Epilepsy Research 147 (2018) 80–86

Contents lists available at ScienceDirect

Epilepsy Research

journal homepage: www.elsevier.com/locate/epilepsyres

Tolerability of adjunctive eslicarbazepine acetate according to concomitant lamotrigine or carbamazepine use: A subgroup analysis of three phase III trials in adults with focal (partial-onset) seizures

Bassel Abou-Khalil[a,*], Pavel Klein[b], Aashit Shah[c], Philippe Ryvlin[d], Luigi M. Specchio[e], Helena Gama[f], Francisco Rocha[f], David Blum[g], Todd Grinnell[g], Hailong Cheng[g], JungAh Jung[g]

[a] Department of Neurology, Vanderbilt University Medical Center, A-0118 Medical Center North, 1161 21st Avenue South, Nashville, TN, 37232, United States
[b] Mid-Atlantic Epilepsy and Sleep Center, Champlain Building, 6410 Rockledge Drive #610, Bethesda, MD 20817, USA
[c] Carilion Clinic Neurology, 3 Riverside Circle, Roanoke, VA 24016, USA
[d] Centre Hospitalo-Universitaire Vaudois (CHUV), Rue du Bugnon 46, Lausanne, 1011, Switzerland
[e] Department of Clinical and Experimental Medicine, University of Foggia, Viale Luigi Pinto 1, Foggia, 71122 Italy
[f] BIAL–Portela & C[a], S.A., Avenida da Siderurgia Nacional, São Mamede do Coronado, 4745-457, Portugal
[g] Sunovion Pharmaceuticals Inc., 84 Waterford Drive, Marlborough, MA 01752, USA

ARTICLE INFO

Keywords:
Antiepileptic drug
Eslicarbazepine acetate
Focal seizures
Lamotrigine
Carbamazepine
Tolerability
Combination therapy

ABSTRACT

Objective: To evaluate and compare the effects of concomitant lamotrigine (LTG) or carbamazepine (CBZ) on the incidence of treatment-emergent adverse events (TEAEs) in patients taking adjunctive eslicarbazepine acetate (ESL) for focal (partial-onset) seizures (FS).

Methods: These post-hoc analyses of data pooled from three randomized, double-blind, placebo-controlled studies of adjunctive ESL (BIA-2093-301, −302 and −304) included adults (≥16 years) with FS refractory to 1–3 antiepileptic drugs (AEDs). Patients were randomized equally to placebo, ESL 400 mg (Studies 301 and 302 only), 800 mg, or 1200 mg once daily (8-week baseline, 2-week titration, and 12-week maintenance periods). TEAEs, TEAEs leading to discontinuation, and serious AEs (SAEs) were evaluated in patients taking, or not taking, LTG (excluding those taking CBZ or phenytoin [PHT]; i.e., the +LTG and −LTG/–CBZ subgroups), or CBZ (excluding those taking LTG or PHT; i.e., the +CBZ and −LTG/–CBZ subgroups) at baseline.

Results: LTG was used concomitantly by 248 patients (+LTG; placebo, $n = 81$; ESL, $n = 167$) and CBZ by 613 patients (+CBZ; placebo, $n = 172$; ESL, $n = 441$); 361 patients were taking neither LTG nor CBZ (−LTG/–CBZ; placebo, $n = 109$; ESL, $n = 252$). The overall incidence of TEAEs with ESL (any dose) was numerically higher for +CBZ (77%) than for +LTG (73%) or –LTG/–CBZ (68%; statistical significance not tested). Among patients taking ESL, dizziness, diplopia, and vomiting were reported more frequently in the +CBZ subgroup (30%, 14%, and 10%, respectively) than in the +LTG (16%, 8%, 5%) or –LTG/–CBZ (11%, 3%, 5%) subgroups. The overall incidence of TEAEs leading to discontinuation with ESL was higher for +CBZ (21%) than for +LTG (13%) or –LTG/–CBZ (15%). Dizziness leading to discontinuation with ESL was reported more frequently in the +CBZ subgroup than in the +LTG or –LTG/–CBZ subgroups (9%, 3%, and 3%, respectively). The overall incidence of SAEs in patients taking ESL was comparable across subgroups (+LTG, 5%; +CBZ, 6%; –LTG/–CBZ, 5%). The results were similar when evaluating placebo-adjusted incidences.

Conclusion: There was a potential pharmacodynamic interaction between AEDs with a putatively similar mechanism of action, with a seemingly lesser interaction between ESL and LTG versus ESL and CBZ. If combining ESL with LTG or CBZ, clinicians should be aware of the potential risk for an increased incidence of TEAEs

Abbreviations: AE, adverse event; AED, antiepileptic drug; CBZ, carbamazepine; +CBZ, patients who were taking concomitant CBZ; –CBZ, patients who were not taking concomitant CBZ; ESL, eslicarbazepine acetate; FS, focal seizures; LEV, levetiracetam; LCM, lacosamide; LTG, lamotrigine; +LTG, patients who were taking concomitant LTG; –LTG, patients who were not taking concomitant LTG; MoA, mechanism of action; OXC, oxcarbazepine; PHT, phenytoin; QD, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event; VGSC, voltage-gated sodium channel; VPA, valproic acid

* Corresponding author.
E-mail addresses: bassel.abou-khalil@vanderbilt.edu (B. Abou-Khalil), kleinp@epilepsydc.com (P. Klein), akshah@carilionclinic.org (A. Shah), philipperyvlin@gmail.com (P. Ryvlin), Luigi.Specchio@unifg.it (L.M. Specchio), Helena.Gama@bial.com (H. Gama), Francisco.Rocha@bial.com (F. Rocha), David.Blum@Sunovion.com (D. Blum), Todd.Grinnell@Sunovion.com (T. Grinnell), Hailong.Cheng@Sunovion.com (H. Cheng), JungAh.Jung@Sunovion.com (J. Jung).

https://doi.org/10.1016/j.eplepsyres.2018.08.011
Received 15 June 2018; Received in revised form 27 July 2018; Accepted 27 August 2018
Available online 29 August 2018

typically associated with voltage-gated sodium channel inhibitors (e.g., dizziness, blurred vision, vertigo, diplopia, headache, or vomiting).

