	0 (0)	0 (0)
Metabolism and nutrition disorders	0 (0)	1 (0.5)
Decreased appetite	0 (0)	1 (0.5)
Reproductive system and breast disorders	0 (0)	1 (0.5)
Erectile dysfunction	0 (0)	1 (0.5)
Respiratory, thoracic and mediastinal disorders	0 (0)	1 (0.5)
Oropharyngeal pain	0 (0)	1 (0.5)

a: MedDRA version 16.1.
b: Recorded for the total treatment phase (titration phase + maintenance period).

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 18: Study SP755, common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 159**	**Placebo** **N = 163**
SP755		
Overall rate of AEs[b]	109 (68.6)	87 (53.4)
NERVOUS SYSTEM DISORDERS	61 (38.4)	41 (25.2)
DIZZINESS	25 (15.7)	8 (4.9)
HEADACHE	13 (8.2)	12 (7.4)
COORDINATION ABNORMAL	10 (6.3)	1 (0.6)
TREMOR	6 (3.8)	2 (1.2)
SOMNOLENCE	6 (3.8)	6 (3.7)
CONVULSION	4 (2.5)	6 (3.7)
INFECTIONS AND INFESTATIONS	26 (16.4)	23 (14.1)
NASOPHARYNGITIS	10 (6.3)	6 (3.7)
INFLUENZA	6 (3.8)	5 (3.1)
UPPER RESPIRATORY TRACT INFECTION	0 (0)	3 (1.8)
GASTROINTESTINAL DISORDERS	26 (16.4)	15 (9.2)
NAUSEA	13 (8.2)	2 (1.2)
VOMITING	9 (5.7)	3 (1.8)
EYE DISORDERS	23 (14.5)	7 (4.3)
DIPLOPIA	16 (10.1)	2 (1.2)
VISION BLURRED	6 (3.8)	2 (1.2)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	22 (13.8)	12 (7.4)
FATIGUE	10 (6.3)	6 (3.7)
Investigations	9 (5.7)	4 (2.5)
Gamma-glutamyltransferase increase	1 (0.6)	6 (3.7)
EAR AND LABYRINTH DISORDERS	14 (8.8)	5 (3.1)
VERTIGO	10 (6.3)	3 (1.8)
PSYCHIATRIC DISORDERS	11 (6.9)	10 (6.1)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	11 (6.9)	8 (4.9)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	8 (5.0)	11 (6.7)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	10 (6.3)	7 (4.3)
METABOLISM AND NUTRITION DISORDERS	9 (5.7)	5 (3.1)
HYPERCHOLESTEROLAEMIA	5 (3.1)	1 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	9 (5.7)	7 (4.3)

(continued)

Table 18: Study SP755, common AEs (in the SOC and in the PT ≥ 3% in at least one study arm) – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 159**	**Placebo** **N = 163**
SP755		
BLOOD AND LYMPHATIC SYSTEM DISORDERS	3 (1.9)	7 (4.3)
NEUTROPENIA	1 (0.6)	3 (1.8)
CARDIAC DISORDERS	5 (3.1)	1 (0.6)

a: MedDRA version 9.0.
b: Recorded for the total treatment phase (titration phase + maintenance period).
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus

Table 19: Study SP755, SAEs – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	Patients with event n (%)	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 159**	**Placebo** **N = 163**
SP755		
Overall rate of SAEs[b]	15 (9.4)	6 (3.7)
NERVOUS SYSTEM DISORDERS	3 (1.9)	4 (2.5)
GRAND MAL CONVULSION	2 (1.3)	0 (0)
EPILEPSY	0 (0)	1 (0.6)
CONVULSION	1 (0.6)	1 (0.6)
SOMNOLENCE	0 (0)	0 (0)
COMPLEX PARTIAL SEIZURES	0 (0)	1 (0.6)
MIGRAINE	0 (0)	1 (0.6)
PARTIAL SEIZURES	0 (0)	1 (0.6)
PSYCHIATRIC DISORDERS	3 (1.9)	0 (0)
PSYCHOTIC DISORDER	2 (1.3)	0 (0)
EPILEPTIC PSYCHOSIS	1 (0.6)	0 (0)
INSOMNIA	0 (0)	0 (0)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	2 (1.3)	0 (0)
MALAISE	1 (0.6)	0 (0)
PYREXIA	1 (0.6)	0 (0)
EAR AND LABYRINTH DISORDERS	2 (1.3)	0 (0)
TYMPANIC MEMBRANE PERFORATION	1 (0.6)	0 (0)
VESTIBULAR DISORDER	1 (0.6)	0 (0)
INVESTIGATIONS	1 (0.6)	0 (0)
ELECTROCARDIOGRAM PR PROLONGATION	1 (0.6)	0 (0)
HEPATIC ENZYME INCREASED	0 (0)	0 (0)
TRANSAMINASES INCREASED	0 (0)	0 (0)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)	0 (0)	0 (0)
FIBROMATOSIS	0 (0)	0 (0)
SALIVARY GLAND ADENOMA	0 (0)	0 (0)
METABOLISM AND NUTRITION DISORDERS	0 (0)	1 (0.6)
DIABETES MELLITUS	0 (0)	0 (0)
HYPONATRAEMIA	0 (0)	1 (0.6)
POLYDIPSIA	0 (0)	1 (0.6)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.6)	0 (0)
THROMBOCYTOPENIA	1 (0.6)	0 (0)
CARDIAC DISORDERS	1 (0.6)	0 (0)
SINUS BRADYCARDIA	1 (0.6)	0 (0)

