Eisai’s R&D Network and Activities

R&D Information Meeting
September 1, 2004

Kentaro Yoshimatsu, Ph.D.
Vice President
Discovery & Development Research Headquarters
Safe Harbor Statement

◆ Materials and information provided during this presentation may contain “forward-looking statements” as defined in the Private Securities Litigation Reform Act of 1995. These statements are based on current expectations, forecasts and assumptions that are subject to risks and uncertainties which could cause actual outcomes and results to differ materially from these statements.

◆ Risks and uncertainties include general industry and market conditions, and general domestic and international economic conditions such as interest rate and currency exchange fluctuations. Risks and uncertainties particularly apply with respect to product-related forward-looking statements. Product risks and uncertainties include, but are not limited to, technological advances and patents attained by competitors, challenges inherent in new product development, including completion of clinical trials; claims and concerns about product safety and efficacy; obtaining regulatory approvals; domestic and foreign healthcare reforms; trends toward managed care and healthcare cost containment, and governmental laws and regulations affecting domestic and foreign operations.

◆ Also, 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.

◆ The Company disclaims any intention or obligation to update or revise any forward-looking statements whether as a result of new information, future events or otherwise.
Global R&D Functions

<table>
<thead>
<tr>
<th>Discovery Research</th>
<th>Non-clinical Development*</th>
<th>Clinical Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tsukuba Kyoto</td>
<td>Tsukuba Kashima Kawashima Honjo</td>
<td>Tokyo</td>
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<tr>
<td></td>
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<td>London</td>
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<td>London</td>
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<tr>
<td>Boston North Carolina (RTP)</td>
<td>Boston</td>
<td>New Jersey</td>
</tr>
</tbody>
</table>

*Process chemistry, Analytical research, Formulation, Safety, Clinical Supply etc.
Eisai Global Clinical Development (EGC) Establishment in May, 2004

Integrated clinical development functions in US/EU
Unified accountability in US/EU

Prompt and efficient decision-making
Close cooperation in US/EU

Director of Clinical Development Europe reports to EGC President

◆ Appointment of Global Therapeutic Area Head
  ➢ CNS, GI, Oncology, Infection

◆ Appointment of Global Functional Head
  ➢ Clinical Pharmacology, Data Management, Biometrics, Project Management
Eisai Research Institute of Boston Expansion

◆ Expand capacity and center a rental laboratory on one campus
◆ Groundbreaking Ceremony - August 23, 2004
◆ Completion of project – Planned for October 2006
◆ Total floor space: 200,000 ft² (18,580 m²)
◆ Staff Capacity for 250 (40% increase)
Outline of PF Plant

- API manufacturing Plant which combined Pilot Plant and Factory
- Total Floor Space : 9,905m²
- Total Cost : 9 billion yen
- Floors : Five stories

Concept

1) Supply high quality API for clinical use by having a cutting edge Pilot Plant which complies with GMP
2) Increase production capacity of Aricept and Aciphex/Pariet and reduce cost of API substantially.
3) Prevent 'health hazard' and 'environmental pollution' by installation of containment equipment.
4) Achieve seamless collaboration between R&D and Production
Current Status of Drug Discovery
## Eisai R&D Product Pipeline

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>GI</td>
<td>E3309 (Hp eradication)</td>
<td>E3810 (US) (Intermittent therapy) E3620 (Prokinetics)</td>
</tr>
<tr>
<td>Immunology/Allergy</td>
<td>E6040 (Autoimmune disease)</td>
<td>E5564 (Sepsis, CABG) D2E7 (Rheumatoid arthritis)</td>
</tr>
<tr>
<td>Anti-cancer</td>
<td>E7389 (Cancer) E7820 (Cancer) E7070 (Cancer)</td>
<td>E7070 (Cancer) E0167 (Cancer)</td>
</tr>
<tr>
<td>CV Metabolic</td>
<td>E5555 (Acute Coronary syndrome) E3030, E3030 (Diabetes)</td>
<td>E0735 (paf/PAF)</td>
</tr>
<tr>
<td>Contrast Media</td>
<td>E7210 (Contrast agent for ultra sound)</td>
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</tr>
</tbody>
</table>
Donepezil has a protective effect against oxygen-glucose deprivation-induced injury to rat primary cultured cortical neurons.

Primary culture of rat cerebral cortical neurons   OGD: oxygen-glucose deprivation
(Eur. J. Pharmacol., 2003; 472: 57-63)
Drug Discovery Approach for Alzheimer’s Disease

Amyloid Precursor Protein

\[ \beta \text{ site} \quad \gamma \text{ site} \]

\[ \downarrow \]

\[ \beta\text{-secretase} \]

\[ \downarrow \]

\[ \gamma\text{-secretase} \]

\[ \ \]

A\(\beta\)

\[ \downarrow \]

Protofibril

\[ \text{Endopeptidase} \]

\[ \downarrow \]

Digested peptide

\[ \rightarrow \]

Acceleration of amyloid degradation

\[ \rightarrow \]

Inhibition of \(\beta\) amyloid production

Inhibition of cell death

Neuronal death

Amyloid deposition

Immunotherapy
Strategy Toward Regenerating CNS Using Neural Stem Cells

1. **Activation of endogenous NSCs**
   - Insult-induced, growth factor infusion
   - Identification of endogenous NSC-activating factors
   - Development of small chemical compounds

2. **Cell Therapy (Transplantation)**
Collaboration with Neurogenetics, Inc.

