UNITED STATES
SECURITIES AND EXCHANGE COMMISSION

Washington, D.C. 20549

FORM 8-K

CURRENT REPORT
Pursuant to Section 13 or 15(d)
of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **September 26, 2016**

FLAMEL TECHNOLOGIES S.A.

(Exact name of registrant as specified in its charter)

Republic of France	**000-28508**	**98-0639540**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(I.R.S. Employer Identification No.)

Parc Club du Moulin à Vent **33, avenue du Docteur Georges Levy** **69200 Vénissieux France**	**Not Applicable**
(Address of Principal Executive Offices)	(Zip Code)

Registrant's telephone number, including area code: **011 +33 472 78 34 34**

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

£ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

£ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

£ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

£ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Item 7.01 Regulation FD Disclosure.

On September 26, 2016, Flamel Technologies S.A. (the "Company") hosted a meeting for investors and analysts in New York City. A copy of the Company's complete slide presentation used at the meeting is being furnished as Exhibit 99.1 to this Current Report on Form 8-K. As previously announced, the meeting was webcast live and was accessible through the Investor section of the Company's website at http://www.flamel.com/investors. A replay of the meeting, together with the complete slide presentation, will be archived and available for at least 30 days on the website following the event.

The information responsive to Item 7.01 of this Form 8-K, including Exhibit 99.1, shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934 (the "Exchange Act") or otherwise subject to the liabilities of that section, nor shall it be deemed incorporated by reference in any filing under the Securities Act of 1933 or the Exchange Act, except as may be expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

99.1		Form of Slide Presentation of Flamel Technologies S.A. as of September 26, 2016.

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned hereunto duly authorized.

FLAMEL TECHNOLOGIES S.A.

By: /s/ Phillandas T. Thompson
Phillandas T. Thompson
Senior Vice President, General Counsel and Corporate Secretary

Date: September 26, 2016

Exhibit Index

99.1		Form of Slide Presentation of Flamel Technologies S.A. as of September 26, 2016.

FLAMEL technologies

Investor & Analyst Day

Forward Looking Statements

This presentation may include "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. All statements herein that are not clearly historical in nature are forward-looking, and the words "anticipate," "assume," "believe," "expect," "estimate," "plan," "will," "may," and the negative of these and similar expressions generally identify forward-looking statements. All forward-looking statements involve risks, uncertainties and contingencies, many of which are beyond Flamel's control and could cause actual results to differ materially from the results contemplated in such forward-looking statements. These risks, uncertainties and contingencies include the risks relating to: our dependence on a small number of products and customers for the majority of our revenues; the possibility that our Bloxiverz® and Vazculep® products, which are not patent protected, could face substantial competition resulting in a loss of market share or forcing us to reduce the prices we charge for those products; the possibility that we could fail to successfully complete the research and development for the two pipeline products we are evaluating for potential application to the FDA pursuant to our "unapproved-to-approved" strategy, or that competitors could complete the development of such products and apply for FDA approval of such products before us; our dependence on the performance of third parties in partnerships or strategic alliances for the commercialization of some of our products; the possibility that our products may not reach the commercial market or gain market acceptance; our need to invest substantial sums in research and development in order to remain competitive; our dependence on certain single providers for development of several of our drug delivery platforms and products; our dependence on a limited number of suppliers to manufacture our products and to deliver certain raw materials used in our products; the possibility that our competitors may develop and market technologies or products that are more effective or safer than ours, or obtain regulatory approval and market such technologies or products before we do; the challenges in protecting the intellectual property underlying our drug delivery platforms and other products; our dependence on key personnel to execute our business plan; the amount of additional costs we will incur to comply with U.S. securities laws as a result of our ceasing to qualify as a foreign private issuer; and the other risks, uncertainties and contingencies described in the Company's filings with the U.S. Securities and Exchange Commission, including our annual report on Form 10-K for the year ended December 31, 2015, all of which filings are also available on the Company's website. Flamel undertakes no obligation to update its forward-looking statements as a result of new information, future events or otherwise, except as required by law.

Flamel Research and Development Update

David Monteith PhD, Vice President – Research and Development

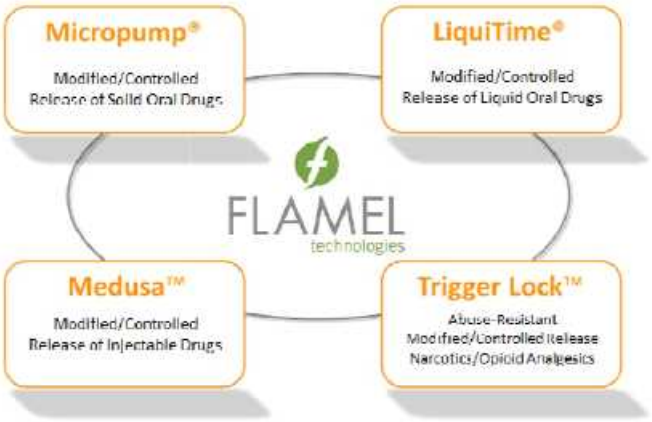
September 26, 2016

Presentation Outline

- Flamel's Proprietary Drug Delivery Platforms
  - **Micropump**
  - **LiquiTime**
  - Trigger Lock
  - Medusa
- Once Nightly Sodium Oxybate
  - Product Profile
  - Studies Conducted To Date
  - Phase III Narcolepsy Trial – Status

