11. Major R&D Pipeline

In-House R&D Pipeline List

	Product Name / Development Code	Additional Indication, etc.*	Development Stage**	Therapeutic Area
New Approval				
○	Halaven (Second-line treatment for breast cancer)	AI	(EU) approved	Oncology and Supportive Care
○	Aricept (Dementia with Lewy bodies)	AI	(JP) approved	Neurology
◎	Pariet (Prevention of recurrence of gastric and duodenal ulcers during treatment with low-dosage aspirin, new 5 mg tablet)	AI, AF	(JP) approved	Gastrointestinal and Hepatic Disorders
Submitted / Preparing for Submission				
	cinitapride (Functional dyspepsia)		(CN) submitted	Gastrointestinal and Hepatic Disorders
	Tambocor (Pediatric fine granule formulation)	AF	(JP) submitted	Vascular and Immunological Reaction
◎	E7080 (Thyroid cancer)		(JP/US/EU/AS) submitted	Oncology and Supportive Care
○	Fycompa (Primary generalized Tonic-Clonic seizures)	AI	(US/EU) submitted	Neurology
○	DC Bead (Transcatheter arterial embolization (TAE) of hypervascular tumors)	AI	(JP) submitted	Oncology and Supportive Care
○	Inovelon/Banzel (Pediatric Lennox-Gastaut syndrome)	AI	(US) submitted	Neurology
Clinical (Phase II or later)				
	Fycompa (Partial-onset seizures)		(JP/CN/AS) PIII	Neurology
	E5501 (Idiopathic thrombocytopenic purpura (ITP))		(US/EU/AS) PIII	Vascular and Immunological Reaction
	E5501 (Thrombocytopenia in chronic liver disease requiring surgery)		(JP/US/EU/AS) PIII	Vascular and Immunological Reaction
	Halaven (Third-line treatment for breast cancer)		(CN) PIII	Oncology and Supportive Care
	E7080 (Hepatocellular carcinoma)		(JP/US/EU/CN/AS) PIII	Oncology and Supportive Care
	Fycompa (Primary generalized Tonic-Clonic seizures)	AI	(JP/AS) PIII	Neurology
	Halaven (Non–small cell lung cancer)	AI	(JP/US/EU/AS) PIII	Oncology and Supportive Care
	Halaven (Sarcoma)	AI	(US/EU/AS) PIII	Oncology and Supportive Care
	Halaven (First-/second-line treatment for HER2-negative breast cancer)	AI	(US) PIII	Oncology and Supportive Care
	Aricept (Severe Alzheimer's disease)	AI	(CN) PIII	Neurology
	Pariet (Maintenance therapy for proton pump inhibitor (PPI)–resistant reflux esophagitis)	AI	(JP) PIII	Gastrointestinal and Hepatic Disorders
	E0302 (Amyotrophic lateral sclerosis (ALS))		(JP) PII/III	Neurology
	BAN2401 (Alzheimer's disease)		(US/EU) PII	Neurology
	E2006 (Insomnia)		(US) PII	Neurology
◎	E2609 (Alzheimer's disease)		(US) PII	Neurology
	E5501 (Thrombocytopenia during interferon therapy (both initiation and maintenance) for hepatitis C)		(US) PII	Vascular and Immunological Reaction
	E6005 (Atopic dermatitis)		(JP) PII	Vascular and Immunological Reaction
	E7080 (Endometrial cancer)		(US/EU) PII	Oncology and Supportive Care
	E7080 (Melanoma)		(US/EU) PII	Oncology and Supportive Care
	E7080 (Non–small cell lung cancer, Third-line, mono-therapy)		(US/EU) PII	Oncology and Supportive Care
	E7080 (Non–small cell lung cancer, RET translocations)		(JP/US/EU/AS) PII	Oncology and Supportive Care
	E7080 (Renal cell carcinoma)		(US/EU) PI/II	Oncology and Supportive Care
	E7820 (Colorectal cancer)		(US/EU) PII	Oncology and Supportive Care
◎	MORAb-003 (Platinum-sensitive ovarian cancer)		(JP/US/EU) PII	Oncology and Supportive Care
	MORAb-003 (Non–small cell lung cancer)		(US/EU) PII	Oncology and Supportive Care
	MORAb-004 (Melanoma)		(US/EU) PII	Oncology and Supportive Care
	MORAb-004 (Colorectal cancer)		(US/EU) PII	Oncology and Supportive Care
	MORAb-004 (Sarcoma)		(US/EU) PII	Oncology and Supportive Care
	MORAb-009 (Mesothelioma)		(US/EU) PII	Oncology and Supportive Care
	Fycompa (Pediatric partial-onset seizures)	AI	(US/EU) PII	Neurology
	Aricept (Regression symptoms in people with Down syndrome)	AI	(JP) PII	Neurology
	Halaven (Sarcoma)	AI	(JP) PII	Oncology and Supportive Care
	Ontak (Melanoma)	AI	(US) PII	Oncology and Supportive Care
	Pariet (Functional dyspepsia)	AI	(JP) PII	Gastrointestinal and Hepatic Disorders
	BELVIQ (Aid for smoking cessation)	AI	(US) PII	Neurology