◆ LOAD program
  – Discovery of genes responsible for Late Onset Alzheimer's Disease (LOAD) to establish valid targets and to facilitate the development of new therapeutic products

◆ Date of contract
  – October 1, 2002

◆ Neurogenetics, Inc.
  – San Diego, founded in April 2000
Exploratory Research for GI Area
-Target diseases and Therapeutic targets-

Gastrointestinal Discomfort (due to GI Motility Dysfunction)

Upper GI Discomfort

Irritable Bowel Syndrome (IBS)

Acid Related Disease

Gastro-Esophageal Reflux Disease (GERD)

Peptic Ulcer Disease

Therapy for GI Disorders related to Gastric Acid Secretion

Therapy for Gastric Dyspepsia and Abdominal Discomfort due to GI Motility Dysfunction

Inflammatory Bowel Disease (IBD)

Crohn’s Disease

Ulcerative Colitis

Therapy for Intractable Bowel Inflammation
Exploratory Research for GI Area

- Therapeutic Approach & Targets -

Gastrointestinal Discomfort (due to GI Motility Dysfunction)

Upper GI Discomfort

GI Motility Approach

E3620

Irritable Bowel Syndrome (IBS)

GI Motility Approach

E3620; Prokinetics

Novel Inflammatory Drug

Acid Related Disease

GERD/ Peptic Ulcer Disease

Acid Suppression Approach

Acid Suppression Research

Inflammatory Bowel Disease (IBD)

Crohn’s Disease Ulcerative Colitis

Inflammatory Suppression Approach
Oncology Projects

Meet Needs for Cancer Treatment by Various Approaches

Tumor regression

- Novel mechanism
  - E7070: Cell cycle G1 phase targeting agent
    US, EU and JP Phase II
  - E7107: Novel antitumor agent derived from fermentation
    Pre-clinical

Novel anti-mitotic

- E7389: Tubulin polymerization inhibitor
  US Phase I
- E7974: Tubulin polymerization inhibitor
  Pre-clinical

Tumor suppression

- Anti-angiogenesis
  - E7820: Integrin α-2 expression inhibitor
    US Phase I
- E7080: VEGF receptor tyrosine kinase inhibitor
  Phase I under preparation

Life-span Prolongation

- Prevention of recurrence
  - E0167: Prevention of recurrence of hepatocellular carcinoma
    by vitamin K₂
    JP, Phase II

Prevention of recurrence

- E7820: Integrin α-2 expression inhibitor
  US Phase I
- E7080: VEGF receptor tyrosine kinase inhibitor
  Phase I under preparation
E7070(indisulam)
G1 Phase Targeting Agent: Ph. II

- Tumor regression of colon, NSCLC, breast and gastric cancer xenografts
- Synergistic effect with irinotecan
  - Down regulation of Topo II
- Additive effect with platinum and 5-FU
  - Down regulation of Glutathione synthetase
  - Down regulation of Thymidylate synthase
Unique Profile of E7070
Study to reveal mechanism is ongoing

Proteome Technology
E7070 binding proteins
More than 10 proteins
For example: cMDH (Cytosolic malate dehydrogenase)
E7070 binds cMDH competitively with NADH

Gene Expression Analysis
E7070 biological Marker
A set of response marker genes
Reduction of Topo II α etc.
In response to E7070 treatment

Bio-pharmacological Approach
E7070 Mode of Action
G1 cell cycle arrest by Induction of CDK inhibitor p21
P21 inhibits G1/S Cell cycle transition
E7389 Tubulin Polymerization Inhibitor: Ph. I

- NCI demonstrated excellent anti-tumor activity of marine natural halichondrin B in several human tumor xenograft models.
- Limited compound supply prevented development of halichondrin B.
- Eisai Research Institute identified pharmacophore.
- E7389 is totally synthetic material.
E7389
Tubulin Polymerization Inhibitor: Ph. I

- Highly effective in several human tumor xenograft models
  - MDA-MB-435 breast
  - COLO 205 colon
  - LOX melanoma
  - OVCAR-3 ovary
  - H522 lung
- Significantly more potent than taxol
- Active against taxol-resistant cancer cells
- Unique mechanism of action among anti-tubulins, taxanes and vinca alkaroids

MDA-MB-435 human breast cancer xenograft model

Average tumor volumes (µl)

0 14 28 42 56 70 84 98

Day

Control

Taxol 25 mg/kg

E7389 1 mg/kg
E7820
Oral Angiogenesis Inhibitor: Ph. I

- Inhibition of capillary tube formation and proliferation of endothelial cells
- Inhibition of integrin $\alpha_2$ expression
- Inhibition of VEGF and FGF-induced angiogenesis

