

OX2R AGONISTS FOR THE TREATMENT OF NARCOLEPSY TYPE 1



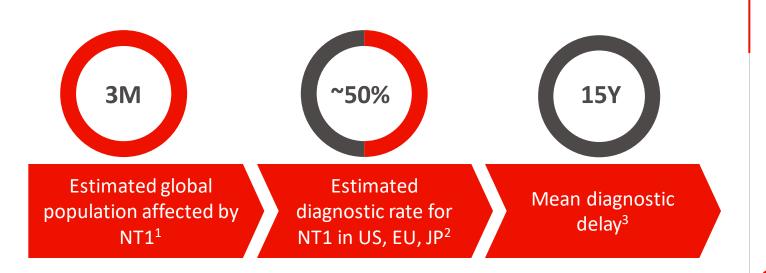
Deborah Hartman, PhD

Global Program Leader, Neuroscience Takeda Pharmaceutical Company Limited New York, NY November 14, 2019

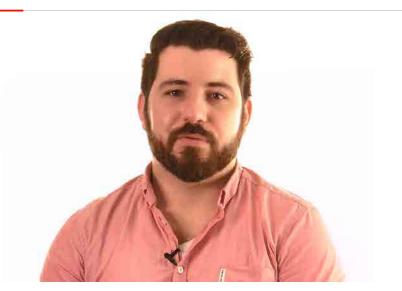
Better Health, Brighter Future

NARCOLEPSY TYPE 1 IS A RARE, ACQUIRED CHRONIC NEUROLOGICAL DISORDER





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



66 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. 99

- Charlie, adviser with NT1

^{1.} Narcolepsy Network. Narcolepsy Fast Facts. Available at: https://narcolepsynetwork.org/aboutnarcolepsy/narcolepsy-fast-facts/. Last Updated June 2015. Last Accessed Sept. 2019

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

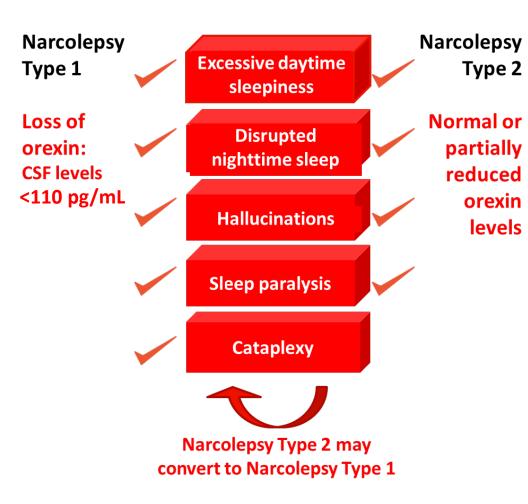
^{3.} Frauscher B, J Clin Sleep Med 2013;9(8):805-12

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

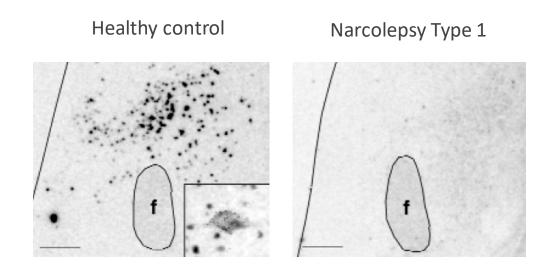
- Idiopathic Hypersomnia
- Residual Excessive Daytime Sleepiness in Obstructive Sleep Apnea¹

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

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

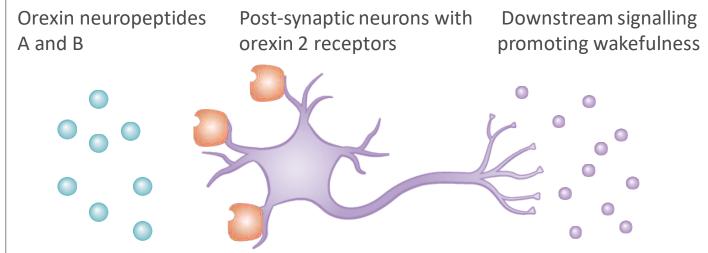


OREXIN mRNA LABELLING OF POSTMORTEM HYPOTHALAMIC SECTIONS



 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

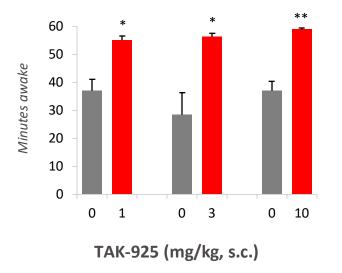
f: fornix 1. Reprinted by permission from Springer Nature. Peyron C, et al. Nat Med. 2000;6:991-997 2. Thannickal TC, et al. *Neuron*.2000;27:469–474

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

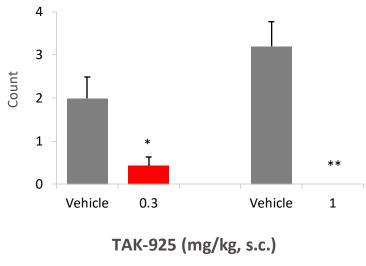
Hypnogram of sleep/wake transitions in NT1 mouse model

