TAK-861 (Lead Oral OX2R Agonist)

Investor Call on Phase 2b NT1 Data Presented at SLEEP 2024

June 3rd, 2024 ET / June 4th, 2024 JST

Better Health, Brighter Future

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Agenda

Today's Topics

Orexin Franchise Overview

Elena Koundourakis
Head of Orexin Franchise Development, Neuroscience TA

Efficacy and Safety Results from the Ph2b Trial of TAK-861 in NT1 Patients

Christian von Hehn
Executive Medical Director, Clinical Science, Neuroscience TA

Q&A Session

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Erika Gill
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TAK-861 has the potential to establish a new standard of care for patients with NT1 – Setting the foundation for Takeda leadership in the orexin field

TAK-861:
First & Fast in NT1

- **First** potential orexin agonist launch — **addressing Orexin deficiency as the underlying pathophysiology in NT1***
- Potential **best-in-class** profile addressing the **entire spectrum of symptoms in NT1**

TAK-360:
Fast following in NT2 & IH

- New chemistry and profile **for Orexin non-deficient indications**
- **Fast track designation received**
- HV study ongoing since April 2024

Additional assets/ indications

- **TAK 925 IV:** Ph2 post-anesthesia recovery in OSA patients**
- Additional differentiated assets in preclinical stage
- Exploration of additional indications based on emerging data

*Dauvilliers, Y., N Engl J Med, 2023; **Suzuki M et al., British Journal of Anaesthesia, 2024; IARS Conference, Denver, 2023; HV: Healthy Volunteer

TAK-861 has the potential to address patient needs across the multiple symptoms of NT1

Current treatments fail to address totality of burden with only partial improvements

>80% of patients **still experience residual symptoms**[1]

Many patients on treatment still take **daytime naps, restrict driving, change school & work plans, avoid strong emotions**[1]

Nearly 60% of diagnosed NT1 patients are on more than one medication to treat their narcolepsy[2]

…Leaving Narcolepsy patients telling us they desire more

- **Sustained Daytime Wakefulness**
- **Functional Improvements**
- **Improved Cognition/ Less "Brain-fog"**
- **Quality of Life**

~120K[3] patients in the US and **~680K[3]** patients globally suffer from NT1

1. [Data on file] Burden of Illness Study among Patients with Central Disorders of Hypersomnolence in Europe; 2. Abioye, I. et al., Sleep Medicine, 2022 100. S152-S153.; 3. *Silber MH et al. Sleep 2002;25:197–202; Heier , M., et al., Acta Neurologica Scandinavica , 2009. 120(4); Hublin , C., et al, Annals of neurology, 1994. 35(6); Wing YK et al. Ann Neurol 2002;51:578–84*

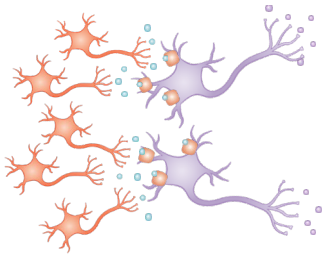
Narcolepsy Type 1 symptoms are a result of loss of orexin neurons

Hallmark NT1 Symptoms

- Excessive Daytime Sleepiness
- Cataplexy
- Disrupted Nighttime Sleep
- Hypnagogic/hypnopompic Hallucinations
- Sleep Paralysis

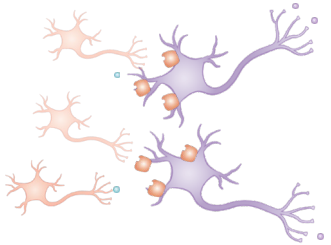
1 Healthy Individual

Healthy orexin neurons with normal postsynaptic downstream neurotransmitter activity



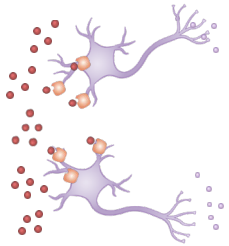
2 Individual with Narcolepsy type 1

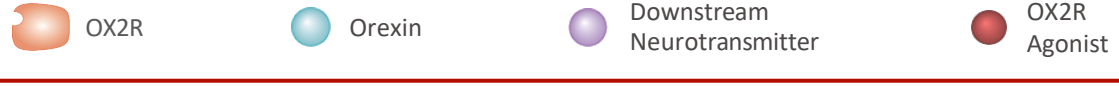
Reduced availability of orexin as orexin neurons are lost reducing downstream neurotransmitter activity



3 Highly Specific OX2R Agonist

Ox2R agonist may **restore downstream neurotransmitter activity** lost when endogenous orexin levels decline





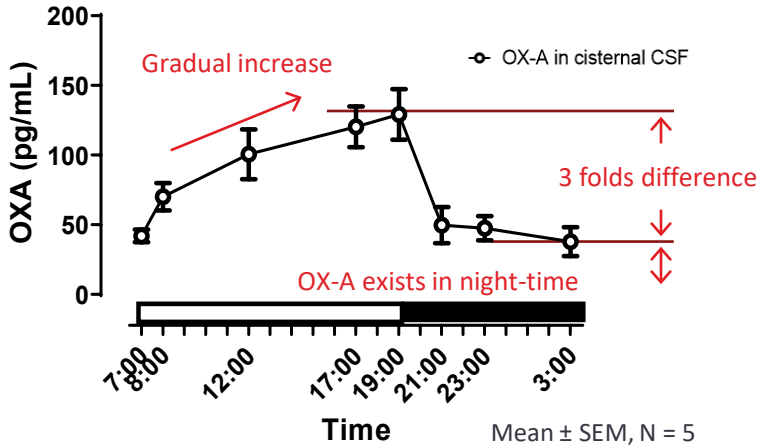
Mahoney CE, et al. *Nat Rev Neurosci.* 2019;20(2):83-93; Chastain EM, et al. *Biochim Biophys Acta.* 2011;1812:265–274; Nishino S. *Sleep Med.* 2007;8(4):373-399; Saper CB, et al. *Trends Neurosci.* 2001;24(12):726-731; Yoshida Y, et al. *Eur J Neurosci.* 2001;14(7):1075-1081; Dauvilliers, Y., N Engl J Med, 2023; 389, 309-321

Optimized dosing regimen is critical to deliver transformative efficacy while minimizing on/off target Adverse Events

Takeda's strategy for achieving efficacy while avoiding unnecessary excessive arousal

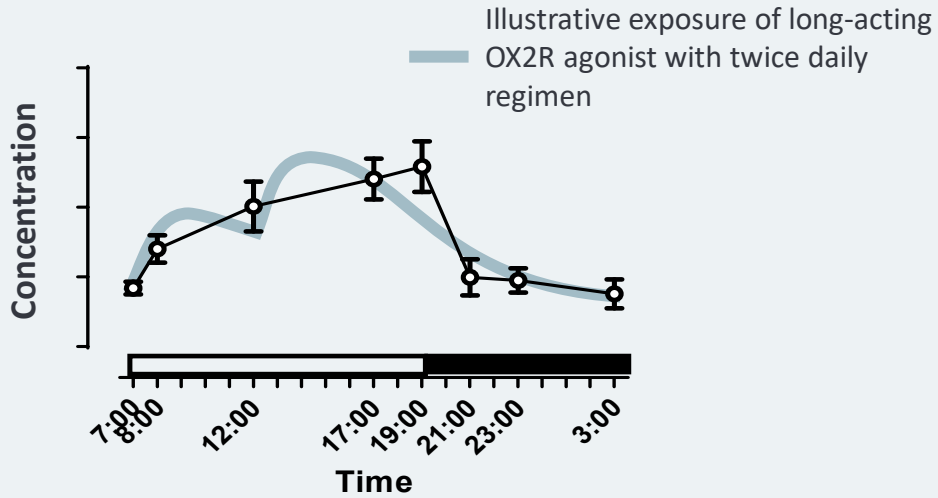
Diurnal fluctuation of Orexin levels in monkey CSF

Takeda's novel method enabled accurate measurement of OX-A*



- OX-A gradually increases in day-time
- OX-A exists even during night-time
- The ratio between maximum and minimum OX-A level is around 3-fold
- Reliable model to predict human PK

Long-acting orexin receptor 2 (OX2R) agonist



- Long-acting orexin 2 receptor agonist with twice daily mimic diurnal orexin fluctuation
- Long half life maintains sufficient exposure during the day
- Exposure levels are reduced at night mimicking the orexin tone

*Narita et al., ACS Chem Neurosci, 2023

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Study Design

Objective: To assess the efficacy, safety, and tolerability of four oral dose regimens of TAK-861 in participants with NT1 in an 8-week, randomized, double-blind, placebo-controlled multicenter study

Randomization 1:1:1:1:1

NT1 patients previously withdrawn from stimulant and anti-cataplectic medication

Ph2b Study 2001
8-week treatment period

- Placebo
- TAK-861 0.5 mg twice daily ~3 hours apart
- TAK-861 2 mg twice daily ~3 hours apart
- TAK-861 2 mg followed by 5 mg ~3 hours apart
- TAK-861 7 mg once daily

Long-Term Extension Study 2003[a]
Treatment to continue until approval

Optional Enrollment in LTE[b]

- 95% of participants that completed the study enrolled in the LTE
- Majority of patients remain in the LTE with some patients reaching 1 year of treatment

[a] Data to be presented at future congress.
[b] After Week 8 visit of 2001, participants will have the option to participate in an LTE study under a separate protocol.

Endpoints

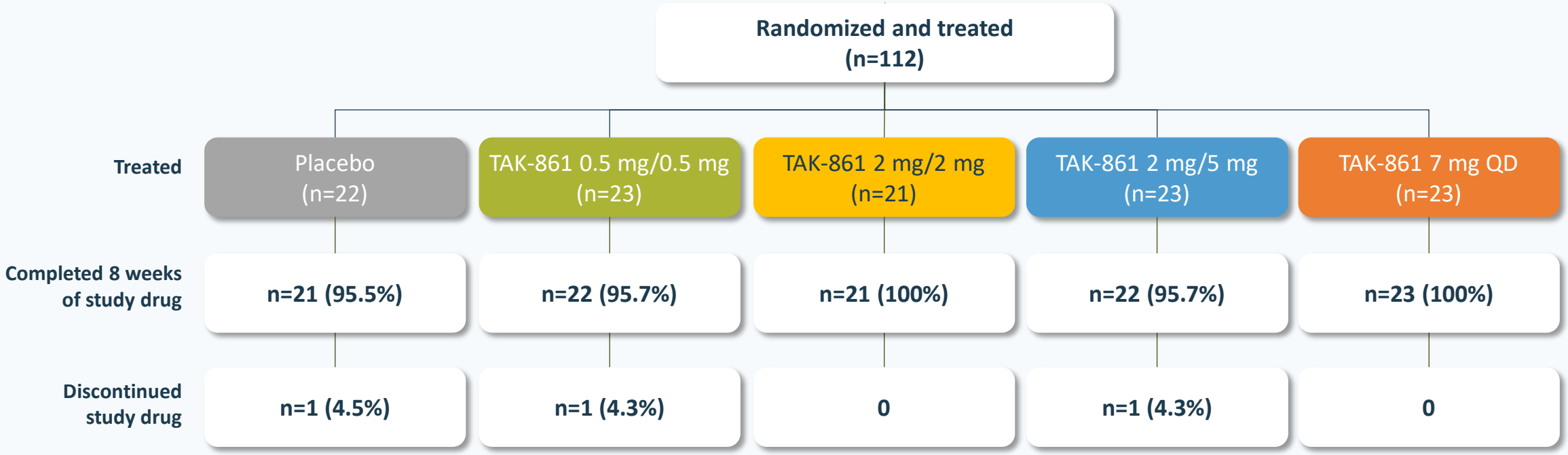
Primary Endpoint

- Change from baseline to Week 8 in mean sleep latency on the **Maintenance of Wakefulness Test (MWT)**

Secondary Endpoints

- Change from baseline to Week 8 in **Epworth Sleepiness Scale (ESS)** total score
- **Weekly cataplexy rate (WCR)** at Week 8
- Frequency of **treatment emergent adverse events (TEAEs)**

