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FULL-LENGTH ORIGINAL RESEARCH

Safety and tolerability of lacosamide monotherapy in the elderly: A subgroup analysis from lacosamide trials in diabetic neuropathic pain

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Summary

Objective: To assess the safety profile of lacosamide monotherapy in elderly (≥65 years) subjects with diabetic neuropathic pain (DNP).

Methods: Of 1,863 DNP subjects in double-blind, randomized, placebo-controlled trials of lacosamide monotherapy (NCT00861445, NCT00235469, NCT00238524, NCT00135109, NCT00350103), 502 were elderly. Safety data from elderly subjects were compared with that of younger subjects (<65 years) within these DNP trials. It should be noted that lacosamide is approved for the treatment of focal (partial-onset) seizures; it is not approved/recommended for the treatment of DNP.

Results: Overall, cardiovascular diseases were prevalent in the DNP population, as was the use of cardiac, blood pressure, diabetes, and cholesterol-lowering medications among both young and elderly subjects. The most frequently reported adverse events (AEs) for lacosamide monotherapy (200, 400, and 600 mg/day combined) in elderly versus younger subjects were dizziness (16.2% vs. 13.2%), nausea (10.0% vs. 9.4%), and headache (8.0% vs. 8.7%). Incidences of cardiac disorder AEs were higher in elderly versus younger subjects receiving placebo (6.2% vs. 3.9%), lacosamide 200 (4.8% vs. 3.3%), lacosamide 400 (7.0% vs. 4.1%), and lacosamide 600 mg/day (7.7% vs. 4.0%). Discontinuation rates because of any AE in the elderly versus younger subjects were similar for placebo (8.8% vs. 7.0%) and lacosamide 200 mg/day (9.6% vs. 11.9%) and higher for lacosamide 400 (25.1% vs. 10.8%) and lacosamide 600 mg/day (52.7% vs. 28.3%).

Significance: Lacosamide monotherapy was well tolerated in elderly subjects with DNP, with an overall AE profile consistent with that reported in epilepsy trials.

KEY WORDS: Lacosamide, Elderly, Epilepsy, Tolerability, Safety.

The elderly population is the fastest growing segment of the global population in many developed countries. New-onset epilepsy incidence is increasing with age mainly owing to cerebrovascular disease.[1–3] In one study using U.S. Medicare beneficiaries 65 years of age and older, the average annual prevalence and incidence rates for epilepsy were 10.8 and 2.4 per 1,000, respectively.[4] The rates were higher for some minorities and increased with age for all gender and race segments.[4] By the year 2020, approximately half of the newly diagnosed subjects with seizures will be 60 years of age and older.[5]

Given that elderly subjects with epilepsy are usually treated with antiepileptic drugs (AEDs) in monotherapy, data on the tolerability of lacosamide as monotherapy in the

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Key Points

- Compared with epilepsy trials, diabetic neuropathic pain trials enrolled higher numbers of elderly, allowing insight into lacosamide safety in the elderly
- Lacosamide monotherapy was well tolerated in the diabetic neuropathic pain population
- Discontinuation rates due to adverse events at a lacosamide dose of 200 mg/day were similar between the elderly and younger diabetic neuropathic pain populations
- The higher discontinuation rate of the elderly vs. younger group on 400–600 mg/day lacosamide supports tailoring dose based on subject response and tolerability
- The choice of an antiepileptic drug in the elderly should be guided by the drug's efficacy, metabolism, pharmacokinetics, and tolerability profile

elderly are informative for clinical practice.[3,6] As people age, they experience more concomitant disease states that typically correlate with an increase in the number of medications taken and increased likelihood of drug-drug interactions.[7] Furthermore, older subjects are more susceptible to drugs' adverse effects because aging is associated with metabolic changes that reduce drug clearance and increase pharmacodynamic sensitivity, thereby decreasing the therapeutic window of a given drug.[8] Therefore, the ideal AED for the elderly should be well tolerated and have a low potential for drug-drug interactions.

