(5) Development activities

■ US/EU/Jpn

Development code/product name <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
TAK-390MR <dexlansoprazole>	Proton pump inhibitor (oral)	Erosive esophagitis (healing and maintenance), Non-erosive gastro-esophageal reflux disease	EU	Approved (Sep 13)*[1]	In-house
SYR-322 <alogliptin>	DPP-4 inhibitor (oral)	Diabetes mellitus	EU	Approved (Sep 13)	In-house
		Diabetes mellitus (Fixed-dose combination with metformin)	EU	Approved (Sep 13)	
		Diabetes mellitus (Fixed-dose combination with pioglitazone)	EU	Approved (Sep 13)	
ATL-962 <cetilistat>	Lipase inhibitor (oral)	Obesity with both type 2 diabetes mellitus and dyslipidemia	Jpn	Approved (Sep 13)	In-license (Norgine BV)*[2]
Lu AA21004 <vortioxetine>	Multimodal anti-depressant (oral)	Major depressive disorder	US Jpn	Approved (Sep 13) P-III	In-license (Lundbeck)
		Generalized anxiety disorder	US	P-III	
MLN0002 <vedolizumab>	Humanized monoclonal antibody against α4β7 integrin (injection)	Ulcerative colitis	US EU Jpn	Filed (Jun 13) Filed (Mar 13) P-I	In-house
		Crohn's disease	US EU	Filed (Jun 13) Filed (Mar 13)	
<lurasidone hydrochloride>	Atypical antipsychotic agent (oral)	Schizophrenia	EU	Filed (Sep 12)	In-license (Dainippon Sumitomo)
		Bipolar disorder	EU	P-III	
SGN-35 <brentuximab vedotin>	CD30 monoclonal antibody-drug conjugate (injection)	Relapsed or refractory Hodgkin lymphoma	Jpn	Filed (Mar 13)	In-license (Seattle Genetics)
		Relapsed or refractory systemic anaplastic large cell lymphoma	Jpn	Filed (Mar 13)	
		Relapsed cutaneous T-cell lymphoma	EU	P-III	
		Post-ASCT Hodgkin lymphoma	EU	P-III	
		Front line Hodgkin lymphoma	EU	P-III	
		Front line mature T-cell lymphoma	EU Jpn	P-III P-III	
BLB-750	Influenza vaccine (injection)	Prevention of pandemic influenza	Jpn	Filed (Mar 13)	In-license (Baxter)
TAK-816	Hib vaccine (injection)	Prevention of infectious disease caused by Haemophilus influenza Type b (Hib)	Jpn	Filed (Sep 13)	In-license (Novartis)
Contrave® <naltrexone SR /bupropion SR>	Mu-opioid receptor antagonist and dopamine/norepinephrine re-uptake inhibitor (oral)	Obesity	US	FDA Complete Response Letter (Jan 11)*[3]	In-license (Orexigen)
TAK-875 <fasiglifam>	GPR40 agonist (oral)	Diabetes mellitus	US EU Jpn	P-III P-III P-III	In-house
TAK-700 <orteronel>	Non-steroidal androgen synthesis inhibitor (oral)	Prostate cancer	US EU Jpn	P-III P-III P-III	In-house
MLN9708 <ixazomib citrate>	Proteasome inhibitor (oral)	Multiple myeloma	US EU Jpn	P-III P-III P-I	In-house
		Relapsed or refractory primary (AL) amyloidosis	US EU	P-III P-III	
		Solid tumors	US	P-I	

*1 Approved in 16 countries in the EU by the decentralized procedure

*2 Alizyme assigned ATL-962 (cetilistat) business to Norgine BV on Oct 15th, 2009

