BACKGROUND
XEN1101 is a novel chemical entity that enhances activation of neuronal K<sub>7.2</sub>/K<sub>7.3</sub> potassium channels and it is currently in clinical development by Xenon Pharmaceuticals as a treatment for epilepsy. The objectives of this first-in-human study were to evaluate the safety, tolerability and pharmacokinetics (PK) of single and multiple ascending doses (SAD and MAD) of oral XEN1101.

METHODS
In the SAD Phase, 32 healthy volunteers were randomized (3:1) to XEN1101 (5, 15, 20, 25, 30 mg) or placebo. The study featured an adaptive design. A crossover food effect cohort (N=10) was also completed with single doses of 20 mg. A sub-set of 8 male subjects were also assessed with Transcranial Magnetic Stimulation (TMS) for effects on cortical excitability (see poster 3.292).

Repeat doses of XEN1101 (15 mg QD) were evaluated in a fasted and fed state over 7 and 10 days, respectively. Repeat doses of XEN1101 (25 mg QD) were also evaluated in a fed state over 10 days.

XEN1101 was formulated as an immediate release capsule. Serial plasma PK samples were collected for all cohorts. Safety evaluations throughout the study included adverse event (AE) monitoring, clinical laboratory tests, vital signs, ECGs, physical examinations and Columbia-Suicide Severity Rating Scale.

PHARMACOKINETICS
XEN1101 displayed a PK profile suitable for once a day dosing with low peak to trough ratio. XEN1101 had less than dose-proportional exposure in the fasted state, with absorption enhanced by food (~1.8 fold for AUC<sub>0-24</sub>). With multiple doses in the fed state, exposure increased in proportion to dose. Apparent steady state was achieved by Day 6-9, based on the 90% CI for the successive day’s exposure ratio within the range 0.8 - 1.25.

SAFETY
Single and multiple doses of XEN1101 were well tolerated at individual C<sub>max</sub> levels up to 104 ng/mL and 107 ng/mL, respectively. The majority of AEs were mild or moderate, resolved spontaneously and were consistent with antiepileptic drugs of this class (e.g., dizziness, sedation). There have been no SAEs, deaths, or clinically significant ECG or laboratory findings.

Adverse Events occurring in ≥2 subjects overall for SAD Cohorts

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Carot 1</th>
<th>Carot 2</th>
<th>Carot 3</th>
<th>Overall</th>
<th>Placebo</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>8</td>
<td>8</td>
<td>8</td>
<td>34</td>
<td>8</td>
<td>10</td>
</tr>
<tr>
<td>N (%) E</td>
<td>4 (50)</td>
<td>7 (87)</td>
<td>5 (62)</td>
<td>6 (18)</td>
<td>1 (13)</td>
<td>4 (20)</td>
</tr>
<tr>
<td>AEs (%)</td>
<td>74</td>
<td>79</td>
<td>79</td>
<td>75</td>
<td>88</td>
<td>82</td>
</tr>
<tr>
<td>Ages (yrs)</td>
<td>23 ± 2</td>
<td>26 ± 2</td>
<td>25 ± 2</td>
<td>25 ± 2</td>
<td>24 ± 2</td>
<td>24 ± 2</td>
</tr>
</tbody>
</table>
| E = number of events; N = number of subjects having an adverse event; N = Number of subjects at risk.

CONCLUSIONS
The current results suggest that XEN1101 is safe and well-tolerated up to doses examined (single doses of up to 30 mg and multiple doses of 25 mg QD).

The PK profile (including an effective half-life ~24 hours), supports a once per day dosing schedule using an immediate release formulation, with attainment of steady state in 1 week without the need for titration.