Keppra
Vimpat
Brivaracetam

2012 Epilepsy Pipeline Update
Conference
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Babak Boroojerdi, MD, PhD, MBA
UCB Clinical Development
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Keppra®
Levetiracetam: Project status

<table>
<thead>
<tr>
<th>Current indication</th>
<th>EU</th>
<th>US</th>
<th>Korea</th>
<th>China</th>
<th>Japan</th>
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</thead>
<tbody>
<tr>
<td><strong>Monotherapy</strong></td>
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<td></td>
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<tr>
<td>• Partial-onset seizures (newly diagnosed epilepsy)</td>
<td>≥16 years</td>
<td>Not approved</td>
<td>≥16 years</td>
<td>Not approved</td>
<td>Not approved</td>
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<tr>
<td><strong>Adjunctive therapy</strong></td>
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<tr>
<td>• Partial-onset seizures</td>
<td>≥1 month and adults</td>
<td>≥1 month* and adults</td>
<td>≥1 month and adults</td>
<td>≥4 years and adults</td>
<td>Adults</td>
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<tr>
<td>• Myoclonic seizures in JME</td>
<td>≥12 years and adults</td>
<td>≥12 years and adults</td>
<td>≥12 years and adults</td>
<td>Not approved</td>
<td>Not approved</td>
</tr>
<tr>
<td>• Primary generalized tonic-clonic seizures in IGE</td>
<td>≥12 years and adults</td>
<td>≥6 years and adults</td>
<td>≥12 years and adults</td>
<td>Not approved</td>
<td>Not approved</td>
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</tbody>
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*Application for 1 month has been approved in December 2011

JME, juvenile myoclonic epilepsy
IGE, idiopathic generalized epilepsy

Keppra® EU SmPC 2011; US PI 2011; Korea PI 2011; China PI; EKeppra® Japan PI 2011
Levetiracetam Phase III–IV development program in East Asia

Two Korean levetiracetam head-to-head comparisons with other AEDs

- **RAPID Study** (N01353)
  - A **RA**andomized, open-label, parallel group, multicenter, comparative, **Phase IV** trial of levet**I**racetam versus **topirimate** as a **D**junctive therapy to evaluate efficacy and safety in adult subjects with refractory POS

- **OPTIMAL Study** (N01367)
  - A multi-center, **OP**en-label, randomized study to evaluate the long term effectiveness of levet**I**racetam as **M**onotherapy in comparison with **oxcarbazepine** in subjects with newly or recently diagnosed parti**AL** epilepsy

Clinical study to evaluate efficacy of Keppra in patients with primary generalized tonic-clonic seizures or POS in China and Japan

- **CJ LINE** (*China-Japan Levetiracetam IN Epilepsy*) (N01159)
  - A double-blind, multicenter, randomized, placebo-controlled study to evaluate the efficacy and safety of adjunctive treatment with oral levetiracetam, in patients with uncontrolled PGTC seizures aged ≥16 years, with generalized tonic-clonic seizures

- **Japanese pediatric extension study for POS** (N01223)
  - An open label, single-arm, multicenter study on the efficacy, safety and pharmacokinetics of levetiracetam in pediatric patients (4–16 years) with partial onset seizures despite treatment with one or two AEDs
Objective

- To assess the long-term effects of levetiracetam on retention rate in patients with refractory POS that are not fully controlled with one to three concomitant AEDs, compared with topiramate as add-on therapy over 52 weeks

Study population

- Refractory epilepsy patients with POS as classifiable by ILAE
- Patients uncontrolled while treated with one to three permitted concomitant AEDs
- Patients with ≥2 POS during 8-week historical baseline AND with ≥1 POS (whether or not secondarily generalized) during 4-week prospective baseline before randomization visit

Sample size

- 340 patients randomized (170 per treatment)
RAPID study: N01353 study design
NCT01229735

1:1 randomization

Visit 1
(-4W)