EEG recordings

REM Vehicle Ž NREM Wake REM Vehicle NT1 mouse model NREM Wake TAK-925 REM NREM Wake ZT13 ZT14 ZT12 Vcataplexy-like event Vehicle or TAK-925 (3 mg/kg)

TAK-925 ABOLISHED CATAPLEXY-LIKE EPISODES

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

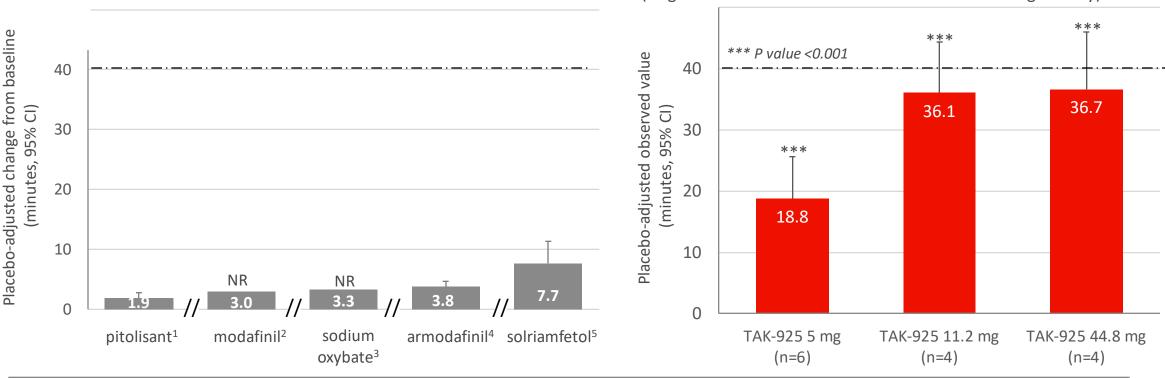


*p<0.05, **p<0.01 vs placebo

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 rot reported

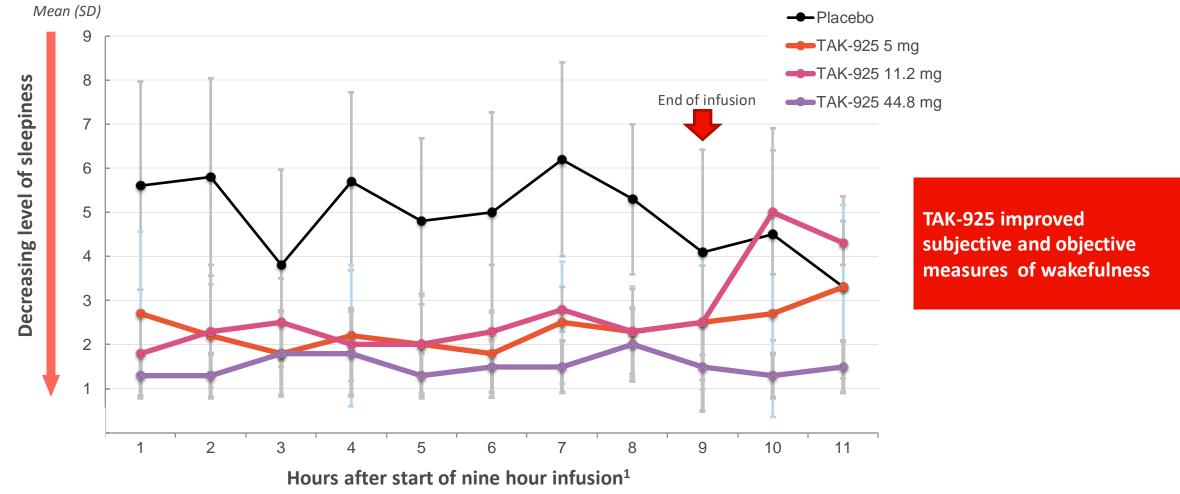
1. Lancet Neurol. 2017 Mar;16(3):200-207; 2. FDA statistical Review: Page 5, 200 mg; 3. Label/Trial N4; 4. Clinicaltrials.gov (NCT00078377); 5. FDA Statistical Review, Study 14-002, 150 mg 6. Evans R, Tanaka S, Tanaka S, et al. 2019. A phase 1 single ascending dose study of a novel orexin 2 receptor 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. <u>http://www.professionalabstracts.com/ws2019/iPlanner/#/presentation/1832</u>

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)



