



OX2R AGONISTS FOR THE TREATMENT OF NARCOLEPSY TYPE 1

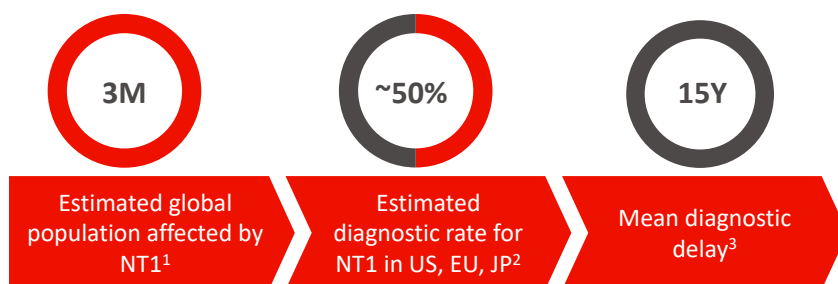


Deborah Hartman, PhD

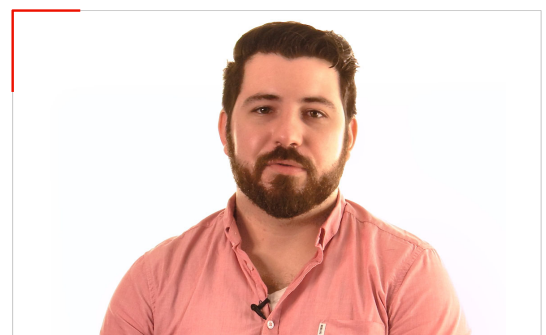
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Better Health, Brighter Future

NARCOLEPSY TYPE 1 IS A RARE, ACQUIRED CHRONIC NEUROLOGICAL DISORDER



- Psychosocially devastating effects
- Current treatments are only partially effective
- Polypharmacy is common



“When I'm awake, sleep is constantly intruding on that part of my life. And when I'm asleep, wakefulness is constantly intruding on that part of my life. It's frustrating because no matter how well you regulate your narcolepsy, you're always tired. You're exhausted.”

- Charlie, adviser with NT1

1. Narcolepsy Network. Narcolepsy Fast Facts. Available at: <https://narcolepsynetwork.org/about-narcolepsy/narcolepsy-fast-facts/>. Last Updated June 2015. Last Accessed Sept. 2019

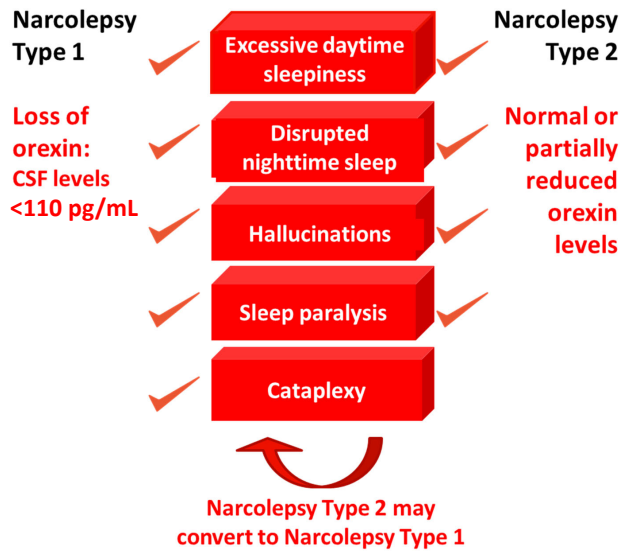
2. Thorpy et al. Sleep Med. 2014 May;15(5):502-7

3. Frauscher B, J Clin Sleep Med 2013;9(8):805-12

NARCOLEPSY TYPE 1 IS DISTINGUISHED BY THE PRESENCE OF CATAPLEXY AND LOW OREXIN LEVELS



“It’s not just about sleep, it’s about quality of wakefulness ... it’s really about partnership with your extended family, your spouse, taking care of your children... it limits my ability to play with my kids.”
-Sara, adviser with NT1



Other hypersomnia disorders

- Idiopathic Hypersomnia
- Residual Excessive Daytime Sleepiness in Obstructive Sleep Apnea¹

