Efficacy and safety of padsevonil as adjunctive treatment for adults with focal epilepsy

A randomized, double-blind, placebo-controlled, proof-of-concept trial

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UCB Pharma

Update in Epilettologia Padova, 9 Febraio, 2019
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AEDs show lack of differentiation for efficacy

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Drug</th>
<th>Delta</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brivaracetam</td>
<td>17.9</td>
<td>35.6</td>
<td>17.7</td>
</tr>
<tr>
<td>Eslicarbazepine</td>
<td>21.5</td>
<td>36.3</td>
<td>14.8</td>
</tr>
<tr>
<td>Gabapentin</td>
<td>9.3</td>
<td>20.3</td>
<td>11</td>
</tr>
<tr>
<td>Lacosamide</td>
<td>22.6</td>
<td>37.8</td>
<td>15.2</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>9</td>
<td>20.6</td>
<td>11.6</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>9.3</td>
<td>34.8</td>
<td>25.5</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>12.7</td>
<td>34</td>
<td>21.3</td>
</tr>
<tr>
<td>Perampanel</td>
<td>19.3</td>
<td>32.9</td>
<td>13.6</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>9.8</td>
<td>36.1</td>
<td>26.3</td>
</tr>
<tr>
<td>Rufinamide</td>
<td>16.3</td>
<td>30.4</td>
<td>14.1</td>
</tr>
<tr>
<td>Topiramate</td>
<td>13.4</td>
<td>43.2</td>
<td>29.8</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>11.3</td>
<td>24.8</td>
<td>13.5</td>
</tr>
</tbody>
</table>

Marson (1997), Marson (2001); for OXC 600 & 1200 mg/d only, Beydoun (2005), Arroyo (2004), French (2003), LCM: 200mg/day and 400mg/day from pooled results, Elger (2009), Ben-Menachem (2010), Gil-Nagel (2009), BRV: 50mg/day and 100mg/day from all fixed dose studies, 3200mg/day with new formulation; Brodie (2009), Biton (2010), Porter (2007), French (2011), Brodie (2010), Jette (2008)
High Unmet Need in Epilepsy Patients
in spite of the multitude of anticonvulsants available

- A good proportion of patients are drug resistant to any currently available AED
- The burden of epilepsy has not changed (1990 – 2016). 80% of the cost of illness is driven by 20% of patients who are treatment resistant
- How to develop AED for treatment resistant patients is not defined.
**Padsevonil: A candidate AED with Dual Mechanism of Action**

- High affinity binding to all three SV2 isoforms (SV2A, SV2B and SV2C)\(^1\), unlike LEV and BRV
- Unique SV2A binding characteristics, relative to LEV and BRV\(^1\)
- Binding affinity for the GABA\(_A\) receptor complex is approx. 100 lower than for SV2\(^1\)
- Partial agonist profile\(^2\)

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2. Wolff C, et al. AES 2017

LEV – levetiracetam
BRV – brivaracetam
Pharmacodynamic interaction between SV2A and GABA\textsubscript{A} ligands

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**Potency**

- Audiogenic seizures in mice

**Tolerability**

- Rota-rod test in mice

**Efficacy**

- Amygdala kindling in rats

- Combination of SV2A (levetiracetam) and GABA\textsubscript{A} ligands (benzodiazepines) offers higher potency and efficacy against seizures with potential for reduced side effects\textsuperscript{1-3}

- Dual SV2A/GABA\textsubscript{A} compound may lead to better seizure control in patients with drug resistant epilepsy

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Dual SV2A and GABA\textsubscript{A} affinities can be engineered into a single molecule

Ligand-based drug design

SV2A selective ligands

GABA\textsubscript{A} (benzodiazepine receptor) selective ligands

First dual hit compound

\textbf{Chemical Structures:}

- **SV2A selective ligands**
  - Rn
  - \textbf{pKi SV2A : 7.3}

- **GABA\textsubscript{A} selective ligands**
  - R4
  - \textbf{pKi BZD: 5.6}

- **First dual hit compound**
  - X
  - X

- **Chemical Compounds:**
  - Zolpidem
  - AHR-14749
Higher level of anticonvulsant activity when compared to drug combinations achieving similar target occupancies