Lacosamide is currently approved for monotherapy (United States up to 400 mg/day; European Union up to 600 mg/day) or adjunctive treatment (United States, European Union, and other countries up to 400 mg/day) of focal epilepsy in adults.[9,10] Lacosamide has a favorable pharmacokinetic profile with low potential for clinically relevant drug-drug interactions.[11] The safety and tolerability of lacosamide were reported in a pooled analysis of pivotal adjunctive clinical trials of generally healthy subjects with focal epilepsy.[12] The most common treatment-emergent adverse events (AEs) associated with lacosamide (up to 600 mg/day) were dizziness (30.6% vs. 8.2% placebo), headache (12.7% vs. 8.8% placebo), nausea (11.4% vs. 4.4% placebo), and diplopia (10.5% vs. 1.9% placebo); except for headache, these AEs appeared to be related to dose.[12] The only AEs leading to at least 5% of subjects in any dose group discontinuing were dizziness and ataxia. The cardiac safety of AEDs affecting voltage-gated sodium channels is of interest, and a study of pooled adjunctive lacosamide safety data has recently been reported.[13] At doses up to 400 mg/day in adjunctive use, lacosamide did not prolong QTc interval or affect heart rate or QRS duration; however, a slight increase in PR interval was observed.[13] This finding may be more relevant for an elderly population.

The number of elderly subjects (≥65 years) enrolled in the pivotal focal epilepsy trials with adjunctive lacosamide[14–16] was limited (n = 18, 1.4%; data on file, UCB Pharma), and there are limited data available in elderly subjects receiving lacosamide in monotherapy for focal epilepsy.[17] However, a large proportion (n = 502, 26.9%) of elderly subjects was enrolled in the lacosamide monotherapy trials for diabetic neuropathic pain (DNP; discontinued development program), which provides an opportunity to increase the number of elderly subjects that can be evaluated for lacosamide safety and tolerability within the dosing range of 200–600 mg/day.[18–22] It should be noted that the U.S. Food and Drug Administration (FDA) stated that lacosamide was not approvable for the treatment of DNP. UCB Pharma does not recommend the use of its products in a manner other than as indicated in the prescribing information or summary of product characteristics. However, because data on the tolerability of lacosamide in the elderly would be informative for clinical practice, a post hoc analysis of pooled safety and tolerability data of lacosamide in monotherapy in the elderly subgroup from the randomized, double-blinded, and placebo-controlled DNP studies was undertaken.

Methods

Study design

Five lacosamide monotherapy DNP trials (NCT00861445, NCT00235469, NCT00238524, NCT00135109, NCT00350103) had similar placebo-controlled, double-blind trial designs, had comparable duration of treatment (titration and maintenance phases), and used similar randomized dosing (200, 400, and 600 mg/day) (Table 1). All studies were phase 2 through phase 3b studies. Within lacosamide dosing of 200–600 mg/day, safety data of the elderly subgroup pooled from the dose-randomized DNP trials were compared with those of the younger subjects (<65 years) pooled from the same DNP trials.

Subject eligibility

Subject eligibility in the DNP trials included ≥18 years of age with symptoms of painful distal diabetic neuropathy for 6 months to 5 years (1–5 years in SP614), a diagnosis of diabetes mellitus (type 1 or type 2), and at least moderate pain defined as an average pain intensity of ≥4 on an 11-point Likert scale (0–10) during the 7 days before randomization.

Statistical analysis

Data from all treated subjects from the double-blind, placebo-controlled trials for DNP were pooled. Descriptive statistics were used to compare subject disposition,

Table 1. Pooled clinical trials of lacosamide monotherapy for diabetic neuropathic pain

Study ID	Phase	Design	Duration (weeks) Baseline/titration[a]/ maintenance	Randomization	Dose groups[b]
SP614[18] NCT00861445	2	Double-blind	1/6[a]/4	1:1	Placebo or lacosamide 400 mg/day
SP742[19] NCT00235469	2b	Double-blind	2/6/12	1:1:1:1	Placebo, lacosamide 200, 400, or 600 mg/day
SP743[20] NCT00238524	3	Double-blind	2/6/12	1:2:2	Placebo, lacosamide 400 or 600 mg/day[c]
SP768[21] NCT00135109	3	Double-blind	2/6/12	1:2:2:2	Placebo, lacosamide 200, 400, or 600 mg/day
SP874[22] NCT00350103	3b	Double-blind	2/4[d]/12	1:1:1	Placebo, lacosamide 400 mg/day ST or FT[d]

FT, fast titration; ST, standard titration.

[a]ST with dose increased to the randomized dose in 100-mg/day weekly increments (beginning with 50 mg twice daily), except for SP614, which started at 100 mg/day for 3 weeks, then titrated by 100 mg/day every week over the next 3 weeks.

