TAKEDA NEUROSCIENCE

BRINGING INNOVATIVE MEDICINES TO PATIENTS FOR WHOM THERE ARE NO TREATMENTS AVAILABLE

EMILIANGELO RATTI, PHD
Head, Neuroscience Therapeutic Area

WE HAVE TAKEN ON THE CHALLENGE TO ALLEVIATE THE IMMENSE PATIENT NEED IN NEUROSCIENCE

MISSION

To bring innovative medicines to patients suffering from neurologic and psychiatric diseases for **whom there are no treatments available**

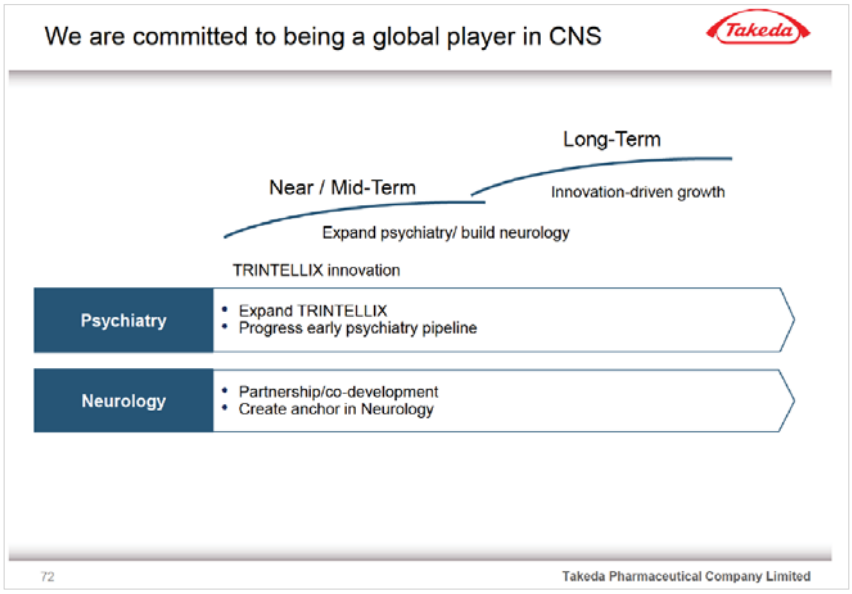
FOCUS

- Treatment Resistant Depression
- Schizophrenia Negative Symptoms & CIAS
- Alzheimer's Disease
- Parkinson's Disease
- ***Selected rare CNS diseases***

CIAS: Cognitive Impairment Associated with Schizophrenia

WE HAVE EXECUTED ON THE ROADMAP DESCRIBED IN 2016

FROM 2016 R&D DAY



KEY COMPONENTS OF ROADMAP

- Differentiate TRINTELLIX
- Advance early pipeline towards POC
- Further expand in neurology and rare CNS diseases through partnerships

BUILDING AN INNOVATIVE PIPELINE ENHANCED WITH EXTERNAL PARTNERSHIPS

	Discovery/Preclinical[1]	Phase 1*	Phase 2	Phase 3	Approved**
Depression		**TAK-653** **AMPA PAM** **Treatment Resistant Depression** *Small Molecule*			**TRINTELLIX** ***Processing Speed sNDA Approved 2018*** **TESD sNDA (US) Submitted** **MDD (JP) To be submitted**
Schizophrenia		**TAK-041** **GPR139 Agonist, 2xFT** *Small Molecule*	**TAK-831** **DAAO Inhibitor, 2xFT** *Small Molecule*		
Parkinson's Disease		AstraZeneca **MEDI1341** **α-synuclein mAb** *Monoclonal Antibody*			teva **AZILECT** **PD (JP) Launched 2018**
Alzheimer's Disease	DENALI **BACE1/TAU, TREM2, Undisclosed** *Antibody Transport Vehicle Monoclonal Antibody*				
Rare CNS Diseases	WAVE **C9orf72, ATXN3, Multiple targets** *Stereopure Antisense Oligonucleotide*	**TAK-925, Narcolepsy, OD** **OX2R Agonist** *Small Molecule* **TAK-418, Kabuki Syndrome, OD** **LSD1 Inhibitor** *Small Molecule* WAVE **WVE-120101; WVE-120102** **Huntington's Disease, OD** *Stereopure Antisense Oligonucleotide*	ovid **TAK-935** **Epileptic Encephalopathy, OD** **CH24H Inhibitor** *Small Molecule* **TAK-831** **Friedreich's Ataxia, OD, FT** **DAAO Inhibitor** *Small Molecule*		

