

Industry perspectives on sleep disturbances in CNS disorders- a window through narcolepsy

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DISCLOSURES/DISCLAIMERS

- Presenter is an employee of Takeda Pharmaceutical Company Ltd. (Takeda)
- Takeda is the sponsor of preclinical studies and clinical trials of TAK-925 (Danavorexton) mentioned within this presentation - TAK-925 was used to illustrate proof of concept as it is the only OX2R agonist with published clinical results
- The views expressed in this presentation are the presenter's and do not necessarily represent the views of Takeda

2023 BREAKTHROUGH PRIZE

Discovering the cause of narcolepsy and orexin system in sleep/wake

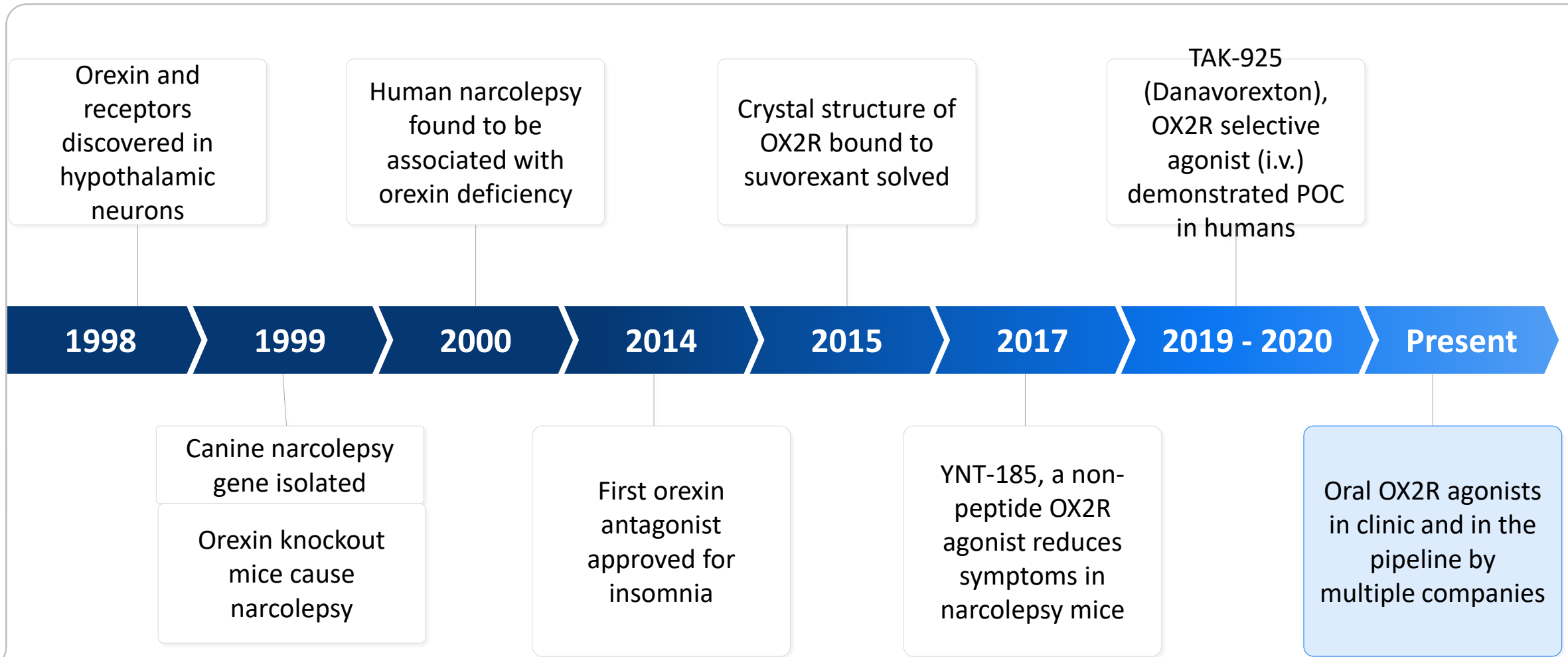


Masashi Yanagisawa



Emmanuel Mignot

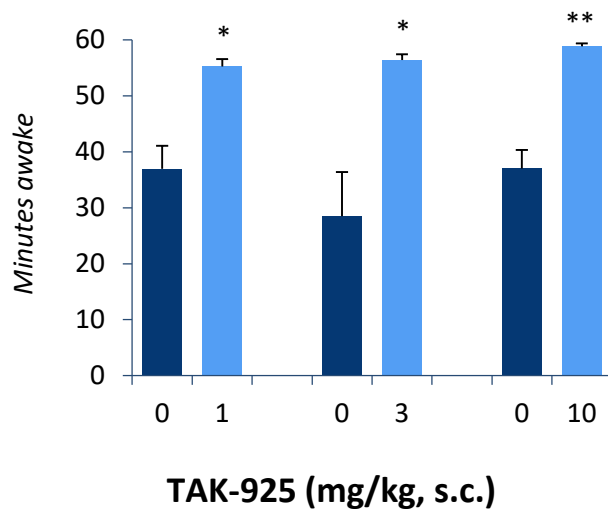
DEVELOPMENT OF OREXIN RECEPTOR AGONIST TAKES TIME AND PERSEVERANCE



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

TAK-925 FULLY RESTORED WAKEFULNESS

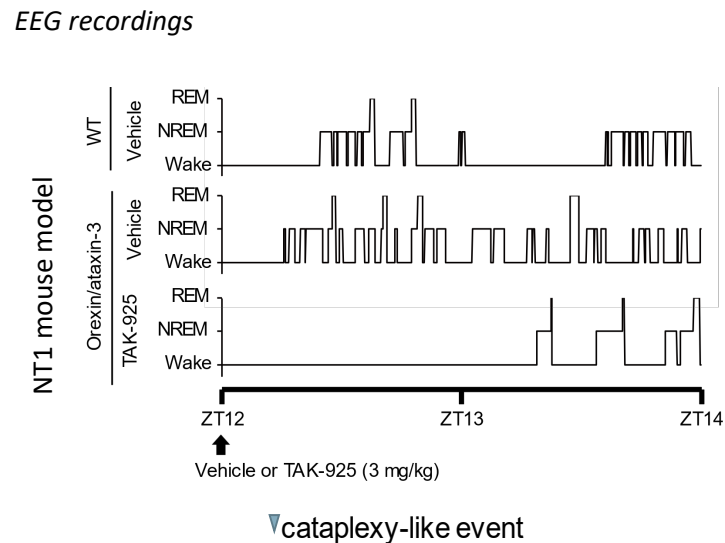
Wakefulness time of NT1 mouse model in active phase for one hour



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

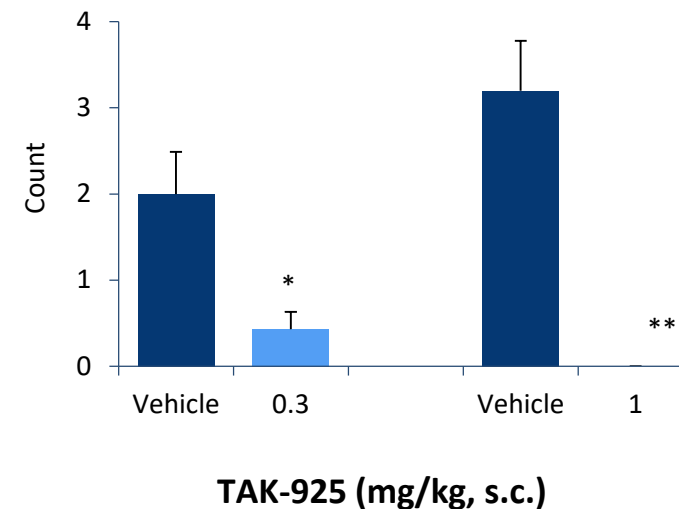
TAK-925 ELIMINATED SLEEP/WAKE TRANSITIONS

