OX2R AGONISTS FOR THE TREATMENT OF NARCOLEPSY TYPE 1

Deborah Hartman, PhD
Global Program Leader, Neuroscience
Takeda Pharmaceutical Company Limited
New York, NY
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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

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

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

NARCOLEPSY TYPE 1 IS CAUSED BY PROFOUND LOSS OF OREXIN-PRODUCING NEURONS

OREXIN mRNA LABELLING OF POSTMORTEM HYPOTHALAMIC SECTIONS

Healthy control Narcolepsy Type 1

- Individuals with NT1 have >85% less orexin neurons than control, which are located in the hypothalamus1, 2

THE OREXIN HYPOTHESIS IN NARCOLEPSY TYPE 1

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

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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**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Placebo-adjusted change from baseline (minutes, 95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Pitolisant¹</td>
<td>NR 3.0</td>
</tr>
<tr>
<td>Modafinil²</td>
<td>NR 3.3</td>
</tr>
<tr>
<td>Sodium Oxybate³</td>
<td>3.3</td>
</tr>
<tr>
<td>Armodafinil⁴</td>
<td>3.8</td>
</tr>
<tr>
<td>Solriamfetol⁵</td>
<td>7.7</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Dose (mg)</th>
<th>Placebo-adjusted observed value (minutes, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>18.8</td>
</tr>
<tr>
<td>11.2</td>
<td>36.1</td>
</tr>
<tr>
<td>44.8</td>
<td>36.7</td>
</tr>
</tbody>
</table>

* 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

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NR: 95% CI not reported

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

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

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

![Graph showing sleepiness scale values](image)

TAK-925 improved subjective and objective measures of wakefulness

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


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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 ADULTS

![Graph showing sleep latency](image)

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

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

Top priority
Other hypersomnia disorders
Additional opportunities for expansion

REM: Rapid eye movement

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

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: NCT04096560
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

- 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


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, 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

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

R&D DAY AGENDA – NEW YORK, NOVEMBER 14, 2019

<table>
<thead>
<tr>
<th>TIME</th>
<th>AGENDA</th>
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<tbody>
<tr>
<td>12:30 – 12:35</td>
<td>Welcome and Opening Remarks</td>
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<tr>
<td></td>
<td>Sheelagh Cowley-Knopf, Head R&amp;D Global Portfolio Strategy</td>
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<tr>
<td>12:35 – 12:45</td>
<td>Takeda: A Global Values-Based, R&amp;D-Driven Biopharmaceutical Leader</td>
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<td>Christophe Weber, President &amp; CEO Takeda</td>
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<td>12:45 – 13:20</td>
<td>Translating Science into Highly Innovative, Life-changing Medicines</td>
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<td></td>
<td>Andy Plump, President R&amp;D</td>
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<td>13:20 – 13:45</td>
<td>Oncology and Cell Therapies with Spotlight on CAR-NK</td>
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<tr>
<td></td>
<td>Chris Arendt, Head Oncology Drug Discovery Unit</td>
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<td>13:45 – 14:05</td>
<td>Spotlight on Oncology Opportunities</td>
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<td></td>
<td>• TAK-788 : Rachael Brake, Global Program Lead</td>
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<td></td>
<td>• Pevonedistat : Phil Rowlands, Head Oncology Therapeutic Area Unit</td>
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<td>14:05 – 14:20</td>
<td>Break</td>
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<tr>
<td>14:20 – 14:45</td>
<td>Rare Diseases &amp; Gene Therapy</td>
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<td></td>
<td>Dan Curran, Head Rare Disease Therapeutic Area Unit</td>
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<tr>
<td>14:45 – 15:00</td>
<td>Spotlight on Orexin2R agonists</td>
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<td>Deborah Hartman, Global Program Lead</td>
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<tr>
<td>15:00 – 15:20</td>
<td>Therapeutic Area Focus in GI with Spotlight on Celiac Disease</td>
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<td></td>
<td>Asit Parikh, Head GI Therapeutic Area Unit</td>
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<td>15:20 – 16:00</td>
<td>Panel Q&amp;A Session</td>
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<tr>
<td>16:00</td>
<td>Drinks reception</td>
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