* Assets shown in discovery/preclinical and Phases 1–3 explicitly refer to new molecular entities

** Some with active development seeking new or supplemental indications, or approvals in new territories

External collaboration FT = Fast Track OD = Orphan Designation *New partnerships since June 2016* *Progress since June 2016 shown in red*

Pipeline as of September 23, 2018

[1] Discovery/preclinical phase: Only external collaborations shown, does not include internal programs

WE HAVE BUILT OUR PORTFOLIO THROUGH THREE MAIN LEVERS

EXECUTED ON OPPORTUNITIES WITH LATE-STAGE ASSETS

- **Successful differentiation of TRINTELLIX**
- Launched AZILECT in Japan

ADVANCED EARLY STAGE PIPELINE TOWARDS POC

- TAK-925 Narcolepsy
- TAK-831 Schizophrenia, Friedreich's Ataxia
- TAK-935 Epileptic Encephalopathy

EXPANDED IN NEURODEGENERATION AND RARE DISEASE WITH WORLD CLASS PARTNERS

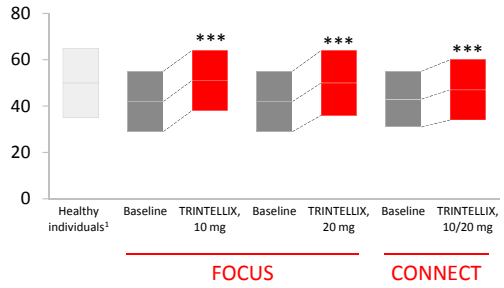
- Denali Therapeutics partnership to address extracellular targets with highly brain penetrant monoclonal antibodies
- Wave Life Sciences partnership to address intracellular targets with stereopure oligonucleotides
- AstraZeneca partnership to treat Parkinson's Disease

TRINTELLIX SHOWS BENEFITS IN PROCESSING SPEED, AN IMPORTANT ASPECT OF COGNITION, AND TREATMENT EMERGENT SEXUAL DYSFUNCTION FOR PATIENTS WITH MDD

COGNITIVE FUNCTION (PROCESSING SPEED)

Digit Symbol Substitution Test (DSST) after 8 weeks of treatment

Total number of correct symbols; mean score with standard deviation



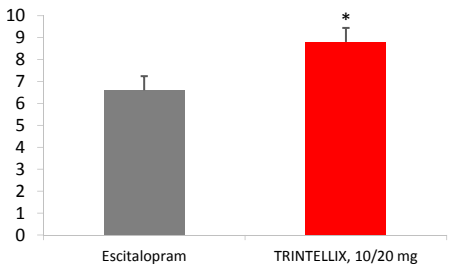
- **In May 2018, FDA approved sNDA that includes DSST, which most specifically measures processing speed, an important aspect of cognition**
- TRINTELLIX® is the first MDD treatment labelled for improvement of processing speed, an important aspect of cognitive function

[1] Normative data from healthy individuals
***p<0.001 vs baseline
Change from baseline was also significant vs placebo in both FOCUS and CONNECT studies
CONNECT study: Mahableshwarkar AR, et al. Neuropsychopharmacology. 2015
FOCUS study: McIntyre RS, et al. Int J Neuropsychopharmacol. 2014
MDD = Major Depressive Disorder

TREATMENT EMERGENT SEXUAL DYSFUNCTION

Changes in Sexual Functioning Questionnaire (CSFQ-14) after 8 weeks of treatment

Change from baseline in CSFQ-14 total score; least squares mean, standard error



- **TRINTELLIX showed statistical superiority to escitalopram in improving sexual dysfunction while maintaining efficacy** in MDD patients with SSRI-induced sexual dysfunction
- **Submitted sNDA to include TESD recovery data in label;** FDA decision expected in 4Q 2018
- Overall, the safety profile of vortioxetine in these studies was consistent with that in the approved vortioxetine label

