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
• **Selected rare CNS diseases**
• Alzheimer’s Disease
• Parkinson’s Disease

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

<table>
<thead>
<tr>
<th>Discovery/Preclinical¹</th>
<th>Phase 1*</th>
<th>Phase 2</th>
<th>Phase 3</th>
<th>Approved**</th>
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<tbody>
<tr>
<td><strong>Depression</strong></td>
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<tr>
<td>TAK-653</td>
<td>AMPA PAM</td>
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<td>Treatment Resistant Depression</td>
<td>Small Molecule</td>
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<td><strong>Schizophrenia</strong></td>
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<td>TAK-041</td>
<td>GPR139 Agonist, 2xFT</td>
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<tr>
<td>Small Molecule</td>
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<td><strong>Parkinson’s Disease</strong></td>
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<td>AstraZeneca</td>
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<tr>
<td>MEDI1341</td>
<td>α-synuclein mAb</td>
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<td>Monoclonal Antibody</td>
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<td><strong>Alzheimer’s Disease</strong></td>
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<tr>
<td>BACE1/TAU, TREM2, Undisclosed Antibody Transport Vehicle Monoclonal Antibody</td>
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<td><strong>Rare CNS Diseases</strong></td>
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<tr>
<td>WVE-120101; WVE-120102</td>
<td>Huntington’s Disease, OD</td>
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<tr>
<td>Stereopure Antisense Oligonucleotide</td>
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<td><strong>External collaboration</strong></td>
<td>FT = Fast Track</td>
<td>OD = Orphan Designation</td>
<td>New partnerships since June 2016</td>
<td>Progress since June 2016 shown in red</td>
</tr>
</tbody>
</table>

### Footnotes:

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

### Notes:

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

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

Pipeline as of September 23, 2018

TRINTELLIX
Processing Speed sNDA
Approved 2018
TESD sNDA (US) Submitted
MDD (JP) Submitted

AZILECT
PD (JP) Launched 2018

TEVA
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

![Graph showing DSST results](image)

**CONNECT study:**
Mahableshwarkar AR, et al. Neuropsychopharmacology. 2015

**FOCUS study:**

MDD = Major Depressive Disorder

• 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

**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

![Graph showing CSFQ-14 results](image)

• 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

In collaboration with Lundbeck
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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.**”

\(^1\) Longstreth. Sleep. 2007;30(1):13
NARCOLEPSY TYPE 1 IS CAUSED BY LOSS OF OREXIN PRODUCING NEURONS

OREXIN mRNA LABELLING OF POSTMORTEM HYPOTHALAMIC SECTIONS\(^1\)

- 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

\(^1\) 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

<table>
<thead>
<tr>
<th>Minutes awake</th>
<th>Vehicle</th>
<th>TAK-925 (0.3 mg/kg)</th>
<th>TAK-925 (1 mg/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
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<tr>
<td>1</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
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<tr>
<td>3</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
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<tr>
<td>10</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
<td>60 ± 10</td>
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* *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

**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
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Monoclonal antibodies can clear pathogenic extracellular proteins

Antisense oligonucleotides can reduce intracellular expression of toxic 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

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

- 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

PARTNERSHIP PROVIDES:

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

Racemic mixture up to >500,000 molecules per sequence

STANDARD OLIGONUCLEOTIDE APPROACHES

Courtesy of Wave Life Sciences
EXPECTED KEY NEUROSCIENCE PORTFOLIO INFLECTIONS AND MILESTONES

Dates in fiscal year (FY) starting April 1st

TRINTELLIX PDUFA
Treatment Emergent Sexual Dysfunction sNDA

2H FY 2018

TAK-831 Friedreich’s Ataxia Phase II

1H FY 2019

TAK-925 preliminary NT1 efficacy data

2H FY 2019

TAK-831 Schizophrenia Phase II

FY 2020

TRINTELLIX JNDA Submission Major Depressive Disorder

WVE-120101, WVE-120102 Phase Ib/Ila top line data

TRINTELLIX JNDA Decision Major Depressive Disorder

MEDI1341 Proof of Mechanism

TAK-935 Pediatric POC in epileptic encephalopathy

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

Regulatory Filing or Anticipated Approval
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<td><strong>1</strong></td>
<td><strong>2</strong></td>
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<tr>
<td>Successful differentiation of TRINTELLIX in processing speed, an important aspect of cognitive function, and treatment emergent sexual dysfunction in MDD</td>
<td>Progressed TAK-925, the first OX2R agonist, as potential transformative therapy for Narcolepsy Type 1</td>
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