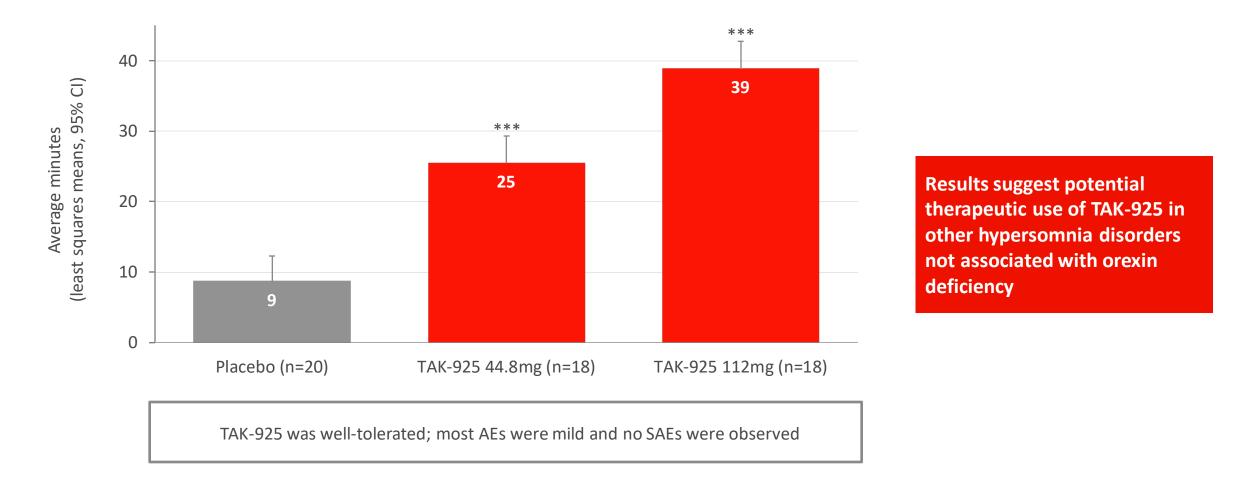
1. TAK-925 effective plasma half-life <2 hours

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

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



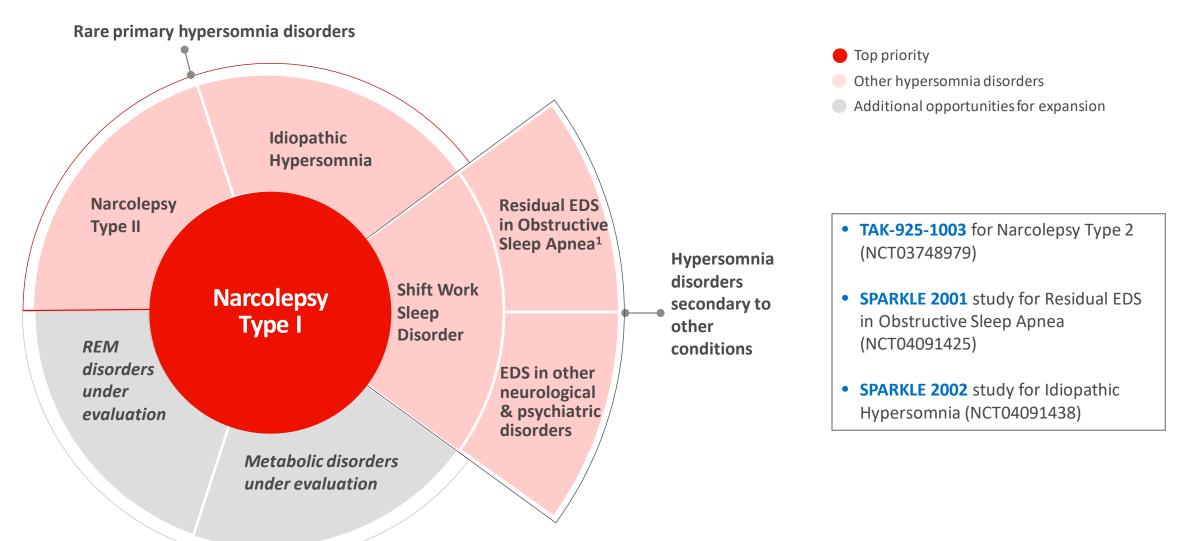
SLEEP LATENCY IN THE MAINTENANCE OF WAKEFULNESS TEST (MWT) IN SLEEP-DEPRIVED HEALTHY ADULTS¹



^{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. <u>http://www.professionalabstracts.com/ws2019/iPlanner/#/presentation/2821</u> 2. Int J Neurosci. 1990 May;52(1-2):29-37

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

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



Takeda

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



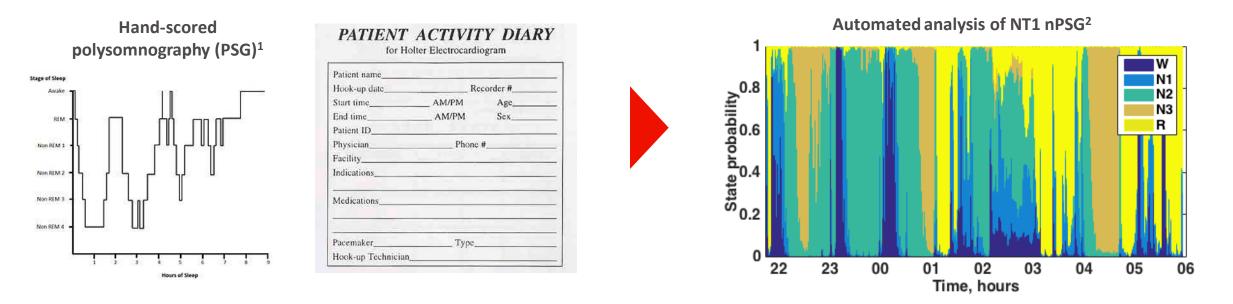
- Multi-center, placebo-controlled trial in North America and Japan
- Enrollment target: 72 adults
- Duration of treatment: 28 days dosing
- Exploratory outcome measures include Maintenance of Wakefulness Test (MWT), Epworth Sleepiness Scale (ESS), and Weekly Cataplexy Rate (WCR)