1. Introduction

Eslicarbazepine acetate (ESL) is a once-daily (QD) oral antiepileptic drug (AED) for the treatment of focal (partial-onset) seizures (FS) as either monotherapy or adjunctive therapy in patients aged ≥4 years. When AEDs are used as adjunctive therapy, potential drug interactions are a concern, including both pharmacokinetic and pharmacodynamic interactions.

Specific combinations of AEDs may increase the frequency of some adverse events (AEs) (Abou-Khalil, 2016; French and Gazzola, 2013). Pharmacodynamic interactions may be of particular importance when combining agents thought to have similar mechanisms of action (MoA). Such interactions have been demonstrated with combinations of two AEDs acting predominantly on voltage-gated sodium channels (VGSCs), such as carbamazepine (CBZ), phenytoin (PHT), oxcarbazepine (OXC), lamotrigine (LTG), and lacosamide (LCM) (Barcs et al., 2000; Besag et al., 1998; Sake et al., 2010). Eslicarbazepine (the primary metabolite of ESL) is also known to inhibit VGSCs, which may contribute to its anticonvulsant effect (Bonifacio et al., 2001). A pharmacodynamic interaction between ESL and CBZ leading to higher incidences of dizziness and diplopia has been previously suggested (Biton et al., 2017); however, other VGSC inhibitors were not excluded from this previous analysis. The effect of concomitant LTG on the tolerability profile of ESL is not known.

We therefore performed an exploratory post-hoc analysis of data pooled from three Phase III studies of ESL to evaluate the impact of concomitant LTG use on the incidence of AEs during adjunctive ESL treatment. The impact of concomitant CBZ use was also evaluated and compared with the impact of LTG. We did not conduct a similar analysis for PHT, as relatively few patients (~9%) were taking PHT at baseline.

2. Methods

Data were pooled from three randomized, placebo-controlled, double-blind trials, as reported previously (Biton et al., 2017). The three Phase III studies (BIA-2093-301 [NCT00957684], −302 [NCT00957047], and −304 [NCT00988429] (Ben-Menachem et al., 2010; Elger et al., 2009; Sperling et al., 2015); registered at ClinicalTrials.gov) were performed in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines, and relevant national, state, and local laws. Study protocols were approved by the relevant independent ethics committees/institutional review boards, and all patients provided written informed consent.

2.1. Study design

The individual study designs, including details of randomization and blinding, have been reported previously (Ben-Menachem et al., 2010; Elger et al., 2009; Sperling et al., 2015). Briefly, each study comprised an 8-week baseline period, a 2-week titration period, and a 12-week maintenance period (Fig. 1). After the baseline period, eligible patients were randomized equally to receive ESL 400 mg QD (Studies 301 and 302 only), 800 mg QD, 1200 mg QD, or placebo. Patients continued to receive stable doses of baseline AEDs throughout the studies. On completion of the 12-week maintenance period, patients entered an ESL taper period (Studies 301 and 304) and exited the study (Fig. 1). The ESL titration and tapering-off schedules differed slightly between studies.

2.2. Patients

Eligible patients were aged ≥16 years (Study 304) or ≥18 years (Studies 301 and 302) and taking 1–3 AEDs at baseline. In addition, patients had ≥4 FS in either the first or last 4 weeks of the baseline period plus no seizure-free period > 21 consecutive days (Studies 301 and 302), or ≥8 FS during baseline (with ≥3 seizures in either the first or last 4 weeks) and no seizure-free period > 28 consecutive days (Study 304). Inclusion and exclusion criteria have been reported previously (Ben-Menachem et al., 2010; Elger et al., 2009; Sperling et al., 2015). Of note, patients taking OXC were excluded from study participation.

2.3. Safety assessments

The safety population comprised all patients who received ≥1 dose of study drug. AEs were considered treatment-emergent (TEAEs) if they began after the first dose of study drug (or if unknown/unclear, after randomization). AEs were recorded and assessed by the investigators and coded using the Medical Dictionary for Regulatory Activities version 13.1. Additional events were detected from audits of investigator records and case report forms, and from review of patient narratives

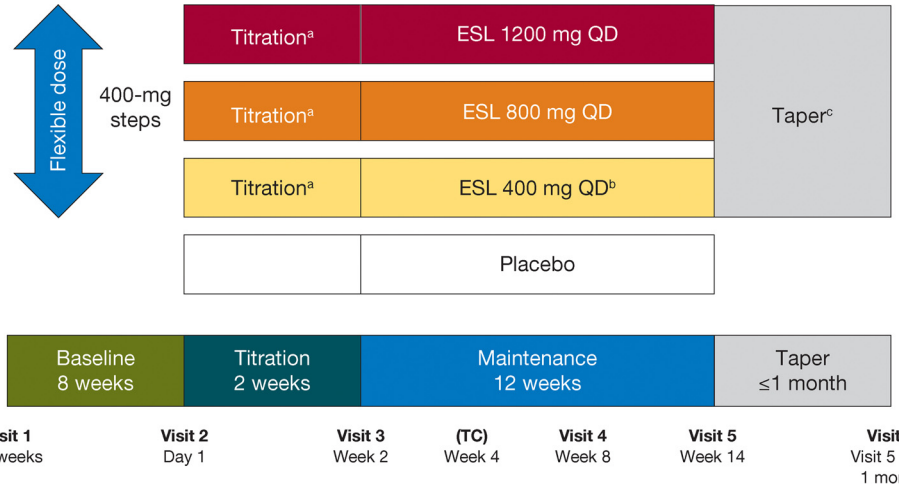

Fig. 1. Design of the Phase III studies.
ESL, eslicarbazepine acetate; QD, once daily; TC, telephone contact. [a]Titration schedules differed between Studies 301, 302, and 304. [b]Studies 301 and 302 only. [c]Patients who did not enter the open-label extension study discontinued ESL (Studies 301 and 304: 2-week down-titration; Study 302: abrupt discontinuation).

and serious AE (SAE) reports. Signs and symptoms relating to any reported diagnoses were recorded as additional TEAEs. Safety endpoints included: overall incidence of TEAEs, TEAEs leading to discontinuation, SAEs, and deaths.