V2
(W0)

V3
(W4)

V8
(W24)

V12
(W52)

Baseline
(4 weeks)

Up-titration
(4 weeks)

Dose-finding period
(20 weeks)

Maintenance
(28 weeks)

Continue
LEV or TPM

500 mg/d

1,000 mg/d

Max 3,000 mg/d

50 mg/d

75 mg/d

100 mg/d

Max 400 mg/d

50 mg/d

75 mg/d

100 mg/d

Max 3,000 mg/d

Max 400 mg/d

Visit 2
(-4W)

Visit 3
(-4W)

Visit 8
(-4W)

Visit 12
(-4W)

LEV

TPM

LEV or TPM

or down-titration

TPM, topiramate
LEV, levetiracetam
Objectives

• To evaluate long-term effectiveness (over 50 weeks) of levetiracetam monotherapy on treatment failure rate in patients with newly diagnosed POS, compared with OXC monotherapy
• To demonstrate that monotherapy with levetiracetam (1,000–3,000 mg/day) is non-inferior to monotherapy with OXC (900–2,400 mg/day)

Study population

• Patients with newly or recently diagnosed epilepsy with unprovoked partial seizures with clear focal origin, classifiable according to ILAE Classification (1981)
  • Patients not clearly defined between primary and secondary generalized seizures could be included
• Patients with \( \geq 2 \) unprovoked seizures \( \geq 48 \) hours apart in the year preceding randomization (\( \geq 1 \) unprovoked seizure in the 6 months preceding randomization)

Sample size

• 352 randomized patients (176 per treatment)
OPTIMAL study: N01367 study design
NCT01498822

Visit 1 (-1W)  V2 (W0)  V3 (W2)  V9 (W50)

Baseline (1 week)  Up-titration (2 weeks)  Treatment (48 weeks)

LEV

500 mg/d  600 mg/d  First level dose: 1,000 mg/d  Max 3,000 mg/d

First level dose: 900 mg/d  Max 2,400 mg/d

OXC

300 mg/d

Continue same commercial medication
Or down-titration

1:1 randomization
Objective

- To evaluate the efficacy of levetiracetam as adjunctive therapy in Japanese and Chinese patients with epilepsy aged ≥16 years with uncontrolled PGTC seizures despite treatment with one or two AEDs
- Primary efficacy variable: percentage reduction in GTC seizure frequency per week from the combined baseline over the 28-week treatment period (dose adjustment + evaluation periods)
- Combined baseline = 4-week retrospective baseline + 4-week prospective baseline

Study population

- Patients with ≥3 PGTC seizures during the 8-week combined baseline period (≥1 PGTC seizure during the 4-week retrospective baseline period and ≥1 PGTC seizure during the 4-week prospective baseline period)
- Patients on stable dose of one or two AEDs for the 4 weeks preceding and during the combined baseline period
- No diagnosis of LGS

Sample size

- Planned number of subjects for the efficacy analyses: 232

PGTC, primary generalized tonic-clonic
GTC, generalized tonic-clonic
CJLine study: N01159 study design
NCT01228747

**Combined baseline period**

- Retrospective baseline (4 weeks)
- Prospective placebo baseline (4 weeks)
- 1,000 mg/d

**Treatment period**

- Dose-adjustment period
  - 3,000 mg/d
  - 2,000 mg/d
- Evaluation period
  - Fall back option

**Conversion to follow up extension**

**Or down-titration**

**Placebo**

- Visit 1 (-4W)
- V2 (0W)
- V3 (4W)
- V4 (8W)
- V5 (12W)
- V6~8 (16W)
- V9 (20~32W)
- V9 (32W)

**1:1 randomization**
Vimpat®
Lacosamide – Structure and Mechanism of Action

Lacosamide (LCM) selectively enhances the slow inactivation of voltage-gated sodium channels\textsuperscript{1,2}

- No effects on fast inactivation, in contrast to older sodium-channel modulators such as carbamazepine, lamotrigine, and phenytoin
- Selectively reduces pathophysiological neuronal hyperexcitability with minimal impact on physiological activity

The precise mechanism by which LCM exerts its antiepileptic effects in humans remains to be fully elucidated

Vimpat® – US Indication

- **Oral lacosamide** is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older.