Over the 8-week study period no participants discontinued due to adverse events

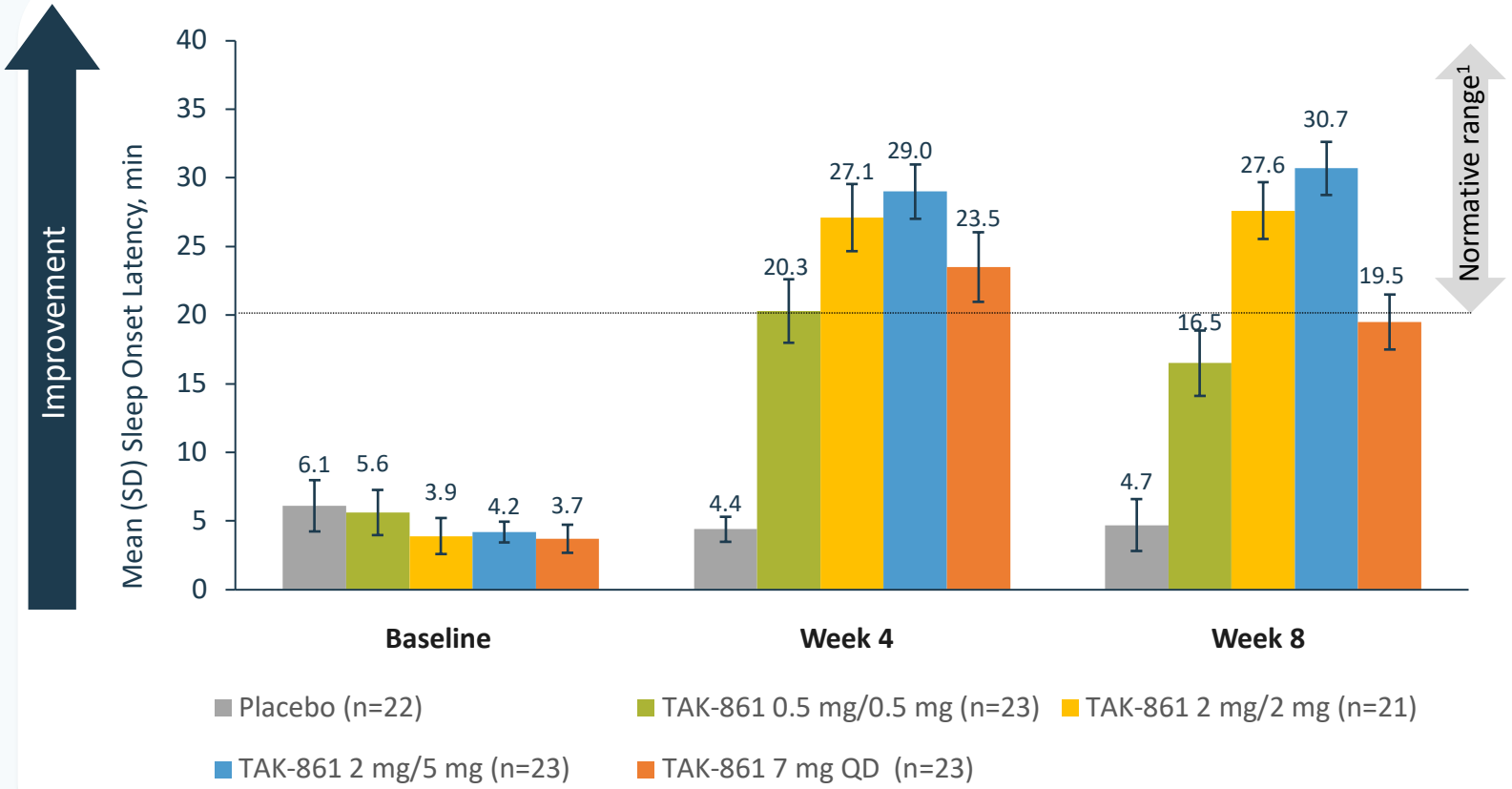


All discontinuations due to protocol deviations

- History of gastric bypass and severe gastroesophageal reflux disease, discontinued at day 43 for not meeting entry criteria (placebo, n=1)
- Urine dip stick positive for amphetamines at Day 14 Visit (0.5mg/0.5mg, n=1)
- Pregnancy detected on Day 42 Visit (2mg/5mg, n=1)

QD, once daily

TAK-861 demonstrated statistically significant and clinically meaningful increased sleep latency on the MWT vs placebo

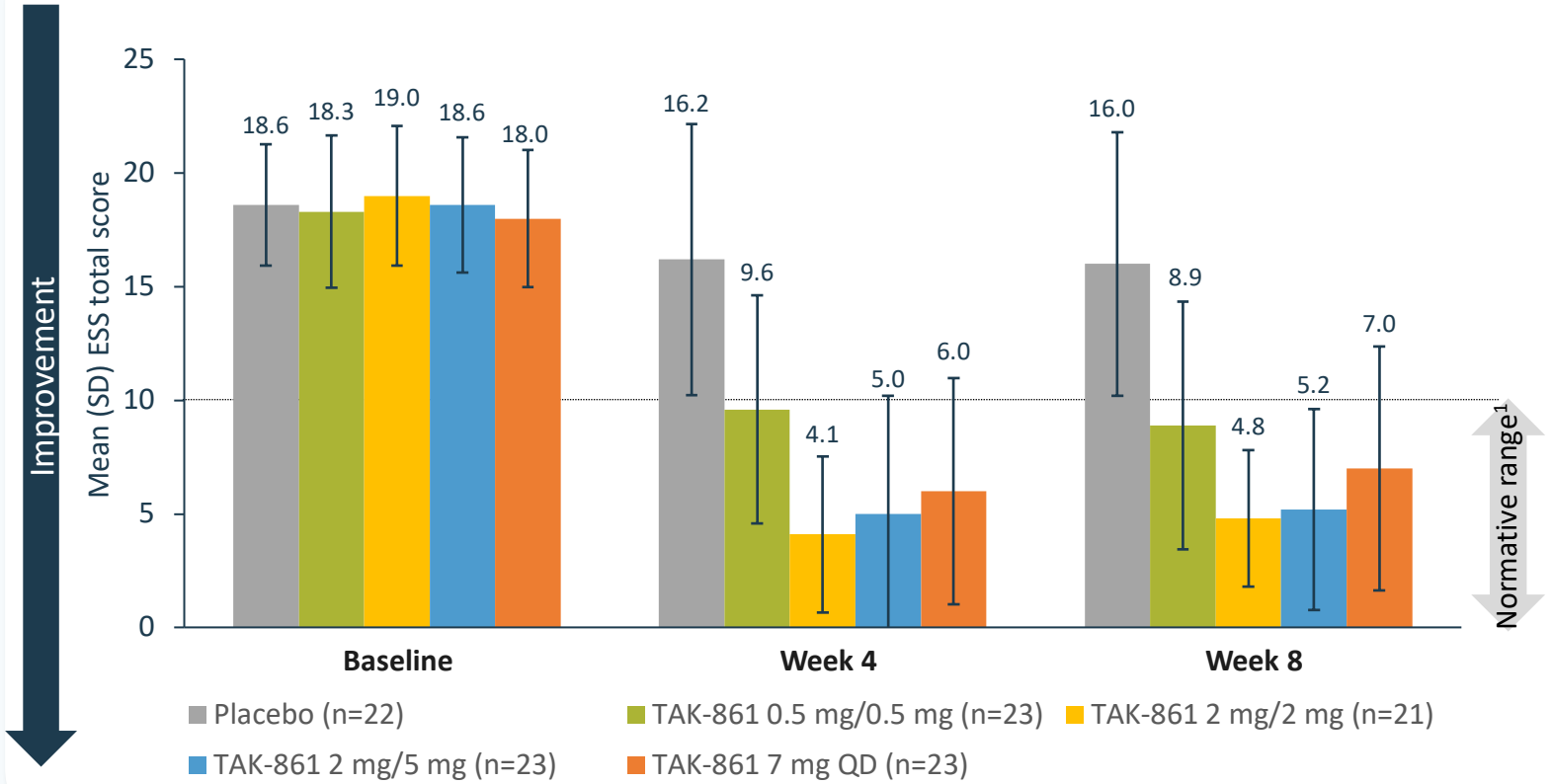


- All doses approached or were in the normative range
- All improvements were sustained over time

QD, once daily; MWT, Maintenance of Wakefulness Test

1. Doghramji K, et al. ,*Electroencephalogr Clin Neurophysiol* 1997; 103: 554-62.

Most participants achieved ESS scores comparable to healthy individuals (≤10) with TAK-861



- All doses of TAK-861 significantly and clinically meaningfully improved subjective wakefulness as measured by ESS
- Week 8: % of participants reaching the normative range w/ESS ≤10
  - Placebo 19.0%
  - 0.5 mg/0.5 mg 66.7%
  - 2 mg/2 mg 95.2%
  - 2 mg/5mg 81.8%
  - 7mg QD 73.9%
- All improvements were sustained over time

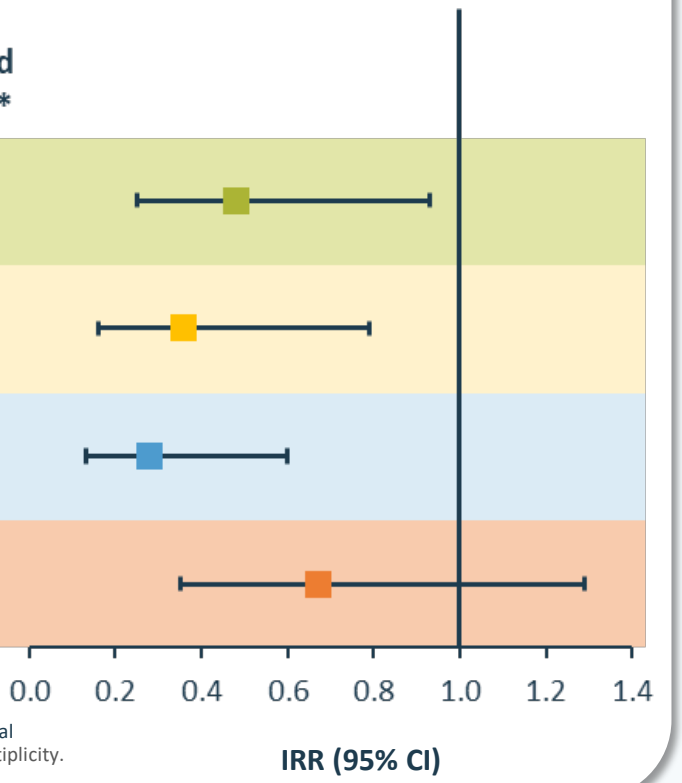
ESS, Epworth Sleepiness Scale; QD, once daily;

1. Johns MW, *Sleep* 1991; 14: 540-5.

TAK-861 significantly reduced cataplexy events compared to placebo

WCR Incidence Rate Ratio Relative to Placebo at Week 8

	IRR	95% CI	p-value	Adjusted p-value*
TAK-861 0.5 mg/0.5 mg	0.48	0.25, 0.93	0.03	0.250
TAK-861 2 mg/2mg	0.36	0.16, 0.79	0.008	0.034
TAK-861 2 mg/5 mg	0.28	0.13, 0.60	0.001	0.003
TAK-861 7 mg QD	0.67	0.35, 1.29	0.233	0.250



IRR: incidence rate ratio; QD: once daily; WCR: weekly cataplexy rate; CI: confidence interval
*Adjusted p-value: smallest significance level used to reject a hypothesis adjusting for multiplicity.

- The twice daily doses significantly reduced cataplexy events close to a weekly rate of zero.
- 8-week: Median WCR
  - Placebo 4.1
  - 0.5mg/ 0.5mg 1.4
  - 2mg/ 2mg 0.7
  - 2mg/ 5mg 0.7
  - 7mg QD 4.3
- All improvements were sustained over time

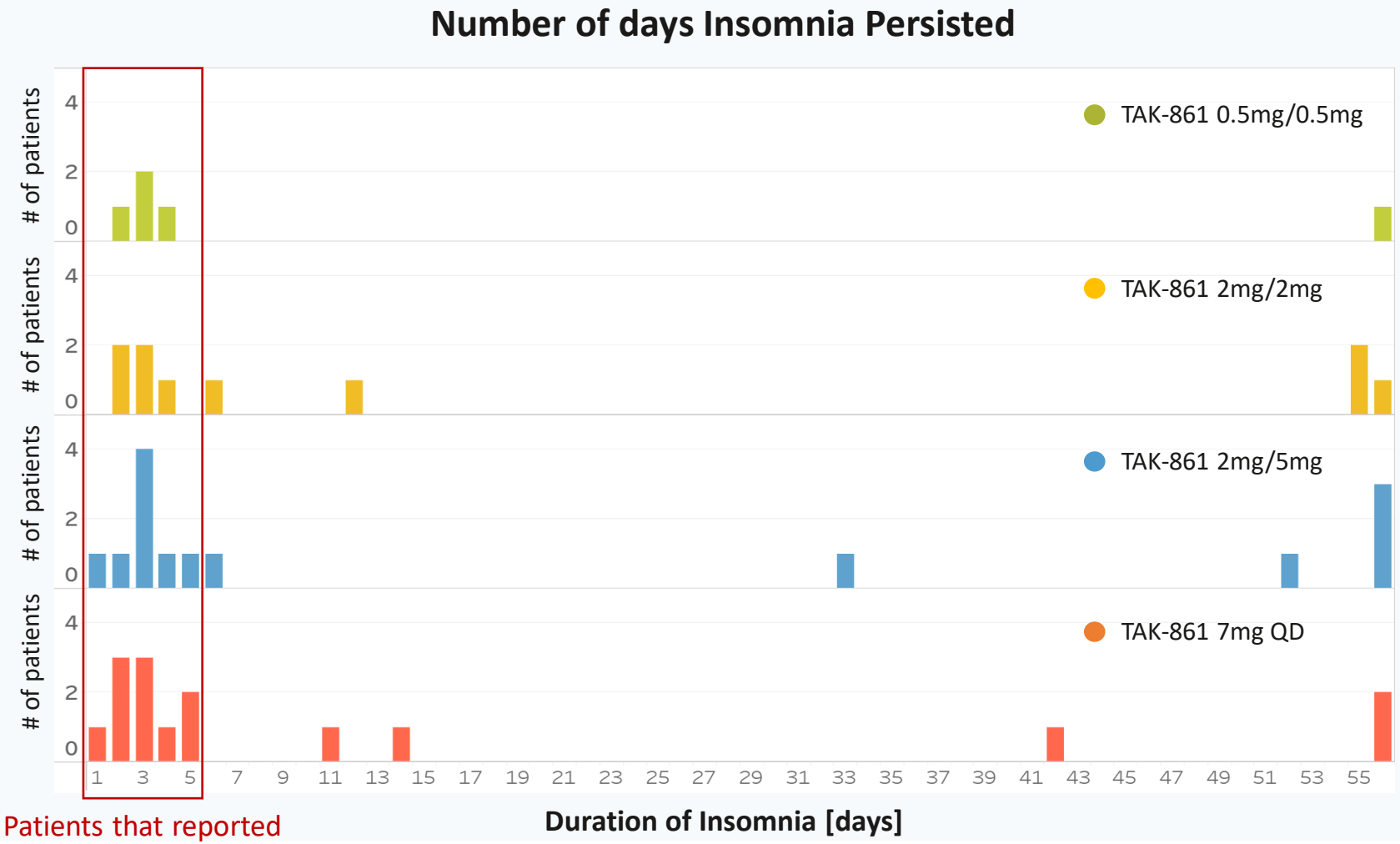
TAK-861 was generally safe and well tolerated in participants with NT1 over 8 weeks

- There were no treatment-related serious TEAEs or discontinuations due to TEAEs during the study
- The most common TEAEs were insomnia, urinary urgency and frequency, and salivary hypersecretion
- Most TEAEs were mild to moderate in severity, occurred within 1-2 weeks of treatment and were transient
- No cases of hepatotoxicity or visual disturbances were reported in Ph2b or in the ongoing LTE

	Placebo (n=22)	TAK-861 0.5 mg/0.5 mg (n=23)	TAK-861 2 mg/2 mg (n=21)	TAK-861 2 mg/5 mg (n=23)	TAK-861 7 mg QD (n=23)
Any TEAE	7 (31.8)	13 (56.5)	15 (71.4)	21 (91.3)	21 (91.3)
• Mild	5 (22.7)	10 (43.5)	6 (28.6)	11 (47.8)	12 (52.2)
• Moderate	2 (9.1)	3 (13.0)	5 (23.8)	8 (34.8)	8 (34.8)
• Severe	0	0	4 (19.0)	2 (8.7)	1 (4.3)
Most common*					
• Insomnia	1 (4.5)	5 (21.7)	10 (47.6)	13 (56.5)	15 (65.2)
• Micturition urgency	1 (4.5)	5 (21.7)	4 (19.0)	12 (52.2)	9 (39.1)
• Micturition frequency	1 (4.5)	3 (13.0)	7 (33.3)	7 (30.4)	12 (52.2)
• Salivary hypersecretion	1 (4.5)	2 (8.7)	2 (9.5)	6 (26.1)	2 (8.7)
Any serious TEAE	0	0	0	1 (4.3)†	0
Any drug-related TEAE	3 (13.6)	12 (52.2)	14 (66.7)	20 (87.0)	20 (87.0)

TEAE defined as an AE whose date of onset occurs on or after the first dose of study of drug.
*Reported in ≥10% of participants overall. †Unrelated to the drug or symptoms of narcolepsy (ankle fracture).
AE, adverse event; QD, once daily; TEAE, treatment-emergent adverse event.