2.4. Statistical analysis

To minimize the potential confounding effect of other putative VGSC inhibitors, patients taking CBZ or PHT at baseline were excluded in the +/–LTG subgroup analyses; similarly, patients taking LTG or PHT at baseline were excluded in the +/–CBZ subgroup analyses. Three patient subgroups were compared descriptively: 1) +LTG subgroup: patients taking LTG without CBZ or PHT; 2) +CBZ subgroup: patients taking CBZ without LTG or PHT; 3) –LTG/–CBZ subgroup: patients not taking LTG, CBZ, or PHT.

Demographic and baseline characteristics, and patient disposition were summarized descriptively for each subgroup (+LTG, +CBZ, –LTG/–CBZ). The numbers and percentages of patients with TEAEs, TEAEs leading to discontinuation, and SAEs were reported. Placebo-adjusted incidences of TEAEs and TEAEs leading to discontinuation were calculated as [incidence with ESL] – [incidence with placebo].

The statistical significance of the TEAE incidence difference between the +LTG and –LTG/–CBZ subgroups, as well as between the +CBZ and –LTG/–CBZ subgroups, was examined by calculating p values, using the chi-square test of independence, or Fisher's exact test (for TEAEs with low incidence, i.e., occurring in five patients or fewer); corrections for multiplicity were not applied. The significance threshold was preset at $p < 0.05$.

3. Results

3.1. Patients

The safety population comprised 1447 patients (placebo: $n = 426$; ESL 400 mg: $n = 196$; ESL 800 mg: $n = 415$; ESL 1200 mg: $n = 410$). There were 248 patients in the +LTG subgroup (placebo: $n = 81$; ESL: $n = 167$), 613 patients in the +CBZ subgroup (placebo: $n = 172$; ESL: $n = 441$), and 361 patients in the –LTG/–CBZ subgroup (placebo: $n = 109$; ESL: $n = 252$).

Baseline demographic and clinical characteristics are presented in Supplemental Table 1, according to subgroup. A greater proportion of patients taking ESL (any dose) were taking two or more AEDs at baseline in the +LTG subgroup (81%) than in the +CBZ (67%) or –LTG/–CBZ (62%) subgroups. A greater proportion of patients taking ESL were receiving CBZ as a monotherapy at baseline (33%) than were receiving LTG as a monotherapy (19%). Baseline use of valproic acid (VPA; 17%, 12%, and 52%) and levetiracetam (LEV; 25%, 9%, 34%) was less frequent in the +LTG and +CBZ subgroups than in the –LTG/–CBZ subgroup. Other baseline demographic and clinical characteristics were similar across subgroups.

Patient disposition is summarized in Table 1, according to subgroup. The proportion of patients that discontinued due to AEs was generally higher with higher ESL doses. A greater proportion of patients taking ESL (any dose) withdrew due to AEs in the +CBZ subgroup (16%) than in the +LTG (10%) or –LTG/–CBZ (10%) subgroups.

3.2. Overall incidence of TEAEs

The incidences of TEAEs in the patient population pooled from Studies 301, 302, and 304 have been reported previously (Biton et al., 2017). The overall incidences of TEAEs with placebo were comparable across the +LTG, +CBZ, and –LTG/–CBZ subgroups (57%, 59%, and 58%, respectively; Table 2). The overall incidence of TEAEs with ESL (any dose) was numerically higher for +CBZ (77%) than for +LTG (72%) or –LTG/–CBZ (68%) (Table 2); the overall placebo-adjusted incidences of TEAEs were 18%, 16%, and 10%, respectively (Fig. 2, Supplemental Table 2). The overall incidence of TEAEs appeared to be related to ESL dose in the +LTG and –LTG/–CBZ subgroups, but not in the +CBZ subgroup (Table 2). Among patients taking the highest ESL dose evaluated (1200 mg QD), the overall incidence of TEAEs was

Table 1
Patient disposition.

n (%)	–LTG/–CBZ					+LTG					+CBZ				
		ESL, mg QD					ESL, mg QD					ESL, mg QD			
	Placebo $n = 109$	400 $n = 37$	800 $n = 116$	1200 $n = 99$	Total $n = 252$	Placebo $n = 81$	400 $n = 32$	800 $n = 64$	1200 $n = 71$	Total $n = 167$	Placebo $n = 172$	400 $n = 99$	800 $n = 174$	1200 $n = 168$	Total $n = 441$
Completed the study	94 (86)	34 (92)	99 (85)	74 (75)	207 (82)	70 (86)	28 (88)	55 (86)	54 (76)	137 (82)	144 (84)	90 (91)	135 (78)	108 (64)	333 (76)
Discontinued during:															
16-week double-blind period	15 (14)	3 (8)	17 (15)	25 (25)	45 (18)	11 (14)	4 (13)	9 (14)	17 (24)	30 (18)	28 (16)	9 (9)	39 (22)	60 (36)	108 (24)
Titration period	2 (2)	0	5 (4)	11 (11)	16 (6)	5 (6)	2 (6)	4 (6)	6 (8)	12 (7)	6 (3)	1 (1)	15 (9)	16 (10)	32 (7)
Maintenance period	12 (11)	2 (5)	12 (10)	14 (14)	28 (11)	6 (7)	2 (6)	5 (8)	11 (15)	18 (11)	19 (11)	8 (8)	24 (14)	42 (25)	74 (17)
Taper period	1 (1)	1 (3)	0	0	1 (< 1)	0	0	0	0	0	3 (2)	0	0	2 (1)	2 (< 1)
Main reason for discontinuation (double-blind period)															
AEs	4 (4)	2 (5)	9 (8)	15 (15)	26 (10)	1 (1)	3 (9)	2 (3)	12 (17)	17 (10)	7 (4)	7 (7)	24 (14)	40 (24)	71 (16)
Withdrawal of consent	3 (3)	1 (3)	2 (2)	6 (6)	9 (4)	4 (5)	1 (3)	4 (6)	3 (4)	8 (5)	8 (5)	2 (2)	5 (3)	9 (5)	16 (4)
Compliance issues	3 (3)	0	1 (1)	0	1 (< 1)	1 (1)	0	0	0	0	4 (2)	0	0	4 (2)	4 (1)
Protocol violation	0	0	1 (1)	2 (2)	3 (1)	1 (1)	0	1 (2)	0	1 (1)	2 (1)	0	2 (1)	1 (1)	3 (1)
Exacerbation of seizures	0	0	0	0	0	0	0	0	1 (1)	1 (1)	1 (1)	0	0	0	0
Pregnancy	2 (2)	0	0	0	0	0	0	0	0	0	0	0	1 (1)	0	1 (< 1)
Administrative reasons	1 (1)	0	1 (1)	1 (1)	2 (1)	1 (1)	0	1 (2)	0	1 (1)	0	0	2 (1)	2 (1)	4 (1)
Other	2 (2)	0	3 (3)	1 (1)	4 (2)	3 (4)	0	1 (2)	1 (1)	2 (1)	5 (3)	0	5 (3)	2 (1)	7 (2)

