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- Furthermore, for products that are approved, there are manufacturing and marketing risks and uncertainties, which include, but are not limited to, inability to build production capacity to meet demand, unavailability of raw materials, and failure to gain market acceptance.

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- The Company discloses its consolidated financial statements according to the International Financial Reporting Standards (IFRS).

- This presentation presents information on investigational agents or investigational uses of approved agents that have not received approval by any regulatory agency.
Eisai Neurology Updates

Eisai Co., Ltd.
## Today’s Presentation on Neurology Pipeline

<table>
<thead>
<tr>
<th>Project</th>
<th>Disease/Disorder</th>
<th>Phase/Status</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Elenbecesat</strong>&lt;sup&gt;1&lt;/sup&gt; BACE inhibitor</td>
<td>Early Alzheimer’s disease</td>
<td>Phase III ongoing</td>
</tr>
<tr>
<td><strong>BAN2401</strong>&lt;sup&gt;1,2&lt;/sup&gt; Anti-Aβ protofibrils antibody</td>
<td>Early Alzheimer’s disease</td>
<td>Phase III ongoing</td>
</tr>
<tr>
<td><strong>E2027</strong> PDE9 inhibitor</td>
<td>Dementia with Lewy bodies</td>
<td>Phase II/III ongoing</td>
</tr>
<tr>
<td><strong>E2814</strong> Anti-tau antibody</td>
<td>Early Alzheimer’s disease</td>
<td>Under preparation for Phase I</td>
</tr>
<tr>
<td><strong>E2511</strong> Synapse regenerant</td>
<td>Alzheimer’s disease, dementia</td>
<td>Preclinical study ongoing</td>
</tr>
<tr>
<td><strong>EphA4 Project</strong>&lt;sup&gt;3&lt;/sup&gt; Synapse modulator</td>
<td>Alzheimer’s disease, dementia</td>
<td>Preclinical study ongoing</td>
</tr>
<tr>
<td><strong>Immuno-Dementia Project</strong>&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Alzheimer’s disease, dementia</td>
<td>Preclinical study ongoing</td>
</tr>
<tr>
<td><strong>Brain Defense Mechanism Research</strong>&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Alzheimer’s disease, dementia</td>
<td>Preclinical study ongoing</td>
</tr>
<tr>
<td><strong>Lemborexant</strong> Dual orexin receptor antagonist</td>
<td>Insomnia disorder, including older patients</td>
<td>Submitted in Japan and U.S.</td>
</tr>
<tr>
<td><strong>E2082</strong> Next-generation AMPA receptor antagonist</td>
<td>Epilepsy and other neurological disorders including dementia</td>
<td>Phase II study ongoing</td>
</tr>
<tr>
<td><strong>E2730</strong> Synaptic functional modulator with novel MOA</td>
<td>Epilepsy and other neurological disorders including dementia</td>
<td>Phase II study ongoing</td>
</tr>
<tr>
<td><strong>E6011</strong> Anti-Fractalkine mAb</td>
<td>Rheumatoid arthritis and other neurological disorders</td>
<td>Phase II ongoing (in rheumatoid arthritis only)</td>
</tr>
</tbody>
</table>
Eisai Neurology Updates

1) Neurology Research Overview

Eisai Co., Ltd.
Wider Scope of Dementia

**Preventive**
- BACE inhibitor Elenbecestat*1
- Anti-Aβ protofibrils antibody BAN2401*1,2
- Anti-tau antibody E2814
- PDE9 inhibitor E2027
- Synapse regenerant E2511
- Synapse modulator EphA4 project*3
- Synaptic functional modulator with novel MOA E2730
- Next-generation AMPA receptor antagonist E2082
- Immuno-dementia therapy*4
- Enhancement of in vivo clearance*5

**Preemptive**
- Dual orexin receptor antagonist Lemborexant
- Synapse regenerant E2511
- Synapse modulator EphA4 project*3

**Restorative**
- TSPO° PET
- Amyloid PET
- CSF*7 tau
- Hypometabolism
- MRI Atrophy
- Cognitive impairment

**Regenerative**
- Neural stem cell revitalization*5

Source: Brain 2017 Mar 1;140(3):792-803 (partially modified) All projects are investigational.
*1: Co-development with Biogen. *2: Antibody for Alzheimer's disease produced as the result of a strategic research alliance between Eisai and BioArctic
*3: Research at KAN Research Institute *4: Research at Eisai Center for Genetics Guided Dementia Discovery (G2D2)
*5: Research at Eisai-Keio Innovation Laboratory for Dementia (EKID) *6: Translocator protein *7: Cerebrospinal fluid
According to AD progression, functional neurons decrease and damaged neurons increase, leading to neuronal death.

- **Early Stage**: Functional neuron
- **Middle Stage**: Damaged neuron, Tau
- **Late Stage**: Activated microglia, Dead neuron

AD Pathogenesis Cascade

Preclinical AD  MCI  Mild AD  Moderate AD  Severe AD
Aim to Delay AD Progression, While Reinnervating to Normal Functions

Provide precision medicines to the patients in every disease stage, rescuing and reinnervating neuronal damage

A: Amyloid beta

T: Tau

N: Neurodegeneration

E2511 EphA4 project

All projects are investigational. * ID: Immuno-Dementia
E2814*

(Anti-tau antibody)

* Investigational
Scientific rationale of tau propagation hypothesis

- Tau pathology spreads in tauopathies as the diseases progress.
- Tau spreads through synaptically connected pathways.
- Tau can form ‘seeds’ which can induce and propagate the pathology.
- Use of a therapeutic antibody to prevent aggregation and transmission of tau seeds may have a disease-modifying effect.

All projects are investigational.
Each Anti-tau Antibody Has Different Epitope

Fragments with MTBR induce neuronal toxicity.

