Pharmacokinetics and formulation selection of FT218
an investigational controlled-release sodium oxybate
formulation designed for once-nightly dosing

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Introduction
Sodium oxybate is indicated for the treatment of excessive
daytime sleepiness (EDS) and cataplexy in patients with
narcolepsy. The currently marketed product, an immediate
release (IR) sodium oxybate is required to be taken twice
nightly: at bedtime and 2.5 to 4 hours later, thus requiring
patients to awaken in the middle of the night.
FT218 is an investigational controlled-release (CR)
formulation of sodium oxybate intended for once-nightly
dosing using Avadel’s proprietary Micropump™ technology.
The efficacy and safety of FT218 is currently being evaluated
in the pivotal, randomized, double-blind, placebo-controlled
Phase 3 REST-ON study.
The pharmacokinetic (PK) performance of three prototypes
of FT218 was evaluated in a PK pilot study (PKFT218-1301).

Objectives
Primary objective: to assess the pharmacokinetic profiles of three CR formulations of FT218.
Secondary objectives: to explore the pharmacodynamic effects of sodium oxybate CR (FT218) versus twice-nightly sodium oxybate IR, and investigate safety and tolerability.

Methods
The study was an exploratory open label, randomized,
crossover study in 16 healthy male and female volunteers.
Each volunteer received 4 different formulations of sodium
oxybate in 4 randomized study periods with a 3 day washout
between periods: a single 4.5g dose of one of the three test
formulations of FT218 or 2 x 2.25g doses of twice-nightly
sodium oxybate IR given 4-hours apart. Pharmacodynamic
effects were explored using the Leeds Sleep Evaluation
Questionnaire (LSEQ) and actigraphy.

Pharmacokinetics
Each of the three FT218 prototypes exhibited a sustained
release profile with Cmax below the global Cmax of
twice-nightly sodium oxybate IR and a Cmin similar to twice-nightly
sodium oxybate IR (Fig. 1).
Prototype 2 was selected for further optimization, as it
provided PK characteristics closest to the desired target
profile. This formulation exhibited a higher Cmax compared to
the other prototypes, and the AUCavg was the closest to the
AUCavg of the twice-nightly sodium oxybate IR (Table 1).

Table 1: PK parameters (mean ± Standard Error)

<table>
<thead>
<tr>
<th></th>
<th>FT218 Type 1</th>
<th>FT218 Type 2</th>
<th>FT218 Type 3</th>
<th>Twice-nightly sodium oxybate IR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cmax (µg/mL)</td>
<td>43 ± 6</td>
<td>46 ± 5</td>
<td>30 ± 4</td>
<td>66 ± 7</td>
</tr>
<tr>
<td>AUCavg (h.µg/mL)</td>
<td>189 ± 28</td>
<td>210 ± 28</td>
<td>153 ± 22</td>
<td>214 ± 27</td>
</tr>
<tr>
<td>Cmin (µg/mL)</td>
<td>6.85 ± 2.09</td>
<td>7.40 ± 1.63</td>
<td>8.33 ± 1.93</td>
<td>9.24 ± 3.15</td>
</tr>
</tbody>
</table>

Sleep quality and alertness on awakening
For each LSEQ domain, there were no clinically meaningful
differences between groups.

Actigraphy
Sleep time over 8 hours after administration was similar
between the treatments.

Safety profile
Four subjects (25%) reported a total of 5 treatment emergent
adverse events (Table 2). All were of mild or moderate
intensity. There were no serious adverse events or adverse
events leading to discontinuation.

Table 2: Incidence of adverse events

<table>
<thead>
<tr>
<th></th>
<th>Type 1 N=15</th>
<th>Type 2 N=14</th>
<th>Type 3 N=15</th>
<th>Twice-nightly sodium oxybate IR N=15, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharyngitis</td>
<td>1 (6.7%)</td>
<td>0</td>
<td>0</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Flu-like syndrome</td>
<td>1 (6.7%)</td>
<td>0</td>
<td>0</td>
<td>1 (6.3%)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>0</td>
<td>0</td>
<td>1 (6.7%)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1 (6.7%)</td>
</tr>
<tr>
<td>Overall</td>
<td>2 (13.3%)</td>
<td>0</td>
<td>1 (6.7%)</td>
<td>4 (25%)</td>
</tr>
</tbody>
</table>

Conclusion
The three FT218 prototypes exhibited CR profiles covering
the entire night (8 hours) with once-nightly dosing. Prototype 2,
compared to twice-nightly sodium oxybate IR, exhibited a
lower overall Cmax and, importantly, a comparable Cmin, while
the AUC was maintained. Between-subject variability of
FT218 and twice-nightly sodium oxybate IR was comparable.
Safety and tolerability was similar between groups. If
approved, FT218 could offer a new option for the treatment
doctoral and cataplexy in narcolepsy with a once-nightly
formulation of sodium oxybate.
The REST-ON pivotal phase 3 study is currently enrolling
patients with narcolepsy to evaluate the efficacy and safety of
FT218. Enrollment is expected to be completed in 2020.