- In the 6 Hz seizure model, at similar in vivo target occupancies, padsevonil protects a greater proportion of mice than LEV, BRV and DZP administered alone or in combination*

* sub-therapeutic doses

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Leclercq K, et al. AES 2017

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SV2A – synaptic vesicle protein 2A  
BZD – benzodiazepine  
PSL – padsevonil  
DZP – diazepam  
LEV – levetiracetam  
BRV – brivaracetam
# High potency and differentiated activity in a range of animal models of acute seizures

<table>
<thead>
<tr>
<th>Seizure model</th>
<th>Levetiracetam</th>
<th>Brivaracetam</th>
<th>Padsevonil</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ED$_{50}$ (mg/kg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6 Hz (44 mA)</td>
<td>19.2</td>
<td>4.4</td>
<td>0.16</td>
</tr>
<tr>
<td>Audiogenic</td>
<td>30</td>
<td>2.4</td>
<td>0.17</td>
</tr>
<tr>
<td>Pilocarpine</td>
<td>7.1</td>
<td>Not effective</td>
<td>0.19</td>
</tr>
<tr>
<td>Pentylenetetrazol</td>
<td>Not effective</td>
<td>30</td>
<td>4.8</td>
</tr>
<tr>
<td>11-deoxycortisol</td>
<td>540^</td>
<td>Not effective</td>
<td>9.9</td>
</tr>
<tr>
<td>Bicuculline</td>
<td>Not effective</td>
<td>Not effective</td>
<td>27.3</td>
</tr>
<tr>
<td>Maximal electroshock</td>
<td>Not effective</td>
<td>113</td>
<td>92.8</td>
</tr>
</tbody>
</table>

Leclercq K, et al. AES 2017

^ - partial efficacy
Padsevonil: efficacy against drug resistant seizures in the rat amygdala kindling model

Among twelve tested AEDs padsevonil is the only compound showing both full efficacy and good tolerability at clinically relevant exposures

5-15x higher than max. clinical exposure
Translating SV2A and cBZD target engagement from rodents to humans

Occupancy at SV2A and cBZD measured in vivo by ligand binding in mice

Target engagement range based on efficacy in the amygdala kindling models

Human SV2A PET > 98% occupancy

Padsevonil (400 mg BID)

Human cBZD PET ~ 5-15% occupancy
Padsevonil

A Rationally Designed New Drug Candidate with Dual Synergistic Mechanism of Action

- High affinity for synaptic vesicle (SV2A, SV2B and SV2C) and low affinity partial agonism for GABA-A

- Robust and broad spectrum effect demonstrated in preclinical studies

- Dose selection for Phase II informed by preclinical and PET imaging data for both targets (SV2A & GABA-A)
Padsevonil – **Trial** Design

**Adult Patients with treatment history > 4 AEDs and > seizures per week**

- **Prospective baseline period (2–3 weeks)**
- **3-week inpatient double blind period with 1 week titration**
  - Titration
  - 400 mg bid
  - 400 mg bid
  - 400 mg bid
- **8-week outpatient maintenance**
  - Placebo
  - Placebo
  - Titration
  - 400 mg bid

N = 55

UCB data on file – EP0069 CSR, Sep 2017, p43–44

Figure adapted from same reference

PSL=padsevonil
OLE=open-label extension
EP0069 – proof-of-concept trial

Patient disposition

All patients in EP0069:
66 patients screened; 55 randomized

Padsevonil (n=28)  Placebo (n=27)

Discontinued
1/28 (3.6%)
Adverse event

Inpatient Period
Entered: 28 (100%)
Completed: 27 (96.4%)

Inpatient Period
Entered: 27 (100%)
Completed: 27 (100%)

Open-label padsevonil (n=53)\(^a\)

Outpatient Treatment
Entered: 53 (96.4%)\(^a\)
Completed: 50 (90.9%)

Discontinued
3/55 (5.5%)
Lack of efficacy

\(^a\)One patient from padsevonil arm completed the inpatient period, but did not start outpatient treatment (due to non-drug-related medical reasons).