* AI: Additional Indication, ADA: Additional Dosage & Administration, AF: Additional Formulation

** P: Clinical Phase; JP: Japan, US: United States, EU: Europe, CN: China, AS: Asia (excluding Japan and China)

- Regarding the aldose reductase inhibitor AS-3201, a Phase II/III study conducted in Europe and the United States was completed, however upon considering the further development strategy based on results, the Company has discontinued development.
- Development was discontinued on the indication of glioma for the anticancer agent E7080, which was at the Phase II trial stage in the United States, due to the revision of development priorities.
- Development was discontinued on the indication of melanoma for the anticancer agent E7016, which was in a Phase II study in the United States.
- Regarding the anticancer agent MORAb-003, after considering further development strategy for the indication of platinum-sensitive ovarian cancer, a new Phase II study was initiated in Japan, Europe and the United States.
- Regarding the development of the higher dose (23 mg) formulation for anti-Alzheimer's agent Aricept, a Phase III trial conducted in Japan did not meet its primary endpoint. Upon receiving these results, the Company decided to discontinue development of the higher dose formulation for Japan.

○ Development progress from April 2014 onwards ◎ Development progress from October 2014 onwards

(1) Oncology and Supportive Care

Development Code: **E7389** Generic Name: **eribulin** Product Name: **Halaven**

Indications / Drug class: Anticancer agent / microtubule dynamics inhibitor				In-house
Description: A synthetic analog of halichondrin B derived from the marine sponge, *Halichondria okadai*. Shows an antitumor effect by arresting the cell cycle through inhibition of the growth of microtubules. Currently being investigated as a potential treatment for various other solid tumors. Approved in 58 countries including in the United States, European Union (EU), Japan and Asia for breast cancer. Also approved in Europe as a second-line treatment for breast cancer in June 2014. Currently approved as a second-line treatment in 39 countries.				
○	Second-line treatment for breast cancer (Additional Indication)	Study 301	EU: approved (June 2014)	Inj.
	Third-line treatment for breast cancer	304	CN: PIII	Submission Target: FY2015	Inj.
	First-/second-line treatment for HER2-negative breast cancer (Additional Indication)	303	US: PIII	Inj.
	Non-small cell lung cancer (Additional Indication)	302	JP/US/EU/AS: PIII	Inj.
	Sarcoma (Additional Indication)	309 217	US/EU/AS: PIII JP: PII	Submission Target: FY2015	Inj.
	Bladder cancer (Additional Indication)	702	US/EU: PI/PII	Inj.
	Liposome formulation (Additional Formulation)		EU: PI	Inj.

・From the results of the Phase III trial in non-small cell lung cancer, the submission target of FY 2014 has been revised and further development strategy is currently under consideration.

