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# Efficacy of lacosamide by focal seizure subtype

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**Summary** The purpose of this post hoc exploratory analysis was to determine the effects of the antiepileptic drug, lacosamide, on focal (partial-onset) seizure subtypes.

Patient data from the three lacosamide pivotal trials were grouped and pooled by focal seizure subtype at Baseline: simple partial seizures (SPS), complex partial seizures (CPS), and secondarily generalized partial seizures (SGPS). Both efficacy outcomes (median percent change from Baseline to Maintenance Phase in seizure frequency per 28 days and the proportion of patients experiencing at least a 50% reduction in seizures) were evaluated by lacosamide dose (200, 400, or 600 mg/day) compared to placebo for each seizure subtype. An additional analysis was performed to determine whether a shift from more severe focal seizure subtypes to less severe occurred upon treatment with lacosamide.

In patients with CPS or SGPS at Baseline, lacosamide 400 mg/day (maximum recommended daily dose) and 600 mg/day reduced the frequency of CPS and SGPS compared to placebo. Likewise, a proportion of patients with CPS and SGPS at Baseline experienced at least a

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50% reduction in the frequency of CPS and SGPS (≥50% responder rate) in the lacosamide 400 and 600 mg/day groups compared with placebo. For both outcomes, numerically greatest responses were observed in the lacosamide 600 mg/day group among patients with SGPS at Baseline. In patients with SPS at Baseline, no difference between placebo and lacosamide was observed for either efficacy outcome. An additional exploratory analysis suggests that in patients with SPS at Baseline, CPS and SGPS may have been shifted to less severe SPS upon treatment with lacosamide. The results of these exploratory analyses revealed reductions in CPS and SGPS frequency with adjunctive lacosamide. Reduction in CPS and SGPS may confound assessment of SPS since the CPS or SGPS may possibly change to SPS by effective treatment.


## Introduction

The treatment of epilepsy can be as complex as the disorder itself, often requiring the use of more than one antiepileptic drug (AED). Though newer AEDs may offer better tolerability than older AEDs (including carbamazepine, phenytoin, and valproate), as many as 30% of patients with focal epilepsy remain resistant to treatment (Mohanraj and Brodie, 2003). Treatment decisions are guided by a number of factors, including the type of seizure (Cretin and Hirsch, 2010; Privitera, 2011). Thus, differentiating between focal or generalized onset seizures has important clinical implications (Ferrie, 2005).

Lacosamide is a mechanistically distinct AED used for the adjunctive treatment of adults with focal (partial-onset) seizures (≥17 years of age in the US, ≥16 years of age in the EU). The approval of lacosamide (200 or 400 mg/day) was based on positive results from three similarly designed multicenter, randomized, double-blind, placebo-controlled pivotal trials (Ben-Menachem et al., 2007; Chung et al., 2010; Halász et al., 2009). The primary outcomes of these and other AED registration trials are designed from a regulatory perspective and though necessary and informative in this context, the outcomes of such trials may not directly address questions that are relevant to everyday clinical practice (Faught, 2012), including those regarding treatment decisions based on an individual patient's seizure subtype.

There is a hierarchy of focal seizure severity, ranging from simple partial to complex partial to secondarily generalized. As the risk for serious consequences increases with increasing severity (Baker, 2002; Berg et al., 2010; Leidy et al., 1999), control of focal seizures—particularly the most severe subtypes—is an important clinical goal. To develop a fuller picture of the therapeutic benefits of lacosamide in the treatment of patients with focal seizures, an exploratory analysis was conducted to determine possible differential effects of lacosamide based on focal seizure subtypes, with a particular emphasis on patients who experienced complex partial seizures (CPS) and secondarily generalized partial seizures (SGPS) at Baseline of the pivotal Phase II/III trials. Though none of the pivotal trials were powered to determine differential effects of lacosamide on the various seizure subtypes by dose, the analysis of efficacy by seizure type was a priori defined in the individual trial protocols and was replicated in this pooled analysis.

## Methods

### Lacosamide pivotal trials

Full details of the individual pivotal trials have been published (Ben-Menachem et al., 2007; Chung et al., 2010; Halász et al., 2009). Briefly, lacosamide was titrated weekly over a period of 4 or 6 weeks in 100 mg increments to the assigned target dose (200, 400, or 600 mg/day). Adult patients with a diagnosis of epilepsy with partial-onset seizures according to the International Classification of Epileptic Seizures (ILAE, 1981) were included. Patients were required to have at least a 2-year history of partial-onset seizures despite prior therapy with at least two AEDs (concurrently or sequentially). In the 8-week period before Baseline and during the 8-week Baseline Phase, patients were to have had at least four partial-onset seizures (either simple partial (SPS) with motor signs, complex partial (CPS), or secondarily generalized (SGPS) seizures per 28 days on average with no seizure-free period longer than 21 days. Patients taking one to three concomitant AEDs (one to two in trial SP667) with or without stable vagus nerve stimulation were maintained on their target lacosamide dose or placebo for a 12-week Maintenance Phase followed by either a 2-week blinded transition to 200 mg/day lacosamide (if entering an open-label extension trial) or a 2—3-week taper off trial medication. The primary efficacy variables assessed in the individual studies were: (1) change in partial seizure frequency per 28 days from Baseline to the Maintenance Phase and (2) the proportion of patients experiencing a 50% or greater reduction in seizure frequency from Baseline to Maintenance Phase (50% responder rate).

### Analysis

Given the similar trial designs and similar patient eligibility criteria, data from the three lacosamide pivotal trials were pooled. The exploratory analyses presented here evaluated the effect of lacosamide on different types of focal seizures by grouping patients according to seizure subtype at Baseline: all SPS (including those with or without focal motor symptoms), CPS, and SGPS (which may be generalized tonic, clonic, tonic—clonic). Patients could experience more than one seizure subtype at Baseline and could therefore be included in more than one subtype group (i.e., the grouping of patients based on Baseline seizure subtypes was