[b]No down-titration was allowed owing to an intolerable adverse event, except for SP614.

[c]Subjects in the 400-mg/day group were further randomized equally to either a slow (100 mg/day for 3 weeks, followed by weekly increases of 100 to 400 mg/day at week 6) or ST scheme.

[d]SP874 FT: started at 200 mg/day for 3 days, increased to 300 mg/day during the next 4 days, and 400 mg/day after 1 week.

demographics, and AEs. Comparisons were made within the DNP population between placebo and lacosamide doses and between age categories (≥65 and <65 years). In post hoc analyses, the relationship between the incidence of AEs and treatment along with a set of covariates was investigated using a negative binomial regression model. In addition, the relationship between AEs leading to discontinuation and treatment along with a set of covariates was explored. A Cox proportional hazards model was used to analyze the time to discontinuation due to AEs and included treatment and a set of covariates. Owing to a statistically significant interaction between treatment and age, the final analysis was performed for each lacosamide dose group (200, 400, and 600 mg/day) using a Cox proportional hazards model to investigate the relationship between discontinuation due to AEs and a set of covariates. The covariates included age (≥65 vs. <65 years), sex, number of concomitant medications, number of concomitant diseases, years with diabetic neuropathy, and treatment duration (only included in the negative binomial regression model).

Results

Subject disposition

A total of 1,863 subjects were enrolled in the double-blind, placebo-controlled DNP trials and were evaluated at either placebo or the lacosamide 200-, 400-, or 600-mg/day dose. Of these, 1,361 were young (<65 years) and 502 were elderly (≥65 years) (Table 2).

Subject demographics and characteristics

Overall, cardiovascular diseases and use of cardiac, blood pressure, diabetes, and cholesterol-lowering medications were prevalent, owing to subjects' older age and underlying diabetes (Table 3). The most concomitant disease states (apart from the underlying diseases of DNP and diabetes) reported as ≥5% of the population were hypertension (68.9%), hyperlipidemia (21.0%), hypercholesterolemia (20.6%), osteoarthritis (14.9%), and obesity (14.7%). Preexisting cardiac disease occurring in ≥5% of a treatment arm was reported for coronary artery disease (placebo, 6.0%; 200, 400, and 600 mg/day lacosamide, 9.8%, 5.5%, 9.6%, respectively [7.0% overall]) and myocardial ischemia (placebo, 4.5%; 200, 400, and 600 mg/day lacosamide, 0%, 5.7%, 4.1%, respectively [4.3% overall]). The elderly subjects tended to have higher frequencies of concomitant diseases and medications compared with the younger subjects (Table 3).

Adverse events during the treatment phase

Dose-response relationships for AEs were analyzed by comparing the incidence of AEs in the lacosamide 200-, 400-, and 600-mg/day groups versus placebo. The most frequently reported AEs for lacosamide monotherapy (all doses combined) in elderly versus younger subjects were dizziness (16.2% vs. 13.2%), nausea (10.0% vs. 9.4%), and

Table 2. Subject enrollment in the pooled clinical trials of lacosamide monotherapy for diabetic neuropathic pain, presented by age (<65 years or ≥65 years)

	Study ID					
	SP614	SP742	SP743	SP768	SP874	Pooled
Total (SS)	119	370	357	468	549	1,863
≥65 years						502 (26.9%)
<65 years						1,361 (73.1%)
Placebo	59	93	74	65	179	470
≥65 years						113 (24.0%)
<65 years						357 (76.0%)
Lacosamide 200 mg/day	n/a	93	n/a	141	n/a	234
≥65 years						83 (35.5%)
<65 years						151 (64.5%)
Lacosamide 400 mg/day	60	91	150	125	370	796
≥65 years						215 (27.0%)
<65 years						581 (73.0%)
Lacosamide 600 mg/day	n/a	93	133	137	n/a	363
≥65 years						91 (25.1%)
<65 years						272 (74.9%)

n/a, not applicable; SS, safety set.

headache (8.0% vs. 8.7%). The incidences of cardiac disorder AEs were higher in elderly versus younger subjects in placebo (6.2% vs. 3.9%), lacosamide 200 mg/day (4.8% vs. 3.3%), lacosamide 400 mg/day (7.0% vs. 4.1%), and lacosamide 600 mg/day (7.7% vs. 4.0%) groups, but there was no difference between the lacosamide and corresponding placebo groups within each age category (Table 4). The incidences of specific cardiac AEs are shown in Table S1. Among other AEs particularly relevant to the elderly, the frequencies of tremor and balance disorder were higher in elderly versus younger subjects and dose-related. Frequencies of fall and gait disturbance were low and similar between elderly and younger subjects (Table 4). The incidence of serious AEs was similar between elderly and younger subjects, and the incidence of serious cardiac AEs was low (Table 4).