Development Code: **E7080** Generic Name: **lenvatinib**

Indications / Drug class: Anticancer agent / molecular targeted drug			In-house
Description: Molecular targeted agent that selectively inhibits receptor tyrosine kinase receptors involved in angiogenesis and tumor proliferation. Exhibits rapid and potent inhibition of kinase activity, simultaneously inhibiting the activity VEGFR, FGFR and RET, which are especially involved in thyroid cancer, and possesses a novel binding mode (Type V) to VEGFR2 which was revealed through co-crystal structural analysis. Also currently being investigated as a potential treatment for various solid tumors.			
	Thyroid cancer	Study 303	○ JP: submitted (June 2014) ○ US: submitted (August 2014), accepted (October 2014) ○ EU: submitted (August 2014), accepted (September 2014) ◎ AS: submitted (November 2014-)	Oral
	Hepatocellular carcinoma	304	JP/US/EU/CN/AS: PIII	Oral
	Endometrial cancer	204	US/EU: PII	Oral
	Melanoma	702	US/EU: PII	Oral
	Non-small cell lung cancer (Third-line, Mono therapy)	703	US/EU: PII	Oral
	Non-small cell lung cancer (RET translocations)	209	JP/US/EU/AS: PII	Oral
	Renal cell carcinoma	205	US/EU: PI/II	Oral

・Development was discontinued on the indication of glioma for the anticancer agent E7080, which was at the Phase II trial stage in the United States, due to the revision of development priorities.

Development Code: **MORAb-003** Generic Name: **farletuzumab**

Indications / Drug class: Anticancer agent / humanized anti-FRA monoclonal antibody				In-house
Description: A humanized IgG1 monoclonal antibody that targets folate receptor alpha (FRA). Expected to show an antitumor effect against carcinomas that over-express FRA.				
◎	Platinum-sensitive ovarian cancer	Study 011	JP/US/EU: PII	Inj.
	Non-small cell lung cancer	009	US/EU: PII	Inj.

・After considering further development strategy for the indication of platinum-sensitive ovarian cancer, a new Phase II study was initiated in Japan, Europe and the United States.

○ Development progress from April 2014 onwards ◎ Development progress from October 2014 onwards

Development Code: **MORAb-004**

Indications / Drug class: Anticancer agent / humanized anti-endosialin monoclonal antibody			In-house
Description: A humanized IgG1 monoclonal antibody that targets Tumor Endothelial Marker 1 (TEM-1) / endosialin. Expected to show an antitumor effect against carcinomas that express endosialin.			
Melanoma	Study 201	US/EU: PII	Inj.
Colorectal cancer	202	US/EU: PII	Inj.
Sarcoma	203	US/EU: PII	Inj.

Development Code: **MORAb-009** Generic Name: **amatuximab**

Indications / Drug class: Anticancer agent / chimeric anti-mesothelin monoclonal antibody			In-house
Description: A chimeric IgG1 monoclonal antibody that blocks the function of mesothelin. Expected to show an antitumor effect against carcinomas that express mesothelin.			
Mesothelioma	Study 003	US/EU: PII	Inj.

Development Code: **E7820**

Indications / Drug class: Anticancer agent / alpha 2 integrin suppressant			In-house
Description: An angiogenesis inhibitor that suppresses the expression of alpha 2 integrin, a vascular endothelial cell adhesion molecule.			
Colorectal cancer	Study 702	US/EU: PII	Oral

Development Code: **E7272** Generic Name: **denileukin diftitox** Product Name: **Ontak**

Indications / Drug class: Anticancer agent / interleukin-2 diphtheria toxin fusion protein			In-house
Description: A fusion protein that combines the interleukin-2 (IL-2) receptor binding domain with diphtheria toxins. Selectively binds to IL-2 receptors on the cell surface, causing diphtheria toxins that have entered cells to inhibit protein synthesis. Already approved in the United States as a treatment for CD25 (a component of the IL-2 receptor) positive cutaneous T-cell lymphoma.			
Melanoma (Additional Indication)	Study 701	US: PII	Inj.