<table>
<thead>
<tr>
<th>Fragment</th>
<th>MTBR</th>
<th>Reported function</th>
<th>Example Reference(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 - x</td>
<td>No</td>
<td>No toxicity reported. Present in AD brain synaptosomes.</td>
<td>Sokolow et al., 2015</td>
</tr>
<tr>
<td>14 - 421</td>
<td>Yes</td>
<td>Induces Tau filament formation. Adversely affects cognition. Associates with tangles in AD brain.</td>
<td>Basurto-Islas et al., 2008; Gamblin et al., 2003; Horowitz et al., 2004</td>
</tr>
<tr>
<td>x - 230</td>
<td>No</td>
<td>Not toxic when expressed in cells. Expression of 45-230 fragment in mice caused neurodegeneration.</td>
<td>Garg et al., 2011; Amadoro et al., 2015</td>
</tr>
<tr>
<td>151 - 391</td>
<td>Yes</td>
<td>Present in AD tangle core. Overexpression in rats induced tangle formation.</td>
<td>Zilka et al., 2006</td>
</tr>
<tr>
<td>187 - 441</td>
<td>Yes</td>
<td>Present in AGD, PSP and CBD but not control brain. Expression induces Tau pathology and cognitive decline. AKA Tau35</td>
<td>Wray et al., 2008</td>
</tr>
<tr>
<td>x - 368</td>
<td>Yes</td>
<td>Toxic to neurons and can form fibrils in vitro.</td>
<td>Zhang et al., 2014</td>
</tr>
</tbody>
</table>

Fragments including MTBR* Recognized by E2814 are Assumed as Tau Propagation Seeds in AD

Key Features of E2814

- Structural biology, genetic and biochemical studies highlight the importance of the MTBR* in the pathogenesis of different tauopathies
- E2814 shows high affinity for full-length human tau with a binding epitope in the MTBR* region
- E2814 inhibits tau aggregation \textit{in vitro} and prevents intracellular tau aggregation in cellular systems
- The murine form of E2814 (clone 2h) reduces tau spreading \textit{in vivo} transgenic mouse models
- E2814 recognises fibrillar tau species derived from AD subject brains and stains pathological tau structures from AD brain-derived tissue sections
- A target engagement biomarker has been developed and confirmed in preclinical studies (e.g. non-human primate)

E2814 demonstrated prevention of tau propagation \textit{in vivo} condition
Phase I study under preparation

All projects are investigational *MTBR: microtubule binding region
E2511*
(Synapse regenerant)
Cholinergic Neurons in AD

Decrease of functional cholinergic pre-synapse number (TrkA* positive pre-synapse number) in AD

Correlation between TrkA level and MMSE score in AD

Cholinergic pre-synapse number (Temporal lobe section)

Normal Adult Brain
Alzheimer's Disease Brain

TrkA
VGlut1 (pre-synaptic marker)
TrkA/VGlut1

Cholinergic neurons are most vulnerable in AD, their dysfunction is correlated with cognitive function

All projects are investigational. * TrkA: Tropomyosin receptor kinase A
In vivo Efficacy of E2511

Show the restorative effect on cholinergic neurons in brain of pathological animals

- Restore damaged cholinergic neuron to functional cholinergic neuron in basal forebrain of tau transgenic animals (P301S)
  
  Once daily dosing (oral dosing)

  4 month (Start) 7 month

  Mice were orally administered with vehicle and E2511 once a day for 3 months (from 4-month-old to 7-month-old). After chronic administration for 3 months, the analysis was conducted. Start: start point

- Potential recovery cholinergic pre-synaptic function in hippocampus of lesion animal models
  
  Once daily dosing (oral dosing)

  Lesion (0day) 7days 21days

  Rats were orally administered with vehicle and E2511 once a day for 14 days (from 7 days after lesion to 21 days). After chronic administration for 14 days, the analysis was conducted.

E2511 revitalizes damaged cholinergic neurons to functionalized neurons, resulting in potentially promoting re-innervation of neurons.

Clinical study initiation planned in FY2019

All projects are investigational. *1 ChAT: choline acetyltransferase  *2 VACHT: Vesicular acetylcholine transporter
E2082*  
(Next-generation AMPA receptor antagonist)  

E2730*  
(Synaptic functional modulator with novel MOA)  

* Investigational
Epilepsy as a Risk Factor for Alzheimer’s Disease; Alzheimer’s Disease as a Risk Factor for Epilepsy

- The incidence of epilepsy among AD patients is approximately seven times higher than non-AD patients*1
- Epilepsy patients significantly show higher amount of senile plaques deposited in brain accompanying increase in age*2
- Accumulation of Aβ is increased in midlife for adult epilepsy patients who experienced onset during childhood, especially patients with APOEε4 gene*3
- Subclinical epileptiform activity is observed in 42% of AD patients*4
- MMSE scores decline faster for AD patients with subclinical epileptiform activity*4

Until recently, it was thought that the onset of epilepsy mainly occurred during the later stages of AD; however, it is suggested that epileptiform activity may be involved even at earlier stages of AD

All projects are investigational.
Suggestion that the Increase of Calcium-permeable AMPA Receptors on Member surface Contributes to Hyper-Excitation in the Brains of AD patients

- Accelerated expression of AMPA receptor GluR1 subunit in early stage AD patients

- In rat hippocampuses, added Aβ and accelerated expression of calcium-permeable AMPA receptors (GluR1, etc.) increase excitatory postsynaptic current

Amount of GluR1 expression on cell surface and peak excitatory postsynaptic current

[Graphs and data from Neurobiology of Aging 2012 33 422e1-10 and Scientific Reports 2015; 5:10934]
E2082, E2730 Being Developed for Potential Preventative/Pre-emptive Treatment of Epilepsy

E2082
Next-generation AMPA receptor antagonist
- E2082 demonstrates a highly-selective, non-competitive inhibitory mechanism against AMPA-type glutamate receptors which play an important role in the onset and propagation of epileptic seizures
- Has a higher affinity for activated synapses compared to perampanel

E2730
Novel synapse function modulator
- Identified from *in vivo* screening of 4,000 compounds
- Verified dose-dependent anti-convulsion mechanism through animal (mouse) models of therapy-resistant psychomotor seizures induced by 6Hz corneal stimulation (figure below)
- Verified synergistic effect to inhibit convulsion in combination with perampanel in lithium-pilocarpine rat epilepsy models

Greater expression of closed-state receptors under physiological conditions
Greater expression of open-state receptors during epileptic seizure

Phase I (First-in-Human) trials completed for both compounds Aiming to establish Proof of Concept (POC) at earlier stage

Seizure Free

(Internal data)

All projects are investigational.
Eisai Neurology Updates

2) Clinical Research
BAN2401*
(Anti-Aβ protofibrils antibody)

* Investigational. Antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen.
Profiles of BAN2401
Targeting Protofibrils

- Low affinity for Aβ monomers and high affinity for aggregated Aβ species (>1000x)
- Preferential activity for Aβ Protofibrils over fibrils (>10x)
- BAN2401 both neutralizes the large soluble aggregates and clears aggregated Aβ species from the brain via FcR-mediated phagocytosis

1) Imbalance between Aβ production and clearance resulting in increased amounts of Aβ monomers, oligomers, insoluble fibrils, and plaques
2) BAN2401 is designed using amyloid proteins with Arctic mutation which highly produce Aβ protofibrils
3) BAN2401 is an antibody which has strong affinity and selectivity to the most toxic Aβ species - Protofibrils

Investigational. Antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen.