The discontinuation rates resulting from any AE in elderly versus younger subjects were similar for placebo (8.8% vs. 7.0%) and lacosamide 200 mg/day (9.6% vs. 11.9%) and higher for lacosamide 400 mg/day (25.1% vs. 10.8%) and lacosamide 600 mg/day (52.7% vs. 28.3%) (Table 4). Discontinuation rates resulting from dizziness were similar between elderly and younger subjects for the lacosamide 200-mg/day group but slightly higher in the elderly for the 400- and 600-mg/day groups (Table 4). Other AEs contributing to a higher discontinuation rate in the 600-mg/day elderly (occurring in ≥3% of the elderly population vs. the younger group) included nausea (8.8% vs. 4.0%), vomiting (5.5% vs. 0.4%), balance disorder (4.4% vs. 1.1%), coordination abnormal (4.4% vs. 0.7%), headache (4.4% vs. 0%), tremor (4.4% vs. 1.5%), and somnolence (3.3% vs. 1.1%). Discontinuations resulting from cardiac AEs were low in both the elderly (2.7%, 2.4%, 2.3%, lacosamide 200, 400, and 600 mg/day, respectively, and 5.5% for placebo) and the younger subjects (2.0%, 0.7%, 0.7%, and 1.5%, respectively). One elderly subject (75 years, lacosamide 200 mg/day) died from a pancreatic carcinoma (causality considered unlikely related). In the younger subject group, one subject (52 years, lacosamide 200 mg/day) committed suicide (causality considered not related) after already being off lacosamide for 72 days; one subject (45 years, lacosamide 400 mg/day) died from worsening coronary artery disease with ventricular fibrillation (causality considered unlikely related), and another subject (48 years, lacosamide 600 mg/day), who had electrocardiogram abnormalities including signs of myocardial infarction at baseline before lacosamide initiation, died from cardiac arrest (causality considered unlikely related).

In the post hoc multivariate regression analysis, age (<65 vs. ≥65 years) was not a statistically significant factor affecting the incidence of AEs. However, as expected, the higher dose group levels (400 and 600 mg/day) showed a greater increase in the incidence of AEs as compared with the placebo group. In addition, the model showed that females had a higher incidence of AEs as compared with males. Other statistically significant factors that had a very small positive increase on the incidence of AEs included the number of concomitant medications, number of concomitant diseases, and years with diabetic neuropathy (Table 5). From the post hoc Cox proportional hazards model, both age and the number of concomitant diseases were statistically significant factors affecting the rate of discontinuation due to AEs for higher lacosamide dose groups (400 and 600 mg/day), but not for the 200-mg/day group. The model showed that older patients (≥65 years) had a higher risk for discontinuation due to AEs than younger patients (<65 years), and a higher number of diseases was associated with a higher risk for discontinuation due to AEs. Other

Table 3. Subject demographics and characteristics in the pooled clinical trials of lacosamide monotherapy for diabetic neuropathic pain