In vitro anti-angiogenic activity in tube formation assay

<table>
<thead>
<tr>
<th>Compounds</th>
<th>Angiogenic factor</th>
<th>IC50 (range) (mg/mL)</th>
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<tr>
<td>E7820</td>
<td>bFGF</td>
<td>0.20 (0.18 - 0.22)</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>0.24 (0.21-0.38)</td>
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<tr>
<td>TNP-470</td>
<td>bFGF</td>
<td>&gt;5</td>
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<tr>
<td></td>
<td>VEGF</td>
<td>&gt;5</td>
</tr>
<tr>
<td>Marimastat</td>
<td>bFGF</td>
<td>&gt;5</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>&gt;5</td>
</tr>
<tr>
<td>SU5416</td>
<td>bFGF</td>
<td>&gt;5</td>
</tr>
<tr>
<td></td>
<td>VEGF</td>
<td>0.19 (0.18-0.19)</td>
</tr>
</tbody>
</table>
E7820
Oral Angiogenesis Inhibitor: Ph. I

- Effective in human pancreatic, breast, colon and renal cancer xenograft models
- Prolongs survival in human breast cancer xenograft model

**Human Pancreatic Cancer (KP-1)**

**Survival curve in MDA-MB-435 human breast cancer xenograft models**
E7080
Oral Angiogenesis Inhibitor: Ph. I (under preparation)

- Highly potent VEGFR tyrosine kinase inhibitor
  VEGF; Vascular endothelial cell growth factor receptor
- Anti-VEGF (Avastin) showed clinical efficacy

<table>
<thead>
<tr>
<th>Inhibition of cell free tyrosine kinase activity</th>
<th>IC50 (nM)</th>
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</thead>
<tbody>
<tr>
<td>SU11248 PTK787 ZD6474 CP-547,632</td>
<td>E7080</td>
</tr>
<tr>
<td>VEGFR</td>
<td>64 124 191 178</td>
</tr>
<tr>
<td>FGFR1</td>
<td>1,500 &gt;10,000 1,400 160</td>
</tr>
<tr>
<td>EGFR</td>
<td>&gt;10,000 &gt;10,000 220 &gt;10,000</td>
</tr>
<tr>
<td>PDGFRb</td>
<td>120 410 6,750 2,000</td>
</tr>
</tbody>
</table>
E7107

Novel Anti-tumor Compound, Derivative of Pladienolide, Derived from Fermentation: Pre-clinical

- Highly potent tumor regression activity; tumor remission was observed in several xenografts

- ‘pRB loss and high cyclin E’ is common feature among tumor cells highly sensitive to E7107; possible predictive factor

*Discovered together with Mercian Corporation
Alliance with Link Genomics

Genome-wide analysis of genetic aberrations in cancer

Genome-wide HR DNA chip

1. “DNA analysis of tumor tissues"
2. “Clinical samples"
3. "Relation of stage, responsibility and prognosis"

Genomic aberration–Cancer stage Data base

Specificities of Tumors and Tissues, Drug response

Novel target genes

Anti-cancer drug in Eisai
E5555
Orally Active PAR-1 Antagonist: Ph I
Indication: Acute coronary syndrome
(ACS)

PAR-1: protease-activated receptor-1

Bleeding
Atherosclerosis
Thrombosis

Thrombin

Fibrin formation
Monocyte/Lymphocyte
Adhesion
Migration
SMC Proliferation

ACS (UA, MI)
**E5555**

Orally Active PAR-1 Antagonist: Ph I

**Indication:** Acute coronary syndrome (ACS)

### Summary of pharmacological studies

<table>
<thead>
<tr>
<th>Test</th>
<th>Human</th>
<th>Monkey</th>
<th>Guinea pig</th>
<th>Rat</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In vitro</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAR-1 Binding (IC50)</td>
<td>19 nM</td>
<td>N.T.</td>
<td>N.T.</td>
<td>N.T.</td>
</tr>
<tr>
<td>PRP aggregation (IC50)</td>
<td>64 nM</td>
<td>12 nM</td>
<td>N.T.</td>
<td>N.T.</td>
</tr>
<tr>
<td>SMC proliferation (IC50)</td>
<td>28 nM</td>
<td>N.T.</td>
<td>N.T.</td>
<td>160 nM</td>
</tr>
<tr>
<td><strong>In vivo</strong></td>
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<tr>
<td>Thrombosis model (30mg/kg)</td>
<td></td>
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</tr>
<tr>
<td>Intimal Hyperplasia model (30mg/kg)</td>
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<tr>
<td>Bleeding Time (1000mg/kg)</td>
<td></td>
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</tbody>
</table>

**Summary:**

- Effective plasma conc.: 56 nM
- Effective
- No prolongation plasma conc.: 281 nM

N.T.: Not Tested
Discovery Research Projects
In Frontier Area

Target: MEKK1, MEK1 and IKK \( \beta \)

- EGF, KGF, ..., IL-1, TNF, LPS, ...

Inflammation pathways
Proliferation pathways

C-RAF \rightarrow MEKK1

MEKK1 \rightarrow MEK1

MEK4/7 \rightarrow IKK \( \beta \)

ERK2

JNK

ELK-1

C-Fos

C-Jun

AP-1

NF-kB

Cytokine

Chemokine

Adhesion Molc.

Cell Growth

Cell Growth
Collaboration with LocomoGene Inc.