* Statistically superior to escitalopram; p<0.05
Jacobsen et al. Journal of Sexual Medicine 2015

In collaboration with Lundbeck

WE HAVE BUILT OUR PORTFOLIO THROUGH THREE MAIN LEVERS

EXECUTED ON OPPORTUNITIES WITH LATE-STAGE ASSETS

- Successful differentiation of TRINTELLIX
- Launched AZILECT in Japan

ADVANCED EARLY STAGE PIPELINE TOWARDS POC

- **TAK-925 Narcolepsy**
- TAK-831 Schizophrenia, Friedreich's Ataxia
- TAK-935 Epileptic Encephalopathy

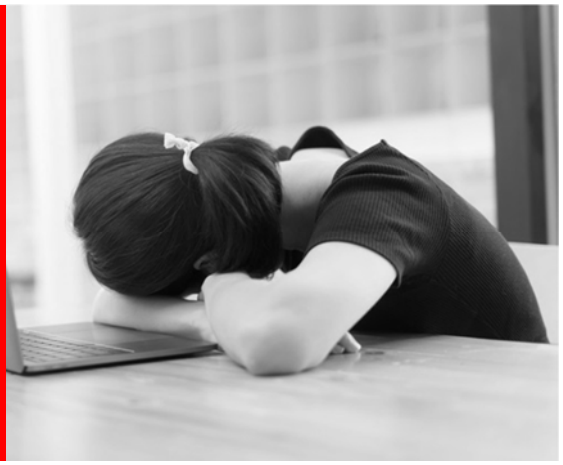
EXPANDED IN NEURODEGENERATION AND RARE DISEASE WITH WORLD CLASS PARTNERS

- Denali Therapeutics partnership to address extracellular targets with highly brain penetrant monoclonal antibodies
- Wave Life Sciences partnership to address intracellular targets with stereopure oligonucleotides
- AstraZeneca partnership to treat Parkinson's Disease

DESPITE CURRENT TREATMENTS, PATIENTS WITH NARCOLEPSY TYPE 1 (NT1) SUFFER FROM A RANGE OF DEBILITATING SYMPTOMS

NARCOLEPSY TYPE 1

- Affects ~100K patients in US (~400K in G-7), with typical disease onset from 7-25 years old[1]
- Symptoms characterized by:
  - Excessive daytime sleepiness
  - Sleep/wake fragmentation
  - Cataplexy
- Current treatments are only partially effective and only provide benefit for some disease symptoms



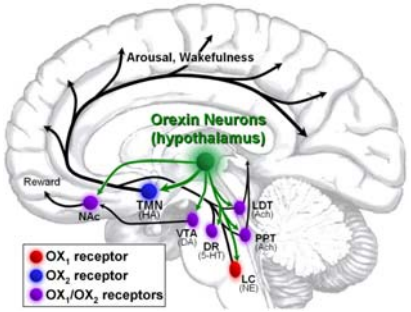
"We take our current meds to **survive.** We want new medications to help us **live.**"

Narcolepsy patient advisor
Patient Advisory Board sponsored by Takeda

[1] Longstreth. Sleep. 2007;30(1):13

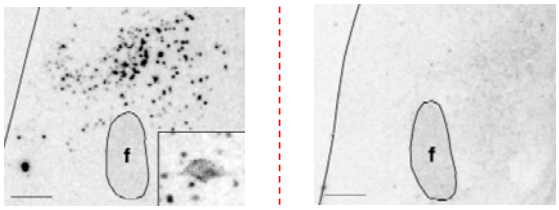
NARCOLEPSY TYPE 1 IS CAUSED BY LOSS OF OREXIN PRODUCING NEURONS

HYPOTHALAMIC OREXIN PRODUCING NEURONS[1]