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



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

OBJECTIVE AND SUBJECTIVE EFFICACY ENDPOINTS IN NARCOLEPSY TRIALS



Maintenance of Wakefulness Test (MWT)

- Subjects sit in bed in dim light, **instructed to try to stay awake** up to 40 minutes
- 4 times every 2h during the day
- Endpoints: mean latency to fall asleep



Epworth Sleepiness Scale (ESS)

- Subjective, self report scale of likelihood to doze off in various circumstances
- Scoring: Normal (0-10); mild (11-14); moderate (15-17); severe (18-24)

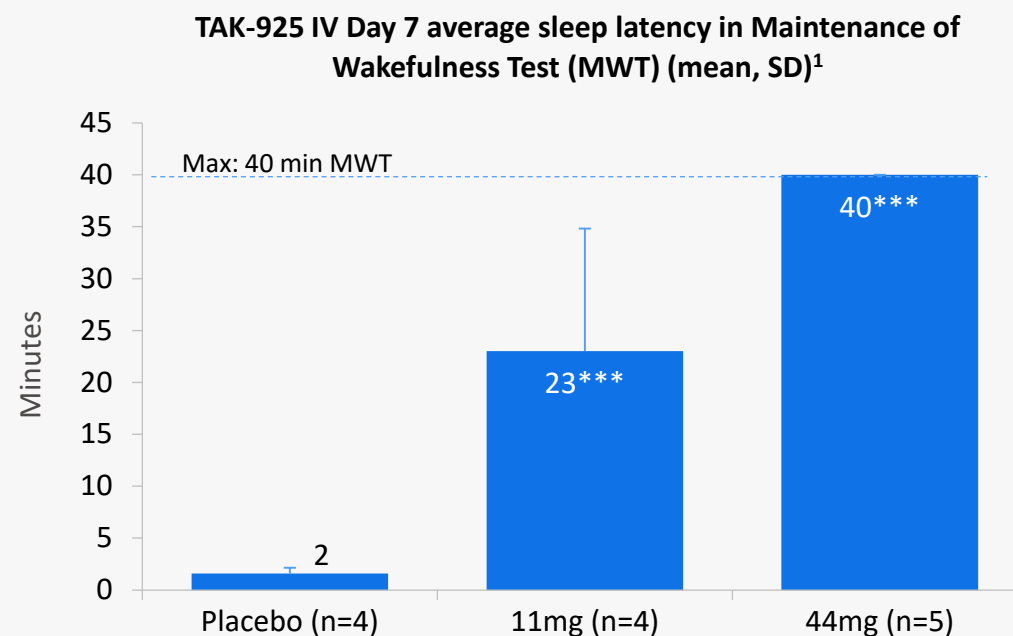
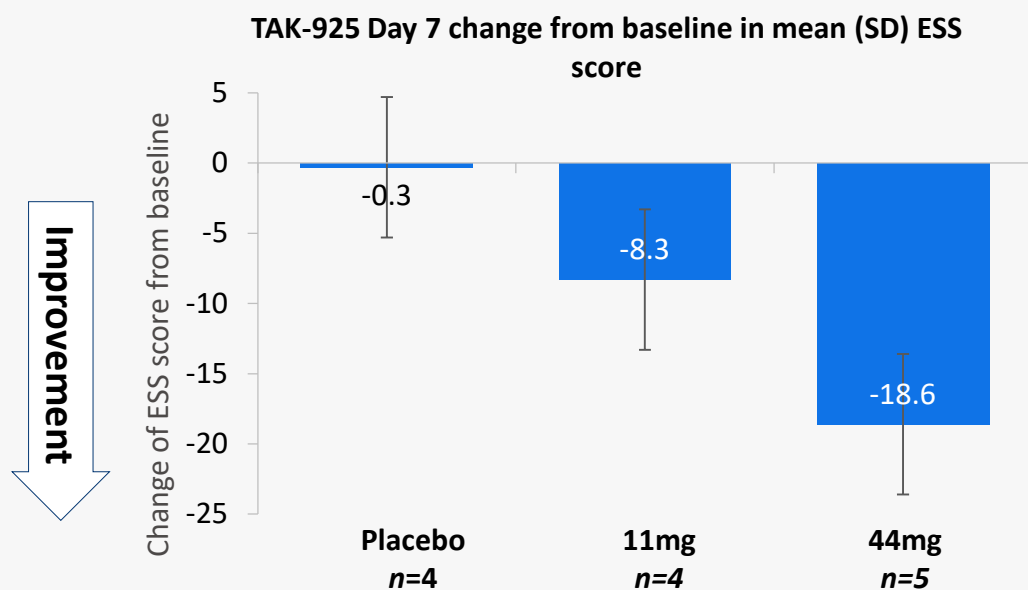