Flamel's Proprietary Drug Delivery Platforms

Advanced Formulation and Delivery Platforms for Better and Safer Drugs



Micropump® Drug Delivery Platform

Modified/Controlled Release of Solid Oral Drugs

Micropump®

Micropump® allows development of modified and/or controlled release of solid, oral dosage formulations of drugs

- Derivative **LiquiTime®** allows development of modified/controlled release of liquid formulations
- Derivative **Trigger Lock™** allows development of tamper-resistant modified/controlled release formulations of narcotic/opioid analgesics

Versatility of Micropump® allows development of differentiated product profiles (SR / DR formulations) under various dosage forms:

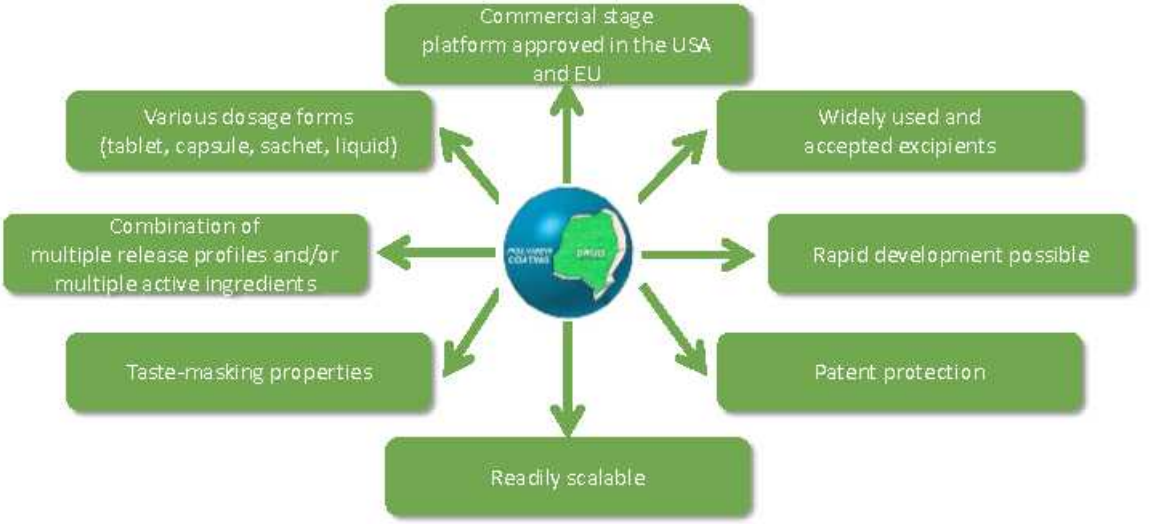
- Capsules, tablets, sachets (sodium oxybate)
- Oral liquid suspensions (LiquiTime®)

Unique formulation used for different dose strengths and forms

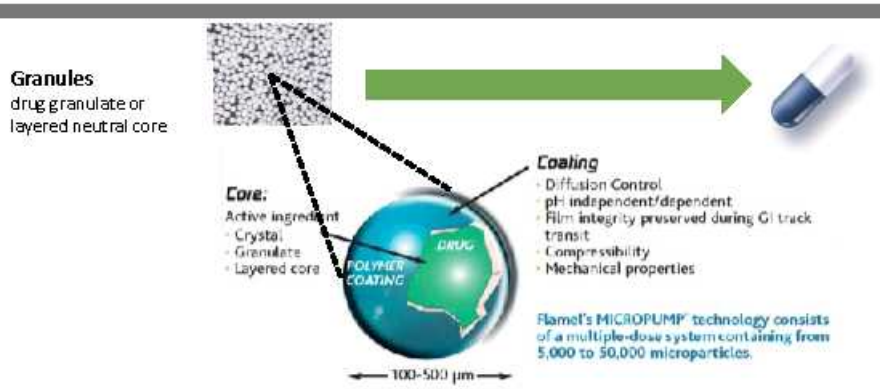
- Same drug with different release profiles or
- Two or more drugs with tailored release profiles for combination therapy

Micropump® Platform at a Glance

- Extended/delayed release of drugs throughout GI Tract
- Precise pharmacokinetics of single or combination drugs in various formats
- Numerous Micropump®-based products have been successfully tested in human clinical trials



Microparticles for Controlled/Modified Release



- Microparticles dispersed in the stomach, pass into the small intestine where each microparticle releases drug at an adjustable rate over an extended period of time (up to 24 hours)
- Drug released at adjustable rate controlled (time dependent release: SR coating) and/or delayed (pH and time dependent release: DR coating)
- Micropump® microparticles can be used separately or together to provide highly specialized delivery profiles

Micropump® – Key Benefits

- Extended release in the GI tract up to 24 hours allowing plasma levels to be extended
- Potentially improved efficacy (by extending therapeutic coverage)
- Potentially reduced toxicity and/or side effects (by reducing Cmax or by reducing intra- and inter-patient variability)
- Improved patient compliance (reducing frequency of administration)
- Applicable to poorly soluble (< 0.01mg/L), highly soluble (> 500g/L), low dose (e.g. 4 mg) or high dose (e.g. 1,000 mg) drugs
- Good mouth feel
- Taste masking properties
- Patent protection

LiquiTime®
Drug Delivery Platform

Modified/Controlled Release of Liquid Oral Drugs

LiquiTime®

- Allows development of modified/controlled release liquid formulations for patients having issues swallowing tablets/capsules
- **Not limited to working solely with ionic drugs as with resin-complex based technologies**
- Readily scalable to commercial quantities
- Easy to swallow, good mouth feel, taste masked - dose flexibility while maintaining accuracy and safety