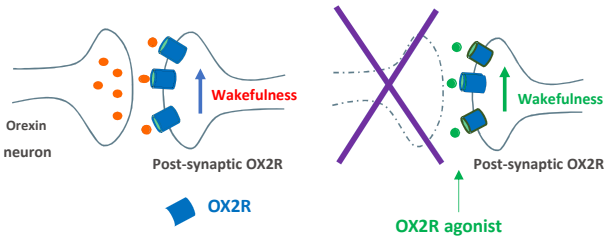


- **OX1Rs:** activate brain's reward systems
- **OX2Rs:** activate arousal and wakefulness

OREXIN mRNA LABELLING OF POSTMORTEM HYPOTHALAMIC SECTIONS[2]



- Orexin mRNA transcripts are detected in control but not in Narcolepsy Type 1 patients
- Orexin receptors may remain functional in Narcolepsy Type 1 patients



LEADING RESEARCH TO SUPPORT THE OREXIN HYPOTHESIS

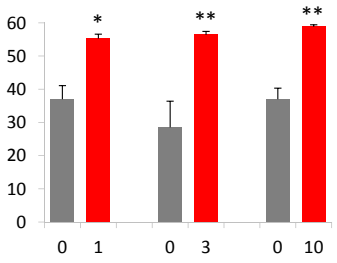
An orexin 2 receptor agonist may mimic the missing endogenous peptide (orexin) and address the neurotransmitter deficiency of Narcolepsy Type 1 leading to reduction in disease specific symptoms

[1] Pharmacol Rev 389–420, 2012
[2] Nature Medicine 2000 Vol 6 p 991-997

TAK-925 IS A SELECTIVE OX2R AGONIST SHOWING REDUCTION IN NARCOLEPSY-LIKE SYMPTOMS IN A MOUSE MODEL

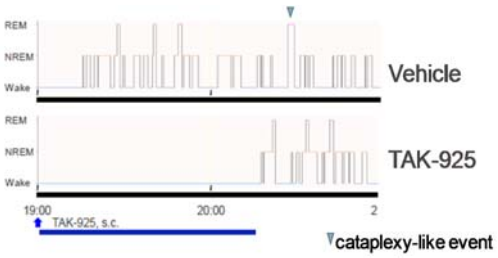
TAK-925 FULLY RESTORED WAKEFULNESS

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



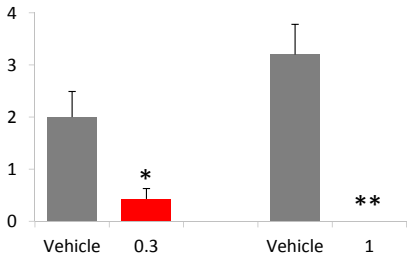
TAK-925 ELIMINATED SLEEP / WAKE TRANSITIONS

Hypnogram of sleep/wake transitions in NT1 mouse model
EEG recordings



TAK-925 ABOLISHED CATAPLEXY-LIKE EPISODES

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



Phase I clinical studies are ongoing to evaluate safety and efficacy of TAK-925

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

WE HAVE BUILT OUR PORTFOLIO THROUGH THREE MAIN LEVERS

EXECUTED ON OPPORTUNITIES WITH LATE-STAGE ASSETS

- Successful differentiation of TRINTELLIX
- Launched AZILECT in Japan

ADVANCED EARLY STAGE PIPELINE TOWARDS POC

- TAK-925 Narcolepsy
- TAK-831 Schizophrenia, Friedreich's Ataxia
- TAK-935 Epileptic Encephalopathy

EXPANDED IN NEURODEGENERATION AND RARE DISEASE WITH WORLD CLASS PARTNERS

- **Denali Therapeutics partnership to address extracellular targets with highly brain penetrant monoclonal antibodies**
- **Wave Life Sciences partnership to address intracellular targets with stereopure oligonucleotides**
- AstraZeneca partnership to treat Parkinson's Disease

ADVANCES IN GENETICS, BIOMARKERS AND ALTERNATIVE MODALITIES DROVE OUR EXPANSION INTO NEURODEGENERATION AND RARE DISEASE

NEURODEGENERATION

Neurodegenerative diseases are **proteinopathies** that can be addressed by **new modalities** with greater precision than before e.g., **monoclonal antibodies and antisense oligonucleotides**