	Total N = 1,863	<65 years N = 1,361	≥65 years N = 502
Age, mean (SD), years	58.1 (10.02)	53.8 (7.85)	69.9 (4.01)
Male/female, %	52.9/47.1	53.0/47.0	52.6/47.4
Concomitant diseases ≥5% in total population, %			
Diabetic neuropathy	99.8	99.9	99.8
Diabetes mellitus—non–insulin-dependent	83.5	79.9	93.0
Hypertension	68.9	64.6	80.7
Hyperlipidemia	21.0	19.9	23.9
Hypercholesterolemia	20.6	18.8	25.3
Osteoarthritis	14.9	12.7	20.7
Obesity	14.7	14.3	15.7
Diabetic retinopathy	11.8	13.5	7.2
Gastroesophageal reflux disease	11.1	9.5	15.5
Depression	10.5	11.4	8.0
Drug hypersensitivity	10.4	9.3	13.1
Diabetes mellitus—insulin-dependent	10.1	12.9	2.6
Insomnia	7.8	7.9	7.8
Hypothyroidism	7.6	6.7	10.2
Seasonal allergy	7.1	7.0	7.6
Coronary artery disease	7.0	5.7	10.6
Back pain	6.9	6.0	9.4
Arthritis	6.0	4.9	9.0
Erectile dysfunction	6.0	5.1	8.6
Asthma	5.8	6.5	3.8
Edema peripheral	5.1	3.9	8.4
Cataract	5.0	3.2	9.8
Concomitant medications taken by ≥10% in total population, %			
Antidiabetics—biguanides	49.9	49.3	51.6
ACE inhibitors	44.0	44.7	42.0
Lipid-lowering agent—statins	39.5	36.9	46.6
Analgesics	38.4	38.3	38.8
Antithrombotic agents	37.8	33.0	51.0
Antidiabetics—sulfonamides	33.9	31.7	39.8
Antidiabetics—insulins fast-acting	32.6	35.9	23.9
Beta-blocking agents	24.6	23.1	28.5
Antidiabetics—insulins intermediate-acting	17.5	18.8	13.9
Calcium channel blockers	14.3	12.4	19.5
Antidiabetics—insulins long-acting	14.2	15.0	12.2
Antidiabetics—thiazolidinediones	14.0	14.3	13.1
Proton pump inhibitors	12.7	11.7	15.5
Angiotensin II antagonists	12.2	10.7	16.5
Diuretics—sulfonamides	10.3	9.0	13.5
Multivitamins	10.3	9.3	12.7

ACE, angiotensin-converting enzyme; SD, standard deviation.

statistically significant factors included years with diabetic neuropathy (only for the 400-mg/day group) and sex (only for the 600-mg/day group). A longer duration of diabetic neuropathy was associated with a higher risk for discontinuation due to AEs for the 400-mg/day group, and females had a higher risk for discontinuation due to AEs than males for the 600-mg/day group (Table 6).

Discussion

Because of low enrollment (1.4%) of elderly subjects in the pivotal clinical trials of adjunctive lacosamide for focal epilepsy, the safety of lacosamide in elderly subjects was examined in the context of DNP studies, which enrolled a more substantial number of elderly subjects. The AE profile in the elderly DNP population was comparable with the known AEs reported from adjunctive lacosamide focal epilepsy trials using similar trial designs and randomized doses.[12] This was true despite the overall older age, higher frequency of concomitant diseases, and higher use of concomitant medications in the DNP population compared with subjects enrolled in epilepsy trials[12] (data on file, UCB Pharma). Dizziness, nausea, and headache were among the most frequently reported AEs in both populations. The

Table 4. AEs and SAEs recorded during the treatment phase (i.e., titration and maintenance phase) with lacosamide monotherapy in subjects with diabetic neuropathic pain, presented by age (<65 years or ≥65 years)