CSF: Cerebral spinal fluid; Orexin also referred to as hypocretin

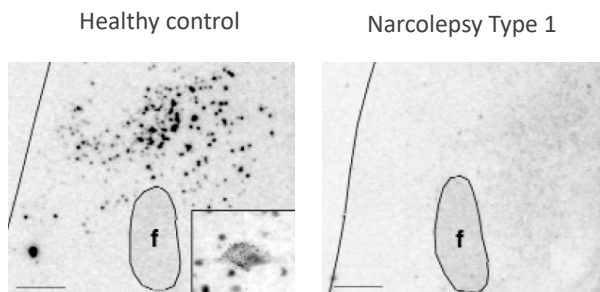
1. Individuals with Obstructive Sleep Apnea who are compliant with use of continuous positive airway pressure at night

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NARCOLEPSY TYPE I IS CAUSED BY PROFOUND LOSS OF OREXIN-PRODUCING NEURONS

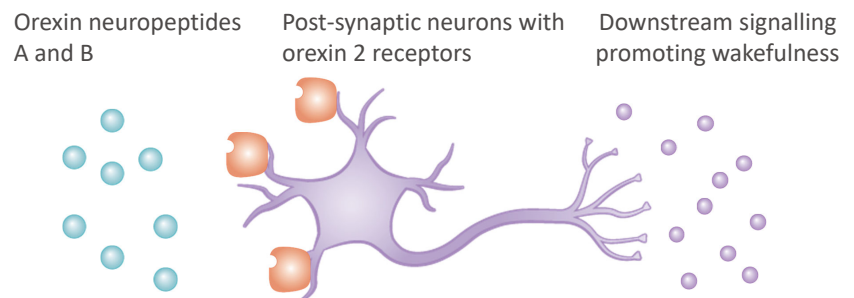


OREXIN mRNA LABELLING OF POSTMORTEM HYPOTHALAMIC SECTIONS



- Individuals with NT1 have >85% less orexin neurons than control, which are located in the hypothalamus^{1, 2}

ACTIVATION OF OREXIN 2 RECEPTOR (OX2R) LEADS TO AROUSAL AND PROMOTES WAKEFULNESS³



THE OREXIN HYPOTHESIS IN NARCOLEPSY TYPE I

An orexin 2 receptor agonist may replace the missing endogenous orexin peptide, addressing the underlying orexin deficiency of Narcolepsy Type 1 and reduce disease specific symptoms

f: fornix

1. Reprinted by permission from Springer Nature. Peyron C, et al. Nat Med. 2000;6:991-997

2. Thannickal TC, et al. Neuron. 2000;27:469-474

3. Tsujino N, et al. Pharmacol. Rev. 2009;61(2):162-176

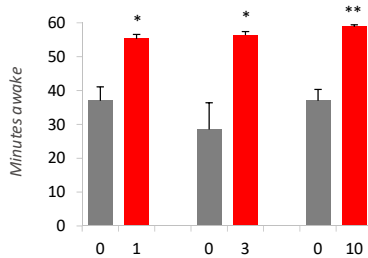
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TAK-925, A SELECTIVE OX2R AGONIST, REDUCES NARCOLEPSY-LIKE SYMPTOMS IN AN OREXIN-DEFICIENT MOUSE MODEL



TAK-925 FULLY RESTORED WAKEFULNESS

Wakefulness time of NT1 mouse model in active phase for one hour

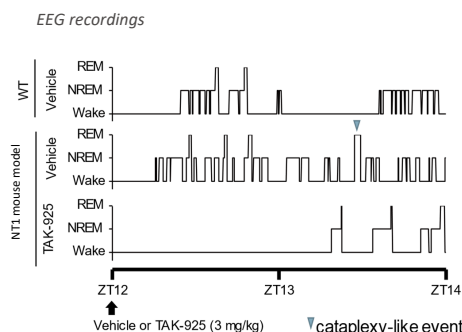


TAK-925 (mg/kg, s.c.)