- **Lacosamide injection for intravenous use** is indicated as adjunctive therapy in the treatment of partial-onset seizures in patients with epilepsy aged 17 years and older when oral administration is temporarily not feasible.

The specific indication statement for lacosamide differs slightly from country to country – local labels should be consulted for further information.
Lacosamide – Overview of Select Ongoing and Planned trials

Monotherapy for patients with partial-onset seizures
- Phase 3, Conversion to monotherapy (US)
- Phase 3, Non-inferiority (EU)

Adjunctive therapy in the pediatric population (1 month – 17 years of age)
- Partial-onset seizures – Phase 2, open-label trial
- Epilepsy – Phase 1, open-label trial

Adjunctive therapy for patients with primary generalized tonic-clonic seizures
- Phase 2, open-label pilot study (clinically complete)
- Phase 3 trial – planned
# Adjunctive Therapy in the Pediatric Population – Phase 1 and 2 Studies

## Design

<table>
<thead>
<tr>
<th>Partial-onset seizures</th>
<th>Epilepsy</th>
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</table>
| Phase 2, open-label trial in children  
1 month – 17 years  
followed by open-label extension study | Phase 1, open-label trial in children  
1 month – 17 years |

## Primary outcome measures

| Safety and tolerability | Pharmacokinetic profile of lacosamide and major metabolite SPM 12809 |

## Planned number of subjects

| N = 42  
FPFV November 2009 | N = 32  
FPFV April 2011 |

OLE = open-label extension; FPFV = first patient first visit
# Monotherapy for Partial-onset Seizures in Adults – Phase 3 Studies

## Conversion to monotherapy – US
Double-blind, historical-controlled conversion to monotherapy in adults followed by open-label extension study

## Non-inferiority – EU
Double-blind, double-dummy, positive-controlled LCM vs. CBZ-CR in adults followed by double-blind extension study

## Primary outcome measure
- **Conversion to monotherapy – US:** Percentage of patients meeting ≥1 predefined exit criteria by Day 112 relative to start of withdrawal of background AED
- **Non-inferiority – EU:** Proportion of patients remaining seizure free for 6 consecutive months (26 weeks) of treatment following stabilization at the last evaluated dose for each patient

## Planned number of subjects
- **Conversion to monotherapy – US:** N = 451 FPFV August 2007
- **Non-inferiority – EU:** N = 878 FPFV April 2011

*CBZ-CR = carbamazepine controlled release; OLE = open-label extension; AED = antiepileptic drug; FPFV = first patient first visit*
Adjunctive Therapy for Primary Generalized Tonic-clonic Seizures

Completed Phase 2, open-label pilot study to assess safety of adjunctive LCM for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy

- Primary Outcome Measures
  - Change in the number of seizure days with absence seizures from the Baseline Phase to the Maintenance Phase
  - Change in the number of seizure days with myoclonic seizures from the Baseline Phase to the Maintenance Phase

- 49 subjects enrolled (LPLV Aug 2011); analysis ongoing
- One-year open-label extension study for patients completing pilot study

Planned Phase 3 study to assess efficacy and safety of adjunctive LCM for uncontrolled primary generalized tonic-clonic seizures in subjects with idiopathic generalized epilepsy
Brivaracetam
Background

Brivaracetam (BRV)
- A novel high-affinity synaptic vesicle protein 2A (SV2A) ligand
- Also displays inhibitory activity at neuronal voltage-dependent sodium channels
- Data from animal models suggested potent and broad spectrum antiepileptic activities