*3 CV study currently ongoing to support re-submission

Development code/product name <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
MLN8237 <alisertib>	Aurora A kinase inhibitor (oral)	Relapsed or refractory peripheral T-cell lymphoma	US EU	P-III P-III	In-house
		Diffuse large B-cell lymphoma, Non-small cell lung cancer, Small cell lung cancer, Gastroesophageal cancer, Head and neck cancer, Breast cancer, Ovarian cancer	US EU	P-II P-II	
		Non-Hodgkin lymphoma	Jpn	P-I	
		Solid tumors	Jpn	P-I	
SYR-472 <trelagliptin>	DPP-4 inhibitor (oral)	Diabetes mellitus	Jpn US EU	P-III P-II P-II	In-house
TAK-438 <vonoprazan>	Potassium-competitive acid blocker (oral)	Acid-related diseases (GERD, Peptic ulcer, etc.)	Jpn	P-III	In-house
<motesanib diphosphate>	VEGFR1-3, PDGFR, c-Kit inhibitor (oral)	Advanced non-squamous non-small cell lung cancer	Jpn	P-III	In-license (Amgen)
AMG 386 <trebananib>	Anti-angiopoietin peptibody (injection)	Ovarian cancer	Jpn	P-III	In-license (Amgen)
<peginesatide>	Synthetic, peptide-based erythropoiesis-stimulating agent (injection)	Anaemia associated with chronic kidney disease in adult patients undergoing dialysis	EU	P-III*[4]	In-license (Affymax)
DENVax	Dengue vaccine (injection)	Prevention of dengue fever caused by dengue virus	-	P-II	In-house
TAK-385 <relugolix>	LH-RH antagonist (oral)	Endometriosis, Uterine fibroids	Jpn	P-II	In-house
		Prostate Cancer	-	P-I	
TAK-361S	Quadruple vaccine (injection)	Prevention of infectious disease caused by Diphtheria, Pertussis, Tetanus, Polio	Jpn	P-II	In-license (Japan Polio)
Norovirus vaccine	Norovirus vaccine (injection)	Prevention of acute gastroenteritis (AGE) caused by norovirus	-	P-I/II	In-house
TAK-733 < - >	MEK inhibitor (oral)	Solid tumors	-	P-I	In-house
TAK-272 < - >	Direct renin inhibitor (oral)	Hypertension	-	P-I	In-house
TAK-063 < - >	PDE10A inhibitor (oral)	Schizophrenia	-	P-I	In-house
TAK-137 < - >	AMPA receptor potentiator (oral)	Psychiatric disorders and neurological diseases	-	P-I	In-house
INV21	EV71 vaccine (injection)	Prevention of hand, foot and mouth disease caused by enterovirus 71	-	P-I	In-house
MLN4924 < - >	NEDD 8 activating enzyme inhibitor (injection)	Advanced malignancies	-	P-I	In-house
MLN0128 < - >	mTORC1/2 inhibitor (oral)	Multiple myeloma, Waldenstrom's macroglobulinemia, Solid tumors	-	P-I	In-house
MLN1117 < - >	PI3Kα isoform inhibitor (oral)	Solid tumors	-	P-I	In-house

*4 Resubmission subject to outcome of ongoing investigation in the US

Development code/ product name <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
MLN0264 < - >	Antibody-Drug Conjugate targeting GCC (injection)	Advanced gastrointestinal malignancies	-	P-I	In-house
MLN2480 < - >	pan-Raf kinase inhibitor (oral)	Solid tumors	-	P-I	In-license (Sunesis)
MT203 <namilumab>	GM-CSF monoclonal antibody (injection)	Rheumatoid arthritis	EU	P-I	In-licence (Amgen)*[5]
Lu AA24530 < - >	Multimodal anti-depressant (oral)	Major depressive disorder, Generalized anxiety disorders	US Jpn	P-I P-I	In-license (Lundbeck)
AMG 403 <fulranumab>	Human monoclonal antibody against human Nerve Growth Factor (NGF) (injection)	Pain	Jpn	P-I	In-license (Amgen)
ITI-214 < - >	PDE1 inhibitor (oral)	Cognitive impairment associated with schizophrenia	-	P-I	In-license (Intra-Cellular)

*5 Deal made with Micromet; on Mar 7th, 2012, Micromet became a wholly owned subsidiary of Amgen