*p<0.05, **p<0.01 vs placebo

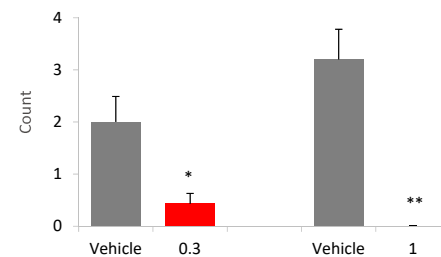
TAK-925 ELIMINATED SLEEP / WAKE TRANSITIONS

Hypnogram of sleep/wake transitions in NT1 mouse model



TAK-925 ABOLISHED CATAPLEXY-LIKE EPISODES

Cataplexy-like episodes in NT1 mouse model for three hours after chocolate



TAK-925 (mg/kg, s.c.)

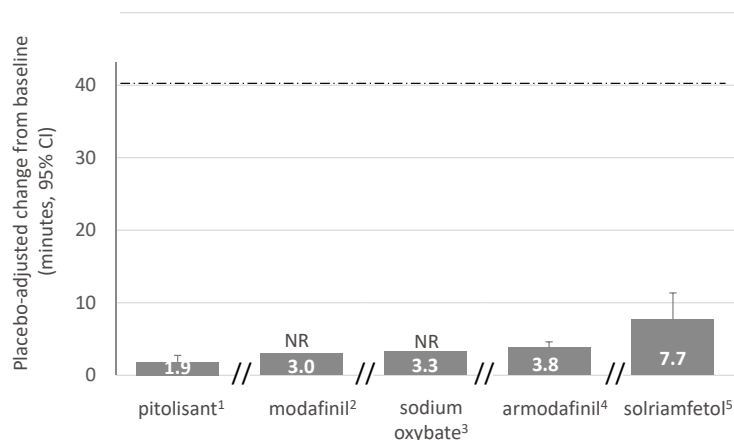
*p<0.05, **p<0.01 vs placebo

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TAK-925 SHOWED PROMISING ABILITY TO MAINTAIN WAKEFULNESS IN AN EARLY PROOF OF CONCEPT STUDY IN NT1 PATIENTS

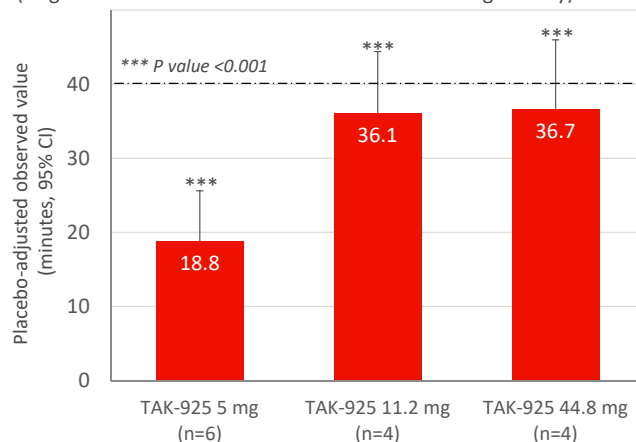


SLEEP LATENCY IN THE MAINTENANCE OF WAKEFULNESS TEST (MWT): CURRENT TREATMENTS



SLEEP LATENCY IN THE MAINTENANCE OF WAKEFULNESS TEST (MWT): TAK-925 (N=14)

(single dose nine hour continuous IV infusion during the day)⁶



- TAK-925 was well-tolerated; most AEs were mild and no SAEs were observed
- In this TAK-925-1001 study, four 40 minute MWTs were conducted per period
- Direct cross-study comparison can not be made between TAK-925 and treatments due to different studies with different designs

NR: 95% CI not reported

1. Lancet Neurol. 2017 Mar;16(3):200-207; 2. FDA statistical Review: Page 5, 200 mg; 3. Label/Trial N4; 4. Clinicaltrials.gov (NCT00078377); 5. FDA Statistical Review, Study 14-002, 150 mg