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

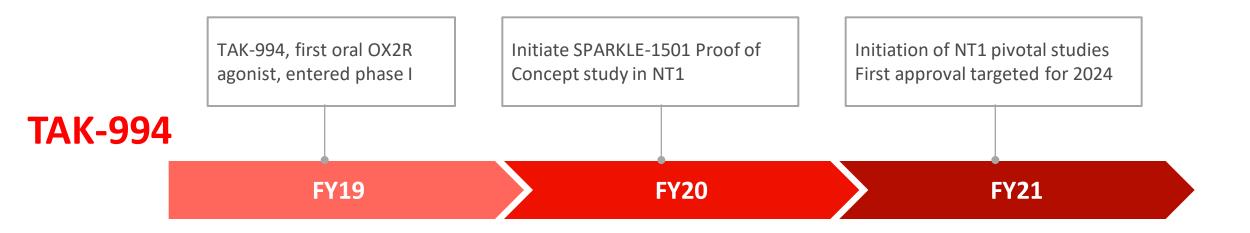
1. Approximately 80% interrater concordance based on Danker-Hopfe et al., J Sleep Res (2009) and Younes & Hanly, J Clin Sleep Med (2016); 2. Analysis shown is based on Stephansen et al., Nature Comm (2018)

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



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



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



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



THERAPEUTIC AREA FOCUS IN GI WITH SPOTLIGHT ON CELIAC DISEASE

Asit Parikh, MD, PhD Head Gastroenterology Therapeutic Area Unit Takeda Pharmaceutical Company Limited

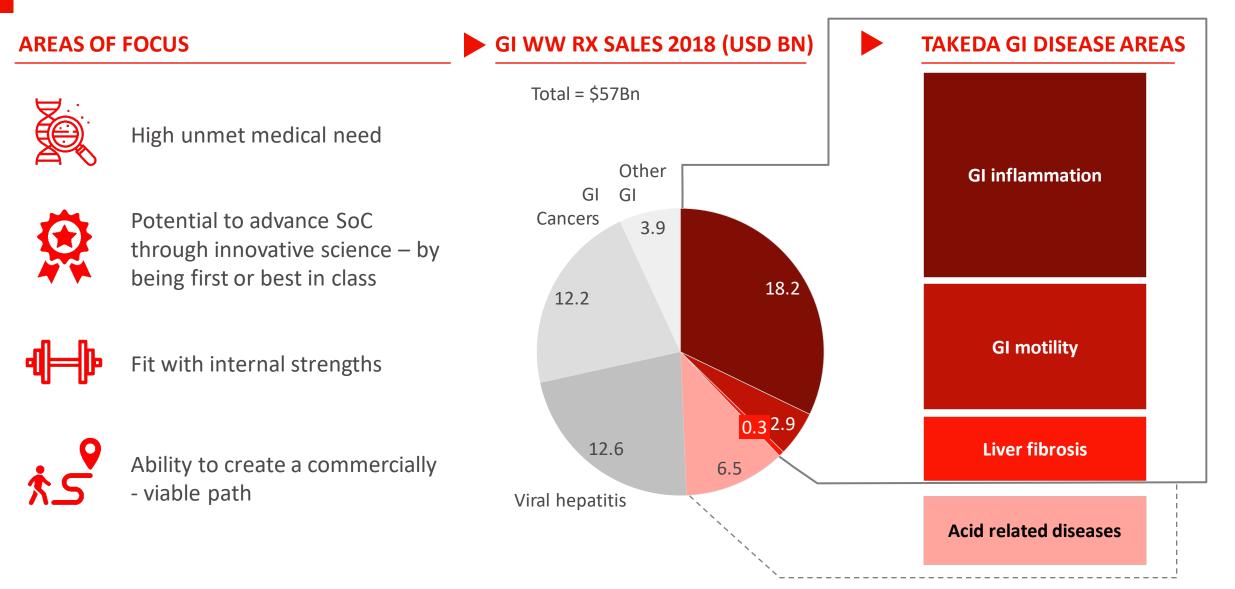
New York, NY

November 14, 2019



WE TARGET UNMET NEEDS THAT ALIGN WITH OUR STRENGTHS





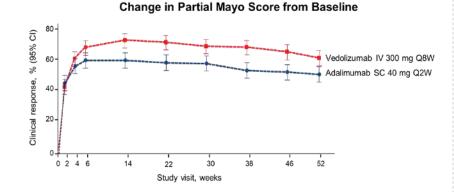
WE STRENGTHEN ENTYVIO BY CONTINUOUSLY IMPROVING **VALUE FOR PATIENTS**



(¥) **COMPETITIVE POSITIONING**

VARSITY: 1st Head-to-Head study in IBD (UC)

- Vedolizumab was superior to adalimumab on the primary endpoint of clinical remission at wk 52
- Onset of action as rapid as anti-TNF



EXPANDED PATIENT POPULATIONS

Entyvio Subcutaneous Development

- Positive VISIBLE UC and CD trials
- Subject to regulatory approval, on track to launch exclusive, digital, needle-free jetinjector by 2022