*1: mAb158 (the murine analog of BAN2401) data produced as the result of a strategic research alliance between Eisai and BioArctic. *2: van Dyck. Biol Psychiatry. 2018;83:311
Study 201: Large Scale Phase II Study in Early AD

Global, placebo-controlled, double-blind, parallel-group, randomized Phase II study

Population and Group

- 856 subjects with early Alzheimer’s disease (mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's dementia)

- Treatment arm(s):
  - BAN2401
    2.5mg/kg biweekly, 5mg/kg monthly, 5mg/kg biweekly, 10mg/kg monthly, 10mg/kg biweekly, and placebo
  - Changed the allocation of subjects in each treatment group at each interim analysis using Bayesian Adaptive Randomization Design

Endpoints

Primary endpoint
- ADCOMS change from baseline at 12 months with Bayesian analysis

Secondary endpoints
- Change from baseline at 18 months with the final analysis:
  - Amyloid plaques levels, as measured by PET (quantitative/qualitative)
  - ADCOMS*1
  - CDR-SB*2
  - ADAS-cog*3
  - Cerebrospinal fluid (CSF) biomarker (Aβ1-42, neurogranin, NfL, t-tau, and p-tau)

Investigational. Antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen.

**Aβ Plaque Reduction through Amyloid PET (Quantitative/Qualitative)**

- **Confirmed dose-dependent reduction of amyloid PET values**
- **10mg/kg biweekly: 81% conversion to amyloid negative by visual read**

**N for treatment arms:**

<table>
<thead>
<tr>
<th></th>
<th>0 month</th>
<th>12 month</th>
<th>18 month</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>98</td>
<td>96</td>
<td>88</td>
</tr>
<tr>
<td>2.5mg/kg biweekly</td>
<td>28</td>
<td>27</td>
<td>44</td>
</tr>
<tr>
<td>5mg/kg Monthly</td>
<td>27</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>5mg/kg biweekly</td>
<td>27</td>
<td>27</td>
<td>25</td>
</tr>
<tr>
<td>10mg/kg Monthly</td>
<td>88</td>
<td>43</td>
<td>83</td>
</tr>
<tr>
<td>BAN2401</td>
<td>24</td>
<td>24</td>
<td>24</td>
</tr>
<tr>
<td>10mg/kg Monthly</td>
<td>82</td>
<td>37</td>
<td>37</td>
</tr>
</tbody>
</table>

Investigational. BAN2401 is an antibody for Alzheimer's disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen. *: Adjusted mean change from baseline by mixed model repeated measures (MMRM). The MMRM uses treatment group, visit, clinical subgroup (MCI due to AD, mild AD), the presence or absence of ongoing AD treatment at baseline, APOE4 status (positive, negative), region, and treatment group-by-visit interaction as factors and baseline value as covariate.
Slowing Disease Progression on Clinical Outcomes at 6, 12 and 18 Months*1

Investigational Antibody for Alzheimer's disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen. Analyses were based on protocol-specified mixed model repeated measures (MMRM) models. All p values described above are nominal ones. Presented at the Clinical Trials on Alzheimer's Disease Conference 2018; Barcelona, Spain. October 25, 2018.

*1: Linear regression model testing the slope of change from baseline. Slopes shown represent change in ADCOMS (Alzheimer's Disease Composite Score) per month

**2: ADCOMS: Alzheimer's Disease Composite Score

**3: ADAS-cog: Alzheimer's Disease Assessment Scale–cognitive subscale

**4: CDR-SB: Clinical Dementia Rating, sum of box

**5: 10 mg/kg bi-weekly

Disease progression

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>10 mg/kg monthly</th>
<th>10 mg/kg biweekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>N WITH DATA</td>
<td>0 MOS</td>
<td>6 MOS</td>
<td>12 MOS</td>
</tr>
<tr>
<td>Placebo</td>
<td>238</td>
<td>216</td>
<td>187</td>
</tr>
<tr>
<td>10 mg/kg monthly</td>
<td>246</td>
<td>208</td>
<td>165</td>
</tr>
<tr>
<td>10 mg/kg biweekly</td>
<td>152</td>
<td>130</td>
<td>93</td>
</tr>
</tbody>
</table>

Slope analysis of ADCOMS*1

Slope = 0.0060

P<0.001

30% LESS DECLINE at 10mg/kg biweekly

P=0.034

47% LESS DECLINE at 10mg/kg biweekly

P=0.017

26% LESS DECLINE at 10mg/kg biweekly

P=0.125

• BAN2401 slows rate of disease progression at the highest dose arm*5 compared to placebo (p<0.001)

• Treatment effect for disease progression of AD during treatment period is observed in BAN2401 arm, and also suggests sustainable treatment effect and potentially expanded treatment effect over time

30% LESS DECLINE at 10mg/kg biweekly

47% LESS DECLINE at 10mg/kg biweekly

26% LESS DECLINE at 10mg/kg biweekly

Placebo

10 mg/kg bi-weekly (N=161)

Slope = 0.0083

P=0.034

47% LESS DECLINE at 10mg/kg biweekly

P=0.017

26% LESS DECLINE at 10mg/kg biweekly

P=0.125
Correlation between Reduction of Aβ Plaques and Change in Clinical Endpoints

Investigational. BAN2401 is an antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen.

*1: \( r_p \) is Pearson's correlation coefficient. Adjusted mean was based on a protocol-specified mixed effects model with repeated measures (MMRM). The MMRM model included baseline as a covariate, with treatment group, visit, region, randomization stratification variables (clinical stage, concurrent AD medication, APOE4 status), and treatment group-by-visit interaction as fixed effects. Data shown are for subjects enrolled in the PET sub-study with PET SUVr and clinical data at 12 or 18 months (N=288).

CSF*1 Biomarkers

Reduction of neurogranin

- Neurogranin is a synaptic protein and a CSF marker of synaptic damage by neurodegeneration
- CSF neurogranin levels are elevated in subjects with early AD*3
- BAN2401 reduces CSF neurogranin levels by 11% (58 pg/ml median reduction from baseline) over 18 months

Reduction of phospho-Tau (p-Tau)

- Phospho-Tau$_{181}$ (p-Tau) is a CSF marker for nerve damage downstream of Tau pathway, that correlates with tau pathology
- CSF p-Tau level is elevated in subjects with AD*4
- BAN2401 significantly reduces CSF p-Tau levels by 13% (12 pg/ml median reduction from baseline) over 18 months

Slowing increase in neurofilament light chain (NfL)

- Neurofilament light chain (NfL) is a neuronal structural scaffold protein and a CSF marker of axonal degeneration*5 by neurodegeneration
- CSF NfL levels are elevated in subjects with AD
- BAN2401 slows increase in NfL in the CSF by 48% (median difference) compared to placebo over 18 months

Investigational. Antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen.

