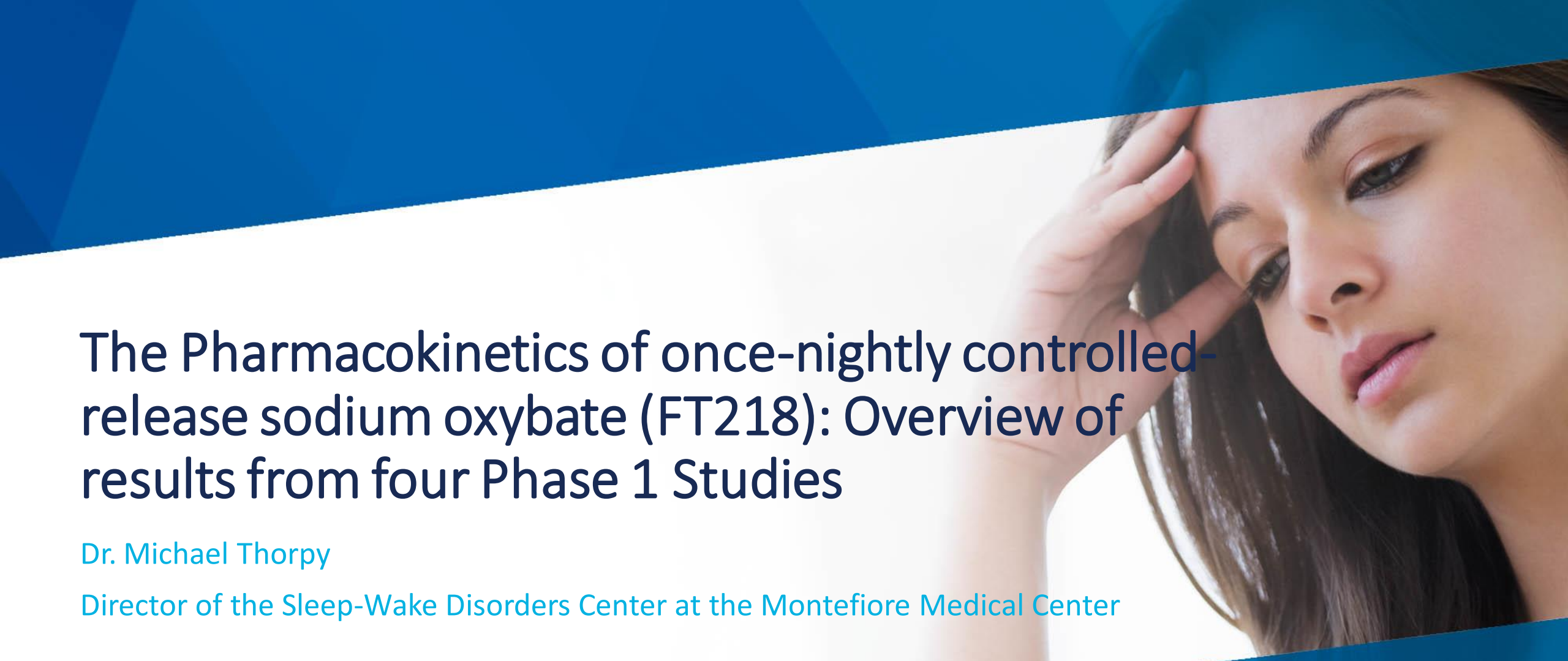
The Pharmacokinetics of once-nightly controlled-release sodium oxybate (FT218): Overview of results from four Phase 1 Studies



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Introduction

- Sodium oxybate is an effective treatment for excessive daytime sleepiness and cataplexy in patients with narcolepsy
- The approved effective doses of sodium oxybate are 6, 7.5 and 9 g per night, divided in two doses – the first taken at bedtime and the second 2.5 – 4 hours later.
- FT218 is an investigational controlled-release formulation of sodium oxybate intended for once-nightly dosing, using Avadel's proprietary Micropump™ technology
- Here we present pharmacokinetic data from four Phase 1 studies of FT218