The majority insomnia were mild or moderate and resolved within 5 days



Patients that reported insomnia for ≤5 days

- No subjects discontinued due to adverse events, including insomnia
- No insomnia events required medical intervention

TAK-861 addresses aspects of disease burden important to people with NT1

Presentation #1318

Primary endpoint:

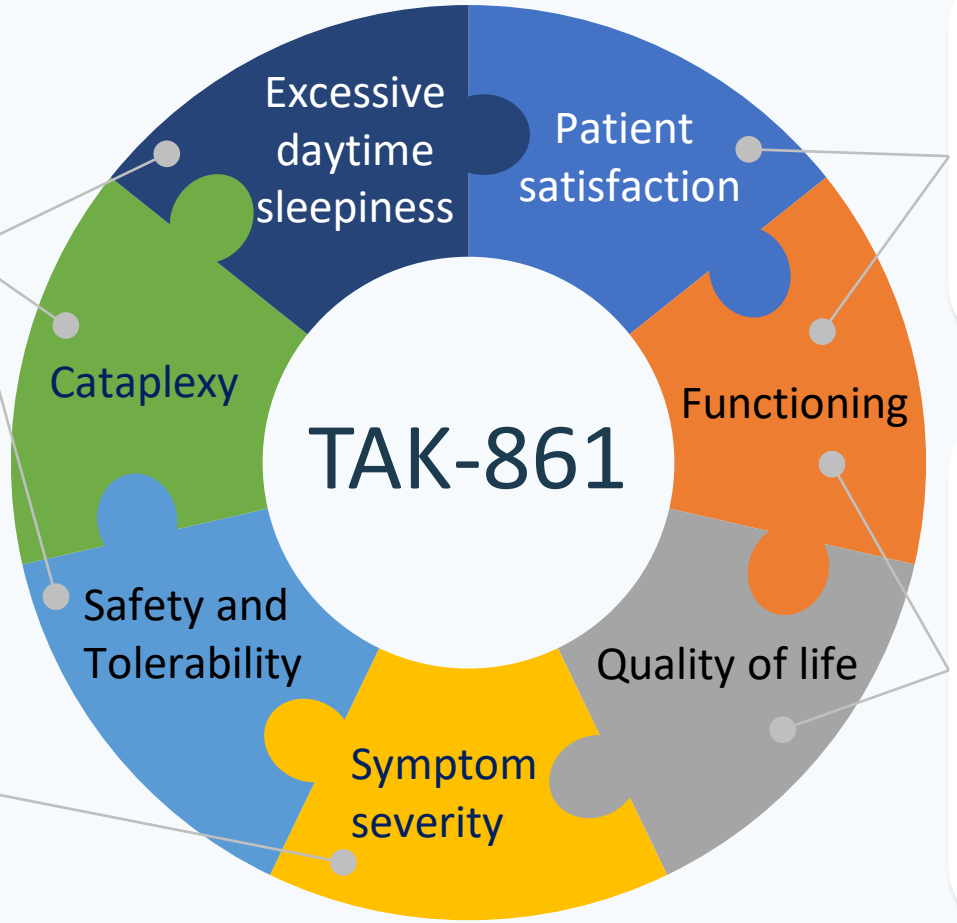
- Improvements in sleep onset latency (MWT)

Secondary endpoints:

- Reductions in self-reported sleepiness (ESS)
- Reductions in cataplexy frequency (WCR)
- No treatment-related serious TEAEs

Presentation #1317

- Improvements in severity of narcolepsy symptoms from both the physician (CGI) and participant perspective (PGI, NSS-CT)



Poster P427

- High treatment satisfaction
- Meaningful improvements in narcolepsy symptoms and functioning according to most participants

Poster P418

- Improvements in narcolepsy-specific functioning (FINI)
- Improvements in general HRQoL assessing mental and physical health (SF-36), and overall health status (EQ-5D-5L)

Conclusions

TAK-861 NT1 phase 2

TAK-861 demonstrated statistically significant and clinically meaningful improvements across multiple objective and subjective endpoints versus placebo over an 8-week treatment period.

- Majority of NT1 patients within normative ranges for ESS and MWT
- Efficacy sustained over the 8-week treatment period and beyond

TAK-861 was generally safe and well tolerated.

- No treatment-related serious TEAEs, and no discontinuations due to TEAEs; majority of TEAEs were mild to moderate in severity and self-limiting
- Frequently reported TEAEs in line with known on-target effects of the drug; no new safety risks were identified in relation to adverse events, vital signs, laboratory, or ECG data
- No cases of hepatotoxicity or visual disturbances reported in Ph2b or in ongoing LTE

TAK-861 optimized profile balances efficacy and on-target & off-target adverse events.

- Based on the results, TAK-861 has the potential to provide transformative efficacy in addressing the overall disease burden in people with NT1.
- TAK-861 will move to Ph3 in H1 FY2024.

Takeda is advancing the field of orexin therapeutics with a multi-asset franchise offering tailored treatments to unlock the full potential of orexin

TAK-861: *Lead Oral*

Potential first-in-class OX2R agonist for the treatment of NT1

- Completed Ph2b development – Jan 2024
- FDA Breakthrough designation – Apr 2024
- Ongoing Long-Term Extension (LTE)
  - Majority of patients in LTE with some patients reaching 1 year of exposure
  - Ongoing until approval
- Next Steps: Initiate Ph3 program – H1 FY2024

TAK-360: *Next Gen Oral*

New chemical series and differentiated profile

- IND approved – Apr 2024
- Fast Track designation – Apr 2024
- Ph1 in HV ongoing
- Next Steps: Ph2 start in NT2/ IH

TAK-925: *IV Formulation*

Fast-acting acute treatment for post-anesthesia recovery in OSA patients

- Ongoing Ph2 post-anesthesia recovery in OSA patients*
  - Proof of concept FY2024
- Next steps: Ph3 program in post-anesthesia recovery and other hospital-based indications based on Ph2 data

Continued commitment to discovering and developing Orexin Therapies

Additional new molecular entities with distinct chemistry and pharmacological profiles in preclinical stage

Exploration of additional indications based on emerging data

Leveraging clinical and novel digital tools to enhance accuracy in diagnosis and improve patients' outcomes

*Suzuki M et al., British Journal of Anaesthesia, 2024; IARS Conference, Denver, 2023

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Appendix

Definitions and Abbreviations

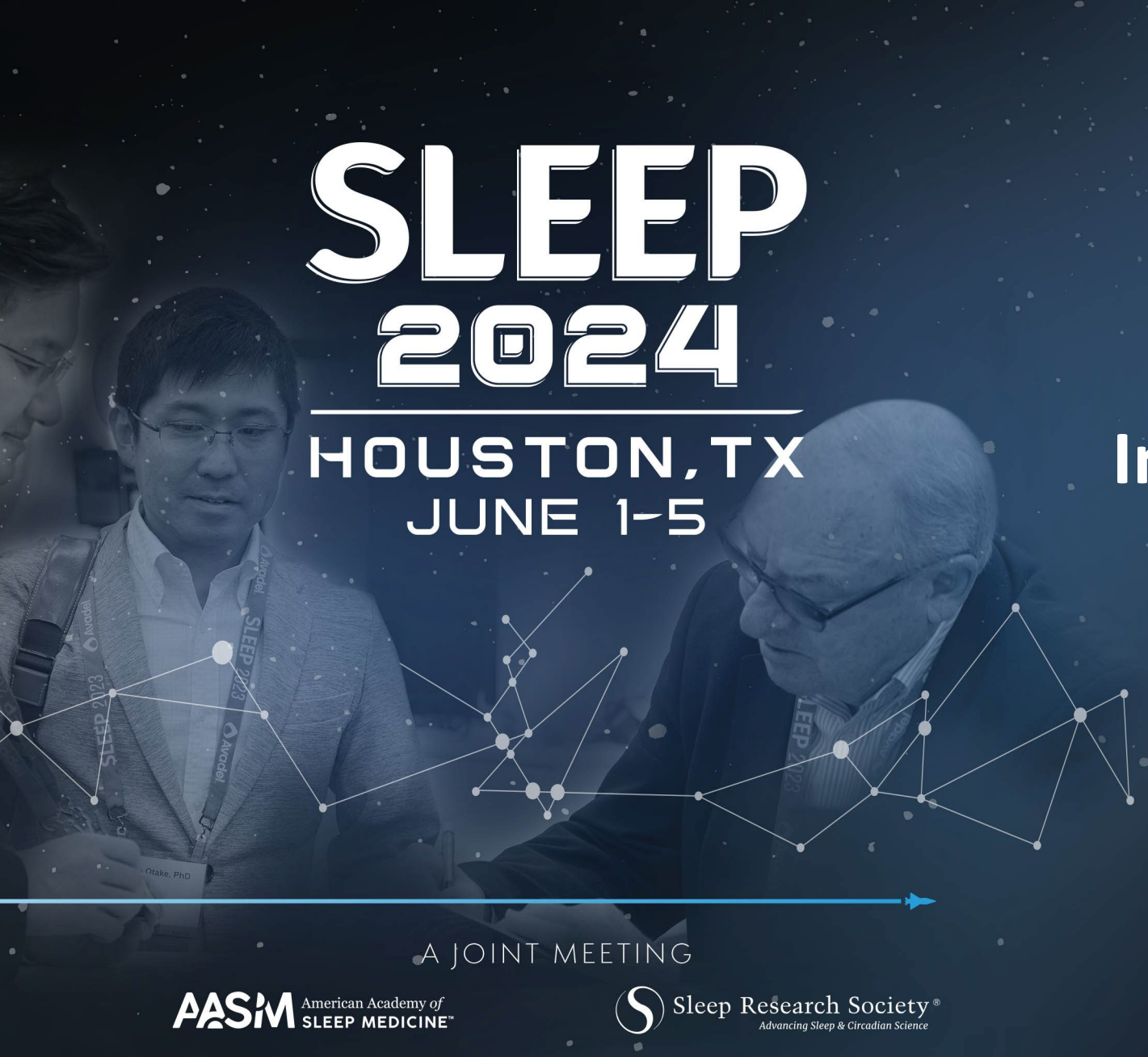
- **The Maintenance of Wakefulness Test (MWT)** is a daytime polysomnographic procedure which quantifies wake tendency by measuring the ability to remain awake during soporific circumstances (sleepiness condition such as dark quiet room).
- **The Epworth Sleepiness Scale (ESS)** is a short self-assessment to identify how likely you are to fall asleep during the daytime and is measured by eight questions. Total score on the Epworth Sleepiness Scale range between 0 and 24 (each question is 0-3). Scores from 0 to 10 reflect normal levels of daytime sleepiness, and scores over 10 are considered to reflect excessive daytime sleepiness.
- **Weekly Cataplexy Rate (WCR)** is the average number of cataplexy (sudden loss of involuntary muscle tone) events per week.

- **Abbreviations**:
  - **CGI-C**: Clinical Global Impression of Change
  - **CI**: Confidence Interval
  - **CSF**: Cerebrospinal Fluid
  - **EQ-5D-5L**: EuroQol-5 Dimensions 5-Levels
  - **ET**: Early Termination
  - **FINI**: Functional Impacts of Narcolepsy Instrument
  - **HLA**: Human Leukocytic Antigen
  - **IRR**: Incidence Rate Ratio
  - **LTE**: long-term extension
  - **NSS-CT:** Narcolepsy severity scale
  - **nPSG**: nocturnal Polysomnography
  - **PGI-C**: Patient Global Impression of Change
  - **PSG**: Polysomnography
  - **QD:** Once Daily
  - **SF-36:** 36-item Short Form Survey
  - **TEAE:** treatment-emergent Adverse Event

Medical Presentations as presented at SLEEP 2024

Slide 24: Efficacy and Safety of TAK-861, an Oral Orexin Receptor 2 Agonist, in Individuals With Narcolepsy Type 1: Results From a Phase 2 Study (LBA1318 Non-CME)

Slide 44: Effect of Oral Orexin Receptor 2 Agonist TAK-861 on the Severity of Symptoms in Individuals With Narcolepsy Type 1: Results From a Phase 2 Study (LBA 1317 Non-CME)



Efficacy and Safety of TAK-861, an Oral Orexin Receptor 2 Agonist, in Individuals With Narcolepsy Type 1: Results From a Phase 2 Study

Yves Dauvilliers, MD, PhD

• This work was funded by Takeda Pharmaceutical Company Limited.

