Clinical trial results:
A Double-blind, Randomized, Placebo Controlled, Two Arm Multi-center Study to Assess the Efficacy and Safety of a Once Nightly Formulation of Sodium Oxybate for Extended-Release Oral Suspension (FT218) for the Treatment of Excessive Daytime Sleepiness and Cataplexy in Subjects with Narcolepsy

Summary

EudraCT number	2016-000359-29
Trial protocol	NL DK DE GB FI CZ FR
Global end of trial date	25 March 2020

Results information

Result version number	v1 (current)
This version publication date	22 January 2022
First version publication date	22 January 2022

Trial information

Trial identification

Sponsor protocol code	CLFT218-1501

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02720744
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Flamel Ireland Limited
Sponsor organisation address	10 Earlsfort Terrace, Dublin, Ireland, 2
Public contact	Clinical Trial Email, Flamel Ireland Limited, +001 636-449-1830,
Scientific contact	Clinical Trial Email, Flamel Ireland Limited, +001 636-449-1830,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	17 April 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	25 March 2020
Global end of trial reached?	Yes
Global end of trial date	25 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Primary Objectives
To compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating excessive daytime sleepiness (EDS) in both type 1 narcolepsy (NT1) and type 2 narcolepsy (NT2) subjects as measured by mean sleep latency on the Maintenance of Wakefulness Test (MWT) and by the Clinical Global Impression (CGI) rating of sleepiness, and to compare the efficacy of 6.0, 7.5, and 9.0 g of FT218 to placebo in treating cataplexy in NT1 subjects as measured by the number of cataplexy attacks (NCA) determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary.

Protection of trial subjects:

A DSMB comprised of independent experts reviewed and assessed study conduct and advised the sponsor and investigators on matters relating to the safety and conduct of the study. The DSMB made recommendations to the sponsor and investigators regarding the continuation, modification, or termination of the study. To achieve this aim the DSMB periodically reviewed and evaluated accumulated study data relevant to subject safety, study progress, and conduct. The DSMB was governed by a charter and the membership of the DSMB reflected necessary clinical, scientific, and related disciplines necessary to interpret data from the clinical study to allow for full evaluation of subject safety.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	11 July 2016
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Netherlands: 1
Country: Number of subjects enrolled	United Kingdom: 2
Country: Number of subjects enrolled	Czech Republic: 2
Country: Number of subjects enrolled	France: 8
Country: Number of subjects enrolled	Germany: 13
Country: Number of subjects enrolled	Australia: 11
Country: Number of subjects enrolled	United States: 116
Country: Number of subjects enrolled	Canada: 59
Worldwide total number of subjects	212
EEA total number of subjects	26

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	11
Adults (18-64 years)	198
From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

This study was conducted at 71 centers in Australia, Canada, Czech Republic, Denmark, Finland, France, Germany, Netherlands, Switzerland, the United Kingdom (UK), and the US. A total of 65 centers enrolled subjects.

Pre-assignment

Screening details:

3 week screening and baseline period, including 2 study visits and completion of the subject daily sleep and symptom diary to collect endpoint data, including cataplexy events for NT1 subjects and weekly ESS for all patients. Subjects were evaluated for eligibility at the end of the screening period.

Pre-assignment period milestones

Number of subjects started	413[1]
Intermediate milestone: Number of subjects	Randomized: 222
Number of subjects completed	212

Pre-assignment subject non-completion reasons

Reason: Number of subjects	Screen Failure: 201

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: A total of 413 patients were screened for the study, however only 222 were randomized. Of the 222 patients randomized, only 212 were actually administered study medication and included in the safety population.

Period 1

Period 1 title	Overall Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

Matched placebo, IRT, central scoring laboratory for the sleep studies i.e. MWT.

Arms

Are arms mutually exclusive?	Yes
Arm title	FT218

Arm description:

Patients treated with FT218, once nightly sodium oxybate granules for oral suspension.

Arm type	Experimental
Investigational medicinal product name	Once Nightly Sodium Oxybate - Granules for oral suspension
Investigational medicinal product code	FT218
Other name	
Pharmaceutical forms	Coated granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Patients were titrated to a maximum 9g stable dose over 13 treatment weeks. FT218 is reconstituted in water and administered once nightly at bedtime.