Applicable to:

Pediatric[1]

- US population younger than 18 years old = 76 million in 2019
- 75% of households with children under 12 purchased an OTC pain reliever over the past 12 months
- Sales of OTC pediatric product in the US = $1.6 B in 2013 ($1.9 B estimated in 2018)

Geriatric

- 810 million people > 60 years in 2012 2 billion expected in 2050[2]
- In 2010 approximately 45-50% of the prescriptions were written for people aged 60 and above and one in three patients took at least 5 drugs or more on a daily basis in the United States[3]

[1] *"OTC Pediatrics – US" (March 2014, Mintel)*
[2] *World Health Organization*
[3] *"Geriatric Medicine Market - Global Industry Analysis, Size, Share, Growth, Trends and Forecast, 2013 – 2019" (Transparency Market Research)*

LiquiTime® – Key Benefits

- Easy to swallow, taste masked and good mouth feel
- Applicable to wide range of drugs, not limited to ionic drugs as with resin-complex based technology
- Combination of immediate release and extended release kinetics possible
- Combination in the same formulation of different drugs with different release kinetics possible
- Widely used and accepted excipients
- Readily scalable to industrial scale
- Clinical Proof of Concept achieved in humans (ibuprofen and guaifenesin)
- Patent protection

Update: Ibuprofen and Guafenesin LiquiTime® Products

- Ibuprofen
  - 12 hour profile developed for pain/fever
  - Regulatory pathway deemed high risk and high cost
- Guaifenesin
  - Successful pilot PK study reported in March 2015
  - Second PK study ongoing
  - Update anticipated in early 2017

Trigger Lock™ Platform

Abuse Deterrent Extended Release of Opioids

Trigger Lock™ for Abuse Deterrence

- **Drug loaded Micropump® microparticles**
  Sustained Release (SR) microparticles individually polymer coated which are resistant to crushing
- **Viscosifying ingredient(s)**
  To prevent abuse by injection after extraction in a small volume of solvent
- **Quenching ingredient(s)**
  To prevent extraction in large volumes of liquid (forming a complex with the opioid preventing its solubilization in aqueous/alcoholic media)

→ **Each microparticle retains its polymer coating**

→ **Trigger Lock™ is virtually impervious to crushing**

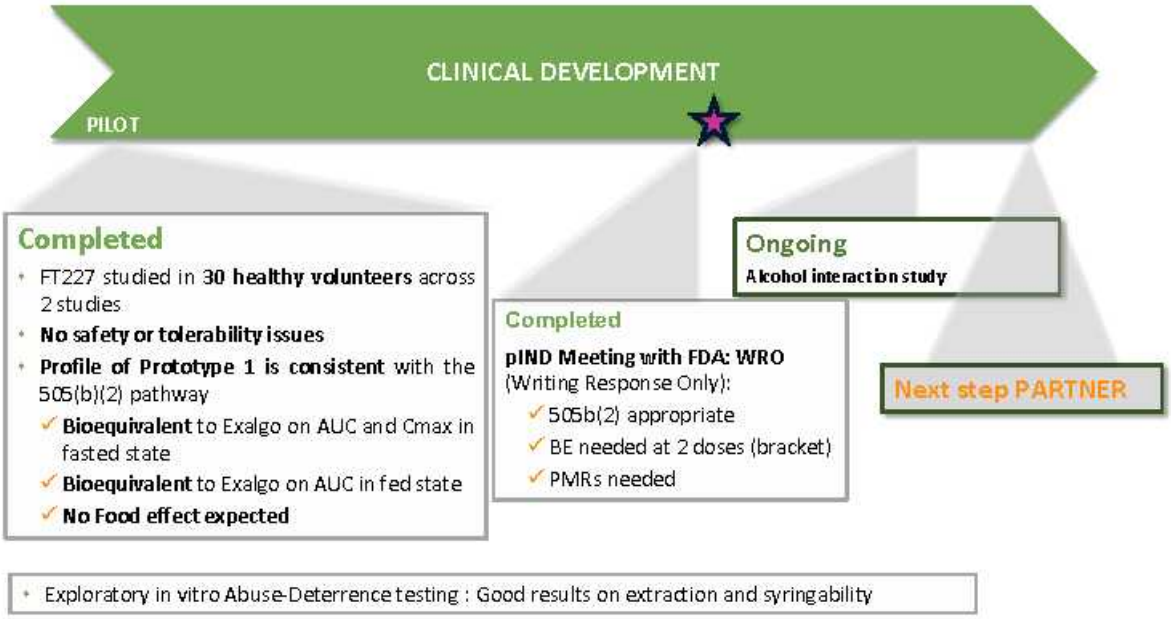
Abuse-Deterrence Category I Studies: *in vitro* Testing

	Physical manipulation		Route specific snorting abuse	Chemical manipulation		Route specific IV Injection
	Mortar/pestle	Coffee grinder		Extraction (RT* and heated) pH2 medium	Extraction (RT* and heated) 40% alcohol	
FT227 vs. Oxycontin	Not Better	Better	Better	Better	Better	Much Better
FT227 vs. Exalgo	Better	Better	Better	Similar/ Better	Better	Much Better

** RT: Room Temperature*

- **Trigger Lock™ has the potential to be more resistant to manipulation and abuse than formulations of opioids that are currently available.**
- **Trigger Lock™ should be eligible for labeling regarding abuse-deterrent properties**