LBA1318 (Non-CME)

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Disclosures

Disclosures

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- Giuseppe Plazzi received consultancy fees from Bioprojet, Jazz Pharmaceuticals, Orexia, and Takeda
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NT1 background

- **Narcolepsy type 1 (NT1)** is a chronic, rare, neurological central disorder of hypersomnolence caused by a significant loss of orexin neurons, resulting in low levels of orexin neuropeptides in the brain and cerebrospinal fluid[1,2]
- **NT1** is typically characterized by symptoms affecting sleep-wake regulation and is associated with cognitive dysfunction and markedly reduced quality of life[1-3]
- No currently available treatments target the underlying pathophysiology of NT1

NT1 Symptoms:


Excessive Daytime Sleepiness (EDS)


Cataplexy


Disrupted nighttime sleep (DNS)


Hypnagogic/hypnopompic hallucinations

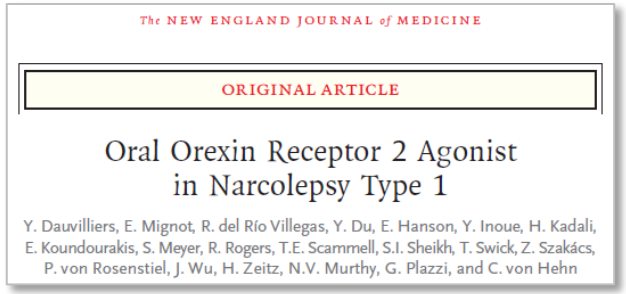

Sleep paralysis

1. Scammell TE, *N Engl J Med* 2015;373:2654–62. 2. International Classification of Sleep Disorders. Third Ed. Darien, IL: AASM; 2014. 3. American Psychiatric Association. Sleep–Wake Disorders; Narcolepsy. In: Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5). Washington, DC: APA; 2013:372-382.

TAK-861 background

Previous orexin receptor 2 (OX2R) agonists showed promising efficacy but clinical development was stopped due to safety concerns[1]

	TAK-994 30 mg BID	TAK-994 90 mg BID	TAK-994 180 mg BID
MWT – LSM change from baseline to week 8	23.9 min	27.4 min	32.6 min
ESS – LSM change from baseline to week 8	–12.2	–13.5	–15.1
WCR – Incidence rate at week 8	0.27	1.14	0.88



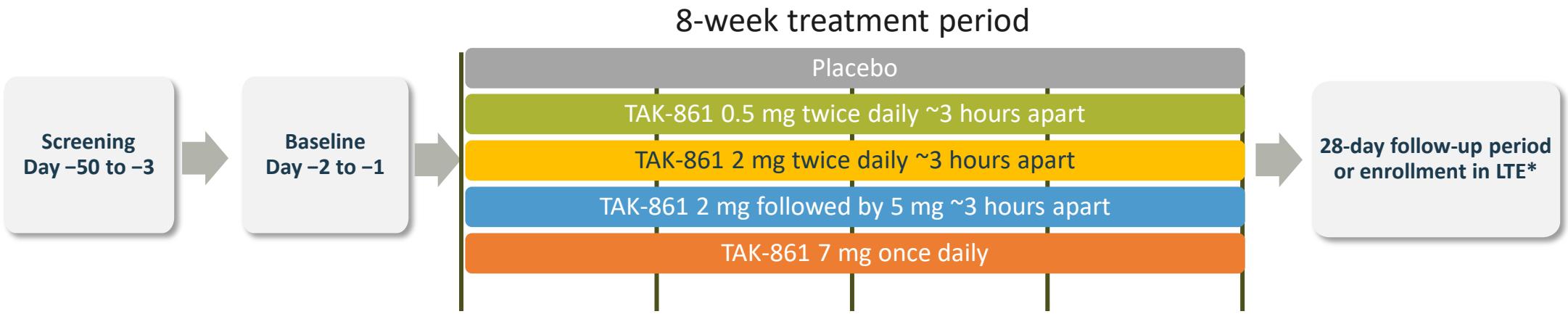
TAK-861 is a next-generation, oral, highly potent, OX2R-selective agonist that was designed to optimize the pharmacokinetic profile and balance between transformative efficacy and on-target and off-target safety[2,3]

TAK-861 has been shown to improve objective and subjective measures of wakefulness (mean sleep latency on the Maintenance of Wakefulness Test [MWT]) and sleepiness (Epworth Sleepiness Scale [ESS]) in sleep-deprived healthy adults and a cohort of patients with NT1 treated for 28 days[4,5]

WCR, weekly cataplexy rate. 1. Dauvilliers et al., *N Engl J Med*, 2023 Jul 27;389(4):309-321 2. Mitsukawa K et al., *Sleep Medicine* 2024;115(S1):12. 3. Kimura H et al., *Sleep Medicine* 2024;115(S1):16. 4. Naylor M. et al., *Sleep Medicine* 2024;115(S1):225. 5. Takeda data on file.

Study design

Objective: To assess the efficacy, safety, and tolerability of 4 oral dose regimens of TAK-861 in participants with NT1 in an 8-week, randomized, double-blind, placebo-controlled, multicenter study



Endpoints		*Baseline*	*Week 2*	*Week 4*	*Week 6*	*Week 8*
Primary	**MWT**	X		X		X
Secondary	**ESS**	X	X	X		X
Secondary	**WCR**	X	X	X	X	X
Secondary	**Adverse events**	X	X	X	X	X

ESS, Epworth Sleepiness Scale; LTE, long-term extension; MWT, Maintenance of Wakefulness Test; WCR, weekly cataplexy rate.
*After the week 8 visit, participants had the option to participate in an LTE study under a separate protocol.

Study population

Inclusion Criteria

- Aged 18–70 years (16–70 in Japan)
- BMI 18–40 kg/m^2
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- Epworth Sleepiness Score >12 on day −1
- ≥4 partial and/or complete episodes of cataplexy/week during screening
- Positive for HLA genotype HLA-DQB1*06:02 OR <110 pg/mL concentration of orexin/hypocretin-1 in cerebrospinal fluid

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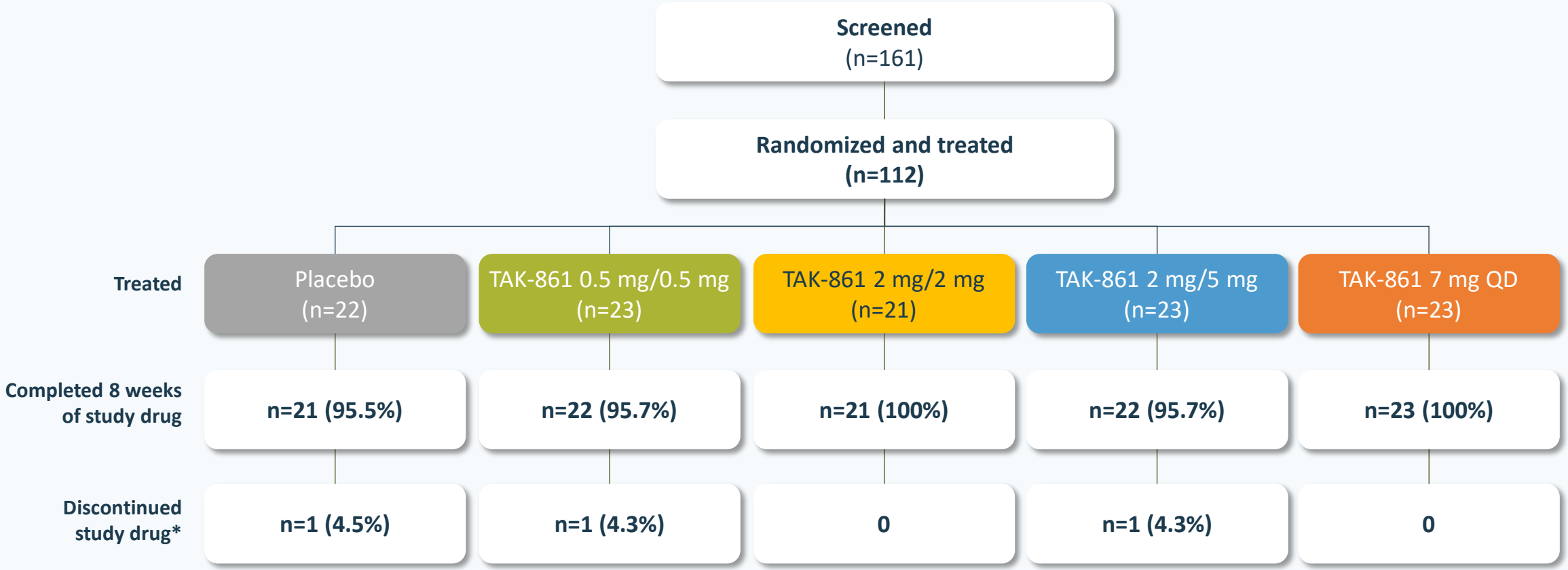
*Based on the ICSD-3 by polysomnography/Multiple Sleep Latency Test, performed in the last 10 years.

Participant disposition



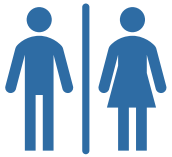
***All discontinuations owing to protocol deviation**

QD, once daily. History of gastric bypass and severe gastroesophageal reflux disease, discontinued at day 43 for not meeting entry criteria (placebo, n=1), urine dip stick positive for amphetamines at day 14 visit (0.5 mg/0.5 mg, n=1), pregnancy detected on day 42 visit (2 mg/5 mg, n=1).

Baseline characteristics

Overall population (n=112)

Mean **34.0** years



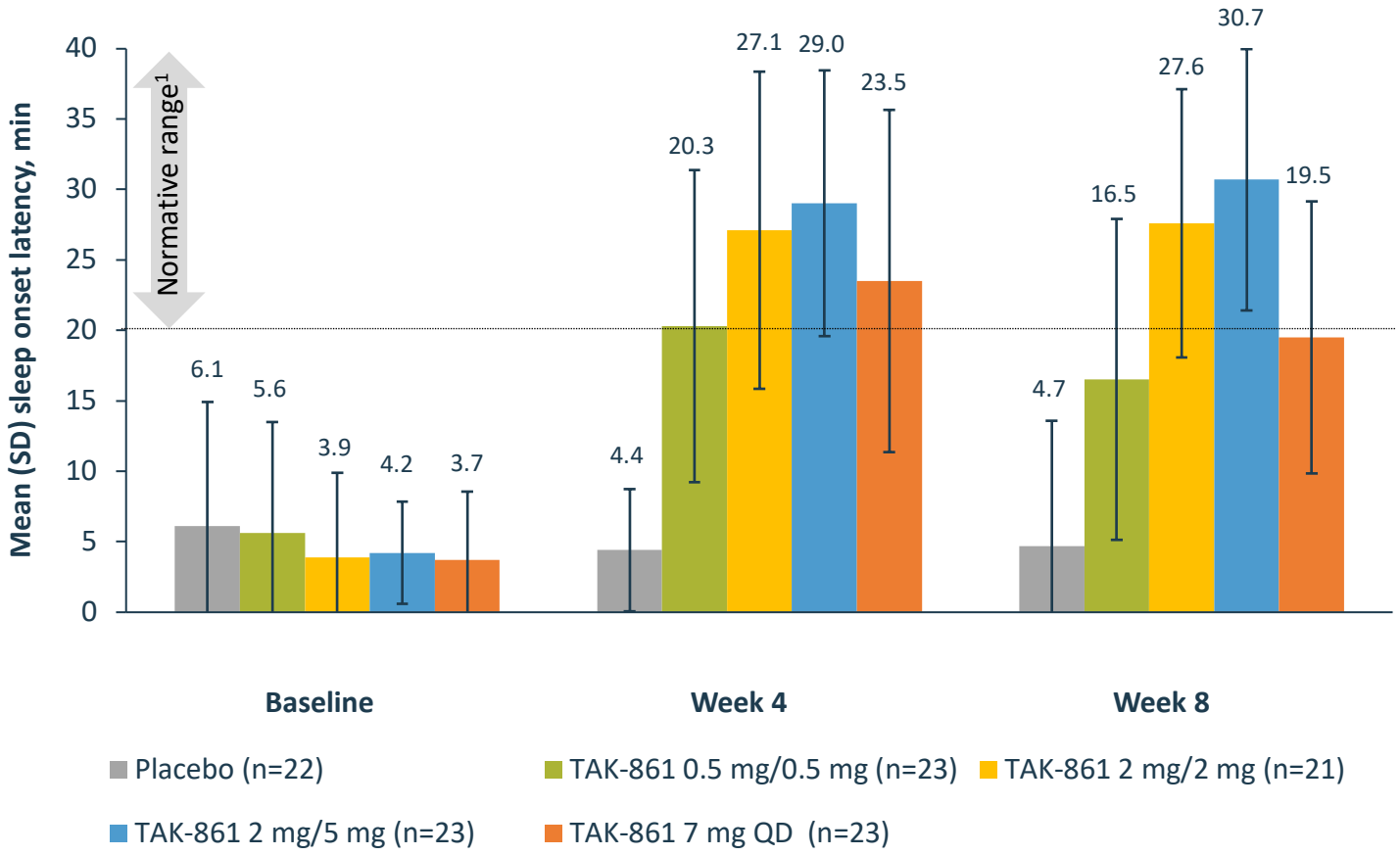
51.8% female

7.1% Asian
5.4% Black/African American
85.7% White

	Placebo (n=22)	TAK-861 0.5/0.5 mg (n=23)	TAK-861 2/2 mg (n=21)	TAK-861 2/5 mg (n=23)	TAK-861 7 mg QD (n=23)
Age (years), mean (SD)	37.5 (11.9)	32.7 (11.1)	31.7 (11.3)	34.7 (11.5)	33.3 (11.9)
Female, n (%)	14 (63.6)	11 (47.8)	9 (42.9)	14 (60.9)	10 (43.5)
Race, n (%)					
Asian	1 (4.5)	2 (8.7)	0	3 (13.0)	2 (8.7)
Black/African American	2 (9.1)	1 (4.3)	2 (9.5)	0	1 (4.3)
White	19 (86.4)	19 (82.6)	19 (90.5)	19 (82.6)	20 (87.0)
BMI (kg/m^2), mean (SD)	28.3 (4.4)	26.7 (5.9)	26.0 (3.4)	28.0 (5.2)	26.3 (4.3)
Years since diagnosis, mean (SD)	10.4 (10.0)	5.6 (4.1)	9.5 (6.6)	8.1 (6.5)	7.4 (7.8)
Sleep latency on the MWT (min), mean (SD)	6.1 (8.8)	5.6 (7.9)	3.9 (6.0)	4.2 (3.6)	3.6 (4.9)
ESS total score, mean (SD)	18.6 (2.7)	18.3 (3.4)	19.0 (3.1)	18.6 (3.0)	18.0 (3.0)
Weekly cataplexy rate					
Mean (SD)	23.1 (25.7)	18.6 (16.9)	21.0 (30.0)	15.7 (13.5)	31.1 (29.1)
Median	13.3	11.0	11.3	9.5	20.0

ESS, Epworth Severity Score; MWT, Maintenance of Wakefulness Test; QD, once daily; WCR, weekly cataplexy rate.