Research program for Rheumatoid Arthritis Treatment

Synovioli

Target

Synovial Cell Growth

Crisis of Rheumatoid Arthritis

LocomoGene Inc.
Established as a research and development venture company to find new genes and proteins related to aging diseases. All shares are held by the investment fund, "The 1st Biotech Healthcare Investment Business Limited Liability Association" supported by Development Bank of Japan.
Global Clinical Research

Jiro Hasegawa, Ph.D.
Vice President, Head of Global Clinical Research,
Eisai Co., Ltd.
September 1, 2004
Clinical Development Priorities in FY2004 (1)

1. Increasing the Probability of Success Future Global Products

- Achievement of Proof of Concept (POC) for the four Global Priority Projects -

- E2007  Phase IIb Study in Parkinson’s disease (EU)
- E5564  Phase II Study in Sepsis (US)
- E7070  Phase IIb Monotherapy in Breast Cancer (US)
- E7389  Phase II Study in Breast Cancer (US)
- Phase II Study in CABG (US)
- Phase IIb Study in CABG (EU)
- Phase II Combination Study with irinotecan in CRC (EU)
Clinical Development Priorities in FY2004 (2)

2. Lifecycle Management Reinforcement for Aricept and Aciphex/Pariet

**Aricept**
Completion of Patient Enrollment in FY2004 of Phase III Studies for:
- Vascular Dementia (US/EU)
- Severe Alzheimer’s Disease (US/EU/JP)
- Dementia associated with Parkinson’s Disease (EU)
Approval of Rapid Disintegrating Tablet and Liquid Formulation (US/EU)  
Filing: FY 2005

**Aciphex/Pariet**
Progress of Phase II Study for Intermittent Therapy (US)
Progress of Phase III Study for s-GERD and H. pylori eradication (JP)
E7070 (indisulam)
Cell Cycle G1 Phase Targeting Agent
Anti-cancer drug
E7070 Clinical Studies

Single agent Phase Ila studies

Completion: Colorectal (EU), Non-small cell lung (EU), Head & Neck (US), Breast (EU), Melanoma (EU), Renal (US/EU)
Under preparation: Stomach (JP)
# Results of 204 Study (Breast, EU) and the Comparison with capecitabine

<table>
<thead>
<tr>
<th>Clinical Phase</th>
<th>E7070</th>
<th>capecitabine</th>
<th>capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers of Patients</td>
<td>II</td>
<td>162</td>
<td>71</td>
</tr>
<tr>
<td>PR rate</td>
<td>15%</td>
<td>20%</td>
<td>17%</td>
</tr>
<tr>
<td>SD rate</td>
<td>40%</td>
<td>40%</td>
<td>38%</td>
</tr>
</tbody>
</table>

PR: Partial Response  
SD: Stable Disease
Current Status of E7070 Clinical Studies

◆ Single agent study
  ■ Initiated Ph IIb for Breast cancer in January, 2004 in the US
  ■ Target NDA/MAA in 2006

◆ Combination study
  ● Combination with irinotecan
    ■ Confirmed the recommended dose in the Ph I (US)
    ■ Partial Responses were observed in colorectal cancer patients
    ■ Initiated the Ph II for colorectal cancer in July, 2004 (EU)
    ■ Target NDA/MAA in FY2006
  ● Combination with capecitabine
    ■ Confirmed the recommended dose in the Ph I study (EU)
    ■ Under preparation for Ph II study for colorectal cancer (EU)
    ■ Under preparation for Ph II study for breast cancer (EU)
  ● Combination with carboplatin
    ■ Confirmed the recommended dose in the Ph I study (EU)
    ■ Initiated the Ph II study for Non-small cell lung cancer (EU)
E7389
Tubulin Polymerase Inhibitor
Anti-cancer drug
E7389 - Phase I

◆ US NCI study
  – NC5730 (Day-1, -8, -15 q28 days, IV bolus)
    – Achieved MTD (Maximum Tolerated Dose)
    – Responses in NSCLC (refractory to taxane)

◆ Eisai study
  – 101 study (Day-1, -8, -15 q28 days, 1 hour infusion)
    – Status: On going
  – 102 study (Day-1 q21 days, 1 hour infusion)
    – Status: On going
E7389 - Phase I, II

Phase I

◆ US NCI study
  – NC5730 (Day-1, -8, -15 q28 days, IV bolus)
    – Achieved MTD
    – Responses in NSCLC (refractory to taxane)

◆ Eisai study
  – 101 study (Day-1, -8, -15 q28 days, 1 hour infusion)
    – Status: On going
  – 102 study (Day-1 q21 days, 1 hour infusion)
    – Status: On going

Phase II

◆ Single agent therapy
  – 201 study (Breast cancer)
  – 202 study (NSCLC)
E2007
AMPA Receptor Antagonist

- Parkinson’s disease
- Epilepsy
- Multiple sclerosis
E2007 Clinical Studies

FY2003 Achievement

- Completion of Phase Ila study for Parkinson’s disease, Epilepsy and Multiple sclerosis in EU

Current status

- Initiated Phase IIb for Parkinson’s disease in EU
- Phase IIb for Epilepsy is in preparation in the US
Anti-Wearing Off Effect of E2007 in Parkinsonian Rats

Advanced Parkinson's disease with E2007

Dyskinesia
Therapeutic Window
on-time
Parkinsonism

Plasma L-DOPA concentration

Time

Day 1
L-DOPA (25mg/kg, i.p.)

