Peripheral Edema and Weight Gain in Adult Patients With Painful Diabetic Peripheral Neuropathy Receiving Gabapentin Enacarbil or Pregabalin Enrolled in a Randomized, Phase 2 Trial

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Disclosures

• AC is a speaker for Depomed, Pfizer, Purdue, Salix, and Teva

• JS served as a consultant for Millennium, XenoPort, Insys, Purdue Frederick, Teva, Empi/Donjoy, Takeda, RS Medical, Covidien, Mallinckrodt, Reckitt Benckiser, and Neurotech

• MJ is a consultant for XenoPort, Inc

• RK and GS are employees of and own stock in XenoPort, Inc
• Gabapentin enacarbil is not approved for use in the treatment of Diabetic Peripheral Neuropathy (DPN)

• Gabapentin enacarbil is approved for the treatment of adults with moderate-to-severe primary Restless Legs Syndrome (600 mg once daily) and for the management of Postherpetic Neuralgia (PHN; 600 mg twice daily).
• Gabapentin enacarbil (GEn) is an actively transported prodrug of gabapentin

• GEn was evaluated in a randomized, phase 2 study in patients with neuropathic pain attributed to Diabetic Peripheral Neuropathy (DPN)\(^1\)

• For the primary efficacy endpoint (change from baseline in the mean 24-hour average pain intensity score), neither the GEn treatment arms (1200 mg, 2400 mg, or 3600 mg per day) nor the control arm (pregabalin 300 mg/day) differed from placebo, mostly due to a high placebo response rate
  – Treatment differences vs. placebo: GEn 1200 mg/day: −0.35; P=0.295
  – GEn 2400 mg/day: −0.02; P=0.946
  – GEn 3600 mg/day: −0.55; P=0.105
  – Pregabalin: 0.43; did not differentiate from placebo

• GEn was well tolerated across all studied doses, even at the highest dose of 3600 mg/day\(^1\)

As this was the first study to assess treatment with GEn compared with the approved dose of pregabalin, two treatment-emergent adverse events of clinical significance commonly reported with treatment with the alpha-2-delta class of drugs, peripheral edema and weight gain, were further examined.
Study Design

Diabetes mellitus (type 1 or 2)
Painful DPN (≥6 mos to <5 yrs)
Stable glycemic control
Baseline avg daily pain score ≥4

N=392

Placebo (n=120)
GEn 1200 mg/day (n=62)
GEn 2400 mg/day (n=56)
GEn 3600 mg/day (n=117)
Pregabalin 300 mg/day (n=66)

Screening
Up to 4 wks
Baseline
1 wk
Up-titration
1 wk
Maintenance treatment
12 wks
Down-titration
1 wk
Post-treatment
7 or 16 days

Treatment period 14 wks

Wk −5 to −2
Wk −1
Day 0
Wk 0
Wk 1
Wks 2−12
Wk 13
Wk 14
Wk 15


a On an 11-point pain intensity numerical rating scale (0=no pain; 10=worst possible pain).
b Randomization occurred at Day 0.
GEn = gabapentin enacarbil; mos = months; wk = week; yrs = years.
**Baseline Characteristics (Safety Population\(^a\))**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (n=120)</th>
<th>1200 mg (n=62)</th>
<th>2400 mg (n=56)</th>
<th>3600 mg (n=116)</th>
<th>Pregabalin (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>60.1 (10.6)</td>
<td>57.5 (10.3)</td>
<td>60.8 (9.0)</td>
<td>57.5 (9.9)</td>
<td>57.7 (10.6)</td>
</tr>
<tr>
<td><strong>Gender, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>61</td>
<td>55</td>
<td>66</td>
<td>61</td>
<td>52</td>
</tr>
<tr>
<td><strong>Race, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>White</strong></td>
<td>82</td>
<td>74</td>
<td>85</td>
<td>79</td>
<td>81</td>
</tr>
<tr>
<td><strong>BMI, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30 kg/m(^2)</td>
<td>27 (23)</td>
<td>16 (26)</td>
<td>22 (39)</td>
<td>39 (34)</td>
<td>17 (26)</td>
</tr>
<tr>
<td>&gt;30 kg/m(^2)</td>
<td>93 (78)</td>
<td>46 (74)</td>
<td>34 (61)</td>
<td>77 (66)</td>
<td>49 (74)</td>
</tr>
<tr>
<td><strong>Baseline 24-h pain score,</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>6.5 (1.3)</td>
<td>6.6 (1.5)</td>
<td>6.3 (1.2)</td>
<td>6.5 (1.4)</td>
<td>6.5 (1.3)</td>
</tr>
<tr>
<td><strong>HbA1c, %</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Mean (SD)</strong></td>
<td>7.5 (1.3)</td>
<td>7.4 (1.3)</td>
<td>7.6 (1.4)</td>
<td>7.6 (1.4)</td>
<td>7.5 (1.3)</td>
</tr>
</tbody>
</table>

\(^a\)421 patients were randomized to treatment; one patient in the GEn 3600-mg group did not take study medication and was excluded from the safety population.