FT-218 PK Data

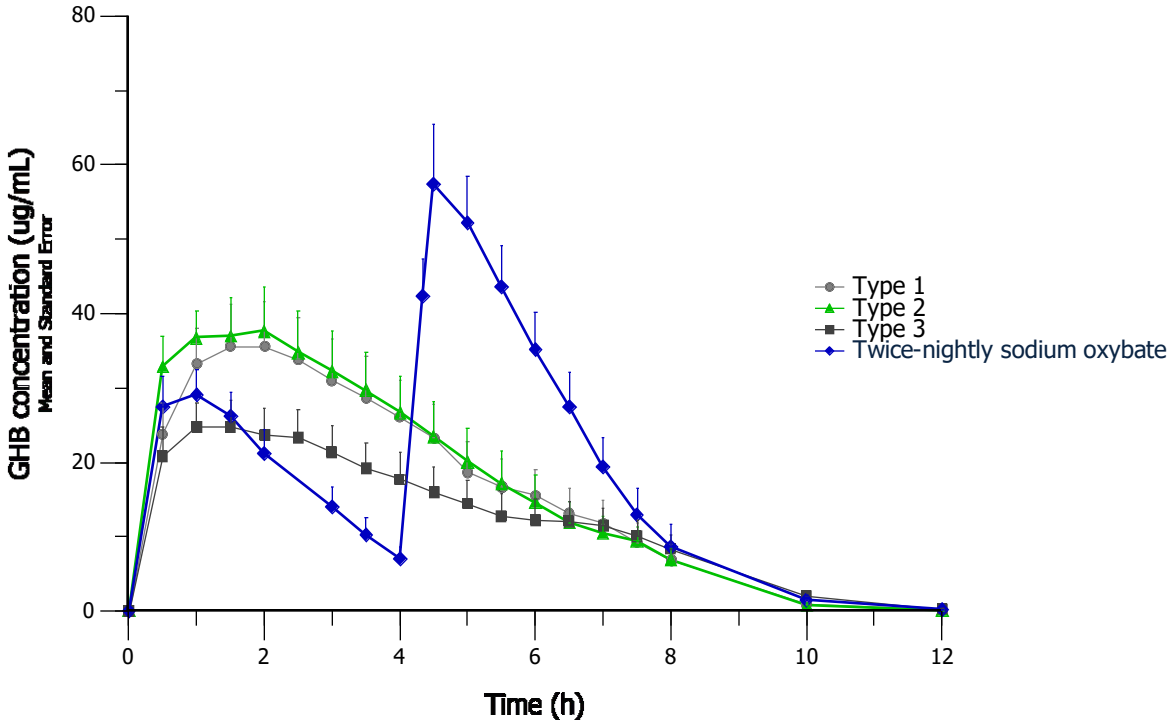
Four crossover, single-dose pharmacokinetic studies were conducted in healthy volunteers

- Pilot PK Study
- Dose Proportionality Study
- Relative Bioavailability Study
- Food Effect Study

Pilot PK Study

Cross Over Study comparing Once Nightly FT218 4.5 g v. Twice Nightly Sodium Oxybate IR 4.5 g (2.25 + 2.25)

Crossover Study of Three Formulations of Once-Nightly (FT218) 4.5 g vs. Twice Nightly Sodium Oxybate IR 4.5 g (2.25+ 2.25): N=16