GEOGRAPHIC EXPANSION

Entyvio IV

- Approved in **68 countries**
- Launched in Japan (UC: Nov 2018, CD: May 2019)

Prefilled syringe

^u	comje		pen	10
	Window	Body	Rear Cap	
		100		

Autoinjector pen				Portal jet-injector
Cap	Window	Body	Rear Cap	•
	\bigcirc		C	•

Gut GvHD prophylaxis

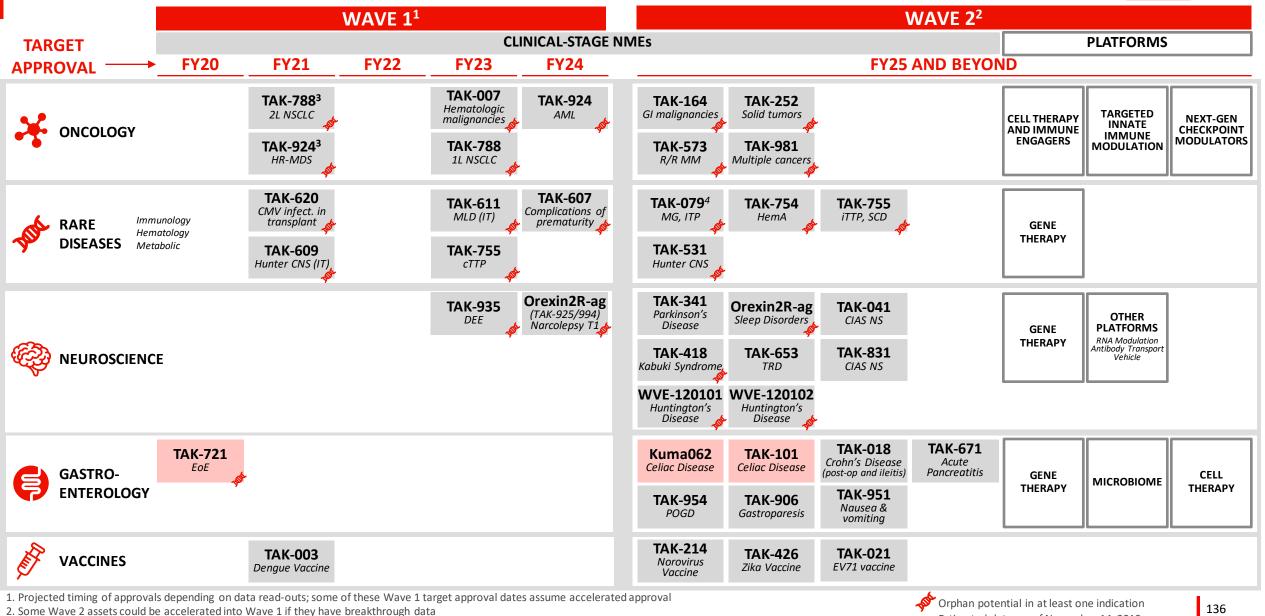
Could **transform SoC** for cancer patients undergoing allo stem-cell transplants

EXPECTED 2019 2020 2021 **MILESTONES (FY)** Entyvio (SC UC) US approval Entyvio (SC CD) US, EU approval **Entyvio GvHD Ph3 readout** Entyvio (SC UC) EU, JP approval Entyvio (IV) CN approval

Source: Sands et al. Vedolizumab versus Adalimumab for Moderate-to-Severe Ulcerative Colitis. N Engl J Med 2019; 381:1215-1226

IBD: Inflammatory Bowel Disease; UC: ulcerative colitis; CD: Crohn's Disease; IV=intravenous; SC=subcutaneous; TNF=tumour necrosis factor; SoC: standard of care; CN: China; JP: Japan; GvHD: graft versus host disease; Clinical remission: Complete Mayo score of ≤ 2 points and no individual subscore >1 point

WE ARE POSITIONED TO DELIVER NEAR-TERM & SUSTAINED GROWTH Takeda



3. Projected approval date assumes filing on Phase 2 data

4. TAK-079 to be developed in Rare Diseases indications myasthenia gravis (MG) and immune thrombocytopenic purpura (ITP) (FPI projected in each indication in 2H FY19)

Estimated dates as of November 14, 2019

TAK-721: ON TRACK TO BE THE FIRST FDA APPROVED AGENT TO TREAT EOSINOPHILIC ESOPHAGITIS (EOE)



ADDRESSES SIGNIFICANT UNMET NEED

- Chronic, allergic, inflammatory condition of the esophagus that results in swallowing dysfunction
- Diagnosed prevalence is expected to increase significantly



No approved US medication SOC is food elimination, off-label use¹



TAK-721 granted breakthrough therapy designation by FDA in 2016

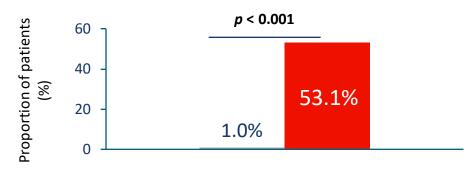
EXPECTED 2019 2020	2021
MILESTONES (FY) Q4: Maintenance Q2: NDA TL results Q4: Approx	e .