BMI = body mass index; GEn = gabapentin enacarbil; HbA1c = glycated hemoglobin; SD = standard deviation.
### Treatment-Emergent Adverse Events Reported in >5% of Patients (Safety Population)

<table>
<thead>
<tr>
<th>Adverse event, n (%)</th>
<th>Placebo (n=120)</th>
<th>GEn 1200 mg (n=62)</th>
<th>GEn 2400 mg (n=56)</th>
<th>GEn 3600 mg (n=116)</th>
<th>Pregabalin (n=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any event</td>
<td>79 (66)</td>
<td>45 (73)</td>
<td>38 (68)</td>
<td>86 (74)</td>
<td>47 (71)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (6)</td>
<td>9 (15)</td>
<td>8 (14)</td>
<td>16 (14)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>5 (4)</td>
<td>2 (3)</td>
<td>7 (13)</td>
<td>14 (12)</td>
<td>9 (14)</td>
</tr>
<tr>
<td>Nausea</td>
<td>9 (8)</td>
<td>7 (11)</td>
<td>4 (7)</td>
<td>7 (6)</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5 (4)</td>
<td>2 (3)</td>
<td>0</td>
<td>11 (9)</td>
<td>11 (17)</td>
</tr>
<tr>
<td>Headache</td>
<td>9 (8)</td>
<td>3 (5)</td>
<td>4 (7)</td>
<td>4 (3)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>Increased weight</td>
<td>1 (&lt;1)</td>
<td>0</td>
<td>2 (4)</td>
<td>5 (4)</td>
<td>5 (8)</td>
</tr>
</tbody>
</table>

Other treatment-emergent adverse events reported in >5% of patients included muscle spasms, diarrhea, urinary tract infection, constipation, fatigue, dry mouth, and pain in extremity.

GEn = gabapentin enacarbil.
Peripheral and Pedal Edema

Peripheral edema as an adverse event

Worsening of pedal edema relative to baseline

\(^a\)Worsening = positive change in grade; GEn = gabapentin enacarbil.
Weight Gain

Weight gain as an adverse event

- Placebo (n=120): 0.83%
- GEn 1200 mg (n=62): 0%
- GEn 2400 mg (n=56): 4%
- GEn 3600 mg\(^{a}\) (n=116): 4%
- Pregabalin (n=66): 8%

\(^{a}\)One subject excluded due to implausible weight change data. GEn = gabapentin enacarbil.

≥7% weight gain at any post-randomization visit

- Placebo (n=116): 3%
- GEn 1200 mg (n=61): 5%
- GEn 2400 mg (n=55): 7%
- GEn 3600 mg\(^{a}\) (n=113): 10%
- Pregabalin (n=62): 15%
Observed mean (±2 SE) change from baseline in weight gain at week 13/ET (LOCF)

Mean Change From Baseline in Weight Gain at Week 13 or Early Termination (LOCF)

- Placebo (n=113) -0.55 kg
- GEn 1200 mg (n=61) 1.22 kg
- GEn 2400 mg (n=50) 1.71 kg
- GEn 3600 mg (n=109) 1.85 kg
- Pregabalin (n=62) 2.65 kg

SE = standard error.

aOne subject excluded due to implausible weight change data
ET = early termination; LOCF = last observation carried forward; SE = standard error.
Mean Change From Baseline in Weight Gain\textsuperscript{a}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
 & W1 & W2 & W5 & W9 & W13 \\
\hline
Placebo & 112 & 108 & 103 & 97 & 90 \\
GEn 1200 mg & 61 & 58 & 57 & 51 & 48 \\
GEn 2400 mg & 49 & 48 & 43 & 40 & 39 \\
GEn 3600 mg & 109 & 106 & 96 & 84 & 81 \\
Pregabalin & 62 & 60 & 55 & 53 & 46 \\
\hline
\end{tabular}
\caption{Patients, N}
\end{table}

\textsuperscript{a}Observed data.

\textsuperscript{b}One subject excluded due to implausible weight change data.

GEn = gabapentin enacarbil; W = week.
Conclusions

• In this phase 2 study in patients with painful DPN, treatment with GEn was associated with overall lower incidences of peripheral edema and weight gain compared with pregabalin
  – This was most evident with GEn 1200 mg, but even the higher doses of GEn were associated with less weight gain and peripheral edema than pregabalin
  – Weight gain in GEn-treated patients appeared to be dose-dependent

• The observed differences in peripheral edema and weight gain between all GEn doses examined and pregabalin are of clinical significance, given that these treatment-emergent adverse events may lead to limitations in patients’ willingness to tolerate and adhere to prescribed regimens

• GEn is approved for the management of PHN in adults at a daily dose of 1200 mg. Additional benefit of using doses greater than 1200 mg/day was not demonstrated, and these higher doses resulted in an increase in adverse reactions
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Backup slides
## Patient Disposition