Day 21

L-DOPA (25mg/kg, i.p.)

E2007 (mg/kg, p.o.)

on-time (mins)

veh 0.3 1.0 3.0

on-time (mins)

**

**

**
E5564 (eritoran)
Endotoxin Antagonist

- Sepsis
- CABG

_Prevention of endotoxin-related complications after coronary artery bypass graft surgery_
**E5564 (Endotoxin Antagonist)**

**Indication:**
- Sepsis
- Coronary artery bypass graft (CABG)
  - Prophylactic use for endotoxemia after Coronary artery bypass graft surgery

**Stage:**
- Sepsis Ph II: Stage 3 on-going in US
- CABG Ph IIa: Stage 3 completed in US
- CABG Ph IIb: On going in EU and Canada

**NDA / MAA:**
- FY2007 (CABG), FY2008 (Sepsis)
E5564 Blocks LPS-induced Symptoms in Phase I Study

E5564 is the only drug which has achieved complete suppression of LPS induced symptoms in human endotoxemia.
Patients (N=301) were evaluated for EndoCAb IgM value and CABG surgical outcome. Major complications were defined by hospital length of stay > 10 days and plotted vs. quartile rank of pre-surgical plasma EndoCAb IgM value. For details see Bennet-Guerrero et al. (1997).
Update

Aciphex/Pariet

Aricept
Recent Regulatory Achievements

- Approval of On Demand Therapy of Pariet (EU) - April 2004 in EU
- Approval of Zollinger-Ellison Syndrome Indication of Pariet (EU) - June 2004 in EU
- Approval of Rapid Disintegration Tablet of Aricept - March 2004 in Japan
- Filing of Rapid Disintegration Tablet of Aricept - December 2003 in EU and US
- Filing of Liquid Formulation of Aricept - December 2003 in US - May 2004 in EU
Aciphex/Pariet
## Aciphex/Pariet Lifecycle Management

<table>
<thead>
<tr>
<th>Compound/Indication</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Submission</th>
<th>Launch</th>
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<tbody>
<tr>
<td>Aciphex/Pariet <em>(H. pylori eradication)</em></td>
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<tr>
<td>US, EU</td>
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<tr>
<td>Aciphex/Pariet <em>(Symptomatic GERD/GORD)</em></td>
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<tr>
<td>US, EU</td>
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<tr>
<td>Pariet <em>(Maintenance Therapy of GERD)</em></td>
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<td>JP</td>
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<tr>
<td>Pariet <em>(On-demand Therapy of GORD)</em></td>
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<td>EU</td>
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<td>Pariet <em>(Zollinger Ellison Syndrome)</em></td>
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<td>EU</td>
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<td>Pariet <em>(H. pylori eradication)</em></td>
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<td>Pariet <em>(Symptomatic GERD)</em></td>
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Aricept
## Aricept Lifecycle Management

<table>
<thead>
<tr>
<th>Compound/Indication</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
<th>Submission</th>
<th>Launch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aricept (Vascular Dementia) US</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Aricept (Severe Alzheimer’s) US, EU, JP</td>
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<tr>
<td>Aricept (Dementia Associated with PD) EU</td>
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<tr>
<td>Aricept (Migraine Prophylaxis) US, EU</td>
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<tr>
<td>Aricept (Rapid Disintegration Tablet) JP</td>
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<tr>
<td>Aricept (Rapid Disintegration Tablet) US, EU</td>
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<tr>
<td>Aricept (Liquid Formulation) US, EU</td>
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</tbody>
</table>
Vascular Dementia
Severe Alzheimer Dementia
(New Indication)

◆ Vascular Dementia
  – US
    – NDA submission: Sep 02
    – Non approvable letter: Jul 03
  – EU
    – MAA submission: Oct 02
    – Withdrawal: Apr 04
  – Future Strategy
    – Complete 3rd pivotal study (E2020-A001-319)
      – US: continue negotiation and submit the 3rd study results to reinforce data set (FY05: expected)
      – EU: Re-submit MAA including the 3rd study results (FY05: expected)

◆ Severe Alzheimer Disease Dementia
  – DON-NY-324 (preliminary study)
    – Moderate to moderately severe AD patient
  – E2020-A001-315 (pivotal study)
    – Severe AD patient
DON-NY-324 (MSAD Study)

Objectives

- Evaluate the safety and efficacy of donepezil in patients with moderate to moderately severe AD (sMMSE = 5 – 17)

Design

- A multicenter, multinational, randomized, double-blind, placebo-controlled 24-week study
- 291 patients with moderate to moderately severe AD
- Randomization was 1:1 (donepezil:placebo)
  - Aricept 5 mg daily for 28 days increased to 10 mg daily for the remainder of the study based on the clinicians judgment
  - 82% of total patients was administered 10 mg daily

Change from Baseline Scores
SIB (Severe Impairment Battery)

Aricept

Placebo

Mean ± SE.