Muglia P, et al. AES 2017; abstract 1.283
### Demographics and baseline epilepsy characteristics

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=27</th>
<th>Padsevonil n=28</th>
<th>All patients N=55</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD), years</strong></td>
<td>35.2 (8.7)</td>
<td>36.2 (11.4)</td>
<td>35.7 (10.1)</td>
</tr>
<tr>
<td><strong>Female, n (%)</strong></td>
<td>14 (51.9)</td>
<td>15 (53.6)</td>
<td>29 (52.7)</td>
</tr>
<tr>
<td><strong>Body mass index, median (range), kg/m²</strong></td>
<td>25.30 (16.9–34.9)</td>
<td>27.55 (18.5–34.7)</td>
<td>26.60 (16.9–34.9)</td>
</tr>
</tbody>
</table>

**History of epileptic seizures**

<table>
<thead>
<tr>
<th></th>
<th>Placebo n=27</th>
<th>Padsevonil n=28</th>
<th>All patients N=55</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age at first seizure, mean (SD), years</strong></td>
<td>13.1 (9.6)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>9.2 (7.7)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>11.1 (8.8)&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>Epilepsy duration, median (range), years</strong></td>
<td>22.1 (1.5–40.6)</td>
<td>26.0 (12.0–49.7)</td>
<td>24.2 (1.5–49.7)</td>
</tr>
<tr>
<td><strong>History of status epilepticus, n (%)</strong></td>
<td>3 (11.1)</td>
<td>3 (10.7)</td>
<td>6 (10.9)</td>
</tr>
<tr>
<td><strong>History of withdrawal seizures, n (%)</strong></td>
<td>3 (11.1)</td>
<td>0</td>
<td>3 (5.5)</td>
</tr>
<tr>
<td><strong>Focal seizures per week at baseline&lt;sup&gt;d&lt;/sup&gt;, median (range)</strong></td>
<td>12.6 (3.0–130.6)</td>
<td>8.0 (3.2–35.7)</td>
<td>8.2 (3.0–130.6)</td>
</tr>
</tbody>
</table>

**Classification of seizures<sup>e</sup> during 2-week prospective baseline<sup>f</sup>, n (%)**

| **Any partial-onset seizure (focal seizures)** | 27 (100)   | 27 (96.4)<sup>f</sup> | 54 (98.2)<sup>f</sup> |
| **Simple partial (focal aware)**                  | 13 (48.1)  | 9 (32.1)       | 22 (40.0)         |
| **Motor symptoms**                                 | 10 (37.0)  | 7 (25.0)       | 17 (30.9)         |
| **Somatosensory or specialized sensory symptoms** | 4 (14.8)   | 3 (10.7)       | 7 (12.7)          |
| **Autonomic symptoms**                             | 1 (3.7)    | 1 (3.6)        | 2 (3.6)           |
| **Psychic symptoms**                               | 0          | 1 (3.6)        | 1 (1.8)           |
| **Complex partial (focal impaired awareness)**    | 22 (81.5)  | 26 (92.9)      | 48 (87.3)         |
| **Partial evolving to secondarily generalized (focal to bilateral tonic-clonic)** | 7 (25.9) | 6 (21.4) | 13 (23.6) |
| **Any generalized seizures**                      | 0          | 0              | 0                 |
| **Unclassifiable**                                 | 1 (3.7)    | 0              | 1 (1.8)           |
| **Clusters**                                       | 1 (3.7)    | 0              | 1 (1.8)           |

*<sup>n=25</sup>; *<sup>n=27</sup>; *<sup>n=52</sup>; bBased on observable focal seizures (focal aware with motor symptoms, focal impaired awareness, and focal to bilateral tonic-clonic); cSeizure types are listed per the International League Against Epilepsy (ILAE 1981) classification, with the newer terminology (ILAE 2017) in parentheses; dMultiple seizure types could be reported. eOne patient lost the prospective baseline diary, but provided retrospective baseline data (with focal seizures).
**Padsevonil POC Patients**