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>GEn 1200 mg</th>
<th>GEn 2400 mg</th>
<th>GEn 3600 mg</th>
<th>Pregabalin</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomized, n (%)</strong></td>
<td>120</td>
<td>62</td>
<td>56</td>
<td>117</td>
<td>66</td>
<td>421</td>
</tr>
<tr>
<td><strong>Completion status, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Completed</td>
<td>90 (75)</td>
<td>47 (76)</td>
<td>37 (66)</td>
<td>79 (68)</td>
<td>47 (71)</td>
<td>300 (71)</td>
</tr>
<tr>
<td>Withdrawn</td>
<td>30 (25)</td>
<td>15 (24)</td>
<td>19 (34)</td>
<td>38 (32)</td>
<td>19 (29)</td>
<td>121 (29)</td>
</tr>
<tr>
<td><strong>Primary reason for withdrawal, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event</td>
<td>11 (9)</td>
<td>5 (8)</td>
<td>12 (21)</td>
<td>21 (18)</td>
<td>6 (9)</td>
<td>55 (13)</td>
</tr>
<tr>
<td>Lack of efficacy</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>0</td>
<td>4 (3)</td>
<td>3 (5)</td>
<td>11 (3)</td>
</tr>
<tr>
<td>Protocol deviation</td>
<td>7 (6)</td>
<td>6 (10)</td>
<td>4 (7)</td>
<td>4 (3)</td>
<td>6 (9)</td>
<td>27 (6)</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>6 (5)</td>
<td>2 (3)</td>
<td>1 (2)</td>
<td>3 (3)</td>
<td>3 (5)</td>
<td>15 (4)</td>
</tr>
<tr>
<td>Investigator discretion</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (2)</td>
<td>0</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>Withdrew consent</td>
<td>3 (3)</td>
<td>1 (2)</td>
<td>2 (4)</td>
<td>4 (3)</td>
<td>1 (2)</td>
<td>11 (3)</td>
</tr>
</tbody>
</table>

GEn = gabapentin enacarbil.
### Adverse Events Leading to Withdrawal

55 patients withdrew from the study due to AE

**List of Preferred Terms for AEs Leading to Withdrawal from the Study (number of days since 1st dose)**

<table>
<thead>
<tr>
<th>Placebo (N=120)</th>
<th>GEN 1200mg (N=62)</th>
<th>GEN 2400mg (N=56)</th>
<th>GEN 3600mg (N=117)</th>
<th>Pregabalin (N=66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>W/D due to AE: 11 (9%)</td>
<td>W/D due to AE: 5 (8%)</td>
<td>W/D due to AE: 12 (21%)</td>
<td>W/D due to AE: 21 (18%)</td>
<td>W/D due to AE: 6 (9%)</td>
</tr>
<tr>
<td>■ Abdominal discomfort (27)</td>
<td>■ Blood creatinine incr. (20)</td>
<td>■ Abdominal pain (5, 13)</td>
<td>■ Affective disorder (5)</td>
<td>■ Affective disorder (16)</td>
</tr>
<tr>
<td>■ Asthenia (2)</td>
<td>■ Blood potassium incr. (20)</td>
<td>■ Ankle fracture (72)</td>
<td>■ Agitation (1)</td>
<td>■ Amnesia (21)</td>
</tr>
<tr>
<td>■ Balance disorder (2)</td>
<td>■ Blood urea incr. (20)</td>
<td>■ Arthralgia (3)</td>
<td>■ Ataxia (12)</td>
<td>■ Constipation (1, 8)</td>
</tr>
<tr>
<td>■ Chronic lymphocytic leukaemia (35)</td>
<td>■ Cellulitis (77)</td>
<td>■ Balance disorder (9)</td>
<td>■ Coronary artery stenosis (64)</td>
<td>■ Dizziness (2)</td>
</tr>
<tr>
<td>■ Constipation (2)</td>
<td>■ Confusional state (78)</td>
<td>■ Bipolar disorder (4)</td>
<td>■ Dizziness (1, 2, 15, 50)</td>
<td>■ Dyspnoea (21)</td>
</tr>
<tr>
<td>■ Diarrhoea (3)</td>
<td>■ Cough (6)</td>
<td>■ Confusional state (9)</td>
<td>■ Eye irritation (50)</td>
<td>■ Fatigue (2, 34)</td>
</tr>
<tr>
<td>■ Dizziness (2, 57)</td>
<td>■ Lethargy (14)</td>
<td>■ Constipation (4)</td>
<td>■ Headache (1, 57)</td>
<td>■ Oedema peripheral (66)</td>
</tr>
<tr>
<td>■ Fatigue (10)</td>
<td>■ Memory impairment (14)</td>
<td>■ Dizziness (4)</td>
<td>■ HbA1c incr. (61)</td>
<td>■ Somnolence (2)</td>
</tr>
<tr>
<td>■ Gastroenteritis viral (30)</td>
<td>■ Nausea (18)</td>
<td>■ Dry mouth (6)</td>
<td>■ Iron deficiency anaemia (57)</td>
<td>■ Weight increased (77)</td>
</tr>
<tr>
<td>■ Lymphocyte count incr. (1)</td>
<td>■ Skin ulcer (77)</td>
<td>■ Headache (9)</td>
<td>■ Middle insomnia (1)</td>
<td></td>
</tr>
</tbody>
</table>