	Placebo	Lacosamide 200 mg/day	Lacosamide 400 mg/day	Lacosamide 600 mg/day	Combined 200 and 400 mg/day	Combined 200, 400, and 600 mg/day
	≥65 years (n = 113) <65 years (n = 357)	≥65 years (n = 83) <65 years (n = 151)	≥65 years (n = 215) <65 years (n = 581)	≥65 years (n = 91) <65 years (n = 272)	≥65 years (n = 298) <65 years (n = 732)	≥65 years (n = 389) <65 years (n = 1,004)
Any AE, n (%)						
≥65 years	74 (65.5)	61 (73.5)	153 (71.2)	76 (83.5)	214 (71.8)	290 (74.6)
<65 years	217 (60.8)	122 (80.8)	364 (62.7)	212 (77.9)	486 (66.4)	698 (69.5)
Common AEs (in ≥10% of subjects in any lacosamide group), n (%)						
Dizziness						
≥65 years	5 (4.4)	2 (2.4)	33 (15.3)	28 (30.8)	35 (11.7)	63 (16.2)
<65 years	13 (3.6)	15 (9.9)	54 (9.3)	64 (23.5)	69 (9.4)	133 (13.2)
Nausea						
≥65 years	7 (6.2)	6 (7.2)	21 (9.8)	12 (13.2)	27 (9.1)	39 (10.0)
<65 years	15 (4.2)	16 (10.6)	36 (6.2)	42 (15.4)	52 (7.1)	94 (9.4)
Headache						
≥65 years	7 (6.2)	5 (6.0)	16 (7.4)	10 (11.0)	21 (7.0)	31 (8.0)
<65 years	27 (7.6)	15 (9.9)	44 (7.6)	28 (10.3)	59 (8.1)	87 (8.7)
Specific AEs (defined as relevant for the elderly population), n (%)						
Tremor						
≥65 years	0	4 (4.8)	18 (8.4)	13 (14.3)	22 (7.4)	35 (9.0)
<65 years	3 (0.8)	3 (2.0)	16 (2.8)	21 (7.7)	19 (2.6)	40 (4.0)
Cardiac disorders[a]						
≥65 years	7 (6.2)	4 (4.8)	15 (7.0)	7 (7.7)	19 (6.4)	26 (6.7)
<65 years	14 (3.9)	5 (3.3)	24 (4.1)	11 (4.0)	29 (4.0)	40 (4.0)
Balance disorder						
≥65 years	0	4 (4.8)	11 (5.1)	11 (12.1)	15 (5.0)	26 (6.7)
<65 years	0	0	5 (0.9)	9 (3.3)	5 (0.7)	14 (1.4)
Fall						
≥65 years	2 (1.8)	1 (1.2)	3 (1.4)	3 (3.3)	4 (1.3)	7 (1.8)
<65 years	1 (0.3)	1 (0.7)	5 (0.9)	7 (2.6)	6 (0.8)	13 (1.3)
Gait disturbance						
≥65 years	0	0	3 (1.4)	2 (2.2)	3 (1.0)	5 (1.3)
<65 years	0	0	1 (0.2)	5 (1.8)	1 (0.1)	6 (0.6)
Any SAE, n (%)						
≥65 years	8 (7.1)	3 (3.6)	19 (8.8)	9 (9.9)	22 (7.4)	31 (8.0)
<65 years	20 (5.6)	7 (4.6)	38 (6.5)	20 (7.4)	45 (6.1)	65 (6.5)
Cardiac SAEs, n (%)						
≥65 years	3 (2.7)	0	2 (0.9)	2 (2.2)	2 (0.7)	4 (1.0)
<65 years	3 (0.8)	1 (0.7)	6 (1.0)	4 (1.5)	7 (1.0)	11 (1.1)
Discontinuation resulting from:						
Any AE, n (%)						
≥65 years	10 (8.8)	8 (9.6)	54 (25.1)	48 (52.7)	62 (20.8)	110 (28.3)
<65 years	25 (7.0)	18 (11.9)	63 (10.8)	77 (28.3)	81 (11.1)	158 (15.7)
Dizziness, n (%)						
≥65 years	0	1 (1.2)	11 (5.1)	11 (12.1)	12 (4.0)	23 (5.9)
<65 years	0	1 (0.7)	9 (1.5)	23 (8.5)	10 (1.4)	33 (3.3)
All cardiac AEs, n (%)						
≥65 years	3 (2.7)	2 (2.4)	5 (2.3)	5 (5.5)	7 (2.3)	12 (3.1)
<65 years	7 (2.0)	1 (0.7)	4 (0.7)	4 (1.5)	5 (0.7)	9 (0.9)

AE, adverse event; SAE, serious adverse event.

[a]Reported MedDRA terms for cardiac disorders: acute myocardial infarction, angina pectoris, angina unstable, arrhythmia, atrial fibrillation, atrial flutter, atrioventricular block first degree, atrioventricular block second degree, bradyarrhythmia, bradycardia, bundle branch block left, bundle branch block right, cardiac arrest, cardiac failure congestive, coronary artery disease, extrasystoles, myocardial ischemia, nodal rhythm, palpitations, sinus tachycardia, supraventricular tachycardia, tachycardia, ventricular extrasystoles, ventricular fibrillation, ventricular hypertrophy.

incidence of dizziness in the overall lacosamide monotherapy DNP trials was lower than when lacosamide was used as adjunctive AED therapy in focal epilepsy trials (30.6%, combined 200-, 400-, and 600-mg/day doses).[12] This difference is likely attributable to the adjunctive nature of the focal epilepsy trials (with overall 84.4% of subjects taking

Table 5. Negative binomial model for overall incidence of adverse events in subjects with diabetic neuropathic pain

Parameter	Incidence rate ratio (95% CI)	p Value
LCM 200 mg/day vs. Placebo	1.085 (0.904,1.302)	0.3806
LCM 400 mg/day vs. Placebo	1.253 (1.096,1.432)	0.0009
LCM 600 mg/day vs. Placebo	1.798 (1.540, 2.100)	<.0001
Age (≥65 vs. <65 years)	0.947 (0.841,1.067)	0.3716
Years with diabetic neuropathy	1.047 (1.020,1.076)	0.0007
Number of concomitant diseases	1.026 (1.012,1.041)	0.0003
Number of concomitant medications	1.097 (1.081,1.113)	<.0001
Sex (female vs. male)	1.203 (1.084,1.334)	0.0005
Treatment duration (days)	0.999 (0.998,1.000)	0.1158

CI, confidence interval; LCM, lacosamide.