1. Swallowed use of glucocorticoids intended for asthma (e.g., home or compounded thickening of budesonide solution, or swallowing fluticasone aerosol).

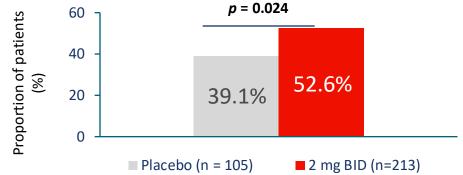
INDUCTION DATA SHOWS SIGNIFICANT HISTOLOGIC AND SYMPTOM RESPONSE

Results presented at presidential plenary at ACG, Texas, Oct 2019

Histologic Response at 12 Weeks (peak ≤ 6 eosinophils/hpf on biopsy)



Symptom Response at 12 Weeks (≥ 30% reduction in DSQ score)

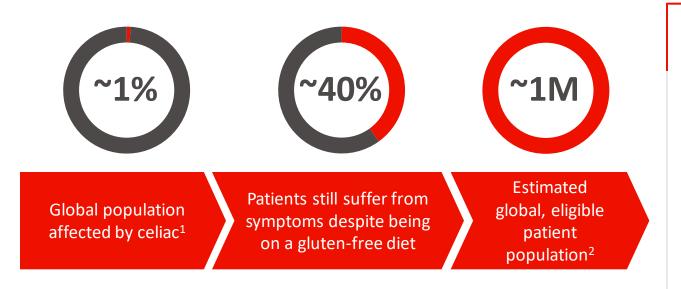


DSQ score: Dysphagia Symptom Questionnaire patient reported outcome score eos/hpf: peak eosinophils per high-powered field from endoscopic biopsies

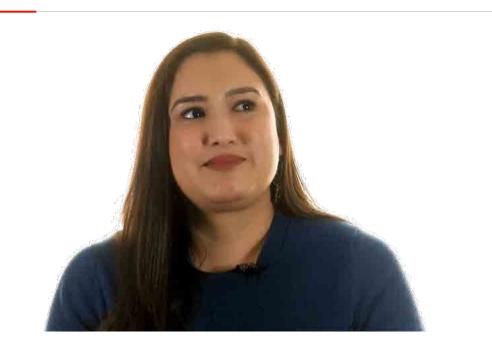
Eos/hpf: eosinophils per high-power field; BID: Twice daily; SOC: Standard of care; NDA: new drug application

CELIAC DISEASE IS AN EXAMPLE OF A HIGH UNMET NEED AREA WITH NO THERAPIES





- Overlooked disease, growing prevalence
- Chronic symptoms
- Higher risk of certain cancers
- High treatment burden affecting the whole family
- No current pharmacologic therapies



 Some of us are so extremely sensitive that one little crumb will make us extremely sick. I'm one of those people, and there is really nothing I can do about it

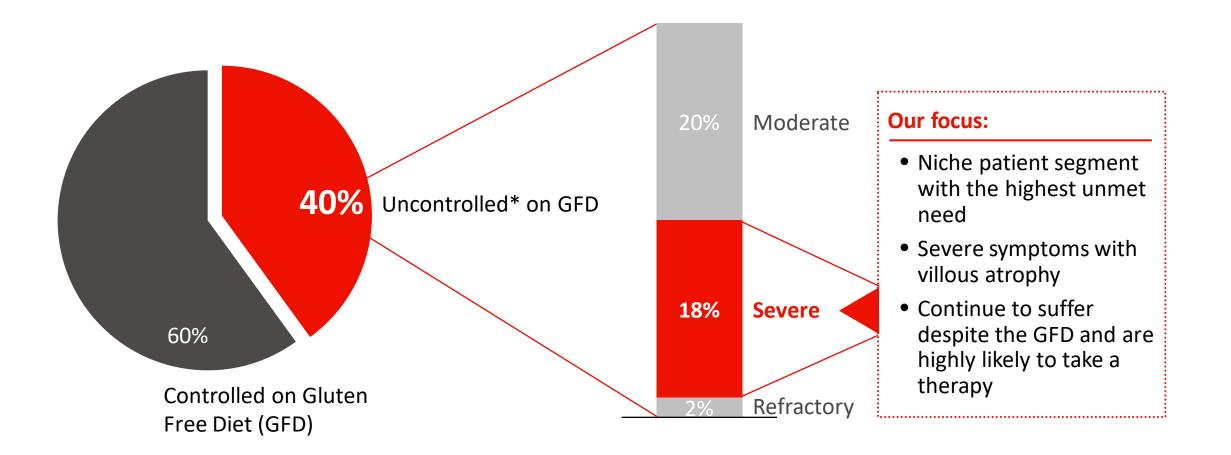
- Delisi, Celiac disease patient

1. Pooled global prevalence; Clin Gastroenterol Hepatol. 2018 Jun;16(6):823-836

2. Estimated number of patients projected eligible for treatment, in markets where the product is anticipated to be commercialized, subject to regulatory approval