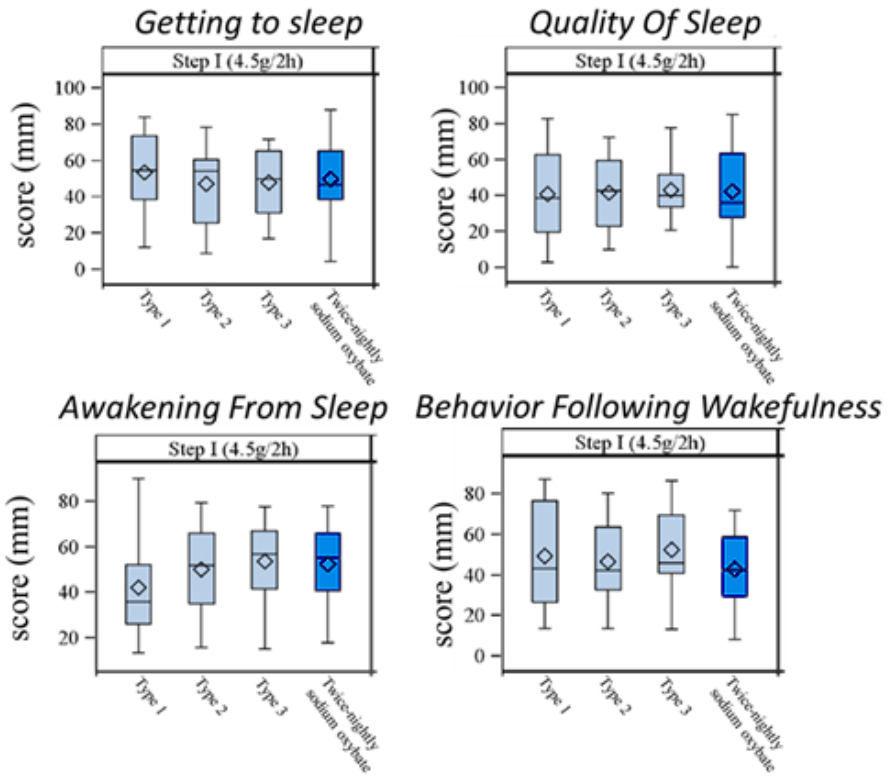


	FT218 Type 1	FT218 Type 2	FT218 Type 3	Twice-nightly sodium oxybate
Cmax (µg/mL)	43 ± 6	46 ± 5	30 ± 4	66 ± 7
AUCinf (h.µg/mL)	189 ± 28	210 ± 28	153 ± 22	214 ± 27
C8h (µg/mL)	6.85 ± 2.09	7.40 ± 1.63	8.33 ± 1.93	9.24 ± 3.15

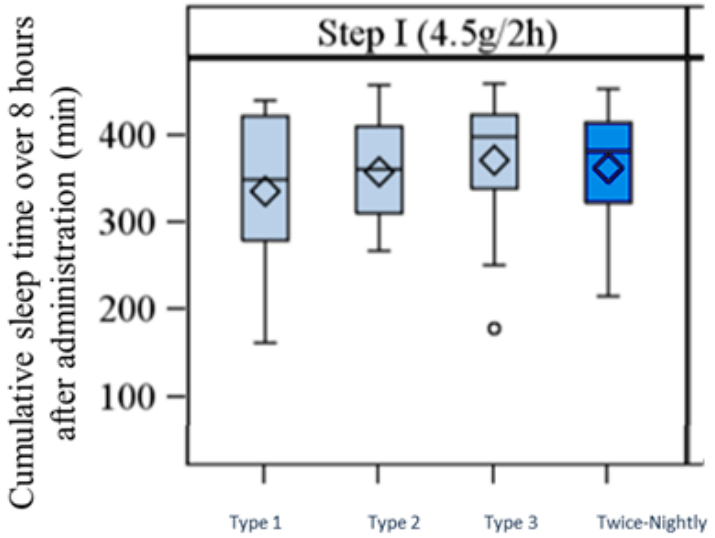
- ✓ Similar overall exposure (AUC) to twice nightly dosing
- ✓ Lower overall peak concentrations (Cmax)
- ✓ Similar morning blood levels (C8h)

Exploratory Endpoints: Leeds Sleep Evaluation Questionnaire – No formal Statistical Analysis