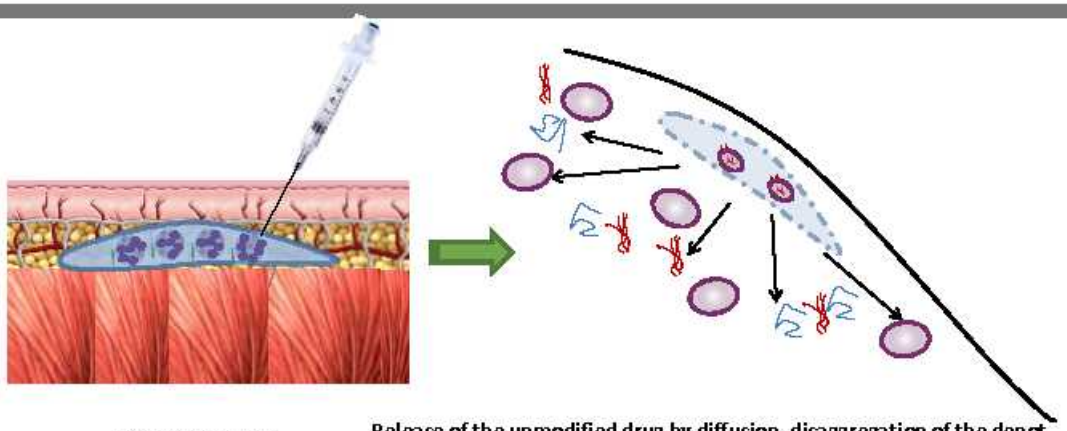
FT227 Clinical Development



Medusa™ Drug Delivery Platform

Modified/Controlled Release of Injectable Drugs

In Vivo Drug Release from Medusa™ Depot



Depot formation

Release of the unmodified drug by diffusion, disaggregation of the depot and competition with endogeneous proteins over several days

Injection — Day 1 — Day X*

Drug

Glutamic acid — Vitamin E

Natural and safe components disappearing progressively

*By adjusting polymer concentration and/or ions content

Phase Ib Outcome

- Safety of exenatide MPF excellent up to 4 weekly administrations of 140 mcg dose in 12 T2DM patients, 30 healthy volunteers administered with escalating doses up to 140 mcg
- The 1st administration leads to continuous release of exenatide observed over a period of 14 days with relative bioavailability close to 100%.
- All biomarkers and surrogate endpoints consistent with effective exenatide MPF after 4 weekly administrations
- PD performance of exenatide MPF is very good in comparison to marketed products, Victoza® (liraglutide IR gold standard) and Bydureon® (exenatide SR), on primary (FPG and HbA1c) and secondary (body weight) therapeutic measures
- **Next Step - Partnering**

Once a Night Sodium Oxybate

(Extended Release Sodium Oxybate Granules for Oral Suspension)

Micropump®

Micropump® allows development of modified and/or controlled release of solid, oral dosage formulations of drugs

- Derivative **LiquiTime®** allows development of modified/controlled release of liquid formulations
- Derivative **Trigger Lock™** allows development of tamper-resistant modified/controlled release formulations of narcotic/opioid analgesics

Versatility of Micropump® allows development of differentiated product profiles (SR / DR formulations) under various dosage forms:

- Capsules, tablets, sachets (sodium oxybate)
- Oral liquid suspensions (LiquiTime®)

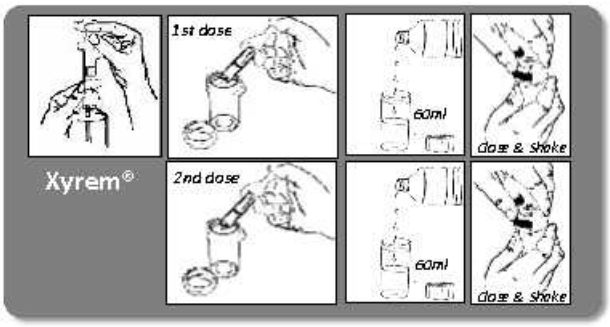
Unique formulation used for different dose strengths and forms

- Same drug with different release profiles or
- Two or more drugs with tailored release profiles for combination therapy

Once Nightly Sodium Oxybate

Therapeutic target	Cataplexy and excessive daytime sleepiness in patients with narcolepsy
Competitor	Xyrem®
Technology®	Micropump®
Dosage	Once at night (2hrs after evening meal)
Dosage Form	Granules for oral suspension
Strength	4.5g – 6g – 7.5g – 9g
Packaging	Stick-pack with child-resistant properties
Dosage units	4.5g – 6g – 7.5g and 9g
Market	US
Regulatory pathway	505(b)(2)
PK Target (BA/BE, Cmax, Tmax)	PK Profile targets a lower Cmax than Xyrem second dose with comparable BA for full night's dose

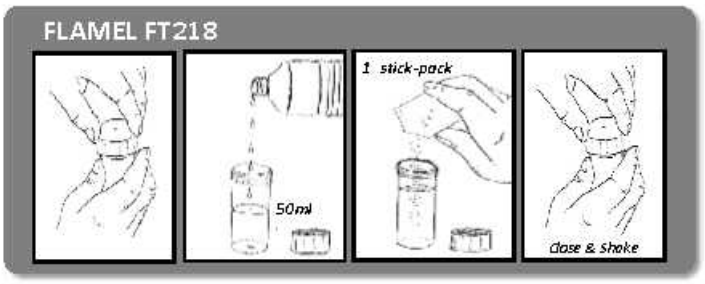
FT218 Expected Dosing



Xyrem®

→ 1st dose taken at bedtime

→ 2nd dose on the nightstand
to be taken 2.5 to 4 hours later



FT218
Only one dose at bedtime!