Development Code: **E7040** Product Name: **DC Bead**

Indications / Drug class: Embolic bead / medical device			In-license (Biocompatibles)
Description: Contains hydrophilic microspherical particles produced from cross-linked polyvinyl alcohol polymer. These embolic beads are injected through a catheter to selectively embolize targeted blood vessels. The beads are microscopic and uniformly spherical in shape, allowing for sustained embolization of targeted vessels based on vascular diameter and tumor size. Approved in Japan as a device for transcatheter arterial embolization (TAE) therapy in patients with hepatocellular carcinoma.			
○ Transcatheter arterial embolization (TAE) of hypervascular tumors (Additional Indication)	Study 301	JP: submitted (September 2014)	Embolic Agent

Development Code: **E7438**

Anticancer agent (EZH2 inhibitor)	PI/II	In-license (Epizyme)	Oral

Development Code: **E7090**

○ Anticancer agent	PI	In-house	Oral.

Development Code: **MORAb-066**

Anticancer agent (Antibody)	PI	In-license (Janssen Biotech)	Inj.

- Development was discontinued on the indication of melanoma for the poly (ADP-ripose) polymerase inhibitor E7016, which was in a Phase II study in the United States.

○ Development progress from April 2014 onwards ◎ Development progress from October 2014 onwards

(2) Neurology

Development Code: **E2020** Generic Name: **donepezil** Product Name: **Aricept**

Indications / Drug class: Anti-Alzheimer's agent				In-house
Description: Increases levels of the neurotransmitter acetylcholine in the brain by inhibiting its breakdown by the enzyme acetylcholinesterase, thereby slowing the overall progression of symptoms associated with Alzheimer's disease (AD). Currently approved in more than 90 countries around the world for the treatment of mild to moderate AD. It is also approved as a treatment for patients with severe AD in numerous countries including the United States, Japan, Canada, and several other Asian and Latin American countries. Also approved in Japan for dementia with Lewy bodies in September 2014.				
○	Dementia with Lewy bodies (Additional Indication)	Study 341	JP: approved (September 2014)	Oral
	Severe Alzheimer's disease (Additional Indication)	339	CN: PIII	Submission Target: FY2014	Oral
	Regression symptoms in people with Down syndrome (Additional Indication)	345	JP: PII		Oral
	Transdermal formulation (E2022, Additional Formulation)		JP: PI	(Collaboration with Teikoku Pharmaceuticals)	Patch

• Regarding the higher dose (23 mg) formulation which previously had a submission target of FY2014, a Phase III study conducted in Japan did not meet its primary endpoint. Upon receiving these results, the Company decided to discontinue development of the higher dose formulation for Japan.

Development Code: **E2007** Generic Name: **perampanel** Product Name: **Fycompa**

Indications / Drug class: Antiepileptic agent / AMPA receptor antagonist				In-house
Description: A selective antagonist against the AMPA receptor (a glutamate receptor subtype). Currently being investigated as a potential adjunctive therapy for partial-onset seizures as well as a treatment for generalized seizures in patients with epilepsy. Approved as an adjunctive therapy for partial-onset seizures in 43 countries including in Europe, the United States, and Canada.				
	Partial-onset seizures	Study 335	JP/CN/AS: PIII	Submission Target: FY2015	Oral
	Primary generalized Tonic-Clonic seizures (Additional Indication)	332	○ US: submitted (August 2014), accepted (October 2014) ○ EU: submitted (August 2014), accepted (September 2014) JP/AS: PIII	Submission Target: FY2015	Oral
	Pediatric partial-onset seizures (Additional Indication)	232	US/EU: PII		Oral

• Simultaneous submission for generalized seizures and partial-onset seizures in Japan is scheduled for FY2015.