AE, adverse event; CBZ, carbamazepine; +CBZ, patients who were taking CBZ at baseline; –CBZ, patients who were not taking CBZ at baseline; ESL, eslicarbazepine acetate; LTG, lamotrigine; +LTG, patients who were taking LTG at baseline; –LTG, patients who were not taking LTG at baseline; QD, once daily.
Data are for patients who received ≥1 dose of study drug (safety population) and who were not taking phenytoin, CBZ (+LTG and –LTG/–CBZ subgroups only), or LTG (+CBZ and –LTG/–CBZ subgroups only) at baseline. Data were rounded to the nearest whole percent.

Table 2
TEAE incidences,[a] according to use of LTG or CBZ at baseline.

	–LTG/–CBZ					+LTG					+CBZ				
		ESL, mg QD					ESL, mg QD					ESL, mg QD			
n (%)	Placebo *n* = 109	400 *n* = 37	800 *n* = 116	1200 *n* = 99	Total *n* = 252	Placebo *n* = 81	400 *n* = 32	800 *n* = 64	1200 *n* = 71	Total *n* = 167	Placebo *n* = 172	400 *n* = 99	800 *n* = 174	1200 *n* = 168	Total *n* = 441
Any TEAE[b]	63 (58)	19 (51)	79 (68)	74 (75)	172 (68)	46 (57)	19 (59)	44 (69)	58 (82)	121 (72)	101 (59)	75 (76)	133 (76)	131 (78)	339 (77)
Somnolence	6 (6)	8 (22)	12 (10)	21 (21)	41 (16)	7 (9)	3 (9)	7 (11)	15 (21)	25 (15)	19 (11)	12 (12)	23 (13)	25 (15)	60 (14)
Nausea	5 (5)	2 (5)	11 (9)	11 (11)	24 (10)	4 (5)	2 (6)	3 (5)	9 (13)	14 (8)	12 (7)	9 (9)	21 (12)	29 (17)	59 (13)
Dizziness	7 (6)	2 (5)	12 (10)	14 (14)	28 (11)	7 (9)	3 (9)	9 (14)	15 (21)	27 (16)	18 (10)	21 (21)	48 (28)	62 (37)	131 (30)
Rash	2 (2)	1 (3)	5 (4)	8 (8)	14 (6)	0	0	0	2 (3)	2 (1)	2 (1)	0	0	2 (1)	2 (< 1)
Vomiting	2 (2)	1 (3)	4 (3)	8 (8)	13 (5)	3 (4)	2 (6)	1 (2)	5 (7)	8 (5)	6 (3)	4 (4)	19 (11)	21 (13)	44 (10)
Diplopia	0	0	5 (4)	3 (3)	8 (3)	4 (5)	2 (6)	3 (5)	8 (11)	13 (8)	5 (3)	9 (9)	24 (14)	28 (17)	61 (14)
Headache	9 (8)	2 (5)	13 (11)	13 (13)	28 (11)	5 (6)	4 (13)	5 (8)	8 (11)	17 (10)	21 (12)	15 (15)	32 (18)	33 (20)	80 (18)
Blurred vision	0	0	2 (2)	3 (3)	5 (2)	2 (2)	2 (6)	4 (6)	3 (4)	9 (5)	1 (1)	7 (7)	12 (7)	8 (5)	27 (6)
Fatigue	4 (4)	0	5 (4)	9 (9)	14 (6)	4 (5)	3 (9)	7 (11)	5 (7)	15 (9)	4 (2)	3 (3)	4 (2)	12 (7)	19 (4)
Vertigo	1 (1)	0	2 (2)	3 (3)	5 (2)	0	2 (6)	1 (2)	7 (10)	10 (6)	1 (1)	4 (4)	4 (2)	11 (7)	19 (4)
Ataxia	1 (1)	0	2 (2)	3 (3)	5 (2)	2 (2)	2 (6)	1 (2)	3 (4)	6 (4)	5 (3)	4 (4)	12 (7)	13 (8)	29 (7)

CBZ, carbamazepine; +CBZ, patients who were taking CBZ at baseline; –CBZ, patients who were not taking CBZ at baseline; ESL, eslicarbazepine acetate; LTG, lamotrigine; +LTG, patients who were taking LTG at baseline; –LTG, patients who were not taking LTG at baseline; QD, once daily; TEAE, treatment-emergent adverse event.
Data are for patients who received ≥1 dose of study drug (safety population) and who were not taking phenytoin, CBZ (+LTG and –LTG/–CBZ subgroups only), or LTG (+CBZ and –LTG/–CBZ subgroups only) at baseline.
Data were rounded to the nearest whole percent.
[a] For TEAEs with an incidence ≥5% (for all ESL doses combined) in either the –LTG/–CBZ, +LTG, or +CBZ subgroup.
[b] Patients with more than one event were only counted once.

numerically higher for +LTG (82%, *n* = 58/71) than for +CBZ (78%, *n* = 131/168) or –LTG/–CBZ (75%, *n* = 74/99; Table 2); overall placebo-adjusted incidences of TEAEs with ESL 1200 mg QD were 25%, 19%, and 17%, respectively (see Supplemental Table 2).