■ Additional indications/formulations of compounds

Development code/ product name <generic name> Brand name (country / region)	Drug Class	Indications or formulations	Stage	In-house/ In-license
AG-1749 <lansoprazole> Takepron® (Jpn) Prevacid® (US) Ogast®, etc. (EU)	Proton pump inhibitor	Fixed-dose combination with low-dose aspirin	Jpn Filed (Mar 13)	In-house
TAK-536 <azilsartan> Azilva® (Jpn)	Angiotensin II receptor blocker	Hypertension (Fixed-dose combination with amlodipine besilate)	Jpn Filed (Apr 13)	In-house
Rienso® <ferumoxytol>	IV iron	Iron deficiency anemia from all causes in patients who have a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used	EU Filed (Jun 13)	In-license (AMAG)
TAP-144-SR <leuprorelin acetate> Leuplin® (Jpn) Lupron Depot® (US) Enantone®, etc. (EU)	LH-RH agonist	Prostate cancer, Premenopausal breast cancer (6-month formulation)	Jpn P-III	In-house
TAK-375SL <ramelteon> Rozerem® (US, Jpn)	MT1/MT2 receptor agonist	Bipolar (sublingual formulation)	US P-III	In-house
VELCADE® <bortezomib>	Proteasome inhibitor	Front line mantle cell lymphoma Relapsed diffuse large B-cell lymphoma	US P-III US P-II	In-house
AD-4833/TOMM40	Insulin sensitizer/ Biomarker assay	Delay of onset of mild cognitive impairment due to Alzheimer's disease	US P- III EU P- III	In-license (Zinfandel)
AMITIZA® <lubiprostone>	Chloride channel activator	Liquid formulation	US P- III	In-license (Sucampo)

■ Recent progress in stage **Progress in stage since release of FY2012 results (May 9th, 2013)**

Development code/ product name <generic name>	Indications	Country/Region	Progress in stage
MLN0002 <vedolizumab>	Ulcerative colitis	US	Filed (Jun 13)
MLN0002 <vedolizumab>	Crohn's disease	US	Filed (Jun 13)
Rienso® <ferumoxytol>	Iron deficiency anemia from all causes in patients who have a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used	EU	Filed (Jun 13)
SGN-35 <brentuximab vedotin>	Front line mature T-cell lymphoma	Jpn	P-III
TAK-390MR <dexlansoprazole>	Erosive esophagitis (healing and maintenance), Non-erosive gastro-esophageal reflux disease	EU	Approved (Sep 13)
SYR-322 <alogliptin>	Diabetes mellitus	EU	Approved (Sep 13)
SYR-322 <alogliptin>	Diabetes mellitus (Fixed-dose combination with metformin)	EU	Approved (Sep 13)
SYR-322 <alogliptin>	Diabetes mellitus (Fixed-dose combination with pioglitazone)	EU	Approved (Sep 13)
ATL-962 <cetilistat>	Obesity with both type 2 diabetes mellitus and dyslipidemia	Jpn	Approved (Sep 13)
Lu AA21004 <vortioxetine>	Major depressive disorder	US	Approved (Sep 13)
TAK-816	Prevention of infectious disease caused by Haemophilus influenza Type b (Hib)	Jpn	Filed (Sep 13)
AD-4833/TOMM40	Delay of onset of mild cognitive impairment due to Alzheimer's disease	US/EU	P-III
AMITIZA® <lubiprostone>	Liquid formulation	US	P-III
TAK-137	Psychiatric disorders and neurological diseases	-	P-I

Progress in stage since the announcement of FY2013 1Q results (July 31st, 2013) are listed under the bold dividing line

■ Discontinued projects **Discontinued since release of FY2012 results (May 9th, 2013)**

