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 C_{max} below the global C_{max} of twice-nightly sodium oxybate IR and a C_{8h} similar to twice-nightly sodium oxybate IR (Fig. 1).

Prototype 2 was selected for further optimization, as it exhibited PK characteristics closest to the desired target profile. This formulation exhibited a higher C_{max} compared to the other prototypes, and the AUC_{inf} was the closest to the AUC_{inf} of the twice-nightly sodium oxybate IR (Table 1).

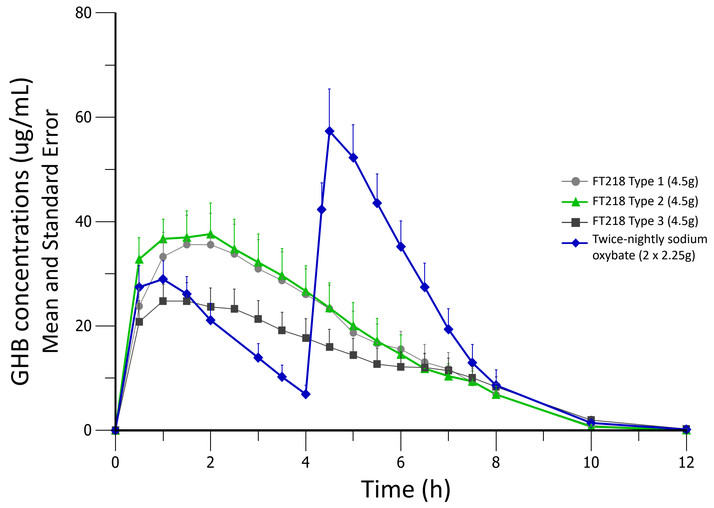

Figure 1: plasma levels of FT218 single dose versus twice-nightly dosing

Table 1: PK parameters (mean ± Standard Error)

	FT218 Type 1	FT218 Type 2	FT218 Type 3	Twice-nightly sodium oxybate IR
C_{max} (µg/mL)	43 ± 6	46 ± 5	30 ± 4	66 ± 7
AUC_{inf} (h.µg/mL)	189 ± 28	210 ± 28	153 ± 22	214 ± 27
C_{8h} (µg/mL)	6.85 ± 2.09	7.40 ± 1.63	8.33 ± 1.93	9.24 ± 3.15

Sleep quality and alertness on awakening

For each LSEQ domain, there were no clinically meaningful differences between groups.

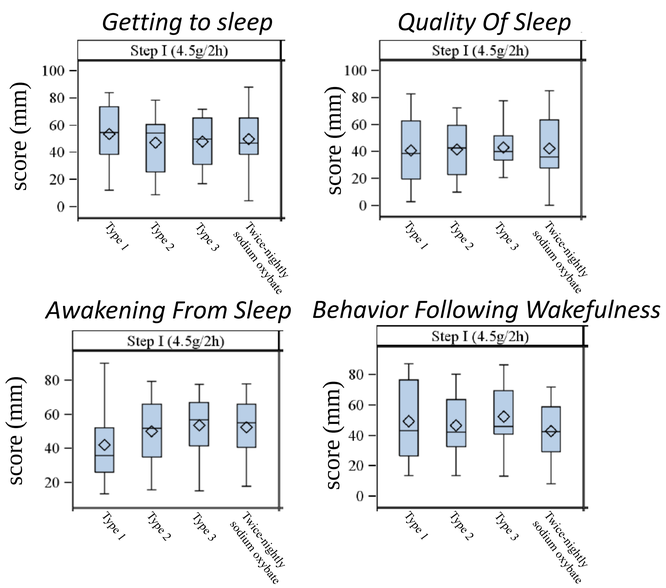

Figure 2: LSEQ results

Actigraphy

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

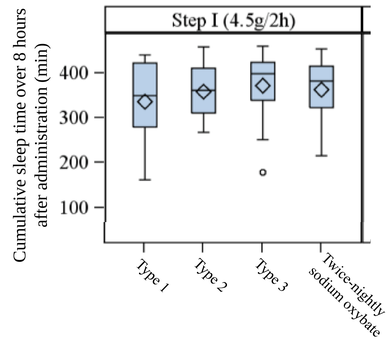

Figure 3: Actigraphy results

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

	Type 1 N=15 n(%)	Type 2 N=14 n(%)	Type 3 N=15 n(%)	Twice-nightly sodium oxybate IR N=15. n(%)	Overall N=16 n(%)
Pharyngitis	1 (6.7%)	0	0	0	1 (6.3%)
Flu-like syndrome	1 (6.7%)	0	0	0	1 (6.3%)
Gastroenteritis	0	0	1 (6.7%)	0	1 (6.3%)
Nausea	0	0	0	1 (6.7%)	1 (6.3%)
Headache	0	0	0	1 (6.7%)	1 (6.3%)
Overall	**2 (13.3%)**	**0**	**1 (6.7%)**	**1 (6.7%)**	**4 (25%)**

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 C_{max} and, importantly, a comparable C_{8h}, 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 of EDS 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.