WE ARE FOCUSING ON THE NARROWEST POPULATION WITH HIGH UNMET NEED

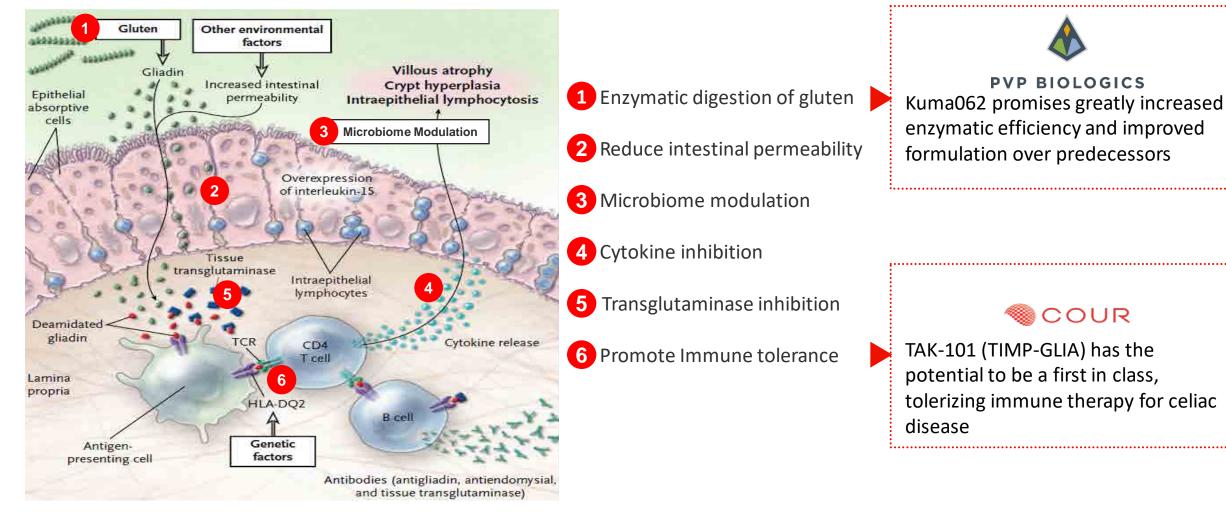




OUR APPROACH TO TREATING CELIAC DISEASE



TREATMENT OPPORTUNITIES FOR CELIAC DISEASE

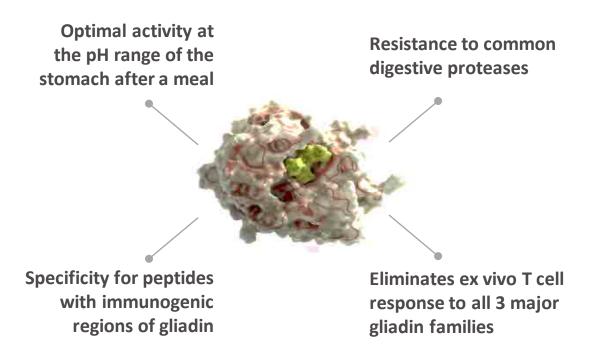


KUMA062: A HIGHLY POTENT ORAL GLUTENASE THAT COULD CHANGE THE STANDARD OF CARE IN CELIAC DISEASE



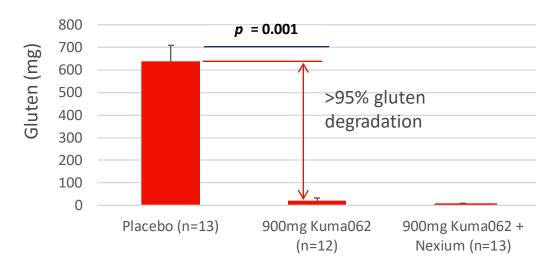
ABOUT KUMA062

- Kuma062 is an oral, computationally-engineered super glutenase
- Enhanced catalytic activity compared to other glutenases



CLINICAL DATA SHOWS KUMA062 CAN DEGRADE >95% OF INGESTED GLUTEN

Gluten recovery in gastric contents aspirated 30mins after meal containing 3g of gluten



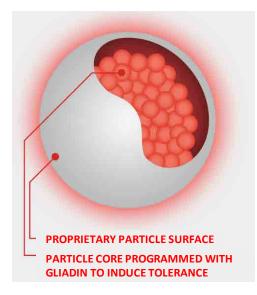
- Kuma well-tolerated, no identified safety concern
- Decision to acquire PVP Biologics expected Q3 FY2019

TAK-101: POTENTIAL BEST-IN-CLASS, INTRAVENOUS THERAPY FOR CELIAC DISEASE DESIGNED TO MODIFY T CELL RESPONSE



ABOUT TAK-101*

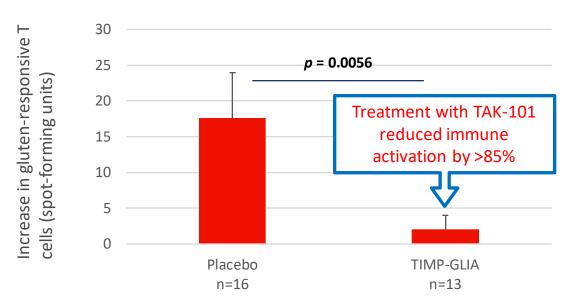
- Biodegradable polymer encapsulating antigen
- Designed to induce tolerance to gluten, reduce T cell responses to gliadin