Development code/ product name <generic name>	Indications (Stage)	Reason
AMG 479 <ganitumab>	Metastatic pancreas cancer (Jpn P-III)	Independent Data Monitoring Committee (DMC) reviewed the interim analysis and concluded that it was unlikely to meet the primary endpoint
TAK-491 <azilsartan medoxomil>	Hypertension (fixed-dose combination with chlorthalidone) (EU P-III)	Discontinued due to a reassessment of the marketing opportunity in the EU
TAK-428 < - >	Diabetic neuropathy (US/EU P-II)	Discontinued based on reassessment of portfolio prioritization
TAK-390MR <dexlansoprazole>	Erosive esophagitis (healing and maintenance), Non-erosive gastro-esophageal reflux disease (Jpn P-II)	Discontinued due to advanced progress of TAK-438 program in Japan
TAK-329 < - >	Diabetes (P-I)	Discontinued due to the clinical data failing to meet the criteria for stage-up

Projects discontinued since the announcement of FY2013 1Q results (July 31st, 2013) are listed under the bold dividing line

■ Revised collaboration agreement **Revised since release of FY2012 results (May 9th, 2013)**

Development code/ product name <generic name>	Indications (Stage)	Reason
Sovrima® <idebenone>	Friedreich's ataxia, Duchenne muscular dystrophy (EU P-III)	Rights for Sovrima returned to Santhera upon Santhera's request and due to a reassessment of portfolio prioritization
<veltuzumab>	Systemic lupus erythematosus (US/EU P-II)	The agreement on veltuzumab with Immunomedics terminated; an arbitration proceeding between the parties is currently on-going

■ Filings and Approvals in Regions other than US/EU/Jpn

Region	Country	Development code / product name (stage)
Americas Ex. US	Argentina	TAK-491*5 (Filed Oct 12)
	Brazil	TAK-491 (Filed Nov 11), SYR-322/metformin (Filed Jun 12), TAK-491/chlorthalidone (Filed Jun 12), SYR-322/pioglitazone (Filed Dec 12), SYR-322 (Filed Feb 13)*6
	Colombia	DAXAS*7 (Approved Jul 13), TAK-491 (Filed Aug 12), SYR-322 (Filed Sep 12), SYR-322/metformin (Filed Sep 12), SYR-322/pioglitazone (Filed Oct 12), TAK-491/chlorthalidone (Filed Oct 12), TAK-390MR (Filed Dec 12(30mg)/Mar 13(60mg))
	Venezuela	mifamurtide*8 (Approved Apr 13), DAXAS (Approved Jul 13), TAK-390MR (Filed Sep 13)
Europe Ex. EU	Albania	DAXAS (Approved Apr 13)
	Montenegro	DAXAS (Filed Jun 11)
	Switzerland	lurasidone hydrochloride (Approved Aug 13), SYR-322 (Filed Jul 12), SYR-322/metformin (Filed Jul 12), TAK-390MR (Filed Sep 12), TAK-491/chlorthalidone (Filed Jan 13), MLN0002 (Filed May 13)
Russia/CIS	Belarus	DAXAS (Filed Apr 13)
	Kazakhstan	TAK-491 (Filed Jan 13)
	Russia	TAK-491 (Filed Apr 13)
	Ukraine	mifamurtide (Approved Jul 13), TAK-491 (Filed Dec 12)
Asia Ex. Jpn	China	SYR-322 (Approved Jul 13), DAXAS (Filed Dec 11)
	Hong Kong	TAK-491/chlorthalidone (Filed Mar 13)
	Indonesia	SYR-322 (Filed Jan 11), TAK-491 (Filed Feb 12), TAK-491/chlorthalidone (Filed Jul 12), TCV-116*9/amlodipine besilate (Filed Oct 12)
	Malaysia	TAK-390MR (Filed Sep 12), TAK-491 (Filed Jan 13), TAK-491/chlorthalidone (Filed Apr 13)
	Philippines	TAK-491/chlorthalidone (Filed Sep 13)
	Singapore	TAK-390MR (Filed Oct 12), TAK-491 (Filed Dec 12), TAK-491/chlorthalidone (Filed Mar 13)
	S. Korea	SYR-322 (Approved May 13), SGN-35 (Approved May 13)
	Taiwan	TAK-491 (Approved Jun 13), SYR-322 (Filed Mar 11), TAK-491/chlorthalidone (Filed May 12), TCV-116/amlodipine besilate (Filed Nov 12)
	Thailand	TAK-390MR (Approved Jun 13), TAK-491/chlorthalidone (Filed Jun 12), TCV-116/amlodipine besilate (Filed Aug 12), SYR-322/pioglitazone (Filed Mar 13)
	Vietnam	DAXAS (Approved Apr 13)
Others	Australia	SYR-322 (Filed Aug 12), SYR-322/metformin (Filed Nov 12), MLN0002 (Filed Jun 13)
	Algeria	DAXAS (Filed Jul 13)
	Botswana	DAXAS (Approved Sep 13)
	Egypt	DAXAS (Filed Jan 12), TAK-491 (Filed Apr 13), TAK-491/chlorthalidone (Filed Jun 13)
	India	DAXAS (Filed Mar 13)
	Jordan	DAXAS (Filed Mar 13)
	Kenya	DAXAS (Filed Jul 12)
	Mauritius	DAXAS (Approved May 13)
	Saudi Arabia	DAXAS (Approved Aug 13)
	Tanzania	DAXAS (Filed Sep 11)
	Uganda	DAXAS (Filed Apr 11)
	UAE	TAK-491 (Filed May 13), TAK-390MR (Filed Jun 13)
	Zambia	DAXAS (Filed Feb 12)