*1:Cerebrospinal fluid  *2: Subjects randomized to 10 mg/kg bi-weekly and 10 mg/kg monthly dose groups combined  *3: Kvartsberg H et al. Alzheimer’s Dementia 2015; 11(10):1180-90
Safety of BAN2401

- Incidence rates of AE, SAE, and TEAE consistent with patient population and balanced across placebo and BAN2401 treatment groups

- Most common TEAEs were infusion-related reactions and ARIA (amyloid-related imaging abnormalities)
  - Incidence of ARIA-E (edema) was 9.9% at the highest treatment dose, and not more than 10% in any of the treatment arms

- No changes in Labs, ECGs, or vital signs

- Dose-dependent ARIA-E* typically resolved within 4-12 weeks
  - ARIA-E* occurred in 48 subjects
    - Headache, visual disturbance and confusion were observed in approx. 10%
    - Approx. 60% of ARIA-E* occurred within first 3 months of treatment
    - Approx. 89% of ARIA-E* were mild to moderate in severity (radiographic)
  - MRI findings typically resolved within 4-12 weeks

Demonstrated acceptable tolerability

Investigational. Antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen.
* ARIA-E: Amyloid Related Imaging Abnormalities-edema
## Achieved POC*1 on Large Scale Phase II Study

### Amyloid ➔ Tau ➔ Neurodegeneration

<table>
<thead>
<tr>
<th>Amyloid</th>
<th>Tau</th>
<th>Neurodegeneration</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Significant amyloid plaques reduction confirmed through PET overall</td>
<td>• Reduction of p-Tau, CSF*4 biomarker that indicates improvement of pathophysiology, indicated inhibition of nerve damage at downstream of Tau pathway</td>
<td>• Reduction of neurogranin and inhibition to increase neurofilament light chain; CSF biomarkers show reduced neurodegeneration versus placebo; and showed inhibition of synapse degeneration and axonal degeneration</td>
</tr>
<tr>
<td>• Over 80% of subjects at highest dose arm*2 converted from amyloid positive to negative confirmed through amyloid PET</td>
<td><img src="Image" alt="Image" /></td>
<td><img src="Image" alt="Image" /></td>
</tr>
<tr>
<td>• Amyloid PET data significant across subgroups*3</td>
<td><img src="Image" alt="Image" /></td>
<td><img src="Image" alt="Image" /></td>
</tr>
</tbody>
</table>

### Clinical outcome

- In highest dose arm, observed 30% less cognitive decline in clinical symptoms evaluated by ADCOMS
- Observed less cognitive decline across subgroups
- Expansion of treatment effect is observed for the entire treatment period

---

Investigational. BAN2401 is an antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen. *1: Proof of Concept *2: 10mg/kg biweekly *3: APOE4 status, clinical stage (MCI due to AD and mild AD), concomitant AD medication *4: Cerebrospinal fluid

Consistent results in clinical effect and ATN biomarker were observed, suggesting disease modifying effect
Clarity AD
Global, placebo-controlled, double-blind, parallel-group, randomized Phase III study

- Based on results from large scale Phase II study, initiation of single confirmatory Phase III study, which could satisfy approval requirements
- Clarity AD was initiated in March 2019
- Selected experienced sites committed to Clarity AD

Population and Group

- 1,566 subjects with early Alzheimer’s disease (mild cognitive impairment (MCI) due to Alzheimer's disease or mild Alzheimer's dementia)
  - Amyloid pathology confirmed
  - Treating early in disease (enriching for mild cognitive impairment)

- Treatment groups: 10 mg/kg bi-weekly of BAN2401 (No titration) and placebo in 1:1 ratio

Endpoints

Primary endpoint
- Change from baseline in CDR-SB at 18 months

Key secondary endpoints
- Changes from baseline to 18 months in:
  - Amyloid plaques levels, as measured by PET
  - ADCOMS
  - ADAS-cog14

Biomarker endpoints
- Cerebrospinal fluid (CSF) biomarker (Aβ1-42, neurogranin, NfL, t-tau, p-tau), and others

Final readout of primary endpoint targeted in 2022
Characteristics of BAN2401

BAN2401 has distinct molecular properties that target the most toxic Aβ species - PROTOFIBRILS with lower affinity to other species, such as monomers and fibrils, leading to differentiated clinical fingerprint including a rapid rate of amyloid clearance and clinical outcome improvement, as well as modest incidence of ARIA-E*1.

BAN2401 has proof of concept with a LARGE PHASE II STUDY showing CONSISTENT RESULTS in the top two highest doses across cognitive and functional improvement, brain amyloid removal, and reduction in CSF biomarkers associated with neurodegeneration.

BAN2401 has an OPTIMIZED PHASE III STUDY DESIGN that enrolls the same enriched patient population as Phase II study, such as early AD subjects with confirmed amyloid pathology in the brain, and studies only the HIGHEST DOSE (10mg/kg biweekly) and placebo from Phase II study without titration in order to maximize potential for rapid treatment effect.

Investigational. Antibody for Alzheimer's disease produced as the result of a strategic research alliance between Eisai and BioArctic. Co-development with Biogen.
*1: van Dyck. Biol Psychiatry. 2018;83:311
Elenbecestat*  
(BACE inhibitor)  

1) Imbalance between Aβ production and clearance results in dynamic equilibrium of Aβ monomers, oligomers, insoluble fibrils, and plaques.

2) Elenbecestat is a novel small molecule BACE1 inhibitor, inhibiting production of all Aβ species including Aβ (1-40) and Aβ (1-42).

* All projects are investigational
Profiles of Elenbecestat

1. Selectivity of BACE1 and BACE2

<table>
<thead>
<tr>
<th>Compound</th>
<th>BACE1</th>
<th>BACE2</th>
<th>BACE2/BACE1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elenbecestat</td>
<td>19</td>
<td>67</td>
<td>3.53</td>
</tr>
<tr>
<td>Ki (nM)*1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Verubecestat</td>
<td>2.2</td>
<td>0.38</td>
<td>0.17</td>
</tr>
<tr>
<td>Ki (nM)*2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lanabecestat</td>
<td>0.4</td>
<td>0.8</td>
<td>2.00</td>
</tr>
<tr>
<td>Ki (nM)*3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1. Depigmentation, as seen in other compounds which have lower BACE1 selectivity, was not observed in preclinical study
2. No depigmentation seen in clinical studies

2. Brain Aβ Reduction

Elenbecestat Rat CSF and Brain Aβ Reduction

Elenbecestat shows high selectivity in BACE1 and dose-dependently reduces brain Aβ
Study 202 (Phase II Study)