6. Evans R, Tanaka S, Tanaka S, et al. 2019. A phase 1 single ascending dose study of a novel orexin 2 receptor agonist, TAK-925, in healthy volunteers (HV) and subjects with narcolepsy type 1 (NT1) to assess safety, tolerability, pharmacokinetics, and pharmacodynamic outcomes. Abstract presented at World Sleep 2019. Vancouver, Canada. <http://www.professionalabstracts.com/ws2019/iPlanner/#/presentation/1832>

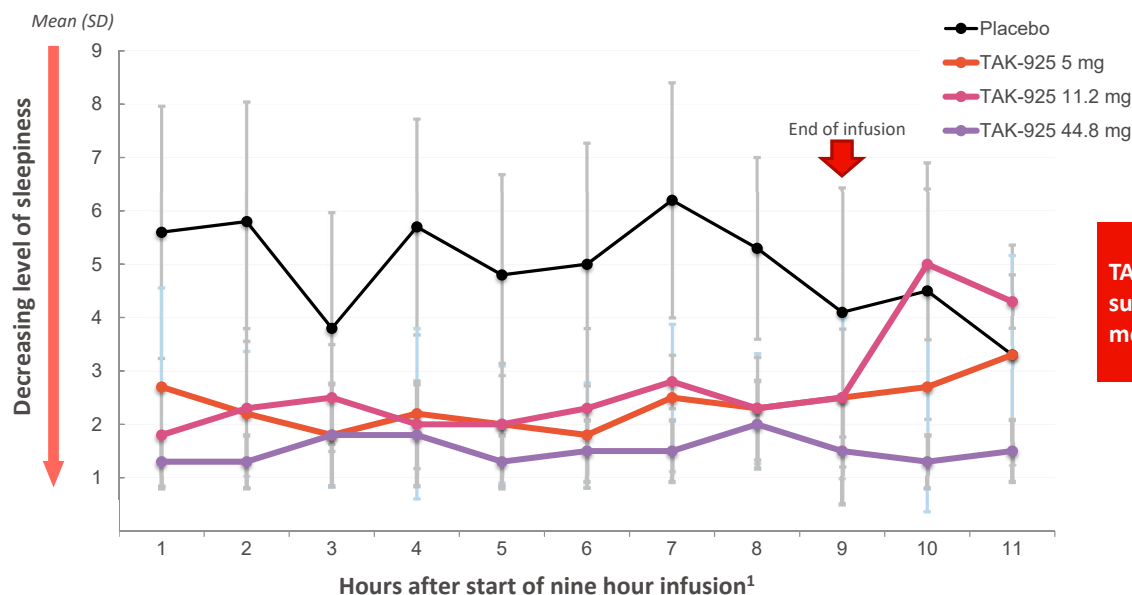
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TAK-925 ALSO REDUCED SUBJECTIVE SLEEPINESS IN THIS EARLY PROOF OF CONCEPT STUDY IN NT1



KAROLINSKA SLEEPINESS SCALE VALUES DURING AND AFTER ADMINISTRATION OF TAK-925

(single dose nine hour continuous IV infusion during the day)



TAK-925 improved subjective and objective measures of wakefulness

1. TAK-925 effective plasma half-life <2 hours

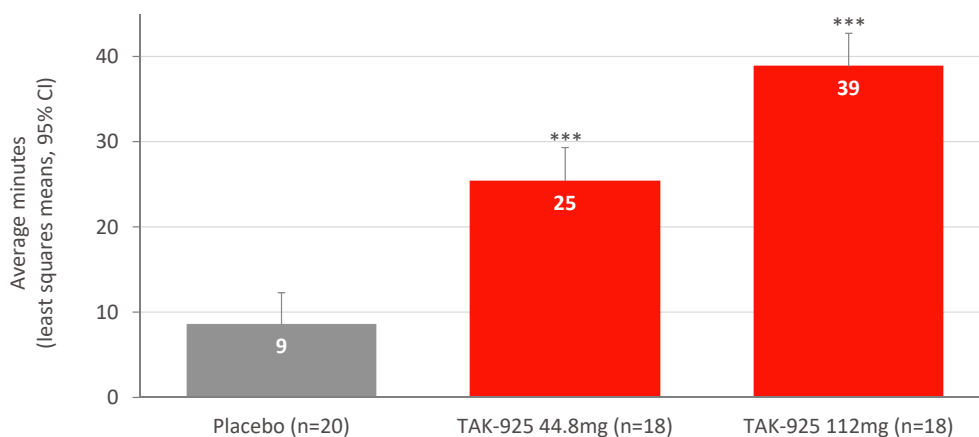
Evans R, Tanaka S, Tanaka S, et al. 2019. A phase 1 single ascending dose study of a novel orexin 2 receptor agonist, TAK-925, in healthy volunteers (HV) and subjects with narcolepsy type 1 (NT1) to assess safety, tolerability, pharmacokinetics, and pharmacodynamic outcomes. Abstract presented at World Sleep 2019. Vancouver, Canada. <http://www.professionalabstracts.com/ws2019/iPlanner/#/presentation/1832>