*5 **TAK-491 <azilsartan medoxomil>** Angiotensin II receptor blocker (oral) for the treatment of Hypertension

*6 Originally filed in August 2011, we refiled in February 2013 due to delay of approval in the US

*7 **DAXAS® <roflumilast>** PDE4 inhibitor (oral) for the treatment of Chronic Obstructive Pulmonary Disease

*8 **<mifamurtide>** Immunostimulant (injection) for the treatment of Non-metastatic osteosarcoma

*9 **TCV-116 <candesartan cilexetil>** Angiotensin II receptor blocker (oral) for the treatment of Hypertension

■ Characteristics of projects

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-390MR	Proton pump inhibitor	Erosive esophagitis (healing and maintenance), Non-erosive gastro-esophageal reflux disease	dexlansoprazole	DEXILANT™ (US, Canada) DEXIVANT™ (Mexico)	Oral

[Mode of action / Supplemental]
TAK-390MR was originally developed by Takeda and is launched in the US, Canada and Mexico, and has been appoved in 16 countries in the EU by the decentralized procedure. It is taken once-daily, and employs a new modified release technology on an enantiomer of lansoprazole. TAK-390MR is the first proton pump inhibitor with a Dual Delayed Release™ formulation designed to provide two separate releases of medication in order to maintain its gastric antisecretory activity.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
SYR-322	DPP-4 inhibitor	Diabetes mellitus	alogliptin	NESINA®(Jpn, US) VIPIDIA™ (EU)	Oral

[Mode of action / Supplemental]
SYR-322 is a DPP-4 inhibitor, taken orally once a day. DPP-4 inhibitors work by blocking Glucagon Like Peptide-1 (GLP-1) degradation to maintain its blood concentration for a longer period of time. GLP-1, which is secreted within the digestive tract, stimulates pancreatic beta cells to increase the secretion of insulin, and GLP-1 has the potential to improve beta cell function itself. SYR-322 was approved in Japan in April 2010, in the US in January 2013, and in the EU in September 2013. Clinical/registration activities are currently ongoing in other regions to support the approval of SYR-322 globally. SYR-322 has also been approved in fixed-dose combinations with pioglitazone (in Japan as LIOVEL®, in the US as OSENI® and in the EU as INCRESYNC™), and metformin (in the US as KAZANO® and in the EU as VIPDOMET™).