FT218 Advantages

Single Dose Nightly Formulation

- Easier for patient (and partners)
- Avoid waking up in the middle of the night and disruption of sleep
- Avoid unattended dose available on nightstand
- Avoid rising and moving in middle of the night (bathroom, kitchen)
- Less water / night compared to 2 doses – potentially fewer incidents of nocturnal enuresis

Potential Benefits

- Potentially better overall patient outcome
- Less side effects due to lower Cmax, particularly avoiding 2nd higher peak (closer to morning)
- Potentially lower-side effect profile allows patient to titrate to effective dose

Dosage form (granules for suspension)

- More convenient for travelling (powder, not liquid > 100ml)
- Individual doses in child–resistant packaging

Summary of PK Data

- Extended Release Sodium Oxybate Granules for Oral Suspension has been studied in 40 healthy volunteers to date across 2 studies
- Results of these studies at 4.5g show:
  - ✓ Expected onset of action similar to Xyrem®
  - ✓ C_{max} lower than the second dose of Xyrem®
  - ✓ Comparable AUC on dose for dose basis
  - ✓ Mean blood concentrations at 7 and 8 hours post dose similar to Xyrem®
  - ✓ No adverse events or tolerability issues
- 6g and 7.5g performed in line with PK expectations based on 4.5g dose
- Profile is consistent with target product profile of a once nightly administration

FT218 – Project Progress to Date

- ✓ Successful Results from the First PK study with 3 prototypes
- ✓ Successful Results from 2nd PK study with 2 prototypes and up to 7.5g
- ✓ Optimized formulation
- ✓ Phase II protocol development and CRO selection
- ✓ P-IND Meeting
- ✓ IND and SPA submission (March 2016) - VHP Europe and Canada submission (Apr 2016)
- ✓ IND and Canadian approval (May 2016) – VHP approval (July 2016)
- ✓ Study site selection and contracting
- ✓ Site Initiation Visits started (Sep 2016)

FT218 – Phase III Narcolepsy Trial Current Status

- Phase III study designed and approved to start in US, Canada and several European countries
- Product scaled and available to start Phase III study
- 56 study sites selected and in various stages of readiness for trial initiation
- First web based Investigator Meeting conducted on Sep 1st, full EU and US Meetings planned in September and October
- First clinical site initiation visits conducted September 2016 in Canada

Patient Recruitment Phase Initiated

Narcolepsy
Clinical Features

Todd J. Swick, M.D.

Assistant Clinical Professor, University of Texas Health Sciences Center,
School of Medicine-Houston

Narcolepsy

- **Lifelong neurologic/sleep disorder characterized by the disruption of the boundaries between sleep and wake states**
- **Classic pentad of signs and symptoms:**
  - Excessive Daytime Sleepiness (EDS)
  - Cataplexy
  - Hypnogogic hallucinations
  - Sleep paralysis
  - Disrupted nighttime sleep (DNS) [nocturnal sleep fragmentation]

Narcolepsy

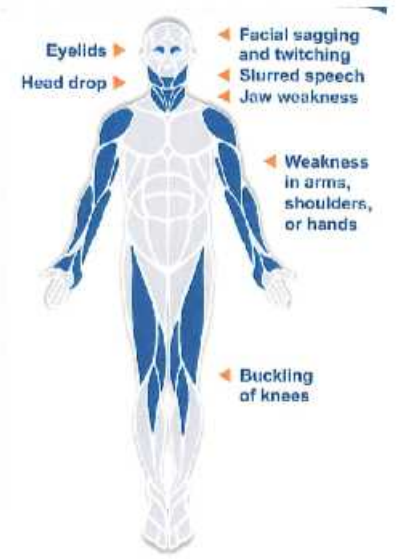
- **Ancillary symptoms:**
  - Automatic behavior
  - Loss of concentration and memory
  - Visual symptoms (blurred vision)
- **There are 2 distinct groups of patients with narcolepsy:**
  - Those with cataplexy (*Type 1 Narcolepsy as per ICSD-3 classification*)
  - Those without cataplexy (*Type 2 Narcolepsy as per ICSD-3 classification*)
- **Can coexist with other sleep disorders**
  - Obstructive Sleep Apnea
  - Restless Legs Syndrome
  - Periodic Limb Movements in Sleep
  - REM sleep behavior disorder
  - Nocturnal eating disorder

Narcolepsy

- **Sleepiness is usually the first symptom**
  - Defined as the irrepressible urge to sleep
  - Daytime lapses into sleep (sleep attacks)
- **Differential dx**
  - Sleep deprivation
  - Obstructive Sleep Apnea
  - Narcolepsy Type 1 (with cataplexy)
  - Narcolepsy Type 2 (without cataplexy)
  - Idiopathic hypersomnia
  - Recurrent hypersomnia (Kleine-Levine Syndrome)

Cataplexy

- **Episodic weakness without altered consciousness lasting seconds to minutes and precipitated by excitement or emotion**
- **May occur several times/day or a few times/year**
- **Sagging of face, eyelid, or jaw; dysarthria (slurred speech- *particularly in children*); head drop; blurred vision; knee bucking; "drop attack"**
- **Can be unilateral**
- **Episodic blurring of vision**
- **Laughter is the most common trigger but can also be triggered by fright, excitement, fear, orgasm**
- **Usually develops within 3 years of EDS symptoms, but may develop 10-40 years later**