LSEQ - Sleep quality and alertness upon wakening



Actigraphy – Total Sleep Time



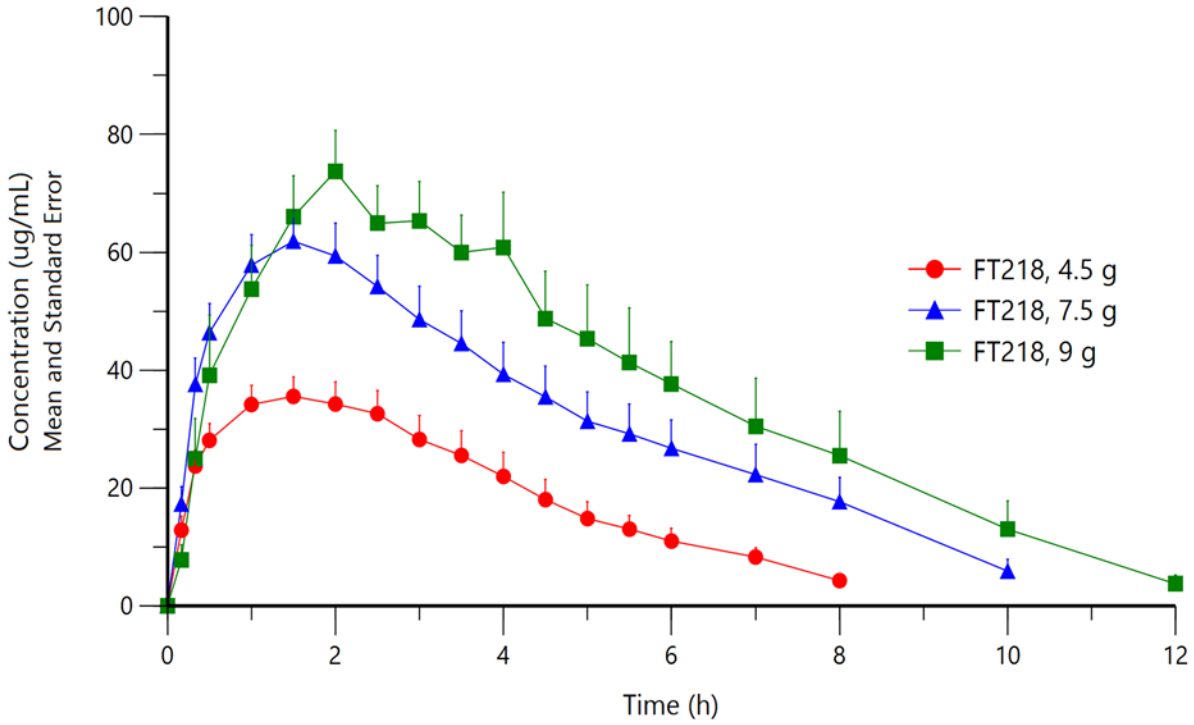
Safety Profile Comparable For Single Dose Administration: All AEs mild to moderate, No SAEs, No discontinuation Due to AE

	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%)**

Dose Proportionality Study

Three Period Single Ascending Dose Study comparing Once Nightly FT218 4.5g, 7.5g and 9g dosages

Three Period Single Ascending Dose Study (n=20): Subjects received single doses of 4.5, 7.5 and 9 g with at least 7 day washout between doses