TAK-861 resulted in significantly increased sleep onset latency on the MWT vs placebo



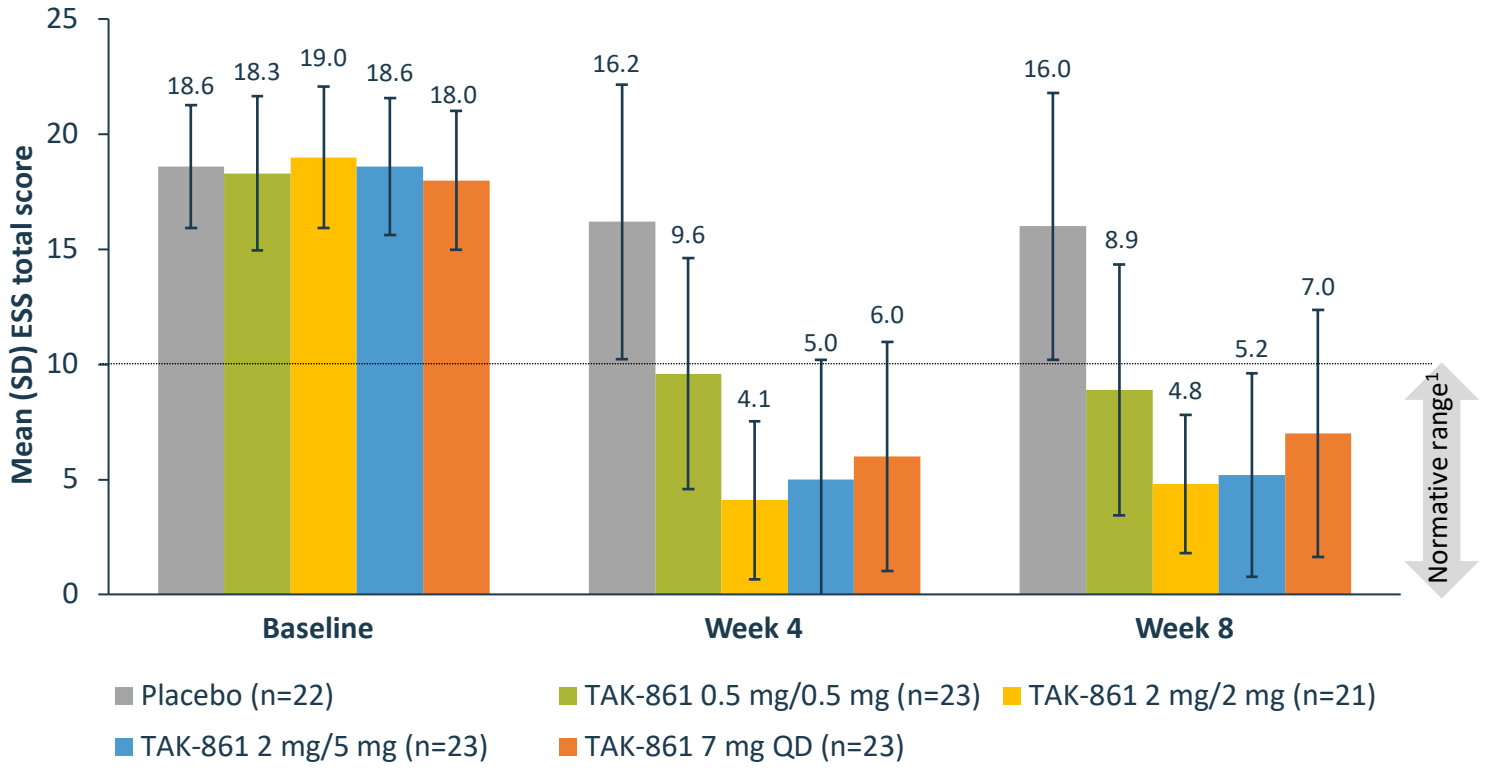
Primary analysis at week 8

	LS mean (SE) change from baseline to week 8	LS mean (95% CI) difference vs placebo at week 8
Placebo	–1.16 (2.06)	—
TAK-861 0.5/0.5 mg	12.49 (2.13)	**13.65** (7.74, 19.57) **P=0.001**
TAK-861 2/2 mg	23.50 (2.04)	**24.67** (18.87, 30.46) **P<0.001**
TAK-861 2/5 mg	25.42 (2.07)	**26.58** (20.81, 32.35) **P<0.001**
TAK-861 7 mg QD	14.96 (1.95)	**16.13** (10.49, 21.76) **P<0.001**

LS, least squares; QD, once daily; MWT, Maintenance of Wakefulness Test. P-values shown have been adjusted for multiplicity.

1. Doghramji K, et al. *Electroencephalogr Clin Neurophysiol* 1997; 103: 554-62.

TAK-861 resulted in significantly decreased ESS total score vs placebo



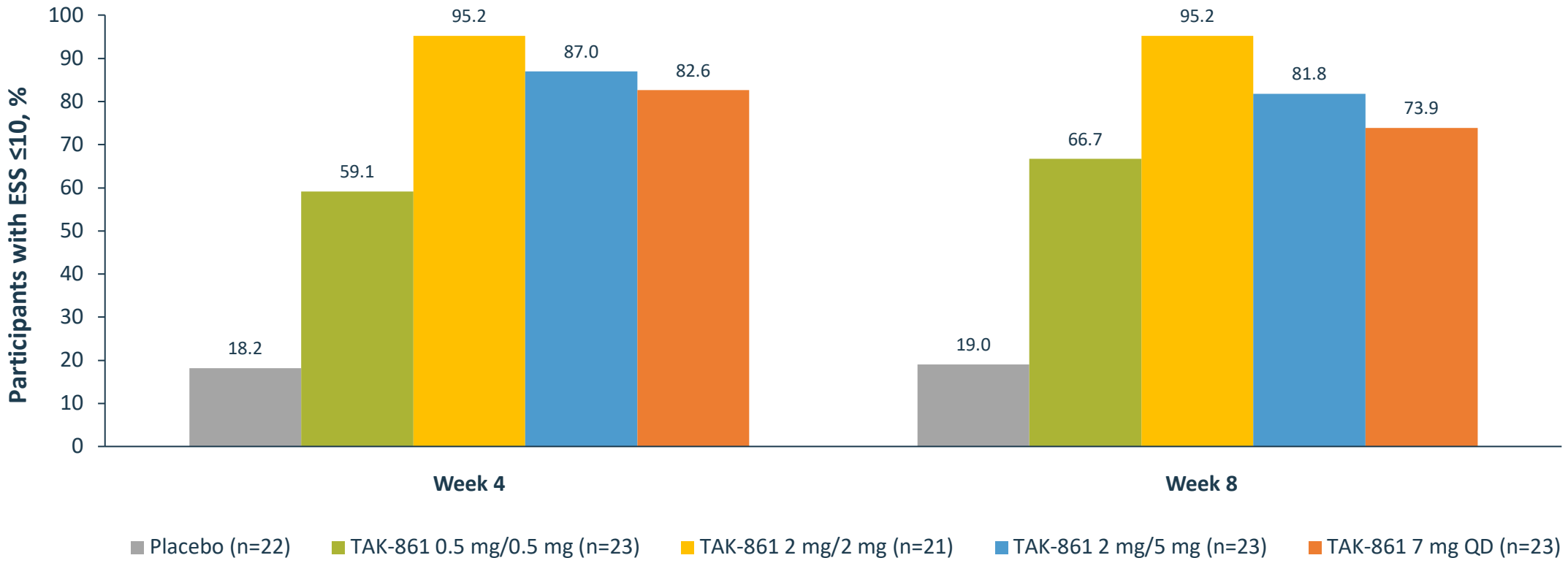
Primary analysis at week 8

	LS mean (SE) change from baseline to week 8	LS mean (95% CI) difference vs placebo at week 8
Placebo	−2.50 (1.11)	—
TAK-861 0.5/0.5 mg	−8.92 (1.09)	−6.42 (−9.53, −3.32) **P=0.004**
TAK-861 2/2 mg	−13.79 (1.12)	−11.30 (−14.44, −8.16) **P<0.001**
TAK-861 2/5 mg	−12.81 (1.07)	−10.31 (−13.35, −7.27) **P<0.001**
TAK-861 7 mg QD	−11.29 (1.06)	−8.79 (−11.84, −5.75) **P<0.001**

ESS, Epworth Sleepiness Scale; LS, least squares; QD, once daily. P-values shown have been adjusted for multiplicity.

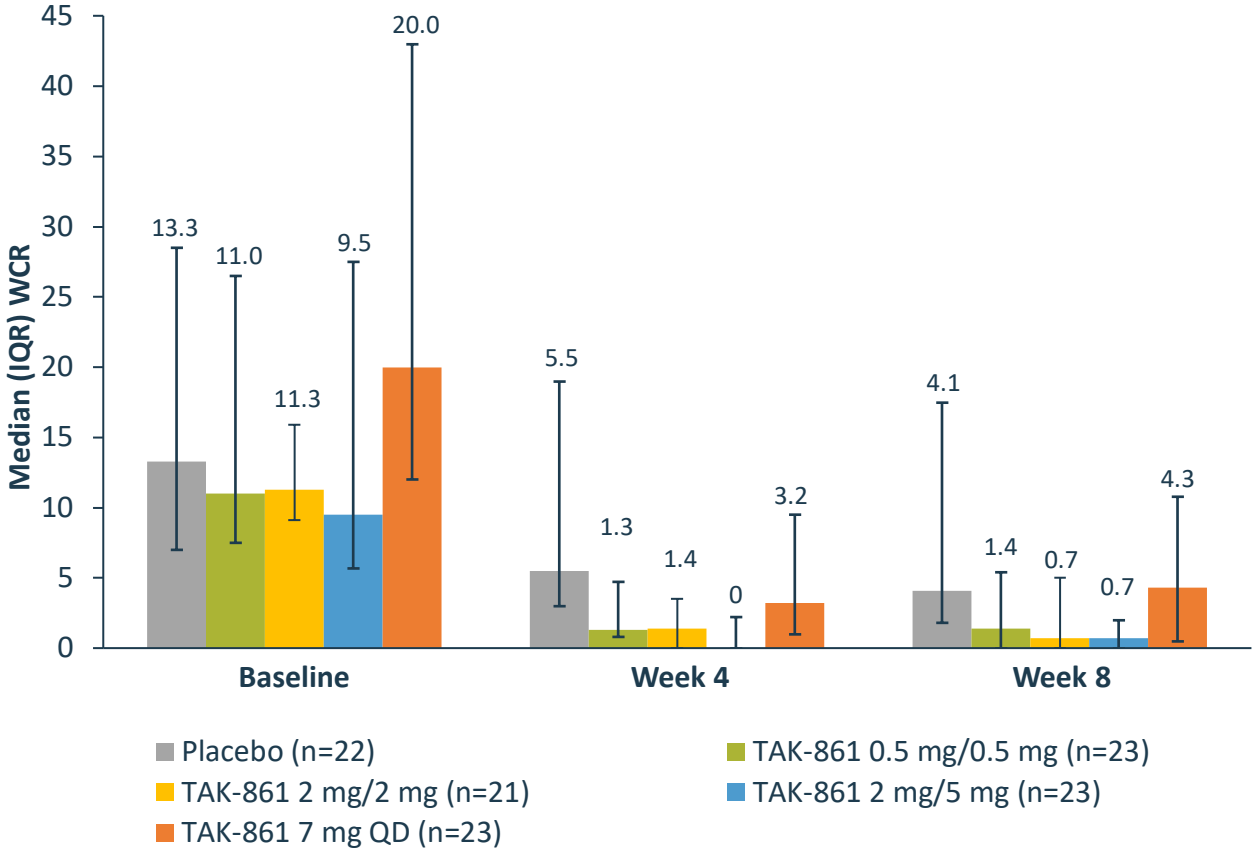
1. Johns MW. *Sleep* 1991; 14: 540-5.

Most participants achieved ESS total score ≤10 with TAK-861



ESS, Epworth Sleepiness Scale.

Twice-daily dosing of TAK-861 significantly reduced cataplexy events compared with placebo



Primary analysis at week 8

	Incidence rate (95% CI) at week 8	Incidence rate ratio vs placebo at week 8
Placebo	8.76 (5.68, 13.51)	—
TAK-861 0.5/0.5 mg	4.24 (2.60, 6.92)	0.48 (0.25, 0.93) **P=0.250**
TAK-861 2/2 mg	3.14 (1.65, 5.98)	0.36 (0.16, 0.79) **P=0.034**
TAK-861 2/5 mg	2.48 (1.30, 4.73)	0.28 (0.13, 0.60) **P=0.003**
TAK-861 7 mg QD	5.89 (3.64, 9.53)	0.67 (0.35, 1.29) **P=0.250**

IQR, interquartile range; QD, once daily; WCR, weekly cataplexy rate.
P-values shown have been adjusted for multiplicity.