3.3. Individual TEAE incidences

Table 2 shows the most frequently reported TEAEs with ESL, defined as an incidence of ≥5% in the total ESL group in any of the +LTG, +CBZ, or –LTG/–CBZ subgroups. These were somnolence, nausea, dizziness, rash, vomiting, diplopia, headache, blurred vision, fatigue, vertigo, and ataxia, with the majority reported more frequently with higher ESL doses in all subgroups.

When all ESL doses were combined, the incidences of the most common TEAEs were similar between the +LTG and –LTG/–CBZ subgroups (Table 2). The exceptions were dizziness, blurred vision, rash, and vertigo, with a difference of ≥5% between subgroups for dizziness. The incidence of dizziness was 16% for +LTG versus 11% for –LTG/–CBZ ($p = 0.1334$; Table 2). The placebo-adjusted incidence of vertigo was 6% for +LTG versus 1% for –LTG/–CBZ (Fig. 2, Supplemental Table 2).

When all ESL doses were combined, the most common TEAEs were generally more frequent in the +CBZ subgroup than in the –LTG/–CBZ subgroup, with ≥5% difference between subgroups for dizziness (30% vs. 11%, $p < 0.0001$), diplopia (14% vs. 3%, $p < 0.0001$), vomiting (10% vs. 5%, $p = 0.0264$), ataxia (7% vs. 2%, $p = 0.0059$), and headache (18% vs. 11%, $p = 0.0141$) (Table 2). Placebo-adjusted incidences of dizziness were 19% and 5% and of diplopia were 11% and

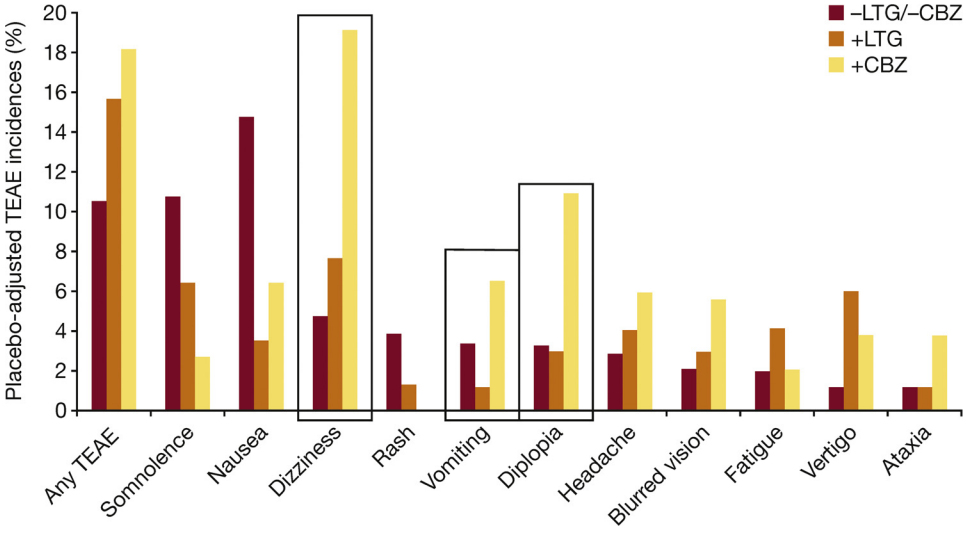

Fig. 2. Placebo-adjusted TEAE incidences,[a] according to use of LTG or CBZ at baseline.
CBZ, carbamazepine; +CBZ, patients who were taking CBZ at baseline; –CBZ, patients who were not taking CBZ at baseline; ESL, eslicarbazepine acetate; LTG, lamotrigine; +LTG, patients who were taking LTG at baseline; –LTG, patients who were not taking LTG at baseline; TEAE, treatment-emergent adverse event.
[a]In the total ESL group, for TEAEs with an incidence ≥5% (for all ESL doses combined) in either the –LTG/–CBZ, +LTG, or +CBZ subgroup.
[b]Patients with more than one event were only counted once.
Data were rounded to the nearest whole percent.
Data are for patients who received ≥1 dose of study drug (safety population) and who were not taking phenytoin, CBZ (+LTG and –LTG/–CBZ subgroups only), or LTG (+CBZ and –LTG/–CBZ subgroups only) at baseline. Placebo-adjusted incidences of TEAEs were calculated as [incidence with ESL] – [incidence with placebo]. Negative incidences are not shown.
Black boxes highlight TEAEs for which the difference in placebo-adjusted incidence between +CBZ and –LTG/–CBZ was ≥5% higher than between +LTG and –LTG/–CBZ.

3% for +CBZ versus –LTG/–CBZ, respectively (Fig. 2, Supplemental Table 2).

At the highest ESL dose (1200 mg QD), incidences of some TEAEs appeared to be higher for +LTG than for –LTG/–CBZ, but the differences between subgroups were not statistically significant (dizziness: +LTG 21%, –LTG/–CBZ 14%, $p = 0.232$; diplopia: +LTG 11%, –LTG/–CBZ 3%, $p = 0.054$; vertigo: +LTG 10%, –LTG/–CBZ 3%, $p = 0.096$). Incidences of some TEAEs also appeared to be higher for +CBZ than for –LTG/–CBZ in the ESL 1200 mg dose group, with dizziness and diplopia statistically significantly more frequent in the +CBZ subgroup than in the –LTG/–CBZ subgroup (nausea: +CBZ 17%, –LTG/–CBZ 11%, $p = 0.174$; dizziness: +CBZ 37%, –LTG/–CBZ 14%, $p = 0.0001$; vomiting: +CBZ 13%, –LTG/–CBZ 8%, $p = 0.262$; diplopia: +CBZ 17%, –LTG/–CBZ 3%, $p = 0.0006$; headache: +CBZ 20%, –LTG/–CBZ 13%, $p = 0.174$).