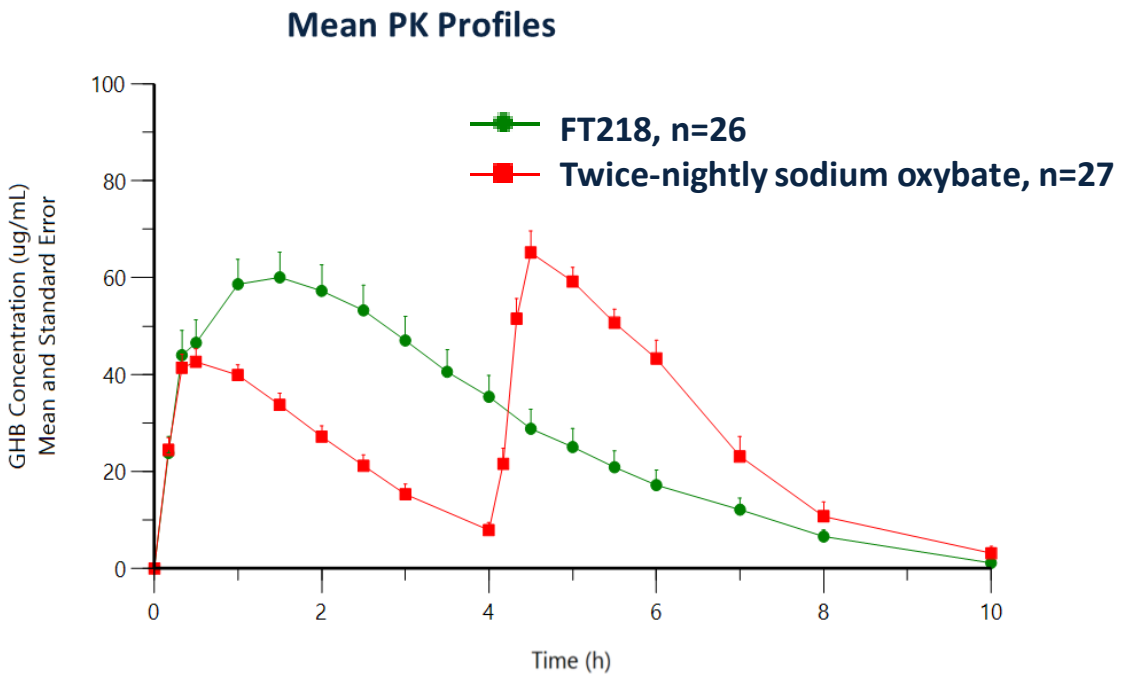


- For the 3 doses, mean pharmacokinetics exhibited similar overall profiles with median Tmax between 1.5 and 2 hours
- FT218 was dose proportional for Cmax
- FT218 was slightly more than proportional for AUC
- Thirteen subjects (65%) reported a total of 31 treatment emergent adverse events:
  - The incidence of AEs increased with increasing doses
  - Most AEs were mild to moderate in severity and consistent with known AEs associated with sodium oxybate
  - The most common AEs (at the 9 g dose) were vomiting (25%), nausea (16.7%), diarrhea (16.7%) and headache (16.7%)

Relative Bioavailability study at 6 g

Two Period Cross Over Study comparing Once Nightly FT218 6 g v. Twice -Nightly Sodium Oxybate IR 6 g (3+3)

Randomized, cross-over, two period, two sequences design of FT218 6 g or twice-nightly sodium oxybate IR 6 g (3 + 3)



MAIN ANALYSIS:

- AUC of FT218 meets bioequivalence criteria compared to AUC of Twice-nightly SO IR
- Cmax of FT218 is lower than overall Cmax of Twice-nightly SO IR

POST-HOC ANALYSIS:

- AUC0-8h meets bioequivalence criteria compared to AUC0-8h of Twice-nightly SO IR
- C8h of FT218 is similar to C8h of Twice-nightly SO IR

Mean PK parameters

Arm	Tmax (h)[a] [min-max]	Cmax (µg/mL) ± SE (CV)	$AUC_{0\text{-}inf}$ (µg/mL.h) ± SE (CV)	$AUC_{0\text{-}8h}$ (µg/mL.h) ± SE (CV)	C8h (µg/mL)[b] ± SE (CV)
FT218 (N=26)	1.5 [0.33-3.5]	64.6 ± 5 (40)	273 ± 27 (51)	267 ± 27 (51)	6.6 ± 1 (108)
Twice-nightly SO IR (N=27)	4.5 [0.33 -7]	70.9 ± 4 (28)	259 ± 22 (44)	248 ± 18 (39)	10.7 ± 3 (145)

Safety Profile

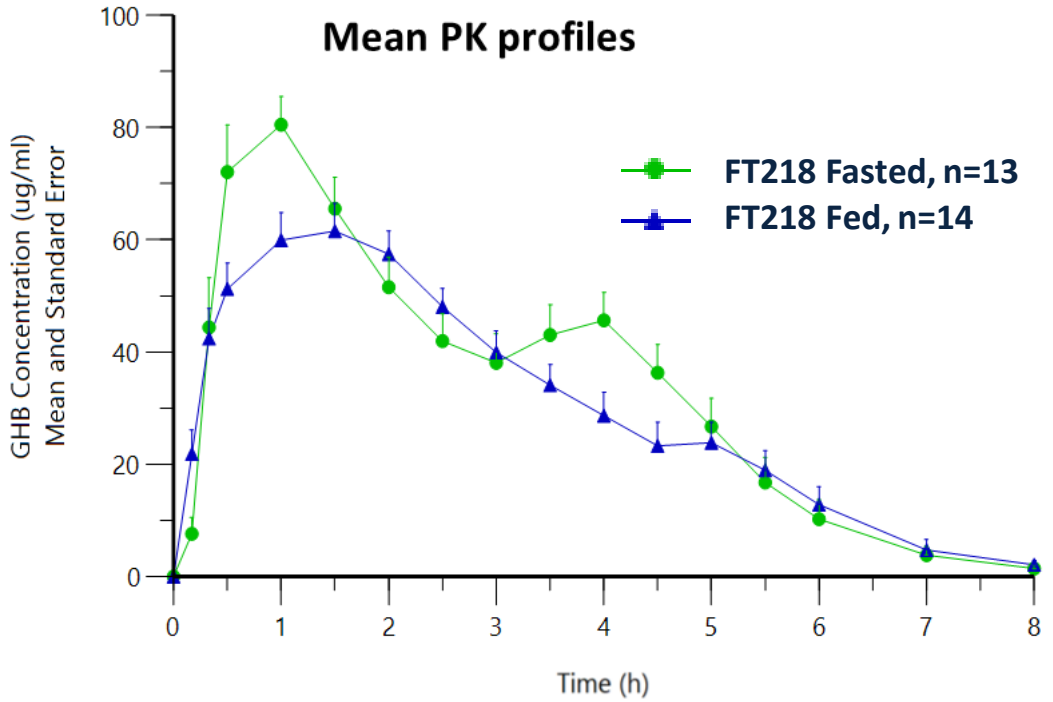
Preferred Term	FT218 6 g (N=27) n (%)	Twice nightly Sodium Oxybate 6 g (3+3) (N=27) n (%)
Somnolence	9 (33.3)	6 (22.2)
Dizziness	1 (3.7)	4 (14.8)
Headache	1 (3.7)	3 (11.1)
Feeling Drunk	3 (11.1)	2 (7.4)
Nausea	3 (11.1)	2 (7.4)
Rhinitis	0 (0)	3 (11.1)
Hyperhidrosis	1 (3.7)	3 (11.1)