Study Week

Aricept 139 130 115 123 119 120 (139)
Placebo 145 139 119 128 128 126 (145)

Severe AD NDA/MAA

◆ E2020-A001-315 study:
  – On-going (study completion: mid FY05)

◆ NDA/MAA: FY05 (expected)
Dementia Associated with Parkinson’s Disease (New Indication)

E2020-E044-316 (PD study)

Objectives

Evaluate the efficacy, tolerability and safety of donepezil in Parkinson’s Disease (PD) patients with dementia

Study Design

◆ E2020-E044-316
  – Clinical phase on going
    – Completion: mid FY05 (expected)

◆ EU MAA: FY05
Working Criteria for MCI

- Subjective memory complaint and objective memory deficit (i.e., delayed recall >1.5 SD below age and education norms)
- Preserved general cognitive ability (Mini-Mental State Examination [MMSE] =24)
- Intact activities of daily living (ADL)
- Not demented (Clinical Dementia Rating [CDR] 0.5)
- MCI may be regarded as incipient or prodromal Alzheimer’s disease (AD)
- Patients with MCI progress to AD at a higher annual rate (10% to 15%) than normal elderly patients (1% to 2%)

Recruit people with MCI

3 treatments
- Vitamin E – 2,000 IU/day
- Donepezil – 10 mg/day
- Placebo
- Open-label donepezil after conversion to AD

Study objectives
- Prevent development of Alzheimer’s disease
- Slow decline on measures of cognition

3-year duration
790 participants
69 centers
Mean Time to Conversion to AD

<table>
<thead>
<tr>
<th></th>
<th>Time to Conversion (mean days ± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aricept (n=63)</strong></td>
<td>661±270*</td>
</tr>
<tr>
<td>Vitamin E (n=76)</td>
<td>540±257</td>
</tr>
<tr>
<td>Placebo (n=73)</td>
<td>484±272</td>
</tr>
</tbody>
</table>

*P=0.0003

177 days
Aricept
Efficacy in Long-term Studies
Objective
Evaluate the Long-term Clinical Efficacy and Safety of Aricept in patients with mild to moderate AD

Study Design
A 52-Week, Randomized, Double-Blind, Placebo-Controlled Study:

- Patients (n = 286, MMSE = 10-26)
  - *Aricept* 10mg (n=142, 5 mg daily for 28 days increased to 10 mg daily based on the clinicians’ judgment) Placebo (n=144)

Study week

Time Course of MMSE

LS mean change from Baseline (mean ± S.E.)

Aricept (n=142)

Placebo (n=144)

End Point (LOCF)

mean ± S.E.

*: p<0.05

**: p<0.01

***: p<0.001

Improvement

Decline

1.0

0

-1.0

-2.0

-3.0

0 12 24 36 52

Study week

End Point (wks)

Aricept Placebo

135 127 121 104 91 135

137 128 120 105 98 137

Objective
Examine the effects of donepezil compared with placebo on the preservation of function in patients with AD

Study Design
- A 1-year double-blind, placebo-controlled study
- Probable AD Patients (n = 431, MMSE=12-20) were randomized
  - donepezil (n = 214, 5 mg/day for 28 days, 10 mg/day thereafter)
  - placebo (n = 217)
- ADL was measured based on instrumental and basic ADL scales widely used in clinical research
- The primary efficacy analysis was the time in days to reach clinically evident functional decline.

Inhibition of ADL Function Decline

The median time to clinically evident functional decline

- Aricept: 357 days
  - Ratio of patients keeping ADL function: 72%
- Placebo: 208 days
  - Ratio of patients keeping ADL function: 35%

Aricept-treated patients maintained their function for significantly longer than Placebo-treated patients: 72% prolongation.*

Placebo
\( \text{Aricept} \)

\( n=217 \) \( n=214 \)

\( p = 0.0019 \)

Nursing Home Study

Objectives

- Assess the relationship between donepezil treatment and time to nursing home placement (NHP) for patients with Alzheimer's Disease

Design

- Patients previously enrolled in one of three placebo controlled studies and participated in subsequent open label extension studies were followed by interviewing caregivers
- Information on the date and reason for each NHP and treatment compliance were obtained
- 671 patients provided complete data for analysis
- Continued treatment of up to 240 weeks in the open label studies were available

Time to First Dementia-related NHP with Increasing Donepezil Exposure

- Maximal (n=310): 66.1 months
- Delayed (n=194): 58.0 months
- Early (n=54): 44.7 months
- Limited (n=113): 44.7 months

21.4 month delay

Median time to first dementia-related NHP (mo)

Error bars represent 95% CIs of median values.

AD2000 Study

◆ Objective
  – Assess the effects of donepezil from the viewpoint such as patient institutionalization

◆ Study Design
  – Double blind, placebo controlled long-term study
  – Patients: selected by DSM-? diagnosis of dementia of Alzheimer type based on uncertainty (mild to moderate patients living in the community)
  – 565 patients enrolled
  – 12 weeks: placebo vs. donepezil (5 mg/day) → 48 weeks: rerandomised to placebo vs. donepezil (5 or 10 mg/day) → 6 weeks washout ? 48 weeks: placebo vs. donepezil → 4 weeks washout → (48 weeks: placebo vs. donepezil → 4 weeks washout) → (repeated)

◆ Primary endpoint
  – Entry to institutional care and progression of disability (BADLS)
AD 2000: Eisai's Statement(1)

- Methods for patient selection
  - Non Eligible: a definite indication for or against donepezil treatment
  - Eligible: "substantially uncertain whether or not a particular patient would derive worthwhile benefit from donepezil"
    - the investigators introduced bias to their results.

- Sample size
  - 3,000 patients (original) → only 566 patients
    - Underpowered study

- Attrition rate
  - Within one year, 48% of patients had discontinued
  - Less than 20% (n=111) remained by the end of year 2.
    - Statistically, this small sample is not sufficient to refute the findings of other published studies
Randomization procedures
- Limited geographic location on subject selection and physician practice patterns
  - Further decrease the conclusion generalization

Multiple washout periods
- Data had been published indicating that such washouts were associated with loss of donepezil treatment benefit
  - This design would be expected to lead to a decreased benefit on cognition, and may impact factors important for institutionalization.
Clinical Research in Japan

Hisashi Tanaka, Ph.D
Vice President, Head of the Clinical Research Center
Eisai Co., Ltd.
September 1, 2004
### Eisai R&D Product Pipeline Projects

<table>
<thead>
<tr>
<th>Category</th>
<th>Clinical</th>
<th>Submission</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Phase I</td>
<td>Phase II</td>
</tr>
<tr>
<td>Neuro</td>
<td>E2051</td>
<td>E2007</td>
</tr>
<tr>
<td></td>
<td>E1049</td>
<td>(AD)</td>
</tr>
<tr>
<td>GI</td>
<td>E3309</td>
<td>E3810</td>
</tr>
<tr>
<td></td>
<td>(Hp eradication) E3620 (Prokinetics)</td>
<td>(US) (Intermittent therapy)</td>
</tr>
<tr>
<td>Immunology/Allergy</td>
<td>E6040</td>
<td>E5564</td>
</tr>
<tr>
<td></td>
<td>(Autoimmune disease) E3620 (Prokinetics)</td>
<td>(Sepsis, CABG) E257 (Rheumatoid arthritis)</td>
</tr>
<tr>
<td>Anti-cancer</td>
<td>E7389</td>
<td>E7070</td>
</tr>
<tr>
<td></td>
<td>(Cancer) E7820 (Cancer) E7070 (Cancer)</td>
<td>(Cancer)</td>
</tr>
<tr>
<td>CV Metabolic</td>
<td>E5555</td>
<td>E0735</td>
</tr>
<tr>
<td></td>
<td>(Acute Coronary syndrome) E3030, E3030 (Diabetes)</td>
<td>(pf/PAF)</td>
</tr>
<tr>
<td>Contrast Media</td>
<td>E7210</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(Contrast agent for ultra sound)</td>
<td>(Anti-obesity)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E2020 (US) (Vascular dementia) E2020 (US, EU) (Liquid formulation)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>E2020 (US, EU) (Rapid disintegrating tablet)</td>
</tr>
</tbody>
</table>

**Red**: Development in Japan  
**Underline**: under preparation
# Outline of D2E7

**Human Anti-TNF-α Monoclonal Antibody**

<table>
<thead>
<tr>
<th>Theme</th>
<th>adalimumab (D2E7)</th>
<th>Note</th>
<th>Co-development with Abbott Japan Co., Ltd. (Launched in US/EU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Rheumatoid Arthritis (moderate to severe)</td>
<td>Supply</td>
<td>Pre-filled Syringe</td>
</tr>
<tr>
<td>Phase</td>
<td>II</td>
<td>NDA target</td>
<td>FY2005</td>
</tr>
</tbody>
</table>
| Merits    | 1) More rapid and sound efficacy than that of DMARDs.  
           | 2) Every other week mono-therapy revealed efficacy with/without MTX.  
           | 3) Ready-to-use liquid formulation suitable for subcutaneous injection. |
## Comparison with Competitors

<table>
<thead>
<tr>
<th>INN</th>
<th>infliximab</th>
<th>etanercept</th>
<th>adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Company</td>
<td>Centocore/ Tanabe</td>
<td>Immunex/ Wyeth</td>
<td>Abbott/ Eisai</td>
</tr>
<tr>
<td>Structure</td>
<td><img src="image" alt="Mouse/human chimera Anti-TNF-alpha Mab" /></td>
<td><img src="image" alt="Soluble TNF receptor Ig-Fc fusion protein" /></td>
<td><img src="image" alt="Fully human Anti-TNF-alpha Mab" /></td>
</tr>
<tr>
<td>Black-area indicates mouse-gene derived parts</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type</td>
<td>Mouse/human chimera Anti-TNF-alpha Mab</td>
<td>Soluble TNF receptor Ig-Fc fusion protein</td>
<td>Fully human Anti-TNF-alpha Mab</td>
</tr>
<tr>
<td>Phase</td>
<td>Launched</td>
<td>Registered</td>
<td>Phase II</td>
</tr>
<tr>
<td>Indication</td>
<td>Rheumatoid Arthritis( inadequate response to at least one DMARD)</td>
<td></td>
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</tbody>
</table>
# Outline of KES524