Table 6. Cox proportional hazards model for discontinuation due to adverse events by lacosamide treatment group in subjects with diabetic neuropathic pain

	Hazard ratio (95% CI)	p Value
Lacosamide 200 mg/day		
Age (≥65 vs. <65 years)	0.825 (0.333,1.873)	0.6576
Number of concomitant diseases	1.039 (0.954,1.104)	0.2980
Number of concomitant medications	0.979 (0.890,1.058)	0.6334
Sex (female vs. male)	0.902 (0.396,1.990)	0.7994
Years with diabetic neuropathy	1.016 (0.775,1.320)	0.9072
Lacosamide 400 mg/day		
Age (≥65 vs. < 65 years)	2.315 (1.591,3.355)	<.0001
Number of concomitant diseases	1.111 (1.069,1.152)	<.0001
Number of concomitant medications	0.978 (0.929,1.029)	0.4044
Sex (female vs. male)	1.349 (0.938,1.950)	0.1077
Years with diabetic neuropathy	1.077 (0.998,1.149)	0.0396
Lacosamide 600 mg/day		
Age (≥65 vs. < 65 years)	2.735 (1.879,3.942)	<.0001
Number of concomitant diseases	1.047 (1.004,1.090)	0.0265
Number of concomitant medications	1.012 (0.968,1.056)	0.5771
Sex (female vs. male)	1.526 (1.070,2.181)	0.0196
Years with diabetic neuropathy	0.977 (0.885,1.059)	0.6115

CI, confidence interval.

two or three concomitant AEDs) and potentially additive effects of sodium-channel-blocking AEDs (taken concomitantly by 82% of the focal epilepsy population[23]). This hypothesis is supported by the similar dizziness rates observed in each of the dose groups of the DNP population as in the subgroup of focal epilepsy subjects adding lacosamide to non-sodium-channel-blocking AEDs.[23]

The number of concomitant diseases or their severity may relate to tolerance of perceived AEs. Because treatment of multiple conditions likely requires several medications, these additional drugs may confound the identification of lacosamide-related AEs. The same lacosamide-related AEs may be more easily identified in subjects with fewer concomitant diseases. The DNP population in this study had a substantial concomitant disease and comedication burden, which is also a common feature of elderly populations. In a study of lamotrigine or sustained-release carbamazepine monotherapy in the elderly with newly diagnosed epilepsy, 63% of elderly subjects had cardiovascular disorders, and approximately half had neurological abnormalities; an average of three comedications were taken at screening.[24] Similarly, in a study of controlled-release carbamazepine, lamotrigine, or levetiracetam in elderly with new-onset focal epilepsy, subjects had a mean of 5.8 concomitant diseases and 5.1 comedications at baseline.[25] A study of adjunctive levetiracetam in elderly with focal epilepsy reported that 83% of subjects had concomitant disease at baseline and 75% received comedications other than AEDs.[26] The most prevalent comorbidities were hypertension (33%), diabetes (12.2%), coronary artery disease (7.5%), and depression (4.5%).[26] Our DNP population had many different comorbidities (mostly related to metabolic, central nervous system, and cardiovascular disorders), which was similar to those reported in elderly focal epilepsy studies.[24–26]

A post hoc multivariate regression analysis for the DNP population revealed that the main factors affecting incidence of AEs included higher doses of lacosamide (400 and 600 mg/day) versus placebo, and female versus male sex; age (<65 vs. ≥65 years) was not a significant factor.