When all ESL doses were combined, the difference in placebo-adjusted incidence between +CBZ and –LTG/–CBZ was higher than between +LTG and –LTG/–CBZ with a ≥5% difference for dizziness, diplopia, and vomiting (difference between +CBZ and –LTG/–CBZ vs. difference between +LTG and –LTG/–CBZ: 14% vs. 3%, 8% vs. 0%, and 4% vs. −2%, respectively; Fig. 2, Supplemental Table 2). This pattern was also apparent in the ESL 800 mg QD (13% vs. 1%, 7% vs. −4%, 5% vs. −4%) and ESL 1200 mg QD (18% vs. 6%, 11% vs. 3%, 3% vs. −3%) dose groups. No other TEAEs were consistently more frequent with concomitant CBZ or LTG across ESL dose groups.

The incidence of the investigator-reported TEAE of hyponatremia was low and similar across subgroups for all ESL doses combined (–LTG/–CBZ 1.6%, +LTG 2.4%, +CBZ 1.1%), with the majority of events occurring at the 800 mg and 1200 mg QD doses.

3.4. Discontinuations, SAEs, and deaths

The overall incidence of TEAEs leading to discontinuation with ESL (any dose) was higher for +CBZ (21%) than for +LTG (13%) or –LTG/–CBZ (15%) (Table 3); placebo-adjusted overall incidences were 13%, 8%, and 6%, respectively. Dizziness (the most frequently reported TEAE leading to discontinuation) was reported more frequently in the +CBZ subgroup than in the +LTG or –LTG/–CBZ subgroups (9%, 3%, and 3%, respectively; Table 3); the placebo-adjusted incidences of dizziness leading to discontinuation were 7%, 3%, and 3%, respectively. In the +CBZ subgroup, the incidence of dizziness leading to discontinuation appeared to be ESL dose-dependent. The overall incidence of SAEs in patients taking ESL (any dose) was comparable across subgroups (+LTG, 5%; +CBZ, 6%; –LTG/–CBZ, 5%; Supplemental Table 3).

There was one death in the –LTG/–CBZ subgroup, due to decreased body temperature (hypothermia); the patient was in the placebo group. Two deaths were reported in the +CBZ subgroup; one in the placebo group (due to pneumonia, septic shock, acute respiratory failure, and decreased oxygen saturation), and one in the ESL 800 mg QD dose group, due to status epilepticus. No deaths were reported in the +LTG subgroup.

4. Discussion

The current analysis suggests possible pharmacodynamic interactions between ESL and both LTG and CBZ. However, the extent of the interaction between ESL and LTG may be lesser than that between ESL and CBZ, despite the fact that both AEDs are thought to act predominantly via a similar MoA (VGSC inhibition).

When treating patients with combinations of AEDs, clinicians should take into account all potential interactions (both pharmacokinetic and pharmacodynamic) between the AEDs in the combination. The concomitant use of AEDs with similar MoAs has been reported to lead to AEs at therapeutic doses/serum concentrations. For example, in a large study of adults with a recent diagnosis of FS, who were taking two different AEDs concomitantly, combinations of AEDs with a similar MoA were associated with shorter persistence and greater risk of discontinuation compared with AED combinations with different MoAs (Margolis et al., 2014). Increased incidences of dizziness, ataxia, and diplopia have been previously reported during use of specific combinations of VGSC inhibitors. The use of CBZ plus LTG has been linked to diplopia and dizziness (Besag et al., 1998). In another study, the incidence of dizziness was considerably higher when LCM was combined with another VGSC inhibitor, versus an AED with a different MoA (Sake et al., 2010). A similar pattern of increased AEs was noted when ESL was combined with CBZ versus other AEDs both in the current analysis, and in Biton et al. (2017). However, in the current analysis, the interaction between ESL and LTG appeared to have a somewhat lesser

Table 3
Incidences of individual TEAEs leading to discontinuation,[a] according to use of LTG or CBZ at baseline.

	–LTG/–CBZ					+LTG					+CBZ				
		ESL, mg QD					ESL, mg QD					ESL, mg QD			
n (%)	Placebo *n* = 109	400 *n* = 37	800 *n* = 116	1200 *n* = 99	Total *n* = 252	Placebo *n* = 81	400 *n* = 32	800 *n* = 64	1200 *n* = 71	Total *n* = 167	Placebo *n* = 172	400 *n* = 99	800 *n* = 174	1200 *n* = 168	Total *n* = 441
Any TEAE leading to discontinuation[b]	9 (8)	4 (11)	12 (10)	21 (21)	37 (15)	4 (5)	4 (13)	4 (6)	14 (20)	22 (13)	14 (8)	10 (10)	33 (19)	48 (29)	91 (21)
Dizziness	0	0	5 (4)	3 (3)	8 (3)	0	0	0	5 (7)	5 (3)	2 (1)	2 (2)	15 (9)	21 (13)	38 (9)
Nausea	1 (1)	0	2 (2)	4 (4)	6 (2)	0	1 (3)	0	4 (6)	5 (3)	0	0	6 (3)	12 (7)	18 (4)
Diplopia	0	0	1 (1)	0	1 (< 1)	0	1 (3)	1 (2)	0	2 (1)	0	2 (2)	5 (3)	9 (5)	16 (4)
Vomiting	1 (1)	0	0	4 (4)	4 (2)	0	1 (3)	0	3 (4)	4 (2)	1 (1)	2 (2)	8 (5)	10 (6)	20 (5)
Ataxia	0	0	0	1 (1)	1 (< 1)	0	2 (6)	0	2 (3)	4 (2)	0	2 (2)	6 (3)	8 (5)	16 (4)
Vertigo	0	0	0	1 (1)	1 (< 1)	0	1 (3)	1 (2)	2 (3)	4 (2)	1 (1)	0	0	2 (1)	2 (< 1)
Somnolence	1 (1)	0	0	5 (5)	5 (2)	0	1 (3)	0	1 (1)	1 (1)	1 (1)	0	5 (3)	5 (3)	10 (2)
Rash	0	0	1 (1)	4 (4)	5 (2)	0	0	0	1 (1)	1 (1)	0	0	0	1 (1)	1 (< 1)
Gait disturbance	0	0	1 (1)	0	1 (< 1)	0	2 (6)	1 (2)	1 (1)	4 (2)	0	0	1 (1)	0	1 (< 1)

CBZ, carbamazepine; +CBZ, patients who were taking CBZ at baseline; –CBZ, patients who were not taking CBZ at baseline; ESL, eslicarbazepine acetate; LTG, lamotrigine; +LTG, patients who were taking LTG at baseline; –LTG, patients who were not taking LTG at baseline; QD, once daily; TEAE, treatment-emergent adverse event.