Placebo-controlled, double-blind, parallel-group, randomized Phase II study

- 21 sites in US
- The results of double-blind period showed significant reduction of Aβ plaques and suggested less decline in clinical symptom
- 24 months open-label extension with 50 mg is ongoing to confirm safety

Population and Group

- 70 subjects with MCI due to AD or mild to moderate Alzheimer’s dementia
  - Subjects 50-85 years old
  - Subjects confirmed as amyloid-PET+
- Treatment groups
  - Core study treatment arms: placebo, 5, 15, and 50/mg daily
  - Subjects in 5 mg and 15 mg groups with ≥3 months of treatment remaining were reassigned to 50 mg

Endpoints

Primary endpoint
- Safety and tolerability, TEAEs and SAEs, laboratory parameters, ECG

Secondary endpoints
- % reduction of Aβ (1-x) and Aβ (1-42) in CSF after at least 4 weeks and 18 months
- The population PK parameters of elenbecestat in CSF and plasma
Study 202 Results

Amyloid PET analysis:
Mean change in Centiloid Values\(^1\) at 18 months from baseline

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Least squares (LS) mean</th>
<th>Treatment difference (LS mean difference)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>elenbecestat 50mg (N=24)</td>
<td>-12.4</td>
<td>-24.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Placebo (N=11)</td>
<td>12.4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Subjects in 50 mg total group showed a reduction in amyloid plaques at 18 months versus placebo of 24.8 units on the Centiloid scale\(^1\)

Less decline trend in clinical symptom

CDR-SB\(^2\)

Placebo

31% less decline

Elenbecestat 50mg total\(^4\)

ADCOMS\(^3\)

Placebo

33% less decline

Elenbecestat 50mg total\(^4\)

Study 202 indicated reduction of Aβ plaque and less decline in clinical symptom
Elenbecestat was generally well tolerated\(^5\)

- No dose dependency observed for TEAEs or SAEs
- No notable safety concerns were observed, including liver toxicity

Investigational. \(^1\): Centiloid scale: an average value of zero in “high certainty” amyloid negative subjects and an average of 100 in “typical” AD patients. Florbetaben and flobetapir were used as PET tracer. \(^2\): Clinical Dementia Rating-Sum of Boxes \(^3\): Alzheimer’s Disease Composite Score \(^4\): For subjects who were reassigned to elenbecestat 50 mg, data before and after dose reassignment were included in the analysis. \(^5\): The six most common adverse events reported were upper respiratory tract infection, abnormal dreams and nightmares, contact dermatitis, headache, diarrhea, and falls.
### Population and Group

- **Early AD**: MCI due to AD or mild Alzheimer’s dementia  
  (1,330 subjects for each study)
  - Amyloid pathology confirmed
  - More than 75% of the randomized subjects diagnosed with MCI due to AD
- Treatment groups: Elenbecestat 50mg and placebo

### Endpoints

**Primary endpoint**
- Change from baseline in CDR-SB at 24 months

**Key secondary endpoints**
- Changes from baseline to 24 months in:
  - ADCOMS
  - ADAS-cog
  - Amyloid plaques levels, as measured by PET

---

**Final readout of primary endpoint targeted in 2021**
Characteristics of elenbecestat observed in previous clinical studies

- Rapid absorption after oral administration
- Possesses half-life and enzyme inhibition profile suitable for simple once daily oral administration
- Observed favorable brain penetration and dose-dependently; decrease A-beta concentration in cerebrospinal fluid (CSF)
- No active metabolite and no accumulation from repeated administration of elenbecestat
- Positive safety profile in therapeutic range

Dose setting

- Dosing was selected in reference to Icelandic Genetic Research. In Amyloid precursor protein (APP) A673T (Icelandic mutation) variant Aβ production was reduced by ~40%; carriers of the variant shows ~75% lower risk of AD*1,2
- Selected optimal single dose of 50 mg based on human biology evidence *1,2 and PK/PD data from Phase I study and Phase II study

MISSION AD
Protocol Enhancement

Combine studies 301/302 into a single database with N~2100

• Primary endpoint remains as CDR-SB at 24 months
• Key secondary endpoints including ADCOMS and PET SUVr 1.2-1.6 at 24 months

Rationale:
• Potentially accelerates submission and increases power of the study
• Potential to support single trial approval by leveraging highly powered combined larger trial database (each study originally powered with 1330 pts)
• Enables internal replication with sub-populations (e.g., PET sub-study, ApoE4+, PET SUVr 1.2-1.6)

At the 8th meeting with the Data Safety Monitoring Board (DSMB), the safety data, including the potential for decline in cognition, was reviewed and the continuation of studies was recommended
E2027*
(PDE9 inhibitor)

* Investigational
1. PDE9 is a principal enzyme to regulate metabolism of cGMP as a second messenger.

2. E2027 would provide therapeutic benefits in cognitive impairment and neuropsychiatric symptoms by inhibiting PDE9.
Relationship of cGMP Increase in CSF Neurophysiological and Behavioral Effects

Observed effect on cognitive function by increasing the threshold of cGMP in CSF in Novel object recognition test* (NOR)

Pharmacodynamic Drug Effect Goal is to achieve at least 150 - 200 % increase in CSF cGMP from baseline
Potential Clinical Efficacy for Patients with Dementia with Lewy Bodies (DLB)

Patients with DLB have been shown to exhibit approx. 13% lower levels of cGMP in CSF.\(^1\)

PDE9 expression level is elevated (1.6 fold) in the frontal cortex in DLB patients compared to healthy elderly control.\(^1\)

Change of cGMP in CSF after administration of E2027 (Phase I Study data).\(^3\)

Confirmed increase of cGMP in CSF after administration of E2027.

Selected DLB as a first indication based on human biology. Phase II/III study ongoing targeting DLB based on the above data.