Arm title	Placebo

Arm description:

Matching Placebo

Arm type	Placebo
Investigational medicinal product name	Matched Placeboo
Investigational medicinal product code	Placebo
Other name	
Pharmaceutical forms	Coated granules in sachet
Routes of administration	Oral use

Dosage and administration details:

Dosage form and administration matched the active FT218 treatment arm.

Number of subjects in period 1	FT218	Placebo
Started	107	105
Completed	69	79
Not completed	38	26
Consent withdrawn by subject	11	11
Lack of Efficacy	2	8
Non-compliance with Study Drug	-	1
Adverse event, non-fatal	21	3
Pregnancy	2	-
other	2	1
Protocol deviation	-	2

Baseline characteristics

Reporting groups	
Reporting group title	FT218
Reporting group description:	
Patients treated with FT218, once nightly sodium oxybate granules for oral suspension.	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo	

Reporting group values	FT218	Placebo	Total
Number of subjects	107	105	212
Age categorical			
Date of Birth (per country regulation) information was collected in the eCRF.			
Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Date of Birth (per country regulations) was collected via the eCRF.			
Units: years			
median	29	30	
standard deviation	± 10.7	± 11.24	-
Gender categorical			
Units: Subjects			
Female	69	75	144
Male	38	30	68
Diagnosis Type			
Narcolepsy Type			
Units: Subjects			
NT1	80	82	162
NT2	27	23	50

Subject analysis sets	
Subject analysis set title	FT218 Safety Group
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects who administered at least 1 dose of study medication (FT218 Group).	
Subject analysis set title	FT218 mITT
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized subjects who were treated with study medication and completed at least 1 efficacy assessment at the 6g dose (FT218 Group).

Subject analysis set title	Placebo Safety Group
Subject analysis set type	Safety analysis

Subject analysis set description:

All enrolled subjects who administered at least 1 dose of study medication (Placebo Group).

Subject analysis set title	Placebo mITT Group
Subject analysis set type	Modified intention-to-treat

Subject analysis set description:

All randomized subjects who were treated with study medication and completed at least 1 efficacy assessment at the 6g dose (Placebo Group).

Reporting group values	FT218 Safety Group	FT218 mITT	Placebo Safety Group
Number of subjects	107	97	105
Age categorical			
Date of Birth (per country regulation) information was collected in the eCRF.			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age continuous			
Date of Birth (per country regulations) was collected via the eCRF.			
Units: years			
median	29	n/a	
standard deviation	± 10.95	±	±
Gender categorical			
Units: Subjects			
Female	144		
Male	68		
Diagnosis Type			
Narcolepsy Type			
Units: Subjects			
NT1	162		
NT2	50		

Reporting group values	Placebo mITT Group		
Number of subjects	93		
Age categorical			
Date of Birth (per country regulation) information was collected in the eCRF.			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			

Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous			
Date of Birth (per country regulations) was collected via the eCRF.			
Units: years median standard deviation	±		
Gender categorical Units: Subjects			
Female Male			
Diagnosis Type			
Narcolepsy Type			
Units: Subjects			
NT1 NT2			

End points

End points reporting groups

Reporting group title	FT218
Reporting group description:	
Patients treated with FT218, once nightly sodium oxybate granules for oral suspension.	
Reporting group title	Placebo
Reporting group description:	
Matching Placebo	
Subject analysis set title	FT218 Safety Group
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects who administered at least 1 dose of study medication (FT218 Group).	
Subject analysis set title	FT218 mITT
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who were treated with study medication and completed at least 1 efficacy assessment at the 6g dose (FT218 Group).	
Subject analysis set title	Placebo Safety Group
Subject analysis set type	Safety analysis
Subject analysis set description:	
All enrolled subjects who administered at least 1 dose of study medication (Placebo Group).	
Subject analysis set title	Placebo mITT Group
Subject analysis set type	Modified intention-to-treat
Subject analysis set description:	
All randomized subjects who were treated with study medication and completed at least 1 efficacy assessment at the 6g dose (Placebo Group).	