(continued)

Table 19: Study SP755, SAEs – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 159**	**Placebo** **N = 163**
SP755		
INFECTIONS AND INFESTATIONS	1 (0.6)	0 (0)
NASOPHARYNGITIS	1 (0.6)	0 (0)
SINUSITIS	1 (0.6)	0 (0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0)	0 (0)
CONCUSSION	0 (0)	0 (0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0)	0 (0)
PAIN IN EXTREMITY	0 (0)	0 (0)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS	1 (0.6)	0 (0)
ABORTION MISSED	1 (0.6)	0 (0)
RENAL AND URINARY DISORDERS	1 (0.6)	0 (0)
NEPHROLITHIASIS	1 (0.6)	0 (0)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS	0 (0)	1 (0.6)
MENORRHAGIA	0 (0)	1 (0.6)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	0 (0)	0 (0)
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	0 (0)	0 (0)
SURGICAL AND MEDICAL PROCEDURES	0 (0)	1 (0.6)
PHYSIOTHERAPY	0 (0)	1 (0.6)
VASCULAR DISORDERS	1 (0.6)	0 (0)
ORTHOSTATIC HYPOTENSION	1 (0.6)	0 (0)

a: MedDRA version 9.0.
b: Recorded for the total treatment phase (titration phase + maintenance period).
MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

Table 20: Study SP755, discontinuations due to AEs – RCT, indirect comparison: brivaracetam vs. lacosamide

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 159**	**Placebo** **N = 163**
SP755		
Overall rate of discontinuations due to AEs[b]	24 (15.1)	8 (4.9)
NERVOUS SYSTEM DISORDERS	8 (5.0)	3 (1.8)
CONVULSION	3 (1.9)	1 (0.6)
DIZZINESS	2 (1.3)	1 (0.6)
TREMOR	2 (1.3)	0 (0)
CEREBELLAR SYNDROME	1 (0.6)	0 (0)
COORDINATION ABNORMAL	1 (0.6)	0 (0)
GRAND MAL CONVULSION	1 (0.6)	0 (0)
HEADACHE	1 (0.6)	0 (0)
COMPLEX PARTIAL SEIZURES	0 (0)	1 (0.6)
GASTROINTESTINAL DISORDERS	4 (2.5)	1 (0.6)
VOMITING	4 (2.5)	1 (0.6)
NAUSEA	2 (1.3)	0 (0)
DIARRHOEA	1 (0.6)	0 (0)
FLATULENCE	1 (0.6)	0 (0)
DRY MOUTH	0 (0)	0 (0)
EYE DISORDERS	5 (3.1)	1 (0.6)
DIPLOPIA	4 (2.5)	1 (0.6)
VISION BLURRED	1 (0.6)	0 (0)
EAR AND LABYRINTH DISORDERS	3 (1.9)	0 (0)
VERTIGO	2 (1.3)	0 (0)
VESTIBULAR DISORDER	1 (0.6)	0 (0)
CARDIAC DISORDERS	3 (1.9)	0 (0)
EXTRASYSTOLES	2 (1.3)	0 (0)
SINUS BRADYCARDIA	1 (0.6)	0 (0)
INVESTIGATIONS	1 (0.6)	1 (0.6)
ELECTROCARDIOGRAM PR PROLONGATION	1 (0.6)	0 (0)
HEPATIC ENZYME INCREASED	0 (0)	0 (0)
TRANSAMINASES INCREASED	0 (0)	0 (0)
WEIGHT DECREASED	0 (0)	0 (0)
NEUTROPHIL COUNT DECREASED	0 (0)	1 (0.6)
General disorders and administration site conditions	2 (1.3)	0 (0)
Malaise	2 (1.3)	0 (0)

(continued)

Table 20: Study SP755, discontinuations due to AEs – RCT, indirect comparison: brivaracetam vs. lacosamide (continued)

Study	**Patients with event n (%)**	
SOC[a] **PT[a]**	**LCM 400 mg** **N = 159**	**Placebo** **N = 163**
SP755		
PSYCHIATRIC DISORDERS	2 (1.3)	0 (0)
BRADYPHRENIA	1 (0.6)	0 (0)
PSYCHOTIC DISORDER	1 (0.6)	0 (0)
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.6)	0 (0)
NEUTROPENIA	0 (0)	0 (0)
THROMBOCYTOPENIA	1 (0.6)	0 (0)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS	0 (0)	0 (0)
CONCUSSION	0 (0)	0 (0)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	0 (0)	1 (0.6)
PAIN IN EXTREMITY	0 (0)	1 (0.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	0 (0)	1 (0.6)
RASH	0 (0)	1 (0.6)
VASCULAR DISORDERS	0 (0)	1 (0.6)
ISCHAEMIA	0 (0)	1 (0.6)

a: MedDRA version 9.0.
b: Recorded for the total treatment phase (titration phase + maintenance period).
AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with (at least one) event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class; vs.: versus