Data are for patients who received ≥1 dose of study drug (safety population) and who were not taking phenytoin, CBZ (+LTG and –LTG/–CBZ subgroups only), or LTG (+CBZ and –LTG/–CBZ subgroups only) at baseline.

Data were rounded to the nearest whole percent.

[a] For TEAEs leading to discontinuation with an incidence ≥2% (for all ESL doses combined) in either the –LTG/–CBZ, +LTG, or +CBZ subgroup.

[b] Patients with more than one event were only counted once.

impact on the frequency and severity of some TEAEs than the interaction between ESL and CBZ.

The overall incidence of TEAEs with ESL (any dose) was numerically higher for +CBZ than for +LTG or –LTG/–CBZ; the relatively higher TEAE incidence in the +CBZ subgroup appeared to be primarily driven by dizziness, diplopia, and vomiting, of which incidences appeared to be ESL dose-dependent. At the highest ESL dose evaluated (1200 mg QD), the overall incidence of TEAEs was numerically higher for +LTG than for +CBZ or –LTG/–CBZ. This may indicate a pharmacodynamic interaction between ESL and LTG, but primarily at the highest ESL dose evaluated. It is possible that a potential interaction between ESL and LTG would have been most marked at higher doses or serum concentrations of LTG; however, we were unable to investigate the impact of LTG dose/serum concentration, as these data were unavailable. Similarly, the impact of CBZ dose/serum concentration could not be evaluated.

As would be expected, in the absence of other VGSC inhibitors (i.e., in the –LTG/–CBZ subgroup), incidences of specific TEAEs typically associated with use of VGSC inhibitors appeared to occur more frequently with higher ESL doses. Incidences of individual TEAEs were generally comparable between the +LTG and –LTG/–CBZ subgroups when all ESL doses were combined. However, at the highest ESL dose (1200 mg QD), incidences of dizziness, diplopia, and vertigo were higher in patients taking LTG than in those who were not (though none of the differences between subgroups were statistically significant). Dizziness, diplopia, and headache occurred more frequently in the +CBZ subgroup than in the –LTG/–CBZ subgroup. In addition, nausea, dizziness, vomiting, diplopia, and headache were more frequent in the +CBZ subgroup than in the –LTG/–CBZ subgroup in the ESL 1200 mg dose group; the differences between subgroups were statistically significant for dizziness and diplopia. Our findings extend those reported by Biton et al. (2017), who completed a similar analysis of LTG using this dataset, but without excluding patients taking other putative VGSC inhibitors (i.e., LTG and PHT). In combination, these data suggest potential pharmacodynamic interactions between ESL and LTG, and ESL and CBZ, possibly due to the shared putative MoA of these AEDs (VGSC inhibition). Incidence differences between the +CBZ and –LTG/–CBZ subgroups were higher than between the +LTG and –LTG/–CBZ subgroups for dizziness, diplopia, and vomiting, across ESL doses, potentially suggesting differences in tolerability between these VGSC inhibitor combinations (CBZ and ESL vs. LTG and ESL).

The overall incidence of TEAEs leading to discontinuation (all ESL doses combined) was higher for +CBZ than for +LTG and –LTG/–CBZ. Discontinuations were most frequent at the highest ESL dose (1200 mg QD) in all subgroups, presumably due to the higher drug load. Dizziness led to discontinuation more frequently in the +CBZ subgroup than in the +LTG and –LTG/–CBZ subgroups, again suggesting potential tolerability differences between VGSC inhibitor combinations. The overall incidences of SAEs (all ESL doses combined) were comparable across subgroups.

One could speculate that the apparently differing levels of pharmacodynamic interaction between ESL and LTG versus ESL and CBZ might relate to differences in MoAs of the drugs. VGSC inhibition is not the sole MoA of LTG, which, unlike CBZ, may act on hyperpolarization-activated cyclic nucleotide-gated channel currents (Grunze et al., 1998; Zona et al., 2002), calcium channels (Dibue et al., 2013), and nicotinic receptors (Valles et al., 2007; Zheng et al., 2010). VGSC-inhibiting AEDs with multiple MoAs (including valproate and topiramate) do not have the same pharmacodynamic interactions with 'classic' VGSC inhibitors as 'classic' VGSC inhibitors do with each other. We are also unable to exclude the possibility that differences between subgroups may have been partly related to average administered doses of CBZ and LTG, as we do not know the doses or serum concentrations of these AEDs for the majority of patients in the current studies.

It is of note that 81% of patients taking ESL in the +LTG subgroup were receiving two or more baseline AEDs, compared with 67% in the +CBZ subgroup, and 62% in the –LTG/–CBZ subgroup. Therefore, it is also possible that patients in the +LTG subgroup were taking higher doses of baseline AEDs than those in the +CBZ or –LTG/–CBZ subgroups, increasing the risk of AEs. These factors may have contributed towards the higher apparent incidences of AEs in the +LTG subgroup, compared with the –LTG/–CBZ subgroup, that would not have affected the +CBZ subgroup.

A limitation of the current analysis is the post-hoc nature of the analyses. Statistical comparisons of TEAE incidences were carried out retrospectively, and the majority of results were compared descriptively between subgroups. Corrections for multiplicity were not applied to the calculated *p* values; therefore, these values merely provide preliminary information on the incidence differences between subgroups that could potentially be examined further in the future. An additional limitation was that the doses and serum concentrations of LTG and CBZ could not be evaluated, such that possible dose/exposure differences between the non-randomized +CBZ and +LTG subgroups could not be accounted for. Nevertheless, our comparison of the ESL–LTG and ESL–CBZ combinations is strongly suggestive of differences that are relevant to clinical practice.

5. Conclusion

Our results suggest a potential pharmacodynamic interaction between AEDs with a putatively similar MoA. However, the pharmacodynamic interaction appeared to differ somewhat between VGSC inhibitors, with a lesser interaction between ESL and LTG versus ESL and CBZ. If combining LTG or CBZ with ESL, clinicians should be aware of the potential risk for an increased incidence of TEAEs typically associated with VGSC inhibitors (e.g., dizziness, blurred vision, vertigo, diplopia, headache, or vomiting). One option for management of such events could be to reduce the dose of either LTG or CBZ.