Primary: Maintainence of Wakefulness Test (MWT)

End point title	Maintainence of Wakefulness Test (MWT)
End point description:	
The MWT is the mean latency across 5 naps, averaged over the test day	
End point type	Primary
End point timeframe:	
Study Visit 8	

End point values	FT218 mITT	Placebo mITT Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	68	78		
Units: Minutes				
arithmetic mean (confidence interval 95%)	15.5 (13.13 to 17.86)	9.39 (7.61 to 11.17)		

Statistical analyses

Statistical analysis title	Maintenance of Wakefulness Test (MWT)

Statistical analysis description:

Maintenance of Wakefulness Test (MWT) Mean Sleep Latency (Minutes) Change from Baseline to the End of 9.0g Treatment Period - MMRM Analysis (mITT Population)

Comparison groups	FT218 mITT v Placebo mITT Group
Number of subjects included in analysis	146
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	6.13
Confidence interval	
level	95 %
sides	2-sided
lower limit	3.52
upper limit	8.75
Variability estimate	Standard error of the mean

Primary: Clinical Global Impression of Improvement

End point title	Clinical Global Impression of Improvement

End point description:

The CGI is the clinician’s global impression of improvement in daytime sleepiness. For the CGI, a GLIMMIX model for binomial data with logit link was used to analyze the categorized CGI response, i.e., the proportions of subjects who were Very Much Improved or Much Improved as compared to baseline

End point type	Primary

End point timeframe:

Study Visit 8

End point values	FT218 mITT	Placebo mITT Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	69	79		
Units: Percentage				
number (not applicable)	72	31.6		

Statistical analyses

Statistical analysis title	Clinical Global Impression (CGI) - Improvement

Statistical analysis description:

Clinical Global Impression - Improvement (CGI-I) by the End of 9.0g Treatment Period - GLIMMIX Model (mITT Population)

Comparison groups	FT218 mITT v Placebo mITT Group
Number of subjects included in analysis	148
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.0001
Method	GLIMMIX
Parameter estimate	Odds ratio (OR)
Point estimate	5.56
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.76
upper limit	11.23

Primary: Number of Cataplexy Attacks

End point title	Number of Cataplexy Attacks

End point description:

The NCA was the mean number of cataplexy events recorded on the SSDD during the treatment period

End point type	Primary

End point timeframe:

Visit 8 - Change from Baseline

End point values	FT218 mITT	Placebo mITT Group		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	54	62		
Units: NCA				
log mean (confidence interval 95%)	-11.521 (-12.960 to -10.081)	-4.938 (-6.206 to -3.669)		

Statistical analyses

Statistical analysis title	Mean Weekly Number of Cataplexy Attacks (NCA)

Statistical analysis description:

Mean Weekly Number of Cataplexy Attacks (NCA) of Each Dosing Period, Change from Baseline to the End of 9.0g Treatment Period - MMRM Analysis (NT1 Subjects in mITT Population)

Comparison groups	FT218 mITT v Placebo mITT Group

Number of subjects included in analysis	116
Analysis specification	Pre-specified
Analysis type	superiority
P-value	> 0.0001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-6.648
Confidence interval	
level	95 %
sides	2-sided
lower limit	-9.315
upper limit	-3.98
Variability estimate	Standard error of the mean
Dispersion value	0.963

Adverse events

Adverse events information

Timeframe for reporting adverse events:

AE data were obtained at all study visits (scheduled or unscheduled) from the time of the signing of informed consent until seven days after the last dose of study drug.

Adverse event reporting additional description:

Safety was evaluated based on reports of AEs either spontaneously reported or observed in clinical laboratory analyses.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.1

Reporting groups

Reporting group title	9g FT218 Group

Reporting group description:

Subjects dosing with FT218

Reporting group title	9g Placebo Group

Reporting group description:

9g dosing period - subjects dosing with placebo

Serious adverse events	9g FT218 Group	9g Placebo Group	
Total subjects affected by serious adverse events			
subjects affected / exposed	5 / 107 (4.67%)	2 / 105 (1.90%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 107 (0.93%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Paraesthesia			
subjects affected / exposed	1 / 107 (0.93%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Immune system disorders			
Drug hypersensitivity			

subjects affected / exposed	0 / 107 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Suicidal ideation			
subjects affected / exposed	1 / 107 (0.93%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Perirectal abscess			
subjects affected / exposed	1 / 107 (0.93%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pelvic inflammatory disease			
subjects affected / exposed	0 / 107 (0.00%)	1 / 105 (0.95%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Diabetes mellitus inadequate control			
subjects affected / exposed	1 / 107 (0.93%)	0 / 105 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	9g FT218 Group	9g Placebo Group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	83 / 107 (77.57%)	50 / 105 (47.62%)	
Cardiac disorders			
Dyspnoea			
subjects affected / exposed	4 / 107 (3.74%)	0 / 105 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Dizziness			