Sleep Paralysis

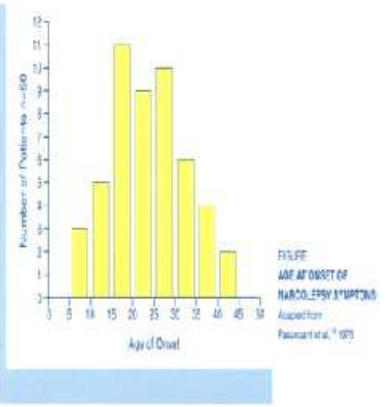
- **The inability to move for a few seconds or minutes during sleep onset or offset**
- **Often occurs in normal individuals on a relatively rare episodic basis but is far more common and almost universal in narcoleptics**
- **Paralysis ends spontaneously (fear reaction is most common) or after mild sensory/tactile stimulation**

Hypnogogic Hallucinations

- **Vivid, "*waking dreams*" that occur during *transitions between* sleep and wakefulness**
  - Hypnogogic (occurring at sleep onset)
  - Hypnopompic (occurring upon awakening)
- **May accompany sleep paralysis or occur independently**
- **May be tactile or auditory**
- **Some awareness of surroundings is preserved**
- **Differentiated from dreaming during sleep**

Narcolepsy-Age of Onset of Symptoms

- **Onset between ages 15 and 30 in 60% of patients**
- **Age range from 5 to 63**
- **Median age of 22**
- **Onset of cataplexy ages 9 to 68**
- **Hypnagogic hallucinations ages 9 to 65**
- **Sleep Paralysis ages 10 to 58**



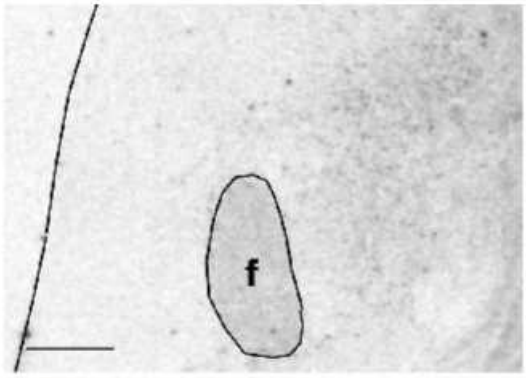
- Age at onset of narcolepsy in two large populations of patients in France and Quebec. Dauvilliers Y, Montplaisir J, et al. Neurology 2001; 57:2029-2033.

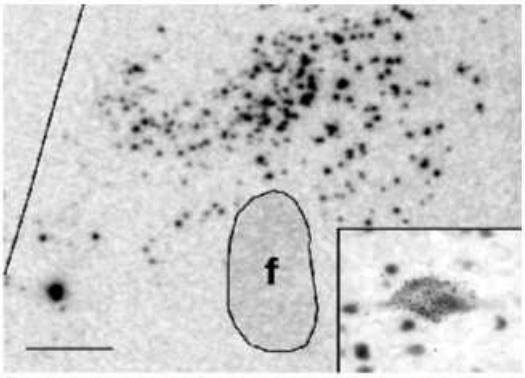
Hypocretins (Orexins)

- **Human narcolepsy/cataplexy (Type 1 Narcolepsy) is caused by loss of hypocretin (orexin) neurons in the dorsolateral hypothalamus (70,000 neurons in a paired set)**
- **Thought to be caused by an autoimmune process directed specifically against hypocretin neurons in the hypothalamus (not by a mutated gene)**
  - The *canine form* (e.g., Doberman Pinchers) of narcolepsy is caused by a single mutated hypocretin receptor 2 gene in an autosomal recessive pattern

De Lecea L, Kilduff TS, Peyron C, et al. The hypocretins: hypothalamic-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA. 1998; 95:322-7.

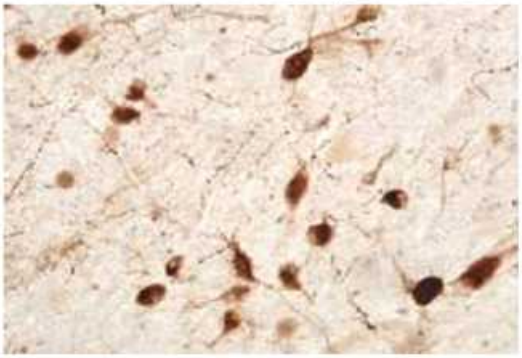
Hcrt loss as the cause of narcolepsy





Normal hypothalamus

Abnormal structure and severe loss of Hcrt peptide staining



Normal Hcrt peptide staining

Hypocretin (Orexin) Cell Loss as the cause of narcolepsy vs. normal tissue

Measuring Sleepiness as an Endpoint for Efficacy of EDS Treatment

- **Subjective scales**
  - Stanford Sleepiness Scale
  - Epworth Sleepiness Scale

- **Objective Testing**
  - Polysomnography/Multiple Sleep Latency Testing (PSG/MSLT)
  - Maintenance of Wakefulness Test (MWT)

Classification of Narcolepsy

- **ICSD-3 (American Academy of Sleep Medicine-2014)**
  - **Narcolepsy Type 1 [Narcolepsy *with* Cataplexy]**
    - Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months
    - Cataplexy *and* a mean SOL of ≤8 min and ≥2 SOREMPs on an MSLT (a SOREMP on the preceding night's PSG can substitute for one of the SOREMPs on the MSLT

      OR
    - CSF HYPOCRETIN-1 concentration of ≤110 pg/mL

American Academy of Sleep Medicine. International Classification of Sleep Disorders, 3rd ed. Darien, IL: American Academy of Sleep Medicine, 2014.