Investigational. *1: Internal data  *2: Including subjects with depression, normal pressure hydrocephalus, vascular diseases and mental illness  *3: Alzheimer’s Association International Conference 2017 “Phase 1 Investigation into the Safety, Tolerability, Pharmacokinetics (PK) and Pharmacodynamics (PD) of E2027, a Selective Phosphodiesterase-9 (PDE9) Inhibitor”
Study 201 (Phase II/III Study)

Study to Evaluate the Efficacy, Safety and Tolerability of E2027 in Participants with Dementia with Lewy Bodies (DLB)

- Study 201 is conducted to compare E2027 to placebo on the cognitive endpoint of eMoCA*1 and the global clinical endpoint of eCIBIC-Plus*2 Caregiver Input in participants with DLB after 12 weeks of treatment.
- Dose rationale based on cGMP levels in Phase I
- Enrollment is ongoing in US, EU and Japan, and will be completed in FY2019
- Enrollment is ahead of the original schedule
- No serious Adverse event (SAE) so far

Population and Group

- 182 subjects With DLB
- Treatment groups
  E2027 50mg and placebo

Endpoints

Primary endpoints
- Change from baseline in eMoCA*1 total score at 12 weeks
- Measure eCIBIC-Plus*2 scale score at 12 weeks

Secondary endpoints
- NPI*3 total score, NPI*3 subscore, NPI*3 caregiver score, MMSE*4 total score, CFI*5 score, CGIC-DLB*6 scale score

Lemborexant*
(Dual orexin receptor antagonist)

* Investigational.
Profiles of Dual Orexin Receptor Antagonist Lemborexant

**Primary Pharmacology**

** Specific for target, OX2R Selective**  
- Binding affinities: hOX1R IC50 6.1 nM; hOX2R IC50 2.6 nM

** Favorable binding kinetics**  
- Fast association/dissociation rates from hOX2R

** Favorable Pharmacokinetics observed in Phase 1 Study**  
- Time-to maximum blood concentration: 1.75 h

---

By reducing the abnormally high wake pressure, lemborexant restores the balance between sleep and wake centers during sleep.

---

Orexin neurons are located upstream of major wake-controlling nuclei

**Orexin peptides and roles of orexin receptors**


---

Investigational
## Study 304/303 (Phase III Studies)

### Study 304 (SUNRISE 1)
- **Population and Group**
  - Insomnia disorder with sleep maintenance complaints. 1,006 subjects were randomized.
  - Older subject; 55 years old and above
  - Treatment groups: Lemborexant 5mg, 10mg, Zolpidem ER 6.25 mg and placebo

- **Endpoints**
  - **Primary endpoint**
    - Latency to persistent sleep (LPS) measured by Polysomnography (PSG) at 1 month
  - **Key secondary endpoints**
    - Sleep efficiency (SE), wake time after sleep onset (WASO) and second half of WASO (WASO2H) measured by PSG at 1 month

### Study 303 (SUNRISE 2)
- **Population and Group**
  - Insomnia disorder with sleep onset and/or sleep maintenance complaints. 949 patients were randomized (full analysis set)
  - 12-month study
    - (placebo-controlled in first 6 months, and placebo re-randomized to Lemborexant 5mg or 10mg after 6 months)
  - Treatment groups: Lemborexant 5mg, 10mg and placebo

- **Endpoints**
  - **Primary endpoint**
    - Subjective sleep onset latency (sSOL) at 6 months
  - **Key secondary endpoints**
    - Subjective sleep efficiency (sSE) and subjective wake time after sleep onset (sWASO) at 6 months
Efficacy Evaluation in Insomnia Disorder in Phase III Study
Primary and key secondary endpoints

Timing of Insomnia Symptoms

- Problems falling asleep
- Get in bed / Lights Off
- Problems staying asleep
- Waking too early

24-hour Sleep/Wake Behavior

Phase III Study Efficacy Measures

- Get out of bed / Lights On
- Sleep Maintenance in the latter half of the night
  - WASO2H
- Sleep Onset
  - Latency to Persistent Sleep
  - sSOL
- Get in bed / Lights Off
- Sleep Efficiency
- Wake After Sleep Onset (WASO)
- sSE
- sWASO

Sleep Opportunity
Out-of-bed behavior/activities
Study 304 Results

Latency to Persistent Sleep (LPS)
Primary Efficacy Results

Sleep Efficiency (SE)
Key Secondary Efficacy Results

Wake After Sleep Onset (WASO)
Key Secondary Efficacy Results

WASO in the 2nd Half of the Night (WASO2H)
Key Secondary Efficacy Results

Lemborexant 5mg and 10mg showed statistically significant improvement vs. placebo and vs. Zolpidem for change from baseline for LPS, SE, WASO and WASO2H (measured by PSG) after last two nights of treatment.

Investigational. LEM5=lemborexant 5 mg; LEM10=lemborexant 10 mg; PBO=placebo; ZOL=zolpidem ER 6.25 mg; PSG=polysomnography; SD=standard deviation; CI=confidence interval; LSM=least squares mean ♦ statistically significant difference vs. PBO (p<0.001) ◇ statistically significant difference vs. PBO (p<0.0001) † statistically significant difference vs. ZOL (p<0.01); ‡ statistically significant difference vs. ZOL (p<0.001)
Study 303 Results

Lemborexant 5mg and 10mg showed statistically significant improvement vs. placebo on change from baseline in sSOL, sSE, sWASO (measured by Sleep Diary) at the end of 6 months of treatment.

Investigational. LEM5=lemborexant 5 mg; LEM10=lemborexant 10 mg; PBO=placebo; CI=confidence interval; LSM=least squares mean; SD=standard deviation

♦ statistically significant difference vs. PBO (p<0.0001)  ♦ statistically significant difference vs. PBO (p<0.001) ; * statistically significant difference vs. PBO (p<0.05)
Driving Study (Study 106)  
Postural Stability Study (Study 108)

Study 106
Any of Lemborexant 2.5mg, 5mg, 10mg arms had an upper bound of the 95% CI for treatment difference from placebo greater than 2.4 cm on Day 2 or Day 9, as measured in the primary endpoint of Standard deviation of lateral position (SDLP).

SDLP 2.4 cm higher than placebo condition = clinically meaningful effect equivalent to that of .05% BAC.

No significant difference in next day driving performance on Lemborexant, as measured by difference from Placebo in SDLP.

Study 108
Both Lemborexant 5mg, 10mg resulted in statistically significant difference with compared to Zolpidem ER in the primary endpoint of postural stability [body sway] during middle of the night (awakening ~4 h post-dose) (p<0.0001).