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TAK-925 MAINTAINED WAKEFULNESS IN SLEEP-DEPRIVED HEALTHY ADULTS IN A SECOND PHASE 1 STUDY



SLEEP LATENCY IN THE MAINTENANCE OF WAKEFULNESS TEST (MWT) IN SLEEP-DEPRIVED HEALTHY ADULTS¹



Results suggest potential therapeutic use of TAK-925 in other hypersomnia disorders not associated with orexin deficiency

TAK-925 was well-tolerated; most AEs were mild and no SAEs were observed

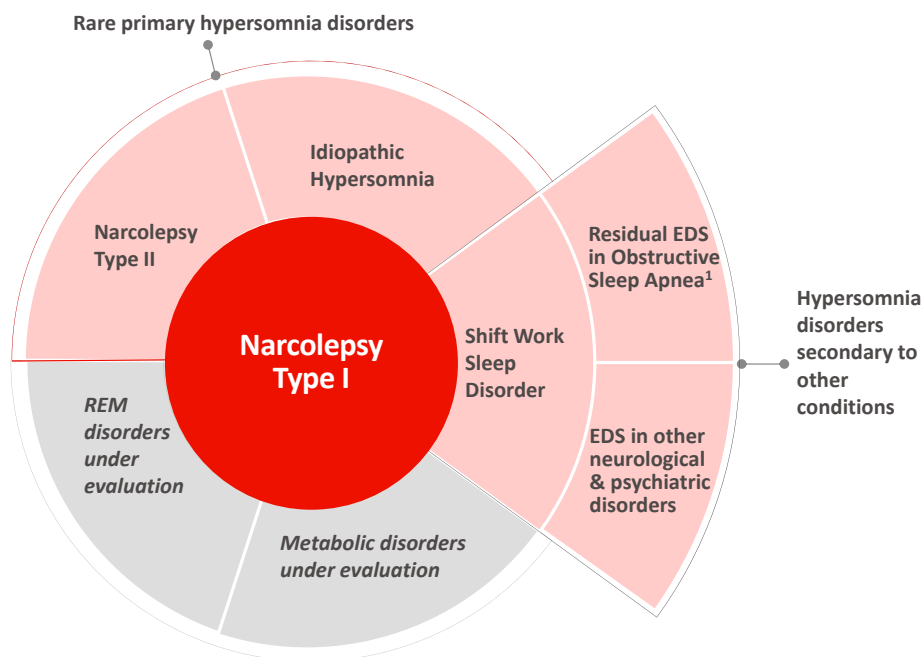
1. Evans R, Hazel J, Faessel H, et al. 2019. Results of a phase 1b, 4-period crossover, placebo-controlled, randomized, single dose study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of TAK-925, a novel orexin 2 agonist, in sleep-deprived healthy adults, utilizing modafinil as an active comparator. Abstract presented at World Sleep 2019. Vancouver, Canada. <http://www.professionalabstracts.com/ws2019/iPlanner/#/presentation/2821>

2. Int J Neurosci. 1990 May;52(1-2):29-37

***: p-value <0.001 relative to placebo

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WE ARE COMMITTED TO LEADING INNOVATION IN OREXIN BIOLOGY AND EXPANDING THERAPEUTIC INDICATIONS FOR OX2R AGONISTS