Development Code: **E0302** Generic Name: **mecobalamin**

Indications / Drug class: Amyotrophic lateral sclerosis				In-house
Description: A mecobalamin (vitamin B_{12} coenzyme) formulation. Restores damaged peripheral nerves and is widely used for the treatment of peripheral neuropathy. Currently being investigated as a potential treatment for amyotrophic lateral sclerosis (ALS).				
	Amyotrophic lateral sclerosis (ALS)	Study 761/762	JP: PII/III	Submission Target: FY2014	Inj.

Development Code: **E2080** Generic Name: **rufinamide** Product Name: **Inovelon/Banzel**

Indications / Drug class: Antiepileptic agent				In-license (Novartis)
Description: A triazole derivative that is structurally unrelated to currently marketed antiepileptic drugs (AEDs). Currently approved in Japan, Europe and the United States as an adjunctive therapy to other AEDs in the treatment of Lennox-Gastaut syndrome (LGS), one of the most severe and intractable forms of childhood-onset epilepsy. The product names are Inovelon in Japan and Europe and Banzel in the United States.				
○	Pediatric Lennox-Gastaut syndrome (LGS) (Additional Indication)	Study 303	US submitted(August 2014), accepted(October 2014)	Oral

○ Development progress from April 2014 onwards ◎ Development progress from October 2014 onwards

Development Code: **BAN2401**

Indications / Drug class: Anti-Alzheimer's agent / humanized anti-Aβ protofibrils monoclonal antibody			In-license (BioArctic Neuroscience)	
Description: A humanized lgG1 monoclonal antibody that targets amyloid beta (Aβ) protofibrils. Expected to be effective in the treatment of Alzheimer's disease by halting disease progression through the elimination of Aβ protofibrils reported to exhibit neurotoxicity.				
Alzheimer's disease	Study 201	US/EU: PII JP: PI		Inj.

Development Code: **E2006**

Indications / Drug class: Anti-insomnia agent / orexin receptor antagonist			In-house	
Description: Anti-insomnia agent with novel mechanism of action. By antagonizing the orexin receptors that maintain wakefulness, it is expected to alleviate wakefulness and thereby induce natural sleep.				
Insomnia	Study 201	US: PII		Oral

Development Code: **E2609**

Indications / Drug class: Anti-Alzheimer's agent / beta secretase cleaving enzyme (BACE) inhibitor			In-house	
Description: BACE inhibitor. By inhibiting beta-site amyloid precursor protein cleaving enzymes (BACE), the agent reduces the amount of amyloid beta in the brain, potentially improving symptoms and slowing the progression of Alzheimer's disease.				
◎ Alzheimer's disease	Study 202	US: PII		Oral

Development Code: **APD356** Generic Name: **lorcaserin** Product Name: **BELVIQ**

Indications / Drug class: Anti-obesity agent / serotonin 2C receptor antagonist			In-license (Arena Pharmaceuticals)	
Description: Anti-obesity agent with novel mechanism of action. By selectively activating serotonin 2C receptors in the brain, it is believed to decrease food consumption and promote satiety. Approved in the United States by the U.S Food and Drug Administration in June 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with an initial body mass index (BMI) of 30 kg/m^2 or greater (obese) or 27 kg/m^2 or greater (overweight) in the presence of at least one weight-related co-morbid condition and launched in the United States in June 2013 after receiving a final scheduling designation from the U.S. Drug Enforcement Administration (DEA). Currently being developed toward receiving indication approval as an aid for smoking cessation.				
Smoking cessation (Additional Indication)	Study 035	US: PII	(co-development with Arena)	Oral
Obesity		JP: PI		Oral

Development Code: **E2307**

○ Alzheimer's disease	PI		In-house	Oral

・Regarding the aldose reductase inhibitor AS-3201, a Phase II/III study of the compound conducted in Europe and the United States was completed, however upon considering the further development strategy, the Company has discontinued development.

