OX2R AGONISTS FOR THE TREATMENT OF NARCOLEPSY TYPE 1

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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

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

Individuals with NT1 have >85% less orexin neurons than control, which are located in the hypothalamus.  

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.

EXTENDED FAMILY
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 Apnea

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

OREXIN mRNA LABELLING OF POSTMORTEM HYPOTHALAMIC SECTIONS

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

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.
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 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 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)

• 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
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)

End of infusion

- Placebo
- TAK-925 5 mg
- TAK-925 11.2 mg
- TAK-925 44.8 mg

TAK-925 improved subjective and objective measures of wakefulness

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


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 ADULTS)

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


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)

**Idiopathic Hypersomnia**

**Narcolepsy Type II**

**Residual EDS in Obstructive Sleep Apnea**

**REM disorders under evaluation**

**EdS in other neurological & psychiatric disorders**

**Shift Work Sleep Disorder**

**Metabolic disorders under evaluation**

**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**

- 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)

Proof of Concept trial: ClinicalTrials.gov identifier: NCT04095660
DIGITAL TECHNOLOGIES ARE ENHANCING THE DEVELOPMENT OF OX2R AGONISTS FOR SLEEP DISORDERS

TRADITIONAL CLINICAL INSTRUMENTS DO NOT FULLY MEASURE SYMPTOMS OF SLEEP DISORDERS

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

Hand-scored polysomnography (PSG)¹

PATIENT ACTIVITY DIARY
for Holter Electrocardiogram

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

Automated analysis of NT1 nPSG²

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)

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, first oral OX2R agonist, entered phase I

TAK-994

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
SUMMARY

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