RARE CNS DISEASES

Genetically defined CNS diseases provide the opportunity to develop targeted therapies employing **new modalities** e.g., **antisense oligonucleotides, gene therapy**

MANY NEURODEGENERATIVE DISEASES CAN BE ADDRESSED WITH ALTERNATIVE MODALITIES TARGETED TO PATHOGENIC PROTEINS

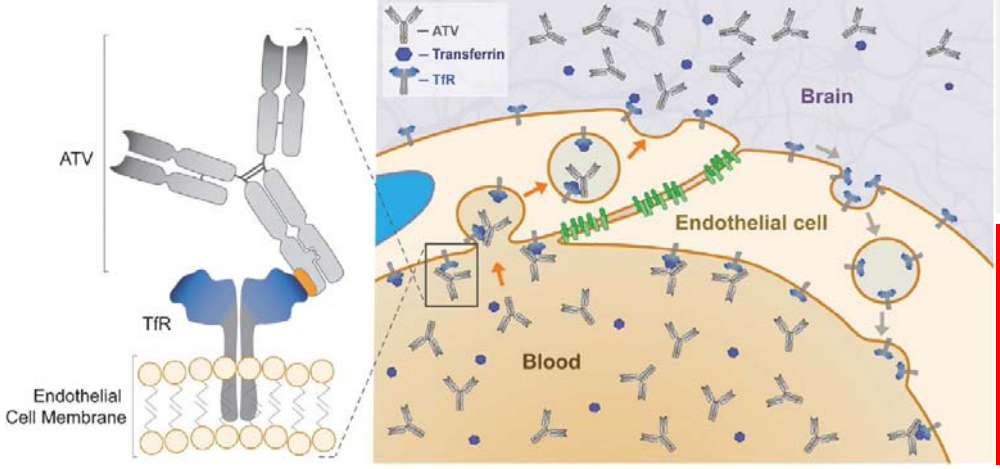
Antisense oligonucleotides can reduce *intracellular* expression of toxic proteins

Monoclonal antibodies can clear pathogenic *extracellular* proteins

ASOs and mAbs could be combined for greater efficacy

Pathogenic protein monomers, oligomers, and fibrils can spread from neuron to neuron and propagate the disease

PARTNERSHIP WITH DENALI HAS REINFORCED OUR ALZHEIMER'S DISEASE PORTFOLIO WITH HIGHLY BRAIN PENETRANT MONOCLONAL ANTIBODIES



Antibody Transport Vehicles (ATVs) enable up to > 20X higher brain penetration of monoclonal antibodies than the same antibody without ATV[1]

Collaboration agreement to co-develop three named programs

- ATV: BACE1 / TAU
- ATV: TREM2
- Additional undisclosed program

[1] Denali Therapeutics S-1/A

PARTNERSHIP WITH WAVE LIFE SCIENCES ENABLES TARGETED THERAPIES TO RARE CNS DISEASES WITH STEREOPURE ANTISENSE OLIGONUCLEOTIDES

SYNTHESIS OF STEREOPURE OLIGONUCLEOTIDES: A SIGNIFICANT IMPROVEMENT IN THE FIELD

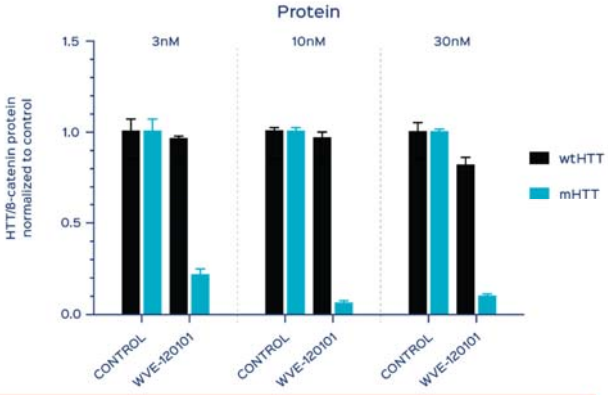
STANDARD OLIGONUCLEOTIDE APPROACHES

Racemic mixture up to >500,000 molecules per sequence

WAVE RATIONAL DESIGN

Selection of 1 stereopure molecule per sequence allows a proper optimization of desired drug properties