○ Development progress from April 2014 onwards ◎ Development progress from October 2014 onwards

(3) Vascular and Immunological Reaction

Generic Name: **flecainide** Product Name: **Tambocor**

Indications / Drug class: Anti-tachyarrhythmia agent				In-house
Description: Suppresses tachyarrhythmia by blocking cardiac sodium channels. The agent was approved for the treatment of tachyarrhythmia (paroxysmal atrial fibrillation/flutter and ventricular tachycardia) in adults and tachyarrhythmia (paroxysmal atrial fibrillation/flutter, paroxysmal superventricular tachycardia and ventricular tachycardia) in pediatric patients.				
Pediatric fine granule formulation (Additional Formulation)		JP: submitted (January 2014)		Oral.

Development Code: **E5501/AKR-501** Generic Name: **avatrombopag**

Indications / Drug class: Treatment for thrombocytopenia / thrombopoietin receptor agonist				In-house
Description: A novel, oral thrombopoietin receptor agonist that stimulates platelet production. Expected to show effects against conditions that are associated with thrombocytopenia.				
Thrombocytopenia in chronic liver disease requiring surgery	Study 310/311	JP/US/EU/AS: PIII	Submission Target: FY2015	Oral
Idiopathic thrombocytopenic purpura (ITP)	302	US/EU/AS: PIII		Oral
Thrombocytopenia during interferon therapy (both initiation and maintenance) for hepatitis C	203	US: PII		Oral

・Japan was added to the global Phase III clinical study of thrombocytopenia in chronic liver disease requiring surgery.

Development Code: **E6005**

Indications / Drug class: Anti-atopic dermatitis / Phosphodiesterase 4 inhibitor				In-house
Description: Inhibits the activity of phosphodiesterase 4, a cyclic AMP-degrading enzyme that acts as an intracellular messenger. Expected to be effective as a treatment to suppress the various symptoms associated with atopic disease.				
Atopic dermatitis	Study 102	JP: PII		Topical

Development Code: **E6011**

Autoimmune disorder/Inflammatory diseases (anti Fractalkine antibody)	PI/II	In-house	Inj.

Development Code: **MORAb-022**

Rheumatoid arthritis (antibody)	PI	In-house	Inj.

Development Code: **E6007**

○	Activated integrin inhibitors	PI	In-house	Oral.

○ Development progress from April 2014 onwards ◎ Development progress from October 2014 onwards

(4) Gastrointestinal and Hepatic Disorders

Development Code: **E3810** Generic Name: **rabeprazole** Product Name: **Pariet/Aciphex**

Indications / Drug class: Proton pump inhibitor				In-house
Description: A proton pump inhibitor approved for the treatment of gastric and duodenal ulcers, reflux esophagitis, eradication of *Helicobacter pylori* infections and triple formulation packs (combination packs) for H. pylori eradication which contain rabeprazole,.etc. Obtained approval for prevention of recurrent gastric or duodenal ulcer caused by low-dose aspirin therapy as well as 5 mg tablet formulation in December 2014.				
◎	Prevention of recurrence of gastric and duodenal ulcers during treatment with low-dosage aspirin, new 5 mg tablet (Additional Indication, Formulation)	Study 308/309	JP: approved (December 2014)	Oral
	Maintenance therapy for proton pump inhibitor (PPI)–resistant reflux esophagitis (Additional Indication)	311	JP: PIII	Oral
	Functional dyspepsia (Additional Indication)	204	JP: PII	Oral

Generic Name: **cinitapride**

Indications / Drug class: Gastroprokinetic agent			In-license (Almirall)
Description: By stimulating 5-HT_2 and 5-HT_4 receptors found in the gastrointestinal tract, the agent increases acetylcholine release and improves upper gastrointestinal motility. Its antidopaminergic effects also help stimulate the release of acetylcholine by blocking dopamine receptors, thereby improving upper gastrointestinal function.			
	Functional dyspepsia	CN: submitted (October 2011)	Oral

○ Development progress from April 2014 onwards ◎ Development progress from October 2014 onwards