- All AEs were mild or moderate in severity
- There were no Serious Adverse Events reported
- 1 subject dropped out in each treatment group due to AE (Nausea for FT218 and influenza for Twice nightly sodium oxybate)
- In general, the safety profile appeared comparable between the two groups

Food-effect study

Two Period Cross Over Study comparing Once Nightly (FT218) 6 g in a Fed and Fasted state

Randomized, Cross-over, two period, two sequences design (N=16) at 6 g:Fed (30 min after high-fat breakfast) vs. Fasted (10-hour Overnight Fast) State



- Cmax in the Fed state is below Cmax in the Fasted state (66.7%)
- AUC in the Fed state is slightly lower than AUC in the Fasted state (PE 86%)
- Tmax in the Fed state longer than Tmax in the Fasted state

Mean PK parameters

Arm	Tmax (h)[a] [min-max]	Cmax (µg/mL) ± SE (CV)	$AUC_{0\text{-}inf}$ (µg/mL.h) ± SE (CV)	$AUC_{0\text{-}8h}$ (µg/mL.h) ± SE (CV)	C8h (µg/mL) ± SE (CV)
FT218 fed n=14	1.5 [0.5 -2.5]	64.0 ± 5 (27.3)	242 ± 24 (36.5)	239 ± 23 (35.5)	2.09 ± 1 (150.5)
FT 218 fasted n=13	0.53 [0.33 – 1]	90.5 ± 4 (17.5)	267 ± 24 (32)	266 ± 23 (31.2)	1.43 ± 1 (142.7)

Safety Profile

Preferred Term	FT218 6 g single dose Fasted (N=16); n (%)	FT218 6 g single dose Fed (N=15); n (%)
Somnolence	13 (81.3)	10 (66.7)
Dizziness	7 (43.8)	3 (20.0)
Nausea	6 (37.5)	1 (6.7)
Headache	4 (25.0)	2 (13.3)
Feeling Drunk	4 (25.0)	4 (26.7)
Vomiting	3 (18.8)	1 (6.7)
Fatigue	3 (18.8)	1 (6.7)

- All AEs were mild or moderate in severity with higher incidences in fasted vs. fed state
- There were no SAEs
- 1 subject discontinued due to vomiting after receiving FT218 in the fasted state

Conclusions

- Once-nightly FT218 at 4.5 and 6 g demonstrated:
  - a lower overall Cmax and equivalent exposure to twice-nightly sodium oxybate IR
  - similar morning plasma levels (C8h) and variability to twice-nightly sodium oxybate IR
- For FT218, Cmax was dose proportional and AUC was slightly higher than dose proportional
- In the Fed state, as expected, AUC and Cmax of FT218 was lower than in the Fasted State
- Up to the 9 g dose level, FT218 was generally well tolerated and the safety profile appeared comparable to twice-nightly sodium oxybate IR at the 4.5 and 6 g dose levels
- The efficacy and safety of FT218 on excessive daytime sleepiness and cataplexy in narcolepsy is currently being evaluated in the pivotal, randomized, double-blind, placebo-controlled Phase 3 REST-ON study
  - Enrollment anticipated to be completed by the end of the year with topline data 2Q 2020