Weekly Cataplexy Rate (WCR) for Narcolepsy Type 1

- Self report of number of episodes of cataplexy per week

TAK-925, A SELECTIVE OX2R AGONIST, IV FORMULATION IMPROVED SUBJECTIVE SLEEPINESS AND SLEEP LANTENCY IN OBJECTIVE MAINTENANCE OF WAKEFULNESS TEST

7-day dosing with 9 h infusion daily in NT1 patients



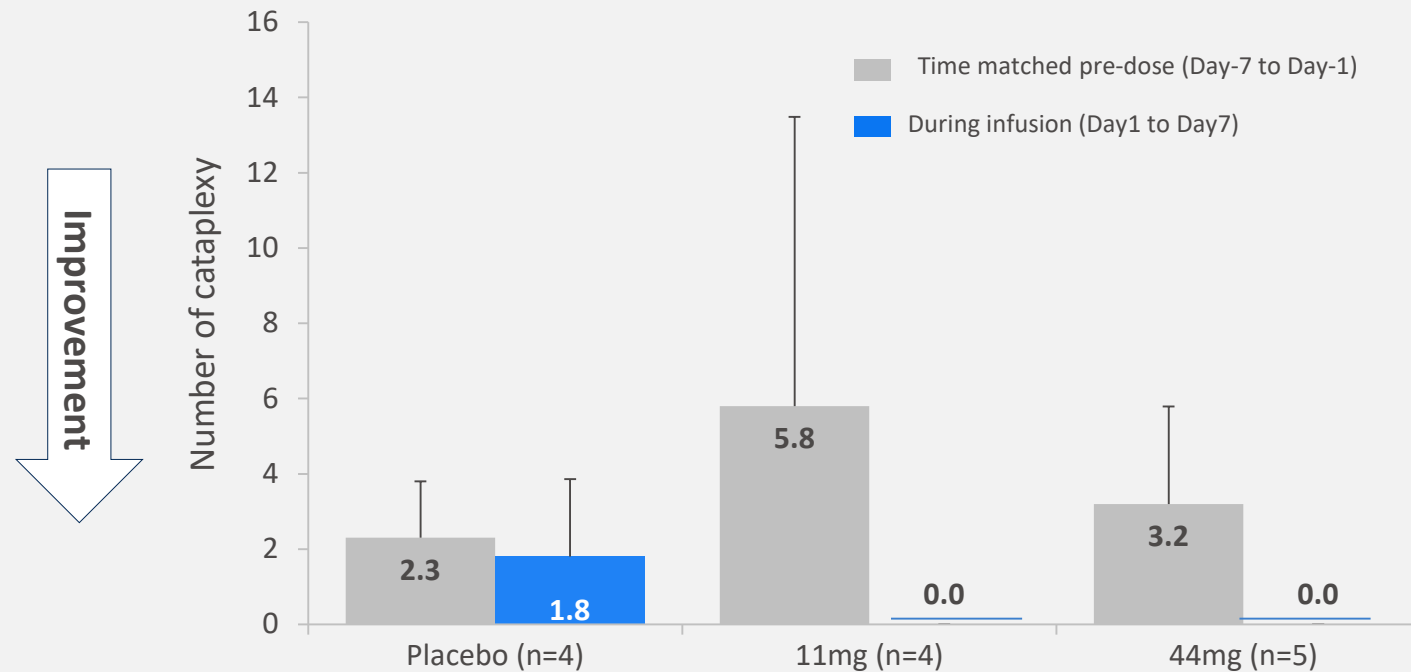
Adapted from Evans R, et al. *Proc Natl Acad Sci U S A*. 2022;119(35):e2207531119. Creative Commons Attribution License (CC BY 4.0) <https://www.pnas.org/doi/epdf/10.1073/pnas.2207531119>

