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

D. Monteith [1], J. Grassot [1], C. Castellan [1], J. Dubow [1], T. Roth [2]

[1] Avadel Ireland, Dublin, Ireland, [2] Sleep Disorders Centre, Henry Ford Hospital, Detroit, United States.

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.

Following the PK pilot PKFT218-1301 study which evaluated the pharmacokinetics (PK) of three prototypes of FT218, the PK and dose proportionality of the optimized formulation of FT218 were evaluated in a Phase I study (PKFT218-1601).

Objectives

Primary objective: to assess the PK of FT218 given as a single dose of 4.5g, 7.5g and 9g.

Secondary objectives:

- To assess the safety and tolerability of FT218.
- To compare PK parameters at the 3 doses and estimate the dose proportionality.

Methods

The study was an open-label, single-dose, 3-sequential period study in 20 healthy volunteers. Subjects received 3 separate single-dose (without titration) administrations of FT218 at bedtime, two hours post-evening meal, in a sequential order of 4.5g, 7.5g and 9g with a minimum 7-day washout between doses. Dose proportionality between the three doses was assessed using the power method. Sensitivity analyses were performed using ANOVA.

Variability of concentrations of FT218 and twice-nightly sodium oxybate IR at 8h and 10h post-dose (when patients typically awaken) in the PK pilot and the present study were compared in terms of standard deviation.

Subject disposition

The study was conducted in 20 healthy volunteers (12 males and 8 females). All subjects completed periods 1 (4.5g) and 2 (7.5g), while 12 subjects completed period 3 (9g).

Pharmacokinetics

For the 3 doses, mean pharmacokinetics exhibited similar overall profiles with median T_{max} between 1.5 and 2 hours (Figure 1). Mean C_{max} increased from 42.9 to 84.5 µg/mL across the increasing doses. Following C_{max}, blood levels gradually decreased overnight. Mean AUC_{inf} was 191, 358 and 443 µg.h/mL for the 4.5, 7.5 and 9g doses respectively. Mean concentrations at 8 hours were 4.8, 19.7 and 25.5 µg/mL for the 4.5, 7.5 and 9g doses respectively.

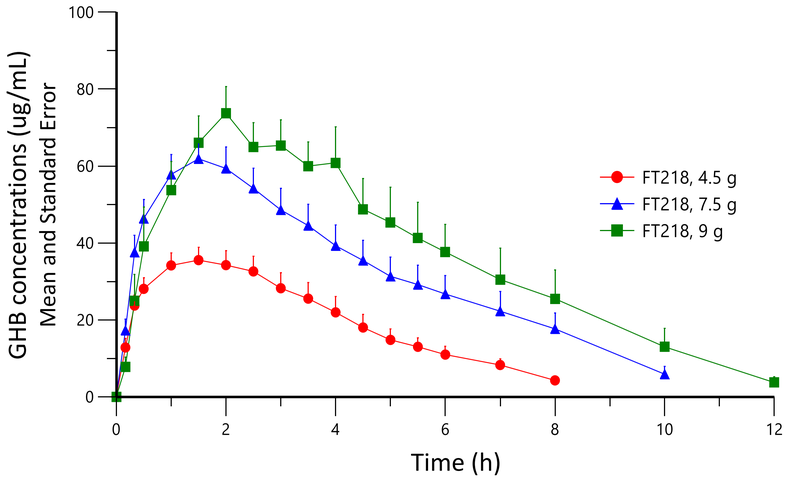

Figure 1. FT218 plasma concentration time curves for rising doses from 4.5g to 9g per night

Table 1. Variability of concentrations at 8h and 10h post-dose for twice-nightly sodium oxybate and FT218 in the PK pilot and dose proportionality studies.

	Twice-nightly sodium oxybate IR	FT218		
	PK pilot study	PK pilot study		Dose proportionality study
		Part 1-Step 1	Part 2	
PK parameter	**2*2.25g n=15**	**4.5g n=14**	**4.5g n=12**	**4.5g n=20**
C_{8h} mean ± SD (µg/mL)				
BQL set to missing	9.24 ± 11.77 (n=14)	7.40 ± 5.88 (n=13)	6.27 ± 5.81	4.76 ± 5.01
BQL set to zero	8.62 ± 11.59	6.87 ± 5.98	6.27 ± 5.81	4.76 ± 5.01
C_{10h} mean ± SD (µg/mL)				
BQL set to missing	2.64 ± 3.84 (n=8)	1.21 ± 1.86 (n=8)	0.94 ± 0.55 (n=7)	0.73 ± 0.41 (n= 9)
BQL set to zero	1.41 ± 3.04	0.69 ± 1.50	0.55 ± 0.63	0.33 ± 0.46

BQL: concentration below quantitation limit.

Variability of C_{8h} and C_{10h}

Mean concentrations at 8h and 10h post-dose for FT218 are at least as low as twice-nightly sodium oxybate IR, regardless of the rule used to address concentrations below quantitation limit (Table 1). Moreover, the variability of the concentrations was similar.

Dose proportionality

Applying the power method, the slope estimate for C_{max} was 1.02 and the confidence interval centered on 1.00 (90% CI: 0.76-1.28). For AUC_{inf}, the estimate was 1.34 (90% CI: 1.19-1.48), indicating that the increase in the AUC is slightly more than proportional. These results were consistent with ANOVA sensitivity analysis results.

Safety profile

Thirteen subjects (65%) reported a total of 31 treatment emergent adverse events:

- 8 TEAEs (mainly headache 5/8) experienced by 7/20 (35%) subjects during the 4.5g period;
- 7 TEAEs (mainly gastrointestinal disorders 4/7) experienced by 4/20 (20%) subjects during the 7.5g period;
- 16 TEAEs (mainly gastrointestinal disorders 8/16) experienced by 6/12 (50%) subjects during the 9g period. One of these, a nervous system disorder (sedation) was a SAE.

The intensity of TEAEs was judged severe for 2/31 TEAEs (both in 9g period), moderate for 10/31 (4 in 4.5g period, 3 in 7.5g period and 3 in 9g period) and mild for 19/31.

All the TEAEs were resolved before the end of the study.

Conclusion

FT218 achieved predictable blood-level profiles, when given at bedtime, consistent with a once-nightly dosing regimen. Dose proportionality was maintained for C_{max} across the dosage range. The safety profile was consistent with what is known for sodium oxybate and most AEs were mild to moderate in severity even without titration.

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 safety and efficacy of FT218 is currently being evaluated in the pivotal, randomized, double-blind, placebo-controlled Phase 3 REST-ON study.