LEM=Lemborexant; PBO=placebo; ZOL=zolpidem ER
* statistically significant difference vs. PBO (p<0.05)
‡ statistically significant difference vs. PBO (p<0.01)
♦ statistically significant difference vs. PBO (p<0.0001)
† statistically significant difference vs. ZOL (p<0.0001)

Investigational
**Study 202 in Patients with Irregular Sleep-Wake Rhythm Disorder (ISWRD) Associated with Alzheimer’s Disease Dementia**

- ISWRD: circadian rhythm sleep disorder
  - Pathology includes
    - Disturbed circadian rhythmicity
    - Neuronal loss in suprachiasmatic nuclei and pineal
    - Recent evidence for dysfunctional orexin system
    - Decreased amplitude of other circadian rhythms such as melatonin, body temperature
  - Affects the entire 24-hour sleep-wake cycle
    - Abnormal sleep at night AND excessive sleep during the day
    - No major sleep period; sleep fragmented
  - No adequate pharmacological or non-pharmacological treatment available
  - Contributes to significant caregiver (family) burden, which often leads to institutionalization of persons with dementia
- ISWRD ≠ Insomnia

**Summary of Study 202 in patients with ISWRD associated with AD**
- Global, multicenter, randomized, double-blind, placebo-controlled, parallel-group Phase II study
- 62 patients 64-89 years of age with ISWRD and mild to moderate Alzheimer’s disease
- Treatment group: Lemborexant 2.5mg, 5mg, 10mg, 15mg and placebo
- Evaluate the change from baseline in circadian rhythm-related parameters, nighttime sleep-related parameters and daytime wake-related parameters using actigraphy over four weeks of treatment

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[Graph showing normal, insomnia, and irregular sleep-wake patterns over three days]


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Results of Study 202 in Patients with Irregular Sleep-Wake Rhythm Disorder (ISWRD) Associated with Alzheimer’s Disease Dementia

Circadian Endpoints

- Relative Amplitude was statistically significantly increased versus Placebo with Lemborexant 5mg and 15mg
- Activity in the Least Active 5 Hours was statistically significantly decreased versus Placebo with Lemborexant 2.5mg, 5mg, and 15mg

Nighttime Sleep Endpoints

- Sleep Fragmentation Index – trend for decrease versus Placebo with Lemborexant 5mg
- Total Sleep Time increased incrementally across the 4 weeks of treatment with both Lemborexant 5mg and 15mg

Proof of concept for ISWRD established
- Improved 24-hour circadian rhythm variables
- Lemborexant helped consolidate nighttime sleep

Lemborexant well-tolerated in patients with Alzheimer’s disease and ISWRD
- No discontinuations from treatment
- Low rate of TEAEs, consistent with insomnia program
Achieved Submission in US and Japan

Insomnia disorder

- Submitted in US in December 2018 and Japan in March 2019. FDA target PDUFA* date within FY2019 and regulatory submissions in other countries will follow.

- The lemborexant clinical development program includes efficacy/safety studies and special population safety studies conducted across Phases I, II, and III, including first ever Head-to-Head trial vs zolpidem as an orexin receptor antagonist.

- Clinical program key efficacy and safety measures have examined sleep onset, sleep maintenance and safety/tolerability in adult and elderly subjects with insomnia disorder, demonstrating superiority to zolpidem.

- Well-tolerated in subjects with Alzheimer’s disease and ISWRD.

* Prescription Drug User Fee Act

Investigational.
Robust Pipeline Aiming at Wider Scope for Dementia

- **Lemborexant**
  - Dual orexin receptor antagonist
  - Discovery: Insomnia disorder, including older patients
  - Phase II/III ongoing: Irregular sleep-wake rhythm disorder (ISWRD) associated with Alzheimer’s disease / dementia

- **Elenbecestat**
  - BACE inhibitor
  - Early Alzheimer’s disease

- **BAN2401**
  - Anti-Aβ protofibrils antibody
  - Early Alzheimer’s disease

- **E2730**
  - Synaptic functional modulator with novel MOA
  - Early Alzheimer’s disease

- **E2027**
  - PDE9 inhibitor
  - Dementia with Lewy bodies (Phase II/III ongoing)

- **E2082**
  - Next-generation AMPA receptor antagonist
  - Epilepsy and other neurological disorders, including dementia

- **E2730**
  - Synaptic functional modulator with novel MOA
  - Epilepsy and other neurological disorders, including dementia

- **E2814**
  - Anti-tau antibody
  - Early Alzheimer’s disease (Under preparation for Phase I)

- **E2511**
  - Synapse regenerant
  - Alzheimer’s disease

- **EphA4 Project**
  - Synapse modulator
  - Alzheimer’s disease

- **Immuno-Dementia Project**
  - Synapse regenerant
  - Alzheimer’s disease

All projects are investigational

*1: Co-development with Biogen.
*2: Antibody for Alzheimer’s disease produced as the result of a strategic research alliance between Eisai and BioArctic.
*3: Research at KAN Research Institute
*4: Research at Eisai Center for Genetics Guided Dementia Discovery (G2D2)
Eisai Neurology Updates

3) KAN Research Institute
EphA4 Project
Preventing Loss of Memory by Maintaining Synapse Connectivity

Eisai Co., Ltd.
KAN Research Institute
Biologic drug creation based on integrative cell biology

- In-house development and new drug creation concept through “integrative cell biology”
- Development of highly original “antibody and nucleic acid medicine creation technologies” for embodiment
- Located in Kobe Biomedical Innovation Cluster, a sector well-known for great scientific achievement, pursue “co-operation with external organizations” taking an advantage of small-size organization with prompt action

Concept of Fractalkine
- Essential mechanism for migration of specific immune cells into tissues
- Development of neutralizing antibody E6011
  Phase II Study for RA and preclinical in neurology

Concept of EphA4
- Synapse revitalization with EphA4 functional modulation
- Preclinical in neurology

Tanaka Y et.al.
Mod Rheumatol 2018 and others

Inoue E et.al.
JCB 2009 and others

Collaboration with external organizations (AMED*1-CiCLE*2)
- Nucleic acid medicine creation utilizing innovative nucleic acid biosynthesis and delivery technology
- Co-development with School of Pharmaceutical Science, Osaka University, National Cancer Center Japan, Tokyo Women’s Medical University, Niigata University School of Medicine with support from AMED
- Development ongoing for clinical introduction aiming for nucleic acid medicine originated in Japan
- Aim to initiate Phase I Study in the near future

All projects are investigational
*1: Japan Agency for Medical Research and Development  *2: Cyclic Innovation for Clinical Empowerment (CiCLE) grant program selected by AMED
Loss of synaptic connectivity (synapse destabilization) is strongly correlated with the level of cognitive impairment*

* S.W. Scheff. et al. Neurology 68, May 1. 2007
Receptor tyrosine kinase EphA4, which is abundant in the hippocampus, is a protein that induces the loss of synapses that functions in neuronal development.

Activated phosphorylated EphA4 is increased in brains affected by Alzheimer's disease.

Huang et al., JEM, 2017
EphA4 Project
Maintenance of Memory through Synapse Stabilization

- Discovered a new EphA4 regulation mechanism involved in synapse stabilization
  - EphA4 is cleaved in neuronal activity-dependent manner

EphA4 modulator (processing enhancer) would potentially realize a new therapeutic paradigm to revitalize synaptic function in patients with Alzheimer's disease.

Clinical study initiation planned in FY2020


All projects are investigational
Eisai Neurology Updates

4) EKID*
Brain Defense Mechanism Research Based on Reverse Translation

Eisai Co., Ltd.