1. Observed mean and standard deviation shown. ***: p-value <0.001 comparing to placebo for MWT

TAK-925 (DANAVOREXTON) ALSO REDUCED WEEKLY CATAPLEXY RATE

7-day dosing with 9h daily infusions in NT1 patients

TAK-925 average number of cataplexy attacks
during 7 day period (mean, SD)



Observed mean and standard deviation shown. No statistical comparison to placebo was done for cataplexy

Adapted from Evans R, et al. *Proc Natl Acad Sci U S A.* 2022;119(35):e2207531119. Creative Commons Attribution License (CC BY 4.0) <https://www.pnas.org/doi/epdf/10.1073/pnas.2207531119>

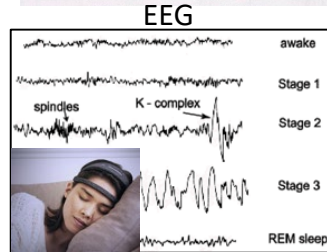
GAPS AND IMPORTANT GOALS IN UNDERSTANDING AND MEASURING EXCESSIVE DAYTIME SLEEPINESS AND IMPACT

Measures of EDS and impact

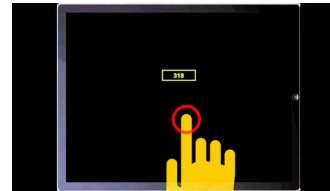
- Objective: MWT (artificial test not used in clinical practice, burdensome to pts)
- Subjective: ESS (need international consensus)
- Other subjective and objective measures in the clinic or at home?

PATIENT ACTIVITY DIARY
for Holter Electrocardiogram

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



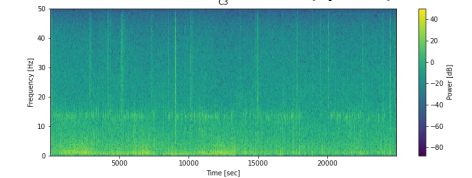
Sustained attention performance test



Real-world data



Quantitative EEG (qEEG)