TAK-861 was generally well tolerated in participants with NT1 over 8 weeks

Adverse events of special interest (AESIs)

- The majority of insomnia and urinary events were mild to moderate, and did not require medical intervention
- There were no blood pressure–related TEAEs. Transient increases in blood pressure were observed after treatment initiation; however, values returned close to baseline values by end of treatment
- One mild event of increased heart rate was reported that resolved the same day. No clinically significant increases in heart rate were noted
- No QT prolongation or any other safety trends were observed with the ECG data
- No safety concerns were noted across all laboratory parameters including LFTs

ECG, electrocardiogram; LFT, liver function test; TEAE, treatment-emergent adverse event.

TAK-861 was generally well tolerated in participants with NT1 over 8 weeks

- There were no treatment-related serious TEAEs or discontinuations due to TEAEs during the study
- One serious TEAE was unrelated to the drug or symptoms of narcolepsy (ankle fracture)
- The most common TEAEs were insomnia, urinary urgency and frequency, and salivary hypersecretion
- Most TEAEs were mild to moderate in severity, most started within 1–2 days of treatment, and most were transient

	Placebo (n=22)	TAK-861 0.5 mg/0.5 mg (n=23)	TAK-861 2 mg/2 mg (n=21)	TAK-861 2 mg/5 mg (n=23)	TAK-861 7 mg QD (n=23)
Any TEAE	7 (31.8)	13 (56.5)	15 (71.4)	21 (91.3)	21 (91.3)
Mild	5 (22.7)	10 (43.5)	6 (28.6)	11 (47.8)	12 (52.2)
Moderate	2 (9.1)	3 (13.0)	5 (23.8)	8 (34.8)	8 (34.8)
Severe	0	0	4 (19.0)	2 (8.7)	1 (4.3)
Most common*					
Insomnia	1 (4.5)	5 (21.7)	10 (47.6)	13 (56.5)	15 (65.2)
Micturition urgency	1 (4.5)	5 (21.7)	4 (19.0)	12 (52.2)	9 (39.1)
Micturition frequency	1 (4.5)	3 (13.0)	7 (33.3)	7 (30.4)	12 (52.2)
Salivary hypersecretion	1 (4.5)	2 (8.7)	2 (9.5)	6 (26.1)	2 (8.7)
Any serious TEAE	0	0	0	1 (4.3)†	0
Any drug-related TEAE	3 (13.6)	12 (52.2)	14 (66.7)	20 (87.0)	20 (87.0)

QD, once daily; TEAE, treatment-emergent adverse event.
TEAE defined as an adverse event for which date of onset occurs on or after the first dose of study of drug.
*Reported in ≥10% of participants overall. †Unrelated to the drug or symptoms of narcolepsy (ankle fracture).

Conclusions

In this trial, TAK-861 demonstrated statistically significant and clinically meaningful improvements in objective measures of wakefulness, subjective measures of sleepiness, and in cataplexy frequency vs placebo over an 8-week treatment period

TAK-861 was generally well tolerated

- There were no treatment-related serious TEAEs, and no discontinuations due to TEAEs. The majority of TEAEs were mild to moderate in severity and self-limiting
- The most frequently reported TEAEs are in line with the on-target effects of the drug. No new safety risks were identified in relation to adverse events, vital signs, laboratory, or ECG data
- No cases of hepatotoxicity or visual disturbances were reported

TAK-861's optimized profile balances efficacy with on-target and off-target safety

- Based on the results, TAK-861 has the potential to provide transformative efficacy in addressing the overall disease burden in people with NT1

ECG, electrocardiogram; NT1, narcolepsy type 1; TEAE, treatment-emergent adverse event.

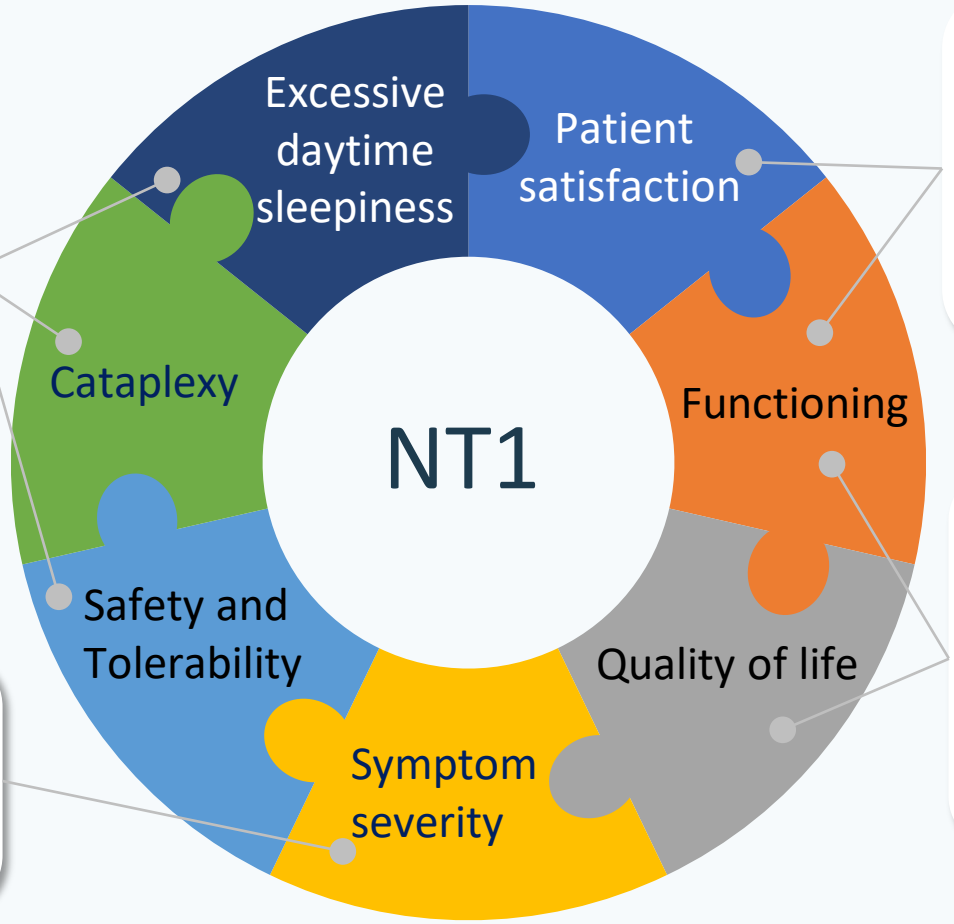
TAK-861 Phase 2 study evaluates aspects of disease burden important to people with NT1

Primary endpoint:

- Improvements in sleep onset latency (MWT)

Secondary endpoints:

- Reductions in self-reported sleepiness (ESS)
- Reductions in cataplexy frequency (WCR)
- Treatment-emergent adverse events



Poster: Treatment satisfaction with oral orexin receptor 2 agonist TAK-861 in patients with narcolepsy type 1: Findings from a phase 2 study (P427)

Poster: Effect of oral orexin receptor 2 agonist TAK-861 on function and health-related quality of life in individuals with narcolepsy type 1: Results from a phase 2 study (P418)

Oral presentation: Effect of oral orexin receptor 2 agonist TAK-861 on the severity of symptoms in individuals with narcolepsy type 1: Results from a phase 2 study

Questions

Effect of Oral Orexin Receptor 2 Agonist TAK-861 on the Severity of Symptoms in Individuals With Narcolepsy Type 1: Results From a Phase 2 Study

Lucie Barateau, MD, PhD

• This work was funded by Takeda Pharmaceutical Company Limited.

LBA1317 (Non-CME)

Contributors

Lucie Barateau,[1,2] Yves Dauvilliers,[1,2] Rachel Neuwirth,[3] Melissa Naylor,[3] Tina Olsson[3]

[1]National Reference Network for Narcolepsy, Sleep and Wake Disorders Centre, Department of Neurology, Gui de Chauliac Hospital, Montpellier, France
[2]University of Montpellier, INSERM Institute for Neurosciences Montpellier, Montpellier, France
[3]Takeda Development Center Americas, Inc., Cambridge, MA, USA

Disclosures

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- Rachel Neuwirth, Melissa Naylor, and Tina Olsson are employees of Takeda Development Center Americas, Inc., and stockholders of Takeda Pharmaceutical Company Limited

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In the TAK-861-2001 phase 2 clinical trial, TAK-861 showed significant improvements in measures of wakefulness and sleepiness and in cataplexy frequency versus placebo, and was generally well tolerated with no treatment-related serious TEAEs over 8 weeks in participants with NT1[5]

In this analysis, the impact of TAK-861 on the severity of narcolepsy symptoms was assessed in the TAK-861-2001 clinical trial using clinical measures including the Narcolepsy Severity Scale for Clinical Trials (NSS-CT)[6] and the Clinical and Patient Global Impression (CGI, PGI) scales

TEAE, treatment emergent adverse event.

1. Mitsukawa K, et al. *Sleep Medicine* 2024;115(S1):12. 2. Kimura H, et al. *Sleep Medicine* 2024;115(S1):16. 3. Naylor, M., et al. *Sleep Medicine* 2024;115(S1):225. 4. Takeda data on file. 5. Dauvilliers Y, et al. LBA1318. Presented at SLEEP 2024; Jun 1-5, 2024; Houston, TX. 6. Dauvilliers Y, et al. *Sleep* 2020;43(6):1-11.

Narcolepsy Severity Scale for Clinical Trials (NSS-CT)

- The **NSS** is a validated, self-administered, 15-item scale evaluating severity, frequency, and impact of 5 narcolepsy symptoms (sleepiness, cataplexy, sleep paralysis, hallucinations, disrupted nocturnal sleep)[1,2]
- The **NSS-CT** used in this study has a 7-day recall

	Scoring	Items, n
Symptoms frequency	6-point Likert scale (0–5)	6
Symptoms consequences on daily life	4-point Likert scale (0–3)	9
Total score = 57		

4 severity levels:	Score
Mild	0–14
Moderate	15–28
Severe	29–42
Very severe	43–57

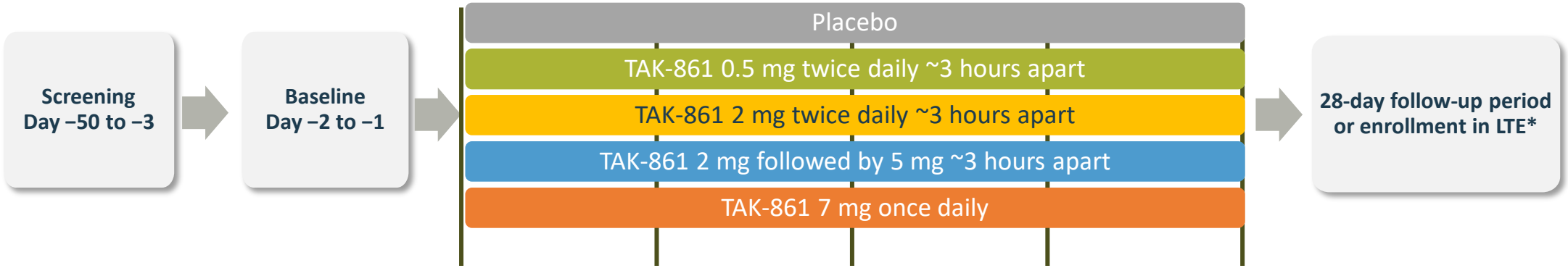
- In adults, 8-point difference between treated and untreated patients is considered clinically meaningful[1,2]
- A pediatric version is also available

The NSS is distributed worldwide by Mapi Research Trust
https://eprovide.mapi-trust.org/instruments/narcolepsy-severity-scale-for-clinical-trials

1. Dauvilliers Y, et al. *Sleep* 2020;43(6):1-11. 2. Dauvilliers Y, et al. *Neurology* 2017;88(14):1358-1365.

Study design

The objective of this analysis was to assess the effect of TAK-861 on measures of symptom severity in participants with NT1



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Primary	MWT	X		X		X
Secondary	ESS	X	X	X		X
Secondary	WCR	X	X	X	X	X
Exploratory	**NSS-CT, CGI-(S/I), PGI-(S/I)**	X		X		X

CGI-(S/I), Clinical Global Impression (Severity/Improvement); ESS, Epworth Sleepiness Scale; LTE, long-term extension; MWT, Maintenance of Wakefulness Test; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; PGI-(S/I), Patient Global Impression (Severity/Improvement); WCR, weekly cataplexy rate. *After the week 8 visit, participants had the option to participate in an LTE study under a separate protocol.