* Eisai-Keio Innovation Lab for Dementia
EKID was established at the Shinano-machi campus of Keio University as an industry-academia collaborative center through a Cyclic Innovation for Clinical Empowerment (CiCLE) grant program selected by the Japan Agency for Medical Research and Development (AMED). This project is aimed at discovery of drug targets for dementia utilizing cross-sectional collaborative research from basic to clinical department of Keio University.

**Perspectives on EKID research and how to proceed**

**Focusing on the homeostasis maintenance mechanism in the brain, it will promote bidirectional translational research (TR) starting reverse TR with clinical samples to TR.**

**Sample management**
- Collection and storage of high-quality and successive samples by standardizing protocols
- Cooperation with Keio-Biobank system

**Omics analysis**
- Measurement the samples with latest LC-MS
- Multiomics (Protein, Lipid, metabolite, mRNA, Genome)
- Global/Focus/Functional omics

**Data science**
- Establishment of pathological models for validation of target and hypothesis.
- Verification of target and hypothesis candidate by intervention experiment in pathological models.

**Hypothesis creation/Target validation**
- Multimodal analysis of combined multiomics data and clinical data (images, dementia score etc)
- Analysis by AI using deep learning and text mining

**Seeking to achieve new drug discovery hypothesis by acquiring and analyzing clinical samples with detailed information and the multidimensional correlation analysis of various omics data and clinical data using AI.**

**Validating the characteristics of drug targets extracted from dementia hypotheses models of cell and animals, as well as further confirming the findings in clinical samples. This would improve the reliability of drug discovery hypotheses and targets, and lead to highly successful drug discovery research.**
Centenarians who possess factors for long life

Healthy individuals

Pathogenic model animals
Brain organoid

Latest Omics technologies
Public big data

Dementia Patients

Keio University School of Medicine, Center for Supercentenarian Medical Research

Keio University Hospital, Memory Center

Eisai’s dementia research knowledge
Eisai’s biomarker research capability

Generate data from high quality and deeply informed clinical samples

Elucidate dementia onset process through integrated analysis of biomarker signatures, and identify candidates for drug discovery targets

Verify quality and potential of drug discovery targets through wet experiments, develop drug treatments

Hypothesis Generation by Reverse Translation for Drug Target Finding for Dementia

Keio University School of Medicine, Center for Supercentenarian Medical Research

Dementia Patients

Healthy individuals

Pathogenic model animals
Brain organoid

Latest Omics technologies
Public big data

Dementia scores
Proteomics

Brain imaging (MRI, PET)
Metabolomics

Various biomarkers
Lipidomics

Utilizing A.I.

Deep learning
Machine learning

Text mining
Network analysis

Enrichment analysis
xQTL analysis

Enrichment analysis

Machine learning

Text mining

Deep learning

Proteomics

Metabolomics

Lipidomics

Dementia scores

Brain imaging (MRI, PET)

Various biomarkers

Utilizing A.I.

Deep learning

Text mining

Enrichment analysis

xQTL analysis

Proceeding the research focused on “enhancing in vivo clearance”, verifying impact on the brain’s lymphatic draining system with in vitro, in vivo pathology models.

Eisai’s biomarker research capability

Eisai’s dementia research knowledge

Generate data from high quality and deeply informed clinical samples

Elucidate dementia onset process through integrated analysis of biomarker signatures, and identify candidates for drug discovery targets

Verify quality and potential of drug discovery targets through wet experiments, develop drug treatments

All projects are investigational

Generation of data from high quality and deeply informed clinical samples

Elucidation of dementia onset process through integrated analysis of biomarker signatures, and identification of candidates for drug discovery targets

Verification of quality and potential of drug discovery targets through wet experiments, development of drug treatments
Target Drug Image and Timeline

Enhancement of protective mechanism through facilitating brain drainage system

**<Dementia/aging>**
Dysfunction in brain drainage system
- Neurodegeneration

- **Blood vessel**
- **Neuron**
- **Astrocyte**

**<Treatment agent aiming for>**
Maintenance of brain environment that neurodegeneration can be suppressed

- **Brain drainage system**

**<Short term>**
Identify candidates for medicine creation targets by integrating existing data and clinical evidence

1. Intracerebral clearance enhancer through reinforcing protective mechanism
2. Brain homeostasis improving agent targeting astrocyte
3. Neural network activation agent

**<Medium term>**
Explore biomarker signature and medicine creation targets by utilizing high-quality data integration and AI

**<Long term>**
Explore medicine creation targets by combining obtained knowledge and new technologies

Aim to identify more than three targets for medicine creation by setting goals for short, medium and long terms

All projects are investigational
Eisai Neurology Updates

5) G2D2
(Eisai Center for Genetics Guided Dementia Discovery)

Genetic Guided Immuno-Dementia Discovery

Eisai Co., Ltd.
Eisai Center for Genetics Guided Dementia Discovery

SCIENCE-FIRST INNOVATION-CENTRED BIOTECH
• New 50,000 SQFT state-of-the-art laboratory located in the Cambridge, Massachusetts, U.S.A. biotech hub
• Sharp focus on multi-disciplinary innovation and entrepreneurial collaborative models to accelerate drug discovery

HUMAN GENETICS & DATA SCIENCE: INCREASED ODDS OF SUCCESS
• Focus not only on how such data help identify and validate therapeutic targets, but also to guide novel approaches to drug such targets and match them to the right patient

DELIVER TAILOR-DESIGNED CUTTING-EDGE MEDICINES
• Precision chemistry strategy in the context of human genetics uniquely positioned to deliver tailor-designed small molecule and anti-sense oligonucleotide solutions for targeted therapeutics

Deliver breakthrough therapeutics that enhance human healthcare by leveraging the power of human genetics, data sciences and precision chemistry
Large-scale genetic studies of AD identify genes related to microglia

Target pathways of microglia to modulate immune functions

AD genetics strongly suggests altered immune function of Microglia (CD33, TREM2, PLCG2, and others) is a high risk factor of AD

Human genetic evidence doubles probability of success


All projects are investigational
TREM2, CD33 and PLCg2, risk genes found at AD GWAS*, are known to exist on the same biological pathway and to relate to maintain homeostasis of microglia functions. Adjustment of these risk factors is considered to normalize microglia functions hyper-activated in accordance with onset or progress of AD, and to provide treatment opportunities for wide disease stage of AD.

Regulation of entire cellular functions in microglia ameliorates brain microenvironment, enabling to slow in AD progression

Opportunity to be industry leader
Plan to initiate clinical study in FY2021

* Genome-wide association studies in Alzheimer's disease