- **TAK-925-1003** for Narcolepsy Type 2 (NCT03748979)
- **SPARKLE 2001** study for Residual EDS in Obstructive Sleep Apnea (NCT04091425)
- **SPARKLE 2002** study for Idiopathic Hypersomnia (NCT04091438)

REM: Rapid eye movement

1. Individuals with Obstructive Sleep Apnea who are compliant with use of continuous positive airway pressure at night

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TAK-994 IS AN ORAL OX2R AGONIST PROGRESSING TO STUDIES IN NARCOLEPSY TYPE 1



TAK-994-1501 PROOF OF CONCEPT STUDY IN NARCOLEPSY TYPE 1



SPARKLE
OREXIN INNOVATION

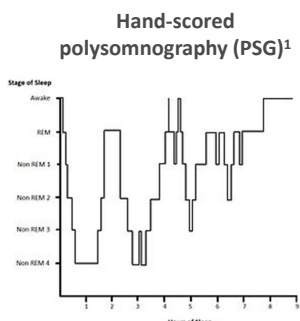
- Multi-center, placebo-controlled trial in North America and Japan
- Enrollment target: 72 adults
- Duration of treatment: 28 days dosing
- Exploratory outcome measures include Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS), and Weekly Cataplexy Rate (WCR)

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DIGITAL TECHNOLOGIES ARE ENHANCING THE DEVELOPMENT OF OX2R AGONISTS FOR SLEEP DISORDERS



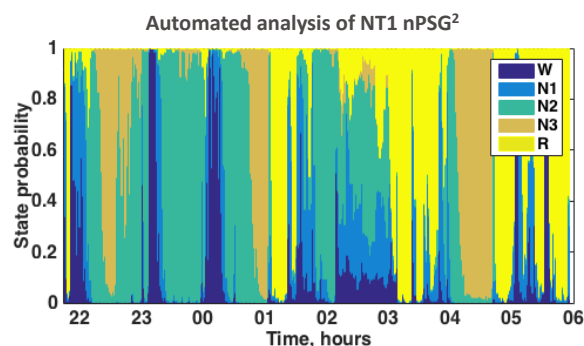
TRADITIONAL CLINICAL INSTRUMENTS DO NOT FULLY MEASURE SYMPTOMS OF SLEEP DISORDERS



PATIENT ACTIVITY DIARY
for Holter Electrocardiogram

Patient name	Recorder #
Hook-up date	Age
Start time	AM/PM
End time	AM/PM
Patient ID	Sex
Physician	Phone #
Facility	
Indications	
Medications	
Pacemaker	Type
Hook-up Technician	

DIGITAL MEASURES WILL FURTHER CHARACTERIZE SLEEP ARCHITECTURE AND SUPPORT CLINICAL TRIAL ASSESSMENTS



- Real-time data capture to understand disease burden and effects of treatment
- Non-invasive measures to optimize therapy
- Patient stratification using digital fingerprints

nPSG – Night time polysomnography

1. Approximately 80% interrater concordance based on Danker-Hopfe et al., J Sleep Res (2009) and Younes & Hanly, J Clin Sleep Med (2016); 2. Analysis shown is based on Stephansen et al., Nature Comm (2018)

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WE ASPIRE TO BRING A POTENTIALLY TRANSFORMATIVE OX2R AGONIST SOLUTION TO INDIVIDUALS WITH NARCOLEPSY TYPE 1



TAK-925

- Achieved early Proof of Concept for NT1
- Awarded Breakthrough Therapy Designation
- Awarded Sakigake Designation
- Launched formulation development activities

TAK-994

TAK-994, first oral OX2R agonist, entered phase I

Initiate SPARKLE-1501 Proof of Concept study in NT1

Initiation of NT1 pivotal studies
First approval targeted for 2024

FY19

FY20

FY21

Thank you to all the study participants who have enrolled in these early OX2R agonist clinical trials

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1

TAK-925 has achieved early Proof-of-Concept for OX2R agonists in Narcolepsy Type 1

2

TAK-925 has demonstrated potential of OX2R agonists for treatment of other sleep-related disorders

3

TAK-994 is an oral OX2R agonist progressing to studies in Narcolepsy Type 1