NextSense Earbud EEG



Important goals

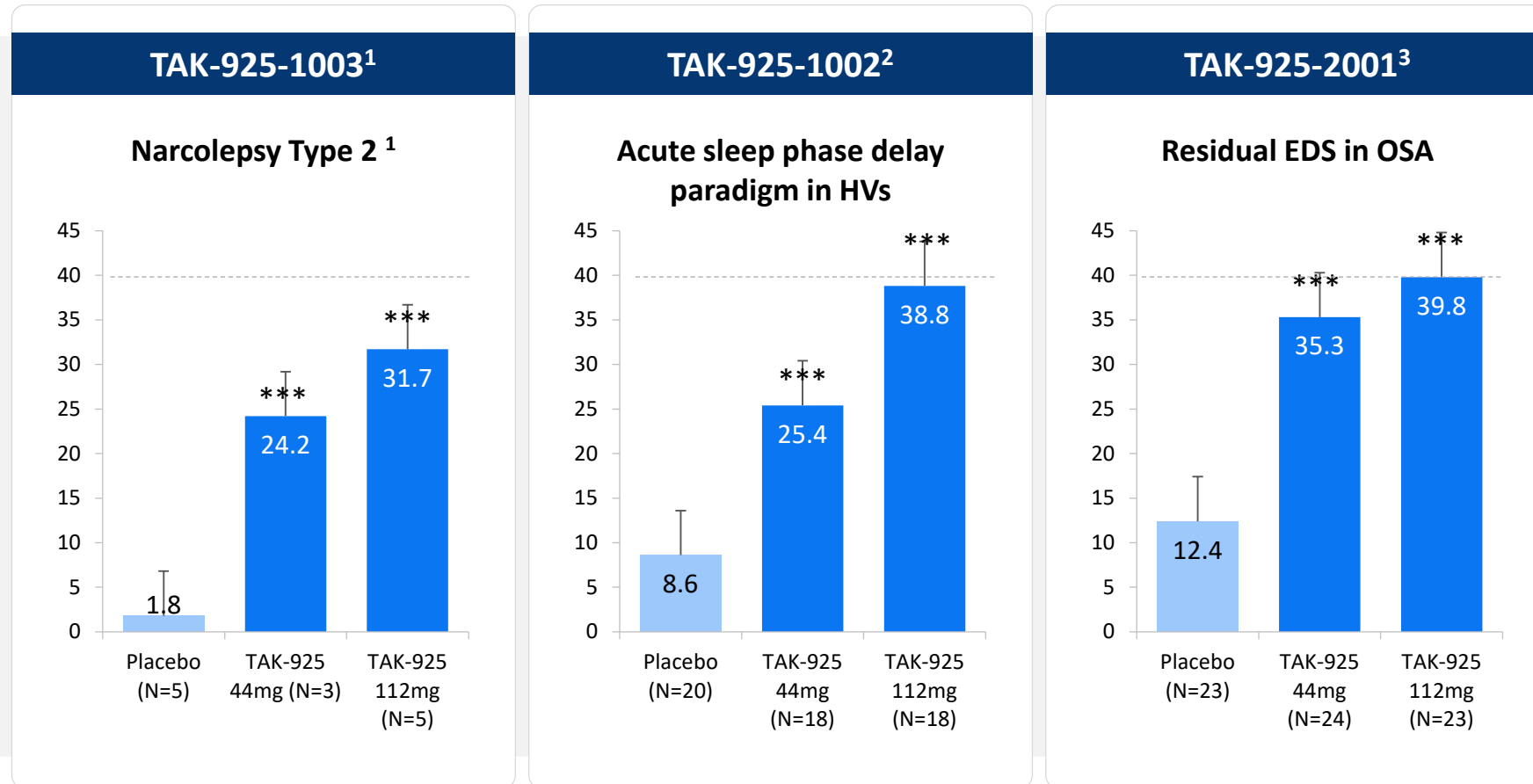
- Develop robust patient relevant measures of sleepiness and quality of wakefulness
 - Validate at home digital measures
 - Measure longitudinally sleep/wake in real world (once validated)
- Understand the relationship between excessive daytime sleepiness and night-time sleep and other factors
- **Select** best measures that are meaningful to patients, robust, least burdensome, equitable for patient access, with international consensus

SUMMARY

- Breakthrough science in orexin system to treatment impacts
- Drug development takes time and perseverance
- OX2R agonist TAK-925 demonstrated POC in the clinic
- Improvement in understanding and measuring daytime sleepiness and impact needed
- Insights relevant for other sleep disturbances in CNS disorders
 - Understand root cause of the sleep disturbance, which may be unique to each disease
 - Determine what the assessments are needed for each disease (unique measures and measures shared across disease)

Backup slide

TAK-925 (DANAVOREXTON) INCREASED SLEEP LATENCY IN MWT IN OREXIN-NORMAL POPULATIONS



Efficacy Endpoint: Mean Sleep onset latency (min) and 95% CI

MWT sleep latency: LS mean (95% CI) sleep onset latency in minutes except for NT2 which is change from baseline at Day 1

***: p-value <0.0001

1. Tanaka S., European Sleep Research Society 2020 Virtual Congress, September 22-24, 2020
2. Evans R., WORLD SLEEP, Vancouver, Canada, September 20-25, 2019
3. Rubens R. American Academy of Neurology (AAN) Annual Meeting April 17-22, 2021