Disclosures

AS has received financial support for research from Lundbeck Pharmaceuticals Ltd., Sunovion Pharmaceuticals Inc., and UCB Pharma. PR has received lecture fees from UCB Pharma and LivaNova PLC; and has acted as a paid consultant for Eisai, UCB Pharma, and LivaNova PLC. HG and FR are paid employees of BIAL – Portela & C[a], S.A. DB, TG, HC, and JJ are paid employees of Sunovion Pharmaceuticals Inc. BA-K, PK, and LS have no conflicts of interest to declare.

Data statement

Sunovion Pharmaceuticals Inc. is part of a clinical trial data sharing consortium that facilitates access for qualified researchers to selected anonymized clinical trial data.

Acknowledgements

Studies 301, 302, and 304 were funded by Sunovion Pharmaceuticals Inc. and BIAL – Portela & C[a], S.A. The sponsors were involved in the design of the studies, in the collection, analysis, and interpretation of data, in writing the report, and in the decision to submit this article for publication. Medical writing support was funded by Sunovion Pharmaceuticals Inc., and was provided by Mallory Gough PhD of FireKite, an Ashfield company, part of UDG Healthcare plc.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2018.08.011.

References

Abou-Khalil, B.W., 2016. Antiepileptic drugs. Continuum (Minneap Minn) 22, 132–156.

Barcs, G., Walker, E.B., Elger, C.E., Scaramelli, A., Stefan, H., Sturm, Y., Moore, A., Flesch, G., Kramer, L., D'Souza, J., 2000. Oxcarbazepine placebo-controlled, dose-ranging trial in refractory partial epilepsy. Epilepsia 41, 1597–1607.

Ben-Menachem, E., Gabbai, A.A., Hufnagel, A., Maia, J., Almeida, L., Soares-da-Silva, P., 2010. Eslicarbazepine acetate as adjunctive therapy in adult patients with partial epilepsy. Epilepsy Res. 89, 278–285.

Besag, F.M., Berry, D.J., Pool, F., Newbery, J.E., Subel, B., 1998. Carbamazepine toxicity with lamotrigine: pharmacokinetic or pharmacodynamic interaction? Epilepsia 39, 183–187.

Biton, V., Rogin, J.B., Krauss, G., Abou-Khalil, B., Rocha, J.F., Moreira, J., Gama, H., Trinka, E., Elger, C.E., Cheng, H., Grinnell, T., Blum, D., on behalf of the Study 301, 302, and 304 Investigators, 2017. Adjunctive eslicarbazepine acetate: a pooled analysis of three phase III trials. Epilepsy Behav. 72, 127–134.

Bonifacio, M.J., Sheridan, R.D., Parada, A., Cunha, R.A., Patmore, L., Soares-da-Silva, P., 2001. Interaction of the novel anticonvulsant, BIA 2-093, with voltage-gated sodium channels: comparison with carbamazepine. Epilepsia 42, 600–608.

Dibue, M., Kamp, M.A., Alpdogan, S., Tevoufouet, E.E., Neiss, W.F., Hescheler, J., Schneider, T., 2013. Cav 2.3 (R-type) calcium channels are critical for mediating anticonvulsive and neuroprotective properties of lamotrigine in vivo. Epilepsia 54, 1542–1550.

Elger, C., Halasz, P., Maia, J., Almeida, L., Soares-da-Silva, P., on behalf of the BIA 2093 301 Investigators Study Group, 2009. Efficacy and safety of eslicarbazepine acetate as adjunctive treatment in adults with refractory partial-onset seizures: a randomized, double-blind, placebo-controlled, parallel-group phase III study. Epilepsia 50, 454–463.

French, J.A., Gazzola, D.M., 2013. Antiepileptic drug treatment: new drugs and new strategies. Continuum (Minneap Minn) 19, 643–655.

Grunze, H., Greene, R.W., Moller, H.J., Meyer, T., Walden, J., 1998. Lamotrigine may limit pathological excitation in the hippocampus by modulating a transient potassium outward current. Brain Res. 791, 330–334.

Margolis, J.M., Chu, B.C., Wang, Z.J., Copher, R., Cavazos, J.E., 2014. Effectiveness of antiepileptic drug combination therapy for partial-onset seizures based on mechanisms of action. JAMA Neurol. 71, 985–993.

Sake, J.K., Hebert, D., Isojarvi, J., Doty, P., De Backer, M., Davies, K., Eggert-Formella, A., Zackheim, J., 2010. A pooled analysis of lacosamide clinical trial data grouped by mechanism of action of concomitant antiepileptic drugs. CNS Drugs 24, 1055–1068.

Sperling, M.R., Abou-Khalil, B., Harvey, J., Rogin, J.B., Biraben, A., Galimberti, C.A., Kowacs, P.A., Hong, S.B., Cheng, H., Blum, D., Nunes, T., Soares-da-Silva, P., on behalf of the 304 Study Team, 2015. Eslicarbazepine acetate as adjunctive therapy in patients with uncontrolled partial-onset seizures: results of a phase III, double-blind, randomized, placebo-controlled trial. Epilepsia 56, 244–253.

Valles, A.S., Garbus, I., Barrantes, F.J., 2007. Lamotrigine is an open-channel blocker of the nicotinic acetylcholine receptor. Neuroreport 18, 45–50.

Zheng, C., Yang, K., Liu, Q., Wang, M.Y., Shen, J., Valles, A.S., Lukas, R.J., Barrantes, F.J., Wu, J., 2010. The anticonvulsive drug lamotrigine blocks neuronal α4β2 nicotinic acetylcholine receptors. J. Pharmacol. Exp. Ther. 335, 401–408.

Zona, C., Tancredi, V., Longone, P., D'Arcangelo, G., D'Antuono, M., Manfredi, M., Avoli, M., 2002. Neocortical potassium currents are enhanced by the antiepileptic drug lamotrigine. Epilepsia 43, 685–690.