subjects affected / exposed	17 / 107 (15.89%)	0 / 105 (0.00%)	
occurrences (all)	20	0	
Somnolence			
subjects affected / exposed	5 / 107 (4.67%)	1 / 105 (0.95%)	
occurrences (all)	6	1	
Headache			
subjects affected / exposed	20 / 107 (18.69%)	12 / 105 (11.43%)	
occurrences (all)	25	13	
Abnormal dreams			
subjects affected / exposed	5 / 107 (4.67%)	0 / 105 (0.00%)	
occurrences (all)	5	0	
Paraesthesia			
subjects affected / exposed	4 / 107 (3.74%)	0 / 105 (0.00%)	
occurrences (all)	4	0	
Hypoaesthesia			
subjects affected / exposed	3 / 107 (2.80%)	0 / 105 (0.00%)	
occurrences (all)	4	0	
Sleep paralysis			
subjects affected / exposed	3 / 107 (2.80%)	0 / 105 (0.00%)	
occurrences (all)	4	0	
Somnambulism			
subjects affected / exposed	3 / 107 (2.80%)	0 / 105 (0.00%)	
occurrences (all)	3	0	
Tremor			
subjects affected / exposed	3 / 107 (2.80%)	0 / 105 (0.00%)	
occurrences (all)	3	0	
General disorders and administration site conditions			
Hyperhidrosis			
subjects affected / exposed	6 / 107 (5.61%)	0 / 105 (0.00%)	
occurrences (all)	6	0	
Asthenia			
subjects affected / exposed	4 / 107 (3.74%)	1 / 105 (0.95%)	
occurrences (all)	4	1	
Fatigue			

subjects affected / exposed	3 / 107 (2.80%)	1 / 105 (0.95%)	
occurrences (all)	3	1	
Pain			
subjects affected / exposed	3 / 107 (2.80%)	0 / 105 (0.00%)	
occurrences (all)	3	0	
Pyrexia			
subjects affected / exposed	3 / 107 (2.80%)	3 / 105 (2.86%)	
occurrences (all)	4	3	
Immune system disorders			
Seasonal allergy			
subjects affected / exposed	3 / 107 (2.80%)	0 / 105 (0.00%)	
occurrences (all)	4	0	
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	19 / 107 (17.76%)	4 / 105 (3.81%)	
occurrences (all)	27	4	
Nausea			
subjects affected / exposed	3 / 107 (2.80%)	4 / 105 (3.81%)	
occurrences (all)	3	4	
Upper Abdominal Pain			
subjects affected / exposed	2 / 107 (1.87%)	0 / 105 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	4 / 107 (3.74%)	0 / 105 (0.00%)	
occurrences (all)	4	0	
Dry mouth			
subjects affected / exposed	4 / 107 (3.74%)	2 / 105 (1.90%)	
occurrences (all)	4	2	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	3 / 107 (2.80%)	4 / 105 (3.81%)	
occurrences (all)	3	4	
Psychiatric disorders			
Enuresis			
subjects affected / exposed	17 / 107 (15.89%)	0 / 105 (0.00%)	
occurrences (all)	23	0	

Anxiety			
subjects affected / exposed	8 / 107 (7.48%)	3 / 105 (2.86%)	
occurrences (all)	8	4	
Depression			
subjects affected / exposed	3 / 107 (2.80%)	1 / 105 (0.95%)	
occurrences (all)	3	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 107 (3.74%)	2 / 105 (1.90%)	
occurrences (all)	5	2	
Pain in Extremity			
subjects affected / exposed	4 / 107 (3.74%)	2 / 105 (1.90%)	
occurrences (all)	4	2	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	6 / 107 (5.61%)	7 / 105 (6.67%)	
occurrences (all)	7	7	
Upper respiratory tract infection			
subjects affected / exposed	3 / 107 (2.80%)	2 / 105 (1.90%)	
occurrences (all)	3	2	
Metabolism and nutrition disorders			
Decreased Appetite			
subjects affected / exposed	13 / 107 (12.15%)	0 / 105 (0.00%)	
occurrences (all)	14	0	
Weight decreased			
subjects affected / exposed	6 / 107 (5.61%)	1 / 105 (0.95%)	
occurrences (all)	6	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported