



R&D Meeting

Major Project Status and Future Plan

August 30, 2005
Eisai Co., Ltd.



Safe Harbor Statement

- Materials and information provided during this presentation may contain so-called “forwardesentatiot



R&D Meeting

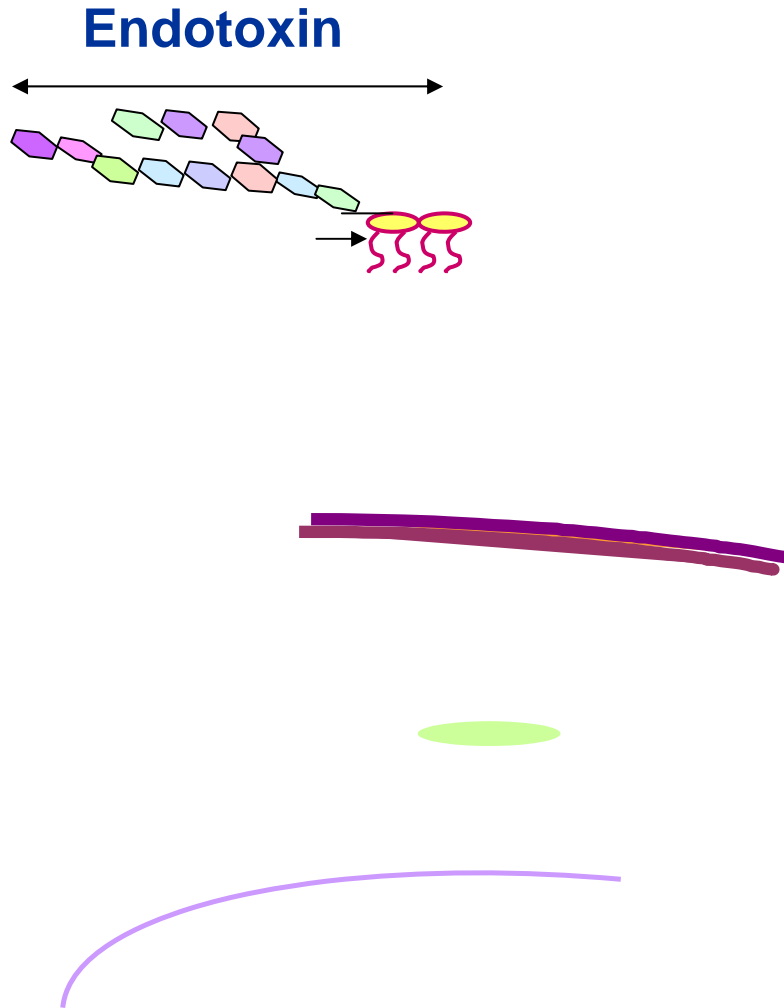
- E5564 Results of Phase II Study
- E2007 Plan for NDA
- E5555 Progress

Jiro Hasegawa
Senior Vice President
Global Clinical Research



E5564 (eritoran)

Inhibitory mechanism of E5564 in TLR4 signal pathway





E5564 (eritoran)

- E5564 synthesized at Eisai Research Institute of Boston, Inc. is a synthetic



History of Clinical Development

- IND Filed: April 1999
- Phase I Initiated: June 1999
- Fast-track Status Granted by FDA: July 1999
- Phase II (201 study) Initiated: January 2002
- 201 Study Clinical Phase Completed: April 2005
- 201 Study Database Lock : July 2005







APACHE II PROM and 28-Day All Cause Mortality in Evaluable Population

	Placebo J3p4 Td30.0607	E5564 45mg 07-0y89	E5564 105mg T50y51-6.n834384
Low PROM (20-50%)			
Number of Patients	38	33	33
Mortality	13.2%	24.2%	12.2%
Difference from Placebo	--	(+11.0%)	(-1.0%)
* P value vs Placebo	--	0.23	0.89
High PROM (51-80%)			
Number of Patients	40	47	43
Mortality	55.0%	38.3%	30.2%
Difference from Placebo	--	(-16.7%)	(-24.8%)
* P value vs Placebo	--	0.12	0.02



Safety

- 6.7% of patients dosed with E5564 through a peripheral vein experienced phlebitis
- Transient elevation in mean value of liver function tests was observed in the high-dose group
- E5564 was well-tolerated



Conclusions

Efficacy

1. ITT population

- The E5564 105 mg group had a 6.4% reduction in mortality vs placebo in treatment of patients with severe sepsis($p=0.34$)
- Treatment effect greater in higher risk patients
The 105 mg group had a 17.6% reduction in mortality vs. placebo ($p=0.07^a$)

2. Evaluable population

- The E5564 105 mg group had a 12.2% reduction in mortality vs placebo ($p=0.09^a$)
- Treatment effect greater in higher risk patients
The 105 mg group had a 24.8% reduction in mortality vs. placebo ($p=0.02^a$)

^a: p-values are of exploratory nature only, no multiplicity adjustment was made

Safety

- E5564 was well-tolerated



E5564 Future Plans

- End-of-Phase II meeting with FDA has been requested
- Plan to meet with regulatory authorities in EU countries and EMEA
- Plans underway to initiate global pivotal Phase III study to start in FY2005





E2007

Schedule of Phase III Study for PD

- **Authorities Status**
 - October 2005: EMEA Response to Phase III plan expected
 - November 2005: End of Phase II Meeting with FDA
- **Phase III**
 - 4Q FY2005 Study will be initiated in EU and US
- **NDA/MAA**
 - 2Q FY2007



E2007

Status and Next Steps for Other Indications

- **Migraine Prophylaxis**
 - Phase IIb study is ongoing
 - Proof of Concept in the first half of FY2006
- **Epilepsy**
 - Phase IIb study is ongoing
 - Proof of Concept in FY2006
- **Multiple Sclerosis**
 - Phase IIb Study is in planning
- **Clinical Development in Japan**
 - Phase I study is ongoing



E5555



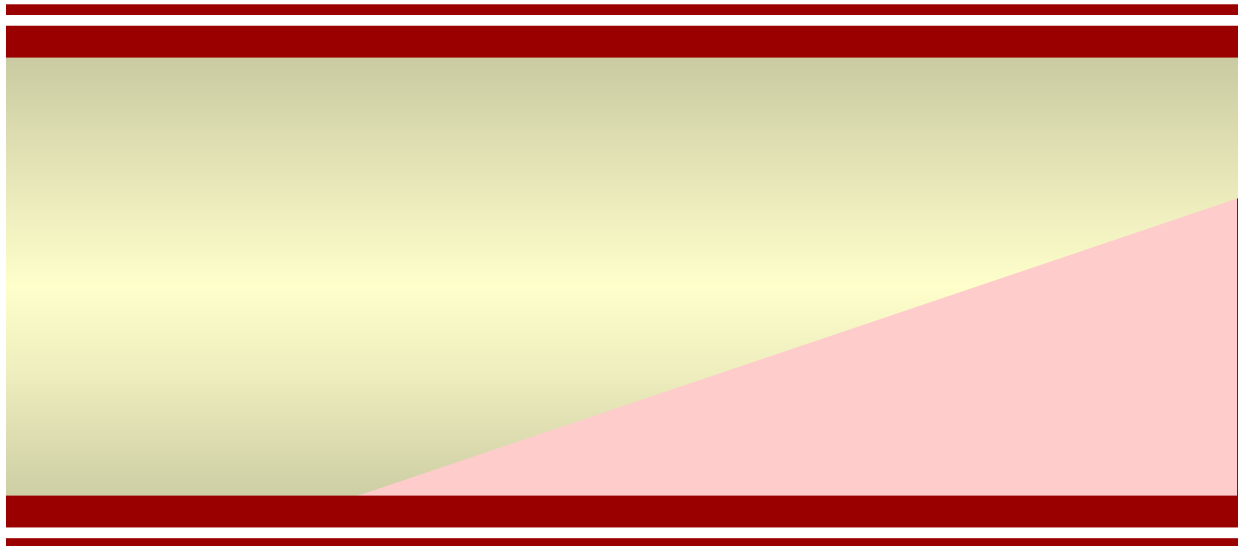
E5555

Orally Active PAR-1 Antagonist

Indication: Acute Coronary Syndrome (ACS), Stable Angina

PAR-1: protease-activated receptor-

E5555



ACS
**(Unstable Angina,
Myocardial Infarction)**



E5555 Future Plan



R&D Meeting

Clinical Development in Japan

Hisashi Tanaka
Vice president
Clinical Research Center





KES524 (Sibutramine)

Indication

Obesity Management

Form

Oral / Capsule

Status

Phase III

Application schedule

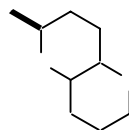
FY 2007





E7389

Microtubule Growth Suppressor

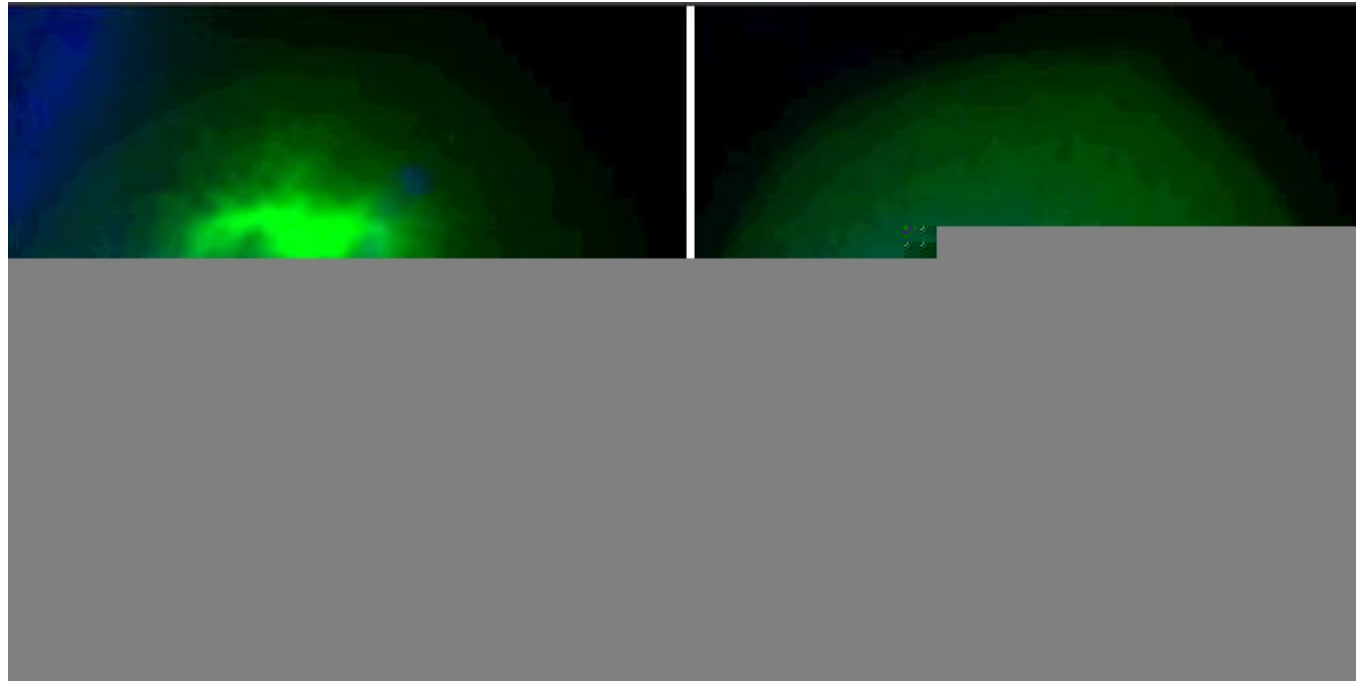
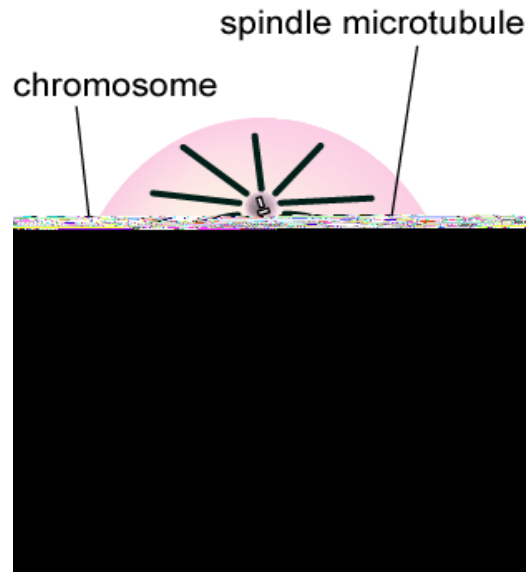




Taxol and E7389 have opposing effects on spindle microtubule dynamics

Taxol enhances spindle-microtubule polymerization.

E7389 induces spindle-microtubule shortening.



Green : microtubule
Blue : chromosome



Antiproliferative Effects of E7389 Against Paclitaxel-Resistant Cancer Cell Lines Expressing Mutation in Beta-tubulin

IC₅₀(nM) SEM 56.76 4a60T9 1 Tf 1w -7.96330 a 21411 745 62 02 w 271.3Tf 1w Resistance Ratio

Compound	A2780/1A9		PTX10		PTX22		PTX10 cells		PTX22 cells	
E7389	0.76	0.16	0.69	0.15	0.65	0.14	0.90	0.12	0.86	0.11
Paclitaxel	3.54	0.85	55.11	9.64	53.54	9.92	16.89	3.48	15.97	2.38



E7389 Interim Analysis for Phase II Study 201 (Breast cancer, Monotherapy)

- Enrollment
 - 71 patients (all taxane resistant)
 - 29 currently evaluable patients
- Efficacy
 - 8 patients with PR
 - 6 confirmed PR (finished cycle 4)
 - 2 unconfirmed PR (before cycle 4)
- Safety
 - Neurotoxicity was infrequent and not severe





E7389 Future Plans

- FDA meeting (end of Phase II meeting; breast cancer) in September 2005
- Initiate registration study (Phase IIb, Phase III) in 3Q FY2005
- Potential Subpart H NDA filing in FY2006
- Initiate clinical studies in EU and Canada
- Initiate clinical studies for Prostate (single), Sarcoma (single) and NSCLC (combination)
- Initiate Phase I studies in Japan



E7070

G1 Phase Targeting Anti-cancer Agent

- **Unique anti-tumor spectrum compared with existing anti-cancer agents; new mechanism of action targeting G1 phase of cell cycle**
- **Synergistic anti-tumor effect by combination with other anti-cancer agents**

<Combination study>

1. Irinotecan

- **Colorectal (Phase II, EU): Enrollment discontinued (35 pts)**
- **Small cell lung: Other administration regimen under investigation (Phase I, US)**

2. Capecitabine

- **Colorectal (Phase I/II, EU): Enrollment discontinued (9 pts)**
- **Breast (Phase II, EU : Enrollment discontinued (62 pts)**

<Single agent study>

- **Gastric (Phase I/II, JP): Ongoing**



E7820 Oral Anti-angiogenesis Agent

- Inhibition of capillary tube formation and proliferation of endothelial cells
- Capillary tube inhibitory action based on inhibition of integrin alpha 2 expression
- Inhibition of VEGF and FGF-induced angiogenesis
- Effective in human pancreatic, breast, colorectal and renal cancer xenograft models
- Inhibition of metastasis in human breast cancer xenograft model
- Synergistic effects with Anti-VEGF antibody, EGFR kinase inhibitor

Current Status: Phase I study is ongoing in US



E7080

Oral Angiogenesis Inhibitor

Highly potent multi-receptor tyrosine kinase inhibitor

Inhibition of cell free tyrosine kinase activity IC50 (nM)