Obesity Management /Central Acting Serotonin & Noradrenaline Reuptake Inhibitor

<table>
<thead>
<tr>
<th>Theme</th>
<th>sibutramine (KES524)</th>
<th>Note</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Obesity</td>
<td>Supply</td>
</tr>
<tr>
<td>Phase</td>
<td>III</td>
<td>NDA Target</td>
</tr>
<tr>
<td>Merits</td>
<td>1) Enhance energy consumption and a feeling of fullness to reduce ingestion and body weight.</td>
<td></td>
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<tr>
<td></td>
<td>2) Expected to reduce body weight and to maintain the reduced weight for a long period.</td>
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<tr>
<td></td>
<td>3) Expected to improve complications related to obesity.</td>
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</tr>
</tbody>
</table>

Exclusive development in Japan (Launched in US/EU)

Capsule

FY2007
%Change of body weight in Phase II study

Change of Body Weight

Weeks after dosing

Placebo
5 mg
10 mg
15 mg

LOCF
### Outline of T-614

**Anti-rheumatic Agent**

<table>
<thead>
<tr>
<th>Theme</th>
<th>iguratimod (T-614)</th>
<th>Note</th>
<th>Co-development with Toyama Chemical Co., Ltd.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indication</td>
<td>Rheumatoid Arthritis</td>
<td>Supply</td>
<td>Tablet</td>
</tr>
<tr>
<td>Phase</td>
<td>Submitted</td>
<td>NDA</td>
<td>FY2003</td>
</tr>
</tbody>
</table>
| Merits         | 1) Suppress antibody production from B cell without inhibiting lymphocyte proliferation.  
               |                    | 2) Suppress cytokine production.           |                                             |
Improvement Rate
based on the ACR Diagnosis Criteria

ACR20 & ACR50 (Non-inferiority analysis set)

ACR20 & ACR50 (Non-inferiority analysis set)

EULAR June-2004
Eisai’s R&D Goals

Kentaro Yoshimatsu, Ph.D.
Vice President,
Discovery & Development Research Headquarter
Eisai Co., Ltd.
September 1, 2004
Eisai’s R&D Goals

◆ Global leader in franchise areas
  – Creation of neurodegenerative diseases treatment through cutting-edge research
  – Strengthen oncology pipeline

◆ Further improve the competitive advantages of Aricept, Aciphex/Pariet
  – Aricept: “Gold standard” of AD treatments
  – Aciphex/Pariet: Strong branding based on evidence

◆ File one NME a year
# Enhanced NME Pipeline

<table>
<thead>
<tr>
<th></th>
<th>Pre-clinical</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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</thead>
<tbody>
<tr>
<td><strong>Neuro</strong></td>
<td>Neurodegenerative diseases † Aβ accumulation suppressor † Neuro cell death inhibitor † Neuro-stem cell activator</td>
<td>E2051 (Acute ischemic stroke) E2070 (Analgesics)</td>
<td>E2007 (MS, PD, EP) TVP1012 (AD) E2014 (Cervical dystonia)</td>
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<tr>
<td><strong>Gl</strong></td>
<td>Acid-related disorders Irritable bowel syndrome IBD</td>
<td>E3309 (H. pylori eradication)</td>
<td>E3620 (Gastroprokinetic)</td>
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<tr>
<td><strong>Anti-cancer</strong></td>
<td>E7080 (Angiogenesis inhibitor) E7107 (pladienolide derivative) E7974 (Tubulin polymerase inhibitor)</td>
<td>E7389 (Tubulin polymerase inhibitor) E7820 (Angiogenesis inhibitor)</td>
<td></td>
<td>E7070 (Cell growth cycle Gl phase inhibitor)</td>
</tr>
<tr>
<td><strong>Frontier</strong></td>
<td>Immunology/Allergy Alimentary tract</td>
<td>E5555 (Acute Coronary syndrome) E6040 (Autoimmune disorders)</td>
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<td></td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td>Diabetes</td>
<td>E3030 (Diabetes)</td>
<td>E7210 (Contrast agent)</td>
<td>KES524 (Obesity)</td>
</tr>
</tbody>
</table>
File One New Molecular Entity (NME) A Year

Submitted

FY2004
- rufinamide (Epilepsy, US and EU)

FY2005
- D2E7 (Rheumatoid Arthritis, JP)
- E2014 (Cervical Dystonia, JP)
- E7210 (Contrast Medium, JP)

FY2006
- E2007 (Parkinson’s disease, US and EU)
- E7070 (Cancer, US and EU)

FY2007
- E7389 (Cancer, US and EU)
- E5564 (Prevention of endotoxin-related complications after coronary artery bypass graft surgery, US and EU)
- KES524 (Obesity Management, JP)

FY2008
- E5564 (Sepsis, US/EU)
- E7070 (Cancer, JP)
- E7070 (Cancer, US and EU)
- E7389 (Cancer, US and EU)
- E2007 (Parkinson’s disease, US and EU)
- E7070 (Cancer, US and EU)
- E7389 (Cancer, US and EU)
- E5564 (Prevention of endotoxin-related complications after coronary artery bypass graft surgery, US and EU)
- KES524 (Obesity Management, JP)