The discontinuation rates resulting from any AE in subjects with DNP receiving 200 mg/day lacosamide were similar between elderly (≥65 years) and younger (<65 years) subjects. However, at higher doses (400 and 600 mg/day) the discontinuation rates resulting from any AE were higher in the elderly versus the younger subjects. A post hoc Cox proportional hazards regression analysis for each lacosamide dose group showed that age and number of concomitant diseases were statistically significant factors affecting the rate of discontinuation due to AEs for higher dose groups (400 and 600 mg/day), but not for the 200-mg/day group. An important limitation to interpreting the safety profile of fixed-dose randomized clinical trials is that drug dosing is entirely based on the predetermined randomization schedule independent of the subject's individual tolerability profile. Such forced dosing may lead to higher overall

discontinuation rates because of AEs, especially at higher doses. In real-life medical practice, most elderly subjects with newly diagnosed epilepsy are expected to require rather low doses of AEDs to maintain seizure control. However, some subjects may still require higher doses to achieve seizure control, and the benefit of higher doses needs to be evaluated as a function of the individual subject's response to efficacy and tolerability. Because higher discontinuation rates would be anticipated in elderly subjects treated with AED polytherapy, studies and guidance have focused on AED monotherapy for elderly subjects newly diagnosed with focal epilepsy.[6] In a study comparing the efficacy of monotherapy AEDs in the elderly with focal epilepsy, discontinuations because of AEs occurred for 32.2% of subjects treated with the continuous-release formulation of carbamazepine and 26.3% of lamotrigine-treated subjects versus 17.2% of levetiracetam-treated subjects.[25] However, it should be noted that once the low target dose was reached for all treatment arms, further dose modifications in that study were performed according to tolerability and seizure control to mimic clinical practice. The finding of similar discontinuation rates between age groups receiving lacosamide 200 mg/day but higher rates in the elderly versus younger subjects receiving 400- or 600-mg/day doses in our dose-randomized studies suggests that a similar flexible and individualized approach should be used in clinical practice when doses higher than 200 mg/day are needed to control seizures.

Our study has several inherent limitations, most notably underlying disease, comorbid diseases, and concomitant medications acting as confounding factors. In the DNP population, the risk of dementia, stroke, and heart disease is high, and AEs may result from the DNP disease process itself rather than from lacosamide treatment. Thus, discerning the disease state itself from lacosamide AEs should be considered when interpreting results. Fixed-drug dose randomization in our trials did not take into account the individual subject's response in contrast to real-life medical practice, where dosing decisions are driven by the individual subject's efficacy needs and tolerability when higher doses are needed. Study interpretation is also limited by the indirect comparison, for which only descriptive statistical analyses were performed.

As the elderly population continues to increase, it is important to maximize safety profiles of AEDs, because epilepsy is the third most common central nervous system disease in the elderly. Older subjects with concomitant disease states, increased comedication burden, and physiologic changes have an increased risk of AEs. Individual trial safety data with the use of lacosamide are limited owing to low elderly enrollment rates. Although lacosamide is not approved for the treatment of DNP, the large number of elderly subjects enrolled in the DNP trials provided an opportunity to assess its tolerability in this age group. Pooled data from DNP trials included safety profiles of 502 subjects who were ≥65 years of age. The most common AEs in the elderly were dizziness, nausea, and headache. No age-specific signal was evident when AEs were compared in subjects ≥65 years versus <65 years of age in the DNP trials; however, a dose-dependent increase was observed in the higher-dose groups.

Discontinuation rates due to AEs for lacosamide 200 mg/day were similar for the elderly and the younger population. The higher discontinuation rate for the elderly versus the younger subjects receiving lacosamide at higher doses suggests that higher doses of lacosamide as monotherapy in elderly subjects needs to be evaluated based on individual subject efficacy response versus tolerability.

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Disclosure of Conflicts of Interest

Jacquelyn Bainbridge has received honoraria for service on advisory boards from Sunovion and UCB Pharma, investigator-initiated grant funding from Supernus and UCB Pharma, and grant support from NINDS. Marc De Backer, Klaus Eckhardt, Frank Tennigkeit, Sabine Bongardt, and Konrad J. Werhahn are all employees of UCB Pharma. David Sen was an employee of UCB Pharma at the time of the study. Aziz Shaibani has no conflict of interest to disclose. Edward Faught has received consulting fees from Eisai, SAGE, Sunovion, UCB, and Upsher-Smith and for service on Data Safety Monitoring Boards from Eisai, Lundbeck, and SK Life Science. Edward Faught has received research support from Brain Sentinel and UCB. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guideline.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Table S1. Specific cardiac AEs recorded during the treatment phase (i.e., titration and maintenance phase) with lacosamide monotherapy in subjects with diabetic neuropathic pain, presented by age (<65 years or ≥65 years).