Inhibition of cell free tyrosine kinase activity IC50 (nM)	

VEGFR2:KDR E7080 inhibits all VEGFR family (VEGFR1: Flt-1, VEGFR3: Flt-4)

In addition, E7080 also potently inhibits other molecules shown to have angiogenic properties (FGFR1, PDGFRb)

Furthermore, E7080 inhibits c-Kit and would be expected to exhibit a significant anti-tumor effect against SCLC that SCF may contribute



E7080

Oral Angiogenesis Inhibitor

- E7080 significantly inhibited the tumor growth of various human cancer in mouse xenograft models, such as colorectal cancer, pancreatic cancer, NSCLC, breast cancer, ovarian cancer, prostate and SCLC, and also significantly induced regression in some models.
- Current Status: Phase I
US: Ongoing, EU: Ongoing, JP: Started
Investigate the biomarkers associated with anti-angiogenic activity
- Future Plan: Phase II single agent studies and Phase Ib combination studies will be started after confirming the recommended regimen by Phase I studies



- Totally synthetic material structurally derived from the marine natural product, Hemiasterlin
- Novel tubulin mechanism: alpha/beta tubulin binder
- Effective tubulin binder to multidrug-resistant cancers



Xenograft model	Comparison of E7974 with			
	Oxaliplatin	5-FU	CPT-11	Paclitaxel
DLD-1	+	+	+	+
HCT-15	+	+	-	+
LoVo	+	+	+	+
SW-620	+	+	+	=
HCC-2998	+	+	=	-

- Current Status

Phase I study is ongoing in US

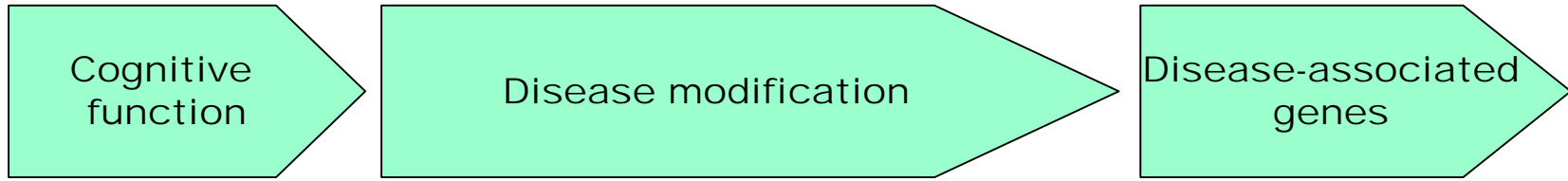
- Future Plan

Phase II single study and Phase Ib combination study are being planned





Trend of Research for Alzheimer's Disease Treatment



Major hypotheses

Choline hypothesis
Cholinergic neuron dysfunction → cognitive dysfunction

Amyloid cascade hypothesis
Beta Amyloid deposit → neuronal death

Multiple associated genes?

Therapeutic approaches

AChE inhibitors
Muscarinic agonists
Nicotinic agonists

Chemicals

Beta secretase inhibitors
Gamma secretase inhibitors
Gamma secretase modulators
Endopeptidase activators
Amyloid polymerization inhibitors
Neuroprotectants

Immunotherapies

Amyloid vaccines
Anti-amyloid antibodies

Eisai's approaches

Aricept
(AChE inhibitor)

E2012
(Gamma secretase modulator)

Immunotherapy
(Collaboration with BioArctic)

Exploration of associated genes
(Collaboration with TorreyPines)



Multidimensional Approach for AD Disease Modifier

APP



A-beta





Point of Difference Between “Modulator” and “Inhibitor”

Modulator does not affect Notch processing
- *No effect on normal cell differentiation* -

Gamma-secretase





Collaboration with BioArctic Neuroscience



Collaboration with Torrey Pines Therapeutics, 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**
- **TorreyPines Therapeutics, Inc**
(renamed from Neurogenetics, Inc.)
 - **San Diego, founded in April 2000**