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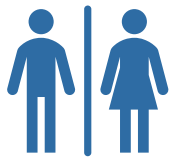

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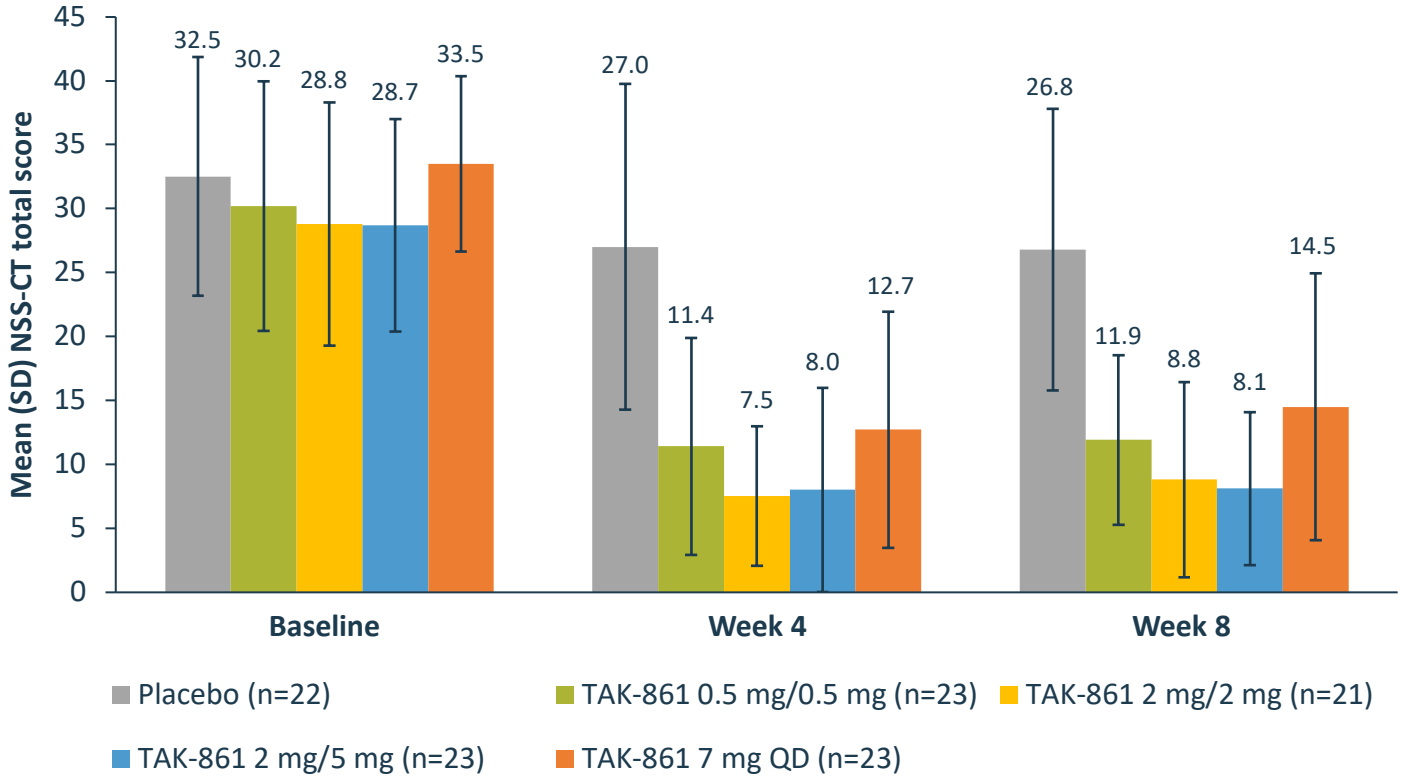
5.4% Black/African American
85.7% White

	Placebo (n=22)	TAK-861 0.5/0.5 mg (n=23)	TAK-861 2/2 mg (n=21)	TAK-861 2/5 mg (n=23)	TAK-861 7 mg QD (n=23)
Age (years), mean (SD)	37.5 (11.9)	32.7 (11.1)	31.7 (11.3)	34.7 (11.5)	33.3 (11.9)
Female, n (%)	14 (63.6)	11 (47.8)	9 (42.9)	14 (60.9)	10 (43.5)
Race, n (%)					
Asian	1 (4.5)	2 (8.7)	0	3 (13.0)	2 (8.7)
Black/African American	2 (9.1)	1 (4.3)	2 (9.5)	0	1 (4.3)
White	19 (86.4)	19 (82.6)	19 (90.5)	19 (82.6)	20 (87.0)
BMI (kg/m^2), mean (SD)	28.3 (4.4)	26.7 (5.9)	26.0 (3.4)	28.0 (5.2)	26.3 (4.3)
Years since diagnosis, mean (SD)	10.4 (10.0)	5.6 (4.1)	9.5 (6.6)	8.1 (6.5)	7.4 (7.7)
NSS-CT total score, mean (SD)	**32.5 (9.3)**	**30.2 (9.8)**	**28.8 (9.5)**	**28.7 (8.3)**	**33.5 (6.9)**

NSS-CT, Narcolepsy Severity Scale for Clinical Trials; QD, once daily.

TAK-861 resulted in clinically meaningful changes in NSS-CT compared with placebo

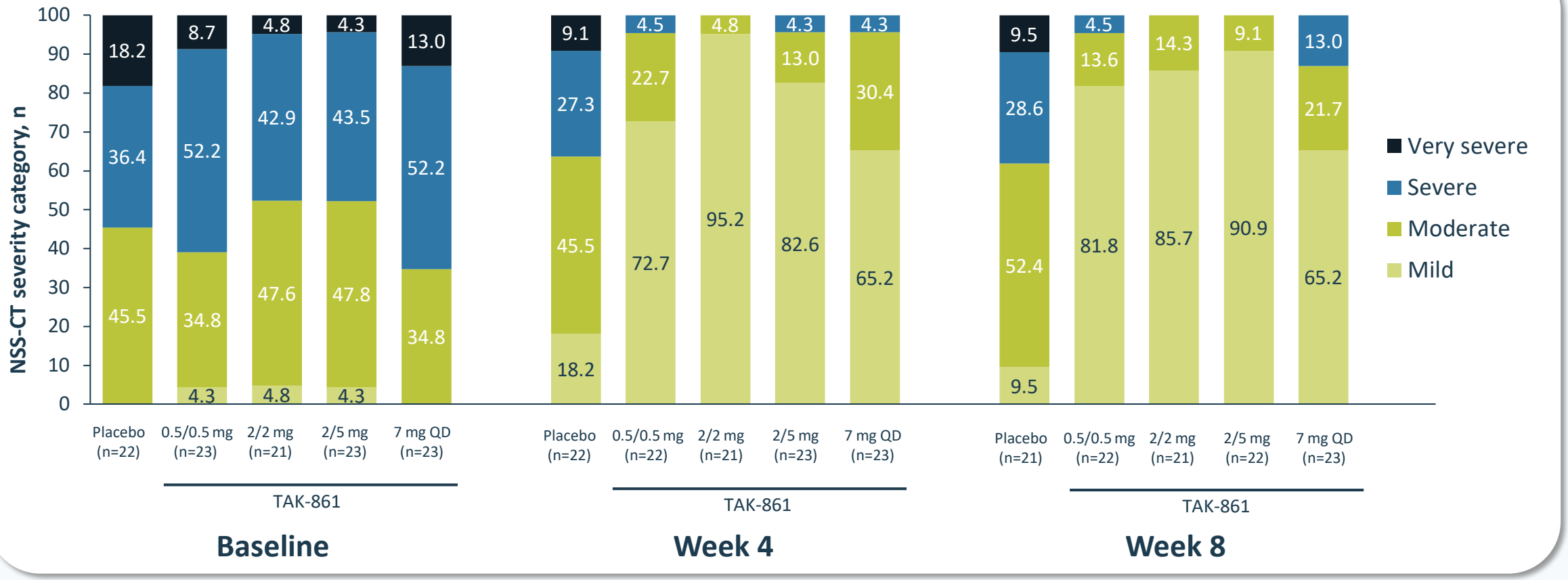


Primary analysis at week 8

	LS mean (SE) change from baseline to week 8	LS mean (95% CI) difference vs placebo at week 8 Nominal P value
Placebo	–3.50 (1.79)	—
TAK-861 0.5/0.5 mg	–18.24 (1.77)	**–14.74** (–19.73, –9.74) **P<0.001**
TAK-861 2/2 mg	–21.03 (1.81)	**–17.53** (–22.60, –12.47) **P<0.001**
TAK-861 2/5 mg	–21.14 (1.75)	**–17.64** (–22.62, –12.66) **P<0.001**
TAK-861 7 mg QD	–17.23 (1.75)	**–13.73** (–18.65, –8.81) **P<0.001**

LS, least squares; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; QD, once daily.
The change from baseline analysis used a linear mixed-effects model for repeated measures with fixed effects for baseline, treatment, visit, and treatment-by-visit interaction.

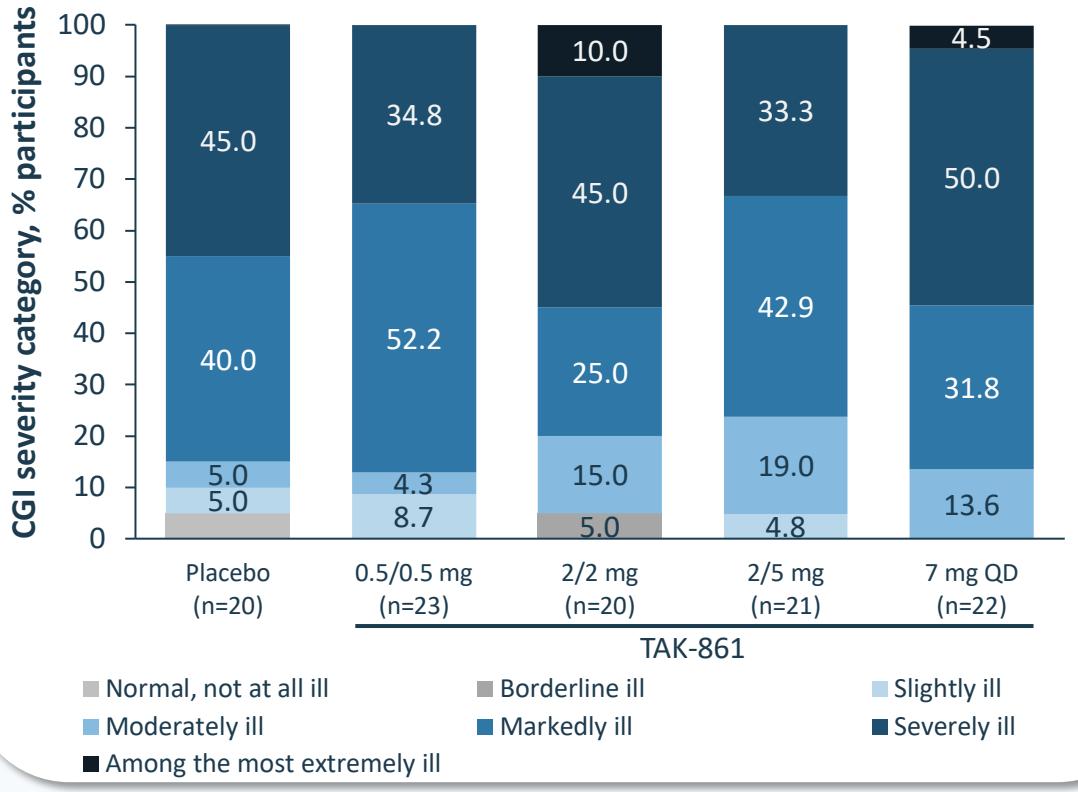
The majority of participants receiving TAK-861 reported mild disease on NSS-CT



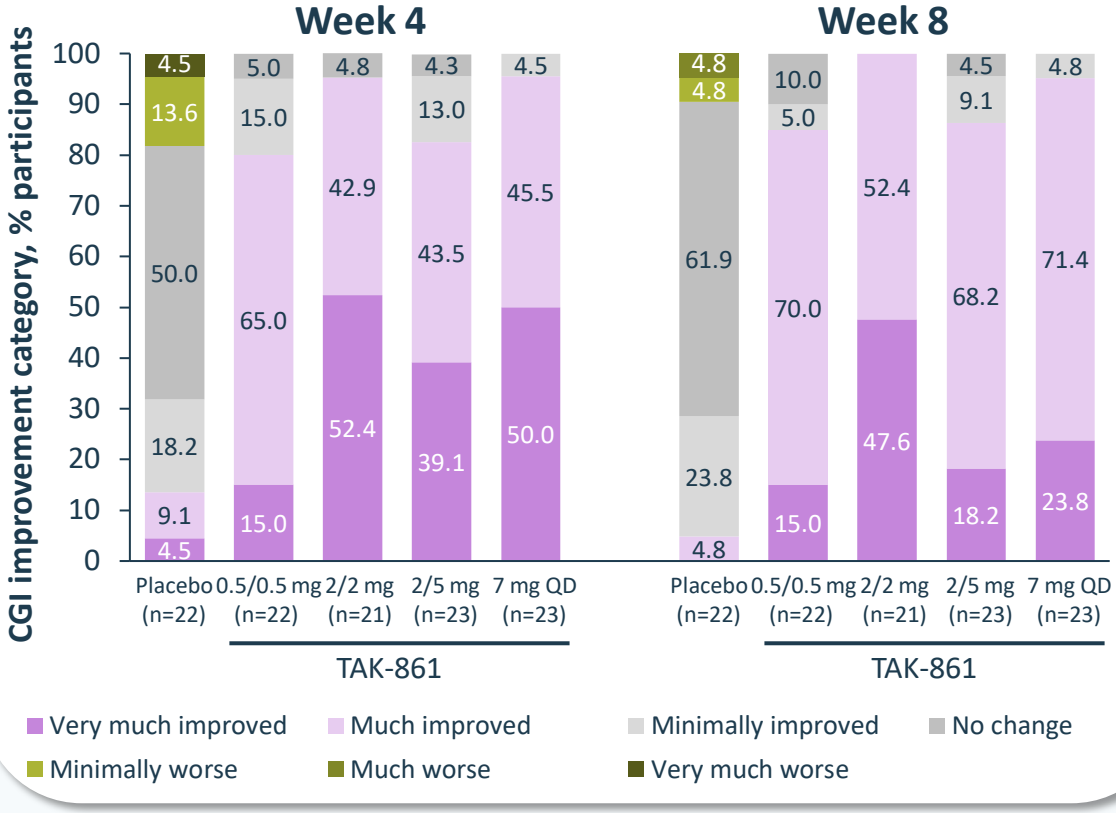
NSS-CT, Narcolepsy Severity Scale for Clinical Trials; QD, once daily.
NSS-CT categories based on total score: Mild=0–14, Moderate=15–28, Severe=29–42, Very severe=43–57.