Adjunctive treatment of adults with POS
- In completed well-controlled trials, adjunctive BRV (50 and 100 mg/day) demonstrated efficacy comparable to recently approved AEDs
- BRV was well tolerated
  - Placebo-like drop-out rate in completed clinical studies (5–150 mg/day)
  - Favorable CNS safety profile across doses and without titration
- One of the Phase III therapeutic confirmatory studies did not meet its primary efficacy endpoint
- UCB is currently conducting another Phase III therapeutic confirmatory study (after consultations with FDA and EMA)

POS, partial-onset seizures
AED, antiepileptic drug
CNS, central nervous system
FDA, Food & Drug Administration
EMA, European Medicines Agency

2. Zona et al. Epilepsy Res 2010;88:46–54
5. Brodsky et al. Epilepsia 2007;48(Suppl. 6):342
Adjunctive treatment for POS in adults therapeutic confirmatory study (N01358)

Safety study for i.v. formulation (N01258)

Pharmacokinetic and safety study in pediatric patients with epilepsy (N01263)
Adjunctive treatment for partial-onset seizures in adults therapeutic confirmatory study (N01358)
NCT01261325

- Double-blind, placebo-controlled, parallel-group, confirmatory study
- Primary objective: to evaluate the efficacy of adjunctive BRV 100 and 200 mg/day compared with placebo in adult focal epilepsy patients with POS
- Primary endpoints:
  - USA: Percent reduction over placebo in POS frequency
  - EU: ≥50% responder rate for POS frequency
- Three treatment arms randomized 1:1:1 (placebo, BRV 100, BRV 200 mg/day)
- 240 patients per arm planned (study total = 720)
- Key inclusion criteria
  - ≥2 POS/month for 3 months prior to entry
  - ≥8 POS during the 8-week prospective baseline
  - Uncontrolled on one to two permitted AEDs
  - Patients on concomitant LEV (or LEV treatment within last 3 months) were excluded
- Status: ongoing
Adjunctive treatment for partial-onset seizures in adults therapeutic confirmatory study (N01358)
NCT01261325

Baseline period (8 weeks) → Treatment period (12 weeks) → Down-titration period (Week 1) → Down-titration period (Week 2) → Down-titration period (Week 3) → Down-titration period (Week 4) → Study drug-free period (2 Weeks)

- **D2 (200 mg/day)**
- **D1 (100 mg/day)**
- **Placebo**

**Visit 1**
- **W1-8**

**V2**
- **W -4**

**V3**
- **W0**

**V4**
- **W2**

**V5**
- **W4**

**V6**
- **W8**

**V7**
- **W12**

**V8**
- **W16**

**Safety visit**
- **W18**

- **Screening**
- **Randomization**
- **Phone call Week 1**

- **Evaluation**

- **Follow-up study**
  - Start dosage 150 mg/day
Multicenter, open-label, four-arm, randomized trial

Primary objective: to evaluate the safety and tolerability of BRV 200 mg/day administered i.v. (infusion or bolus) according to an initiation or a conversion scheme, during repeated dosing (100 mg/administration b.i.d for 4.5 days) as an adjunctive treatment in adult patients with localization-related or generalized epilepsy

100 subjects will be randomized

Status: ongoing
Pharmacokinetic and safety study in pediatric patients with epilepsy (N01263)
NCT00422422

- Open-label, single-arm, multicenter, pharmacokinetic, safety and efficacy study of adjunctive BRV in patients with epilepsy aged from ≥1 month to <16 years

- Primary objective: to characterize the steady-state pharmacokinetics of BRV and its metabolites, evaluate their relationship with physiological developmental variables and develop dosing adaptations in patients aged ≥1 month to <16 years

- Doses: three dose levels for each patients. All doses will be adjusted by body weight, with similar exposure to adult doses of 50 mg/day, 100 mg/day, and 200 mg/day

- Sample size: 100 patients

- Status: ongoing
Questions?