STEREOPURE APPROACH ENABLES ALLELE-SPECIFIC TARGETING OF DISEASE GENES



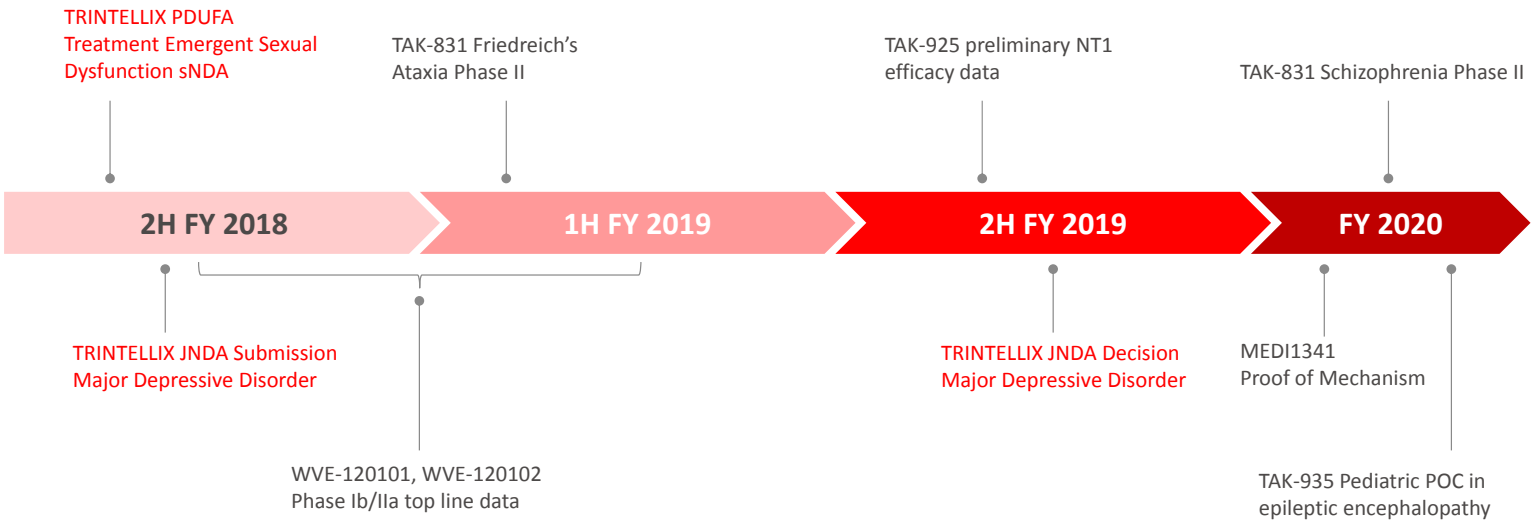
PARTNERSHIP PROVIDES:

- **Option to co-develop and co-commercialize programs for rare CNS diseases (Huntington's Disease, Amyotrophic Lateral Sclerosis, Frontotemporal Dementia and Spinocerebellar Ataxia Type 3)**
- **Exclusive license to research, develop, and commercialize multiple additional programs for CNS indications**

Courtesy of Wave Life Sciences

EXPECTED KEY NEUROSCIENCE PORTFOLIO INFLECTIONS AND MILESTONES

Dates in fiscal year (FY) starting April 1st



Regulatory Filing or Anticipated Approval

Projected timelines as of September 23, 2018, subject to change

CONCLUSION

1. Successful differentiation of TRINTELLIX in processing speed, an important aspect of cognitive function, and treatment emergent sexual dysfunction in MDD

2. Progressed TAK-925, the first OX2R agonist, as potential transformative therapy for Narcolepsy Type 1

3. Expanded in neurodegeneration and CNS rare disease with world-class partners (exemplified by Wave and Denali partnerships)