CGI-I scores were ‘much’ or ‘very much’ improved for most participants who received TAK-861

CGI-S Baseline



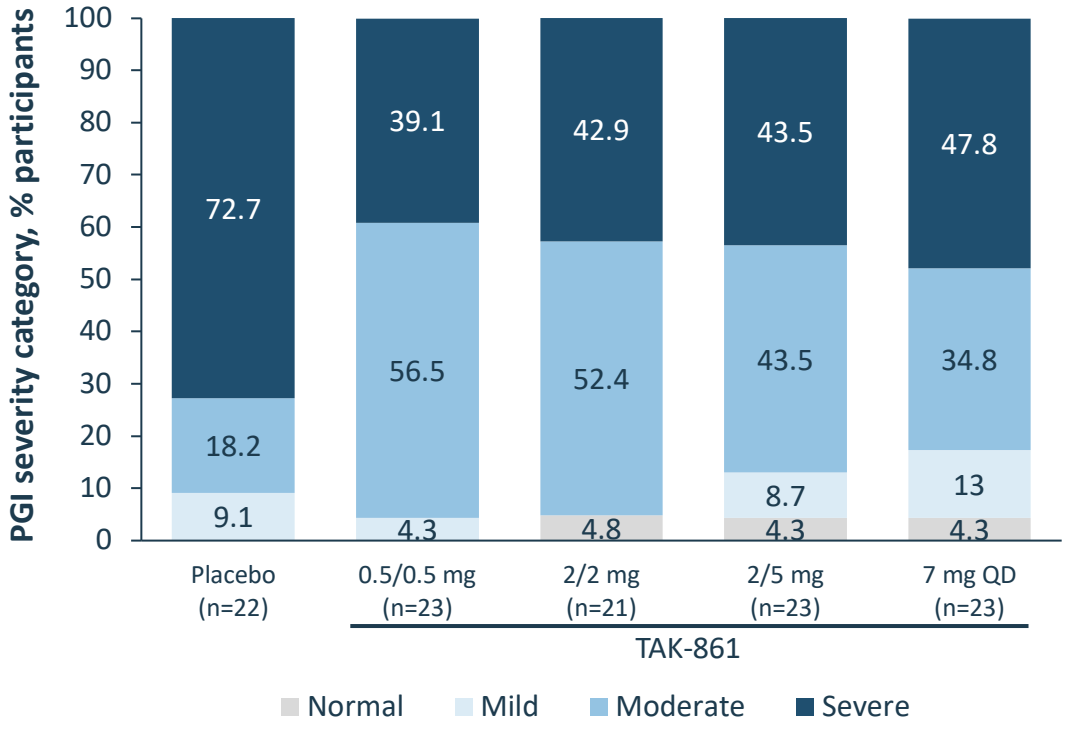
CGI-I



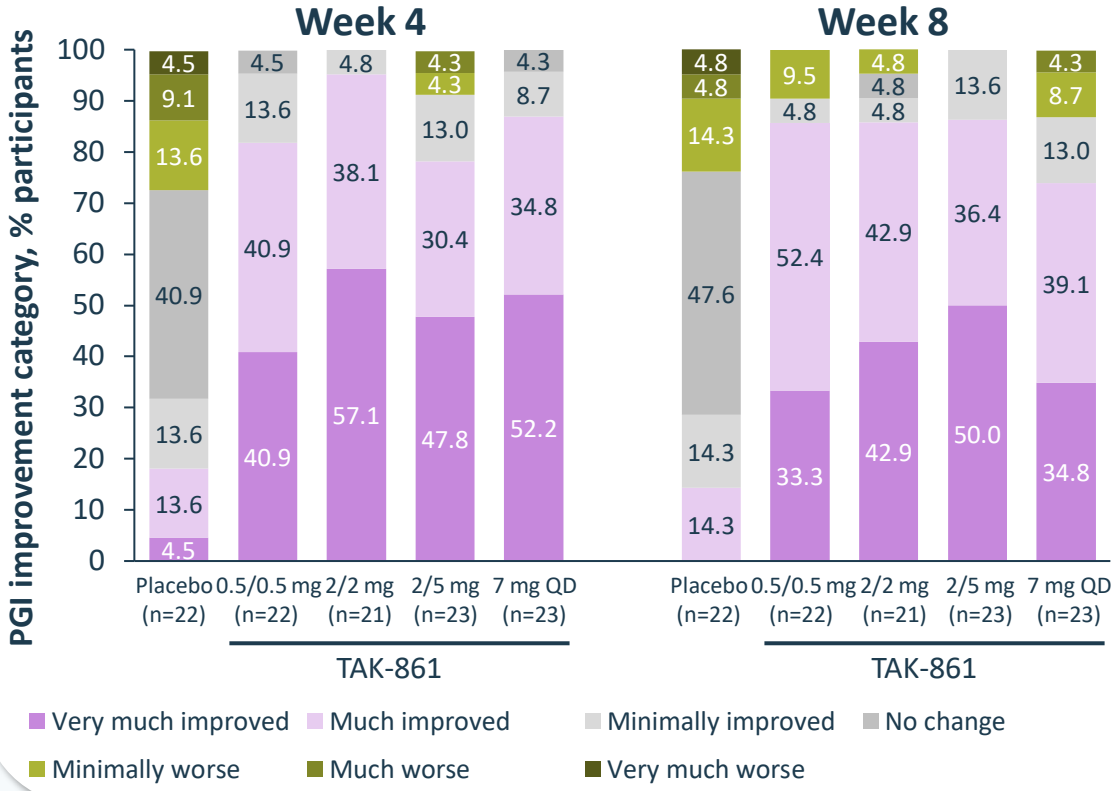
CGI-I, Clinical Global Impression - Improvement; CGI-S, Clinical Global impression – Severity; QD, once daily.
The statistical analysis was based on the comparison of much or very much improved. For CGI-I, at week 4 values across doses are statistically significant at P<0.001 (nominal p value).

PGI-I scores were ‘much’ or ‘very much’ improved for most participants who received TAK-861

PGI-S Baseline



PGI-I



PGI-I, Patient Global Impression - Improvement; PGI-S, Patient Global Impression – Severity; QD, once daily.
The statistical analysis was based on the comparison of much or very much improved. For PGI-I, all week 8 values across doses are statistically significant at P<0.001 (nominal value).

TAK-861 was generally well tolerated in participants with NT1 over 8 weeks

- There were no treatment-related serious TEAEs or discontinuations due to TEAEs during the study
- One serious TEAE was unrelated to the drug or symptoms of narcolepsy (ankle fracture)
- The most common TEAEs were insomnia, urinary urgency and frequency, and salivary hypersecretion
- Most TEAEs were mild to moderate in severity, most started within 1–2 days of treatment, and most were transient

TEAE, treatment-emergent adverse event.
TEAE defined as an adverse event for which date of onset occurs on or after the first dose of study of drug.

Conclusions

TAK-861 significantly improved both physician- (CGI) and participant-reported (PGI, NSS-CT) measures of overall treatment experience and disease severity across the spectrum of narcolepsy symptoms in participants with NT1 over 8 weeks

These findings supplement primary and secondary results from the trial, which show that TAK-861 significantly improves objective and subjective measures of EDS, decreases cataplexy frequency, and was generally well tolerated in participants with NT1

CGI, Clinical Global Impression; EDS, excessive daytime sleepiness; NSS-CT, Narcolepsy Severity Scale for Clinical Trials; NT1, narcolepsy type; PGI, Patient Global Impression.

TAK-861 phase 2 study evaluates aspects of disease burden important to people with NT1

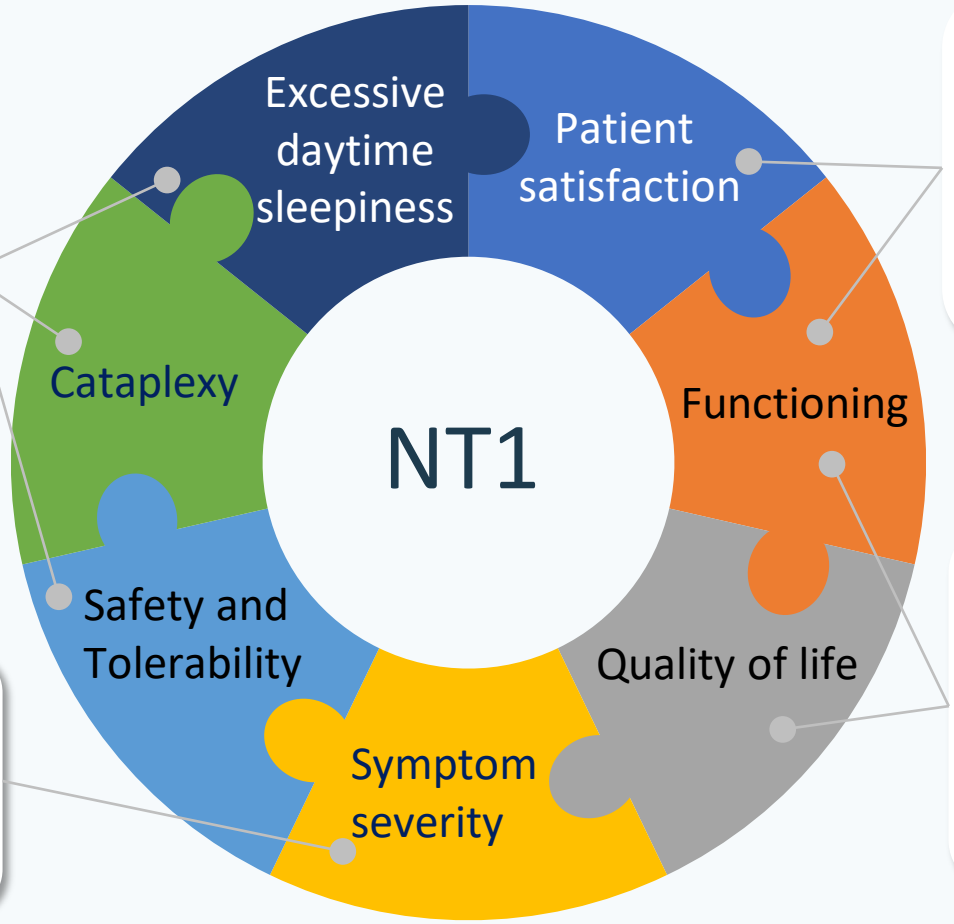
Primary endpoint:

- Improvements in sleep onset latency (MWT)

Secondary endpoints:

- Reductions in self-reported sleepiness (ESS)
- Reductions in cataplexy frequency (WCR)
- Treatment-emergent adverse events

- Improvements in **severity of narcolepsy symptoms** from both the physician (CGI) and participant perspective (PGI, NSS-CT)



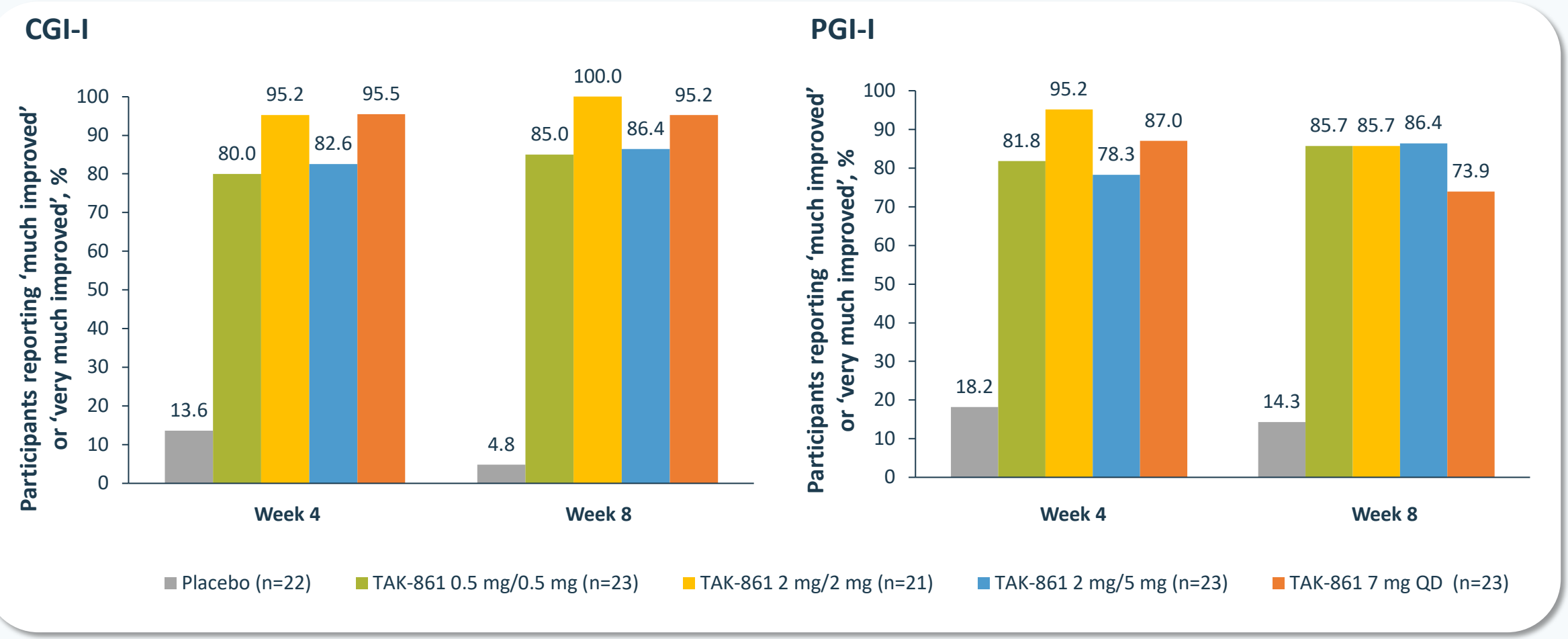
Poster: Treatment satisfaction with oral orexin receptor 2 agonist TAK-861 in patients with narcolepsy type 1: Findings from a phase 2 study (P427)

Poster: Effect of oral orexin receptor 2 agonist TAK-861 on function and health-related quality of life in individuals with narcolepsy type 1: Results from a phase 2 study (P418)

Questions

Back Up

Most participants who received TAK-861 were responders on the CGI-I and PGI-I



CGI-I, Clinical Global Impression - Improvement; PGI, Patient Global Impression - Improvement; QD, once daily.
Responders were defined as participants considered or who reported being much improved or very much improved. Analyses at week 8 were not evaluable for statistical significance.