Classification of Narcolepsy

- **ICSD-3 (American Academy of Sleep Medicine-2014)**
  - **Narcolepsy Type 2 [Narcolepsy *without* Cataplexy] (*All* criteria must be met)**
    - Patient has daily periods of irrepressible need to sleep or daytime lapses into sleep occurring for ≥3 months
    - Mean SOL=≤8 min and ≥2 SOREMPs (a SOREMP on the preceding PSG can count as one SOREMP for the MSLT)
    - Cataplexy is absent
    - CSF has NOT been measured or is >110 pg/mL
    - The hypersomnia is not better explained by another sleep disorder, medical, psychiatric or neurological disorder

Incidence of Narcolepsy

- Data from the Mayo Clinic from (1960-1989)
  - Narcolepsy without cataplexy (1.37/100,000)
  - Narcolepsy with cataplexy (0.74/100,000)
- Following 2010 (post H1N1 infection/immunization) there was a profound increase in the incidence of narcolepsy with cataplexy
  - Finland saw a 17 fold increase in the incidence in children ages 2-17 and adolescents from 17-19 years of age saw a three fold increase
  - Sweden saw the incidence rise in 2-17 year olds from 0.26/100,000 to 6.6/100,000 a 25 fold increase

Narcolepsy Management

- **Treatment of excessive daytime sleepiness (EDS)**
  - Stimulants (methylphenidate, amphetamines)
  - modafinil (Provigil®)-racemic mixture of "r" and "s" forms of modafinil
  - armodafinil (Nuvigil®)-pure "r" isomer of modafinil
- **Treatment of Cataplexy**
  - Tricyclic antidepressants (TCAs)
  - Selective Serotonin Reuptake Inhibitors (SSRIs)
  - Selective Serotonin Noradrenergic Reuptake Inhibitors (SSNRIs)
- **Both EDS and Cataplexy**
  - Sodium Oxybate

Goals of Treatment

- **Reduce daytime sleepiness**
- **Reduce/eliminate cataplexy**
- **Control ancillary symptoms**
  - Nightmares and unpleasant frequent dreams
  - Hallucinations
  - Sleep paralysis
  - Disturbed nocturnal sleep
- **Improve cognitive, psychosocial and work functioning**
- **Improve safety of patient and public**

Widespread Underdiagnosis of Narcolepsy

- **Only 50,000 of the estimated 200,000 Americans with narcolepsy have been correctly diagnosed**
- **Almost as common as Multiple Sclerosis**
- **Can go 10 to 15 years after symptoms start before correct diagnosis is made**
- **A patient with narcolepsy/cataplexy sees an average of 5-7 physicians before a proper diagnosis is made**

- Delayed diagnosis of narcolepsy: characterization and impact. Thorpy and Krieger. Sleep Med 15 (2014) 502-507.

Challenges to Effective Treatment

- Under diagnosis and/or misdiagnosis of narcolepsy is VERY frequent
  - Daydreaming
  - Insomnia
  - Drug Abuse
  - Depression/Bipolar disorder
  - Apathy
  - ADD
  - Seizures
- Insufficient exposure to patients with narcolepsy in sleep fellowships
- Inadequate education of sleep fellows
  - >70% of sleep fellowships in USA are run by pulmonary medicine departments and pulmonary/critical care physicians

Challenges to Effective Treatment

- Too many "sleep physicians" are afraid to prescribe sodium oxybate
- Myths about sodium oxybate
  - Health Care Practitioners think they are prescribing "GHB"
  - They think that sodium oxybate carries the same risks as GHB
    - Overdose/Coma
    - Addiction
    - Utility as a date-rape drug
- **Less than 15% of currently diagnosed narcoleptics are currently being treated with sodium oxybate**

Treatment is Often Less than Effective

- **"Wake Up Narcolepsy" survey of patients [2013-2014] (n= 2017; data were analyzed of 1697 respondents along with information from their direct care givers)**
  - 62% were between the ages of 25-54
  - 78% had narcolepsy symptoms for ≥8 years (prior to diagnosis)
  - 59% had cataplexy
- **"Improved" *EDS* with FDA approved medications: 85.4% However only**
  - 42.3% had improved cognition
  - 51.8% improved fatigue
- ***Despite treatment most patients continue to struggle with daily symptoms***
  - **Residual EDS symptoms in 64.8%**
  - **Constant fatigue 37.4%**
  - **Cognitive impairment 40.8%**
- **Cognitive symptoms are very common and are under-appreciated by clinicians**

Efficacy of current narcolepsy treatments: are we setting the bar too low? Maski KP et al. Sleep 37: A222; 2014 (abs)

Sodium Oxybate

- Na^+ salt of gamma hydroxybuterate (GHB)
- Only drug to be FDA approved to treat ***both*** excessive daytime sleepiness and cataplexy in patients with narcolepsy
- ½ life 30-60 min
- Allow at least 2 hours ***after*** eating to time of first dose
- Nocturnal dosing (as a split dose)
  - ½ of the full dose at bedtime
  - ½ of full dose 3-4 hours after taking the bedtime dose