• Expected to provide durable (3 months or longer) down regulation of T cell responses to immunogenic gliadin peptides

TAK-101 REDUCES IMMUNE ACTIVATION AFTER GLUTEN EXPOSURE

Interferon-gamma ELISPOT measurement of gluten-responsive T cells



TAKEDA ACQUIRED EXCLUSIVE GLOBAL LICENSE TO TAK-101



WE ARE LEADING THE SCIENCE IN CELIAC DISEASE WITH A NEW AI - BASED TOOL AND INGESTIBLE DEVICE





Innovative, non-invasive, patented method of measuring total burden of intestinal disease

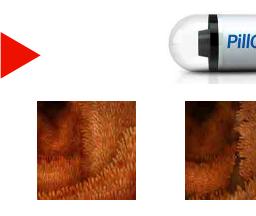


- Ingestible high resolution camera pill ۲
- Modern machine-learning/ AI based image processing

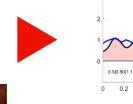


Pioneering Automated Image assessment quantifies disease burden

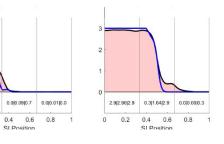


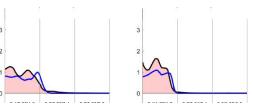






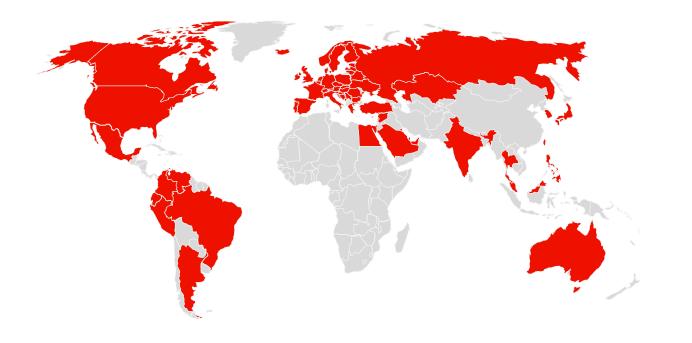
02





TAKEDA IS THE BEST COMPANY TO BRING CELIAC THERAPIES TO PATIENTS

World-class, fully connected GI commercial infrastructure across 65+ countries that supports \$6bn+ revenues



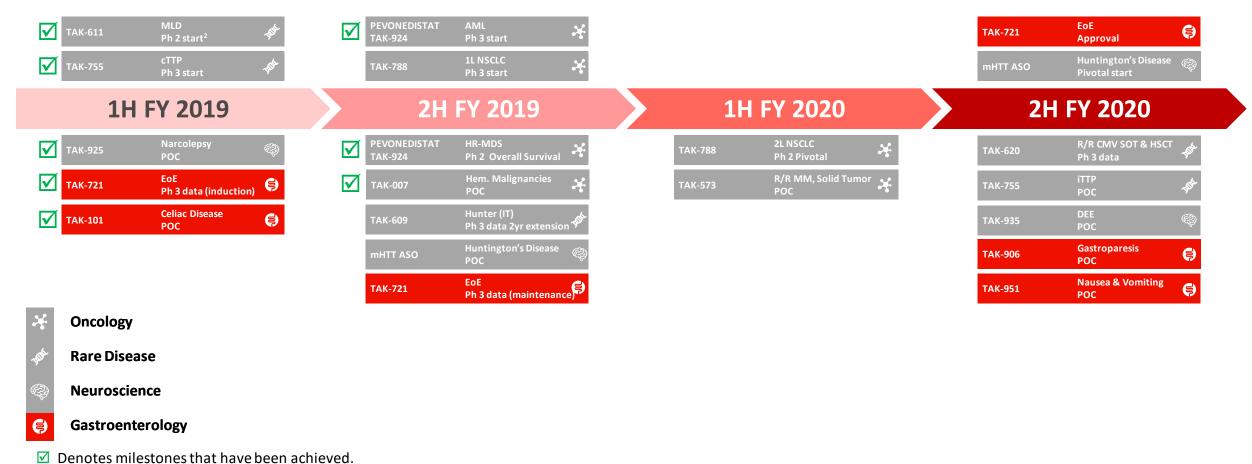


- Extensive GI clinical footprint
- Strong reputation for scientific excellence
- Lauded for calculated risk-taking by the GI community
- Experience with redefining guidelines and treatment paths

NME MILESTONES ACHIEVED IN FY19 AND LOOKING AHEAD TO OTHER POTENTIAL MILESTONES¹ THROUGH FY20



PIVOTAL STUDY STARTS, APPROVALS



KEY DATA READOUTS

1. Potential key milestone dates as of November 14, 2019. The dates included herein are estimates based on current data and are subject to change 2. Potentially registration enabling

SUMMARY



1

We have built an industry-leading portfolio rooted in unparalleled scientific excellence and outstanding global commercial strength

2

We are well positioned to bring the first therapies to celiac patients that could change the standard of care

3

We have multiple milestones, including expected key approvals in the next 2 years that will be transformative for patients

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



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

Panel Q&A Session