**3 times ↑ seizure frequency than typical trial patient population**

<table>
<thead>
<tr>
<th></th>
<th>Padsevonil (n = 55)</th>
<th>Lacosamide (n = 1,308)</th>
<th>Brivaracetam (n = 760)</th>
<th>Cenobamate* (n = 679)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure / 28 days (Median Baseline Freq.)</td>
<td>32</td>
<td>11.5</td>
<td>9.6</td>
<td>5.5-11</td>
</tr>
</tbody>
</table>

High seizure frequency at baseline is associated with lower response to AEDs
• (Berg et al. 1996, Schiller 2009)

Brivaracetam has 4 times lower chance of achieving at least 50% seizure reduction when baseline median seizure frequency is 32 vs. 9
• (Schoemaker, Wade and Stockis *J Clin Pharm* 2016)

* Phase 3 study SK Biopharmaceuticals Co., LTD
Efficacy Variables – double-blind inpatient treatment period

2-week focal seizure frequency during treatment vs 2-week prospective baseline

- ≥75% responder rate
  - Odds ratio 4.14 (95% CI 0.9, 19.1)
  - p=0.0679

- Percent reduction in seizure frequency
  - Median difference 34.0 (95% CI 3.0, 67.5)
  - p=0.026*
Efficacy Variables – outpatient treatment period

- **≥75% responder rate**
  - PSL: n=51, 31.4%

- **Percent reduction in seizure frequency**
  - PSL: n=51, 55.2%
## Safety overview – incidence of TEAEs

### Treatment-emergent adverse events (TEAEs) with PSL (SS)

<table>
<thead>
<tr>
<th>Patients, n (%)</th>
<th>All patients (n=55)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TEAEs</td>
<td>50 (90.9)</td>
</tr>
<tr>
<td>Drug-related TEAEs</td>
<td>47 (85.5)</td>
</tr>
<tr>
<td>Severe TEAEs</td>
<td>8 (14.5)</td>
</tr>
<tr>
<td>Serious TEAEs</td>
<td>2 (3.6)</td>
</tr>
<tr>
<td>TEAEs requiring dose change</td>
<td>18 (32.7)</td>
</tr>
<tr>
<td>Discontinuations due to TEAEs</td>
<td>1 (1.8)</td>
</tr>
</tbody>
</table>
Levetiracetam, the most Common Concomitant AEDs, is not influencing response.

Most Common Concomitant AEDs:
- LEV
- LCM
- OXC
- VPA
- LTG
- PER
- ESL

Seizure Frequency Reduction in Patients with concomitant LEV:

EP0069: Percent Reduction from Baseline in Seizure Frequency
Focal seizure type - Period = Last 4-week out-patient - broken down by level
Padsevonil 400 mg BID achieved targeted SV2A and GABA-A occupancies

Model based PK/ PD/ Receptor Occupancy Analyses

- Observed average concentrations from NCA after 400 mg bid: $C_{av} = 440.8$ ng/mL (177.2 – 1436.7 as 90% CI)
- Estimated daily average concentration for 50% of the maximum reduction seizure counts: $EC_{50} = 190.6$ ng/mL

**Human SV2A PET**: > 98% occupancy

**Human cBZD PET**: ~ 5-15% occupancy
Conclusions

• Clinically meaningful reduction of seizure frequency in patient with frequent seizures

• Initial data suggest maintenance of effect for 8-11 weeks

• No new or unexpected safety signals – acceptable tolerability and safety profile in the studied population

• Most frequent TEAEs: somnolence, dizziness, headache, fatigue, and irritability

• Phase IIb study ongoing
Acknowledgement

Patients and Families

Investigators

P.I.s, Investigators, and all staff at the recruiting sites

Discovery

- Rafal Kaminski
- Benoit Kenda
- Henrik Klitgaard
- Alain Matagne
- Philippe Michel
- Laurent Provins
- Yannick Quesnel
- Laurent Turet
- Martyn Wood
- Michel Gillard

Proof of concept

- Massimo Bani
- Hugues Chanteux
- Anna Colzi
- Miranda Cornet
- Steven de Bruyn
- Colin Ewen
- Jonas Hannestad
- Pierandrea Muglia
- Christian Otoul
- Marie-Luce Rosseels
- David Sciberras
- Françoise Stiernet
- Marc Watling
- Elizabeth Webster
- Konrad Werhahn