Sodium Oxybate

- Increases slow wave sleep
- Decreases time to sleep onset and decreases wakefulness after sleep onset
- Needs to be titrated upwards over 4-8 weeks (max total nightly dose=9 gm)
- Cannot be used with other CNS depressants or alcohol

Sodium Oxybate

- **Issues related to split night dosing**
  - Need to prepare both doses before bedtime (time consuming and increases the potential for dosing errors)
  - Proportion of patients who miss the second dose either because they can't wake up with an alarm or who sleep through the alarm
  - In a college dorm risk of keeping a bottle of medication on nightstand literally unattended during deep sleep
  - Waking up for second dose, taking it, and then going to restroom where individual can inadvertently fall asleep either on the commode or standing in front of it

Thomas Roth

Sleep Disorders and Research Center

Henry Ford Hospital

REST-ON Trial

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

Study Objectives

- Primary objectives:
  - To compare efficacy of 6.0, 7.5 and 9.0 g of FT218 to placebo in treating **EDS** in both NT1 and 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
  - 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 number of cataplexy attacks (NCA) determined from the cataplexy frequency item in the Sleep and Symptom Daily Diary

Creating an Efficient Protocol

- No placebo group for stimulant. Very big issue
- In majority of sites 16-18 (prime age for narcolepsy onset) will be included
- Doses evaluated in crossover design not parallel group
- Major efforts in recruitment and retention

Unique Efficient Study Design

- Only two groups, one active one placebo, thus overall fewer subjects needed
- Dose is studied within active group with all receiving 6, 7.5 and 9 grams
- Duration of treatment for any given dose is therefore less
- Screening period is carried out over time with extensive ongoing monitoring of eligibility and subjects compliance with protocol requirements

Inclusion Criteria

- For NT1 only, current continuing presence of cataplexy as defined by subject report for the last 3 months
- Subjects may use concomitant stimulants, but must comply with the following:
  - They must be on a stable dose of stimulants for at least 3 weeks prior to starting the screening process for this study

AND

  - They must use the same stimulant regimen throughout the entire study period, including during screening and post-treatment periods
  - They must discontinue all anti cataplexy drugs

Study Population

- 264 study subjects, randomized across approximately 60 centers in USA, Canada, Europe
- Subjects randomized 1:1 (NT1/NT2, single parallel group design)
- Minimum 107 subjects for each arm will have both EDS and cataplexy

Site Selection

- Sites selected from United States, Europe and Canada
- Total 56 sites: 31 US, 25 non US
- Sites selected which had extensive experience in Narcolepsy and Narcolepsy Clinical Trails
- Major Academic Narcolepsy Sites Participating

  France - Montpellier

  Italy – Bologna Neurology institute

  US - Stanford

  US - Yale

Regulatory Approvals

- United States
- Canada
- Virtually all EU sites

Rest-ON Global Study Specific Recruitment Methods

Flamel has established a robust subject recruitment and retention framework.

Establishment of a study specific Patient Advisory Group mediated via the Narcolepsy Network. *Inaugural PAG Meeting Hosted by Flamel April 2016:*

- ✓ Provide insight into patient decision making relative to disease trajectory and clinical trial requirements i.e. *placebo design, visit & dosing schedule, unique patient group needs*
- ✓ Advisory on group strategies to create widespread CLFT-218-1501 trial awareness in Narcolepsy community
- ✓ Advisory on key messaging and creative strategy of planned social media campaign and web-site for relevance and acceptability in the Narcolepsy community
- ✓ Editorial on trial specific patient facing materials to be used at site level to match express needs of the Narcoleptic subject

Rest-ON Global Study Specific Recruitment Methods

Social Media Campaign:

- ✓ Link2Trials focused social media campaign service for subject recruitment and retention:
  - ✓ Country specific web-site
  - ✓ Subjects directed to site (*via social media campaign etc.) where interested subjects complete an on-line pre-screen questionnaire*
  - ✓ *Completed questionnaires filtered for suitability*
  - ✓ *Dynamic subject referral. On-line respondents with likely suitability directed to clinical trial site close to where they live*
  - ✓ *Site flagged of potential subject for on-site pre-screen eligibility assessment*

Flamel Specific web-site

- ✓ Link to Flamel site hosted on Narcolepsy Network web-site and other aligned patient group and trial on-line sites
  - ✓ Flamel site will have a link to Link2Trials site to allow "*push*" for dynamic subject referral

What Narcolepsy Patients Want

- Summarizing the results from a patient survey with 1350 responses in preparation for the FDA meeting

- "A drug that would provide consistent and adequate control of the daytime sleepiness without the hard crash and one that would require 1 dose taken at bedtime resulting in 8 hours of restorative sleep"

- Wake Up Narcolepsy Inc. Patient-focused narcolepsy survey: interim analysis. 2013; http://www.unitenarcolepsy.org/wp-content/uploads/Interim-Survey-Analysis-v1.pdf. Accessed May 10, 2015

Potential Advantages for Patients

- Convenience
- No disturbance of sleep for second dose
- Less water intake
- Potential greater efficacy with decreased risk of missing second dose
- Greater safety

Potential Safety Differences

- No unattended doses on night stand (concern with children in house or roommates)
- Not arising during night thereby decreasing risk of fall accidents or amnestic episodes
- Performance including driving at 6 hours post bed time
- Less Suppression of arousal response at peak plasma (Tmax) thus greater safety in sleep apnea and COPD patients. This is an important issue as there is an increased prevalence of sleep apnea in narcolepsy
- Consistency of blood levels from night to night and between patients given variable ingestion times of second dose