Development code	Drug Class	Indications	Generic name	Brand name	Administration
ATL-962	Lipase inhibitor	Obesity with both type 2 diabetes mellitus and dyslipidemia	cetilistat	OBLEAN® (Jpn)	Oral

[Mode of action / Supplemental]
ATL-962 is a gastro-intestinal lipase inhibitor, designed to decrease weight by reducing the digestion and thus the absorption of fat from the diet. In P-III trials, ATL-962 demonstrated a statistically significant greater reduction in bodyweight from baseline compared to placebo, with a good safety and tolerability profile. In September 2013, Takeda obtained marketing approval for ATL-962 from the Japanese Ministry of Health, Labour and Welfare.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Lu AA21004	Multimodal anti-depressant	Major depressive disorder, Generalized anxiety disorder	vortioxetine	BRINTELLIX® (US)	Oral

[Mode of action / Supplemental]
Lu AA21004 is an inhibitor of serotonin (5-HT) reuptake and that is thought to be a mechanism of its action. It is also an agonist at 5-HT1A receptors, a partial agonist at 5-HT1B receptors and an antagonist at 5-HT3, 5-HT1D and 5-HT7 receptors. In vivo nonclinical studies have demonstrated that Lu AA21004 enhances levels of the neurotransmitters serotonin, noradrenaline, dopamine, acetylcholine and histamine in specific areas of the brain. In September 2013, Takeda obtained approval from the FDA for Lu AA21004 for the treatment of Major Depressive Disorder.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN0002	Humanized monoclonal antibody against α4β7 integrin	Ulcerative colitis, Crohn's disease	vedolizumab	Not decided yet	Injection

[Mode of action / Supplemental]
MLN0002 is a humanized monoclonal antibody that specifically antagonizes the α4β7 integrin, inhibiting the binding of α4β7 integrin to intestinal mucosal cell adhesion molecule (MAdCAM-1). MAdCAM-1 is preferentially expressed on blood vessels and lymph nodes of the gastrointestinal tract. The α4β7 integrin is expressed on a subset of circulating white blood cells, and these cells have been shown to play a role in mediating the inflammatory process in ulcerative colitis and Crohn's disease. P-III studies have shown that MLN0002 demonstrates statistically significant improvement in clinical remission in patients with ulcerative colitis and Crohn's disease at 52 weeks versus placebo. In March 2013, Takeda filed a Marketing Authorisation Application in the EU for the treatment of ulcerative colitis and Crohn's disease, and in June 2013, Takeda filed a Biologics License Application (BLA) in the US for the same indications. In September 2013, the US FDA granted Priority Review status for the BLA for the treatment of ulcerative colitis.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	Atypical antipsychotic agent	Schizophrenia, Bipolar disorder	lurasidone hydrochloride	Not decided yet	Oral

[Mode of action / Supplemental]
Lurasidone is an atypical antipsychotic agent, developed originally by Dainippon Sumitomo Pharma Co., Ltd. with an affinity for dopamine D2, serotonin 5-HT_{2A} and serotonin 5-HT_7 receptors where it has antagonist effects. In addition, lurasidone is a partial agonist at the serotonin 5-HT_{1A} receptor and has no appreciable affinity for histamine or muscarinic receptors. In September 2012, Takeda filed a Marketing Authorisation Application in the EU for the treatment of schizophrenia.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
SGN-35	CD30 monoclonal antibody-drug conjugate	Relapsed or refractory Hodgkin lymphoma, Front line Hodgkin lymphoma, Post-ASCT Hodgkin lymphoma, Relapsed or refractory systemic anaplastic large cell lymphoma, Front line mature T-cell lymphoma, Relapsed cutaneous T-cell lymphoma	brentuximab vedotin	ADCETRIS® (EU)	Injection

[Mode of action / Supplemental]
SGN-35 is an antibody-drug conjugate (ADC) comprising an anti-CD30 monoclonal antibody attached by an enzyme cleavable linker to a potent, synthetic drug, monomethyl auristatin E (MMAE) utilizing Seattle Genetics' proprietary technology. The ADC employs a novel linker system that is designed to be stable in the bloodstream but to release MMAE upon internalization into CD30-expressing tumor cells. This approach is intended to spare non-targeted cells and thus may help minimize the potential toxic effects of traditional chemotherapy while allowing for the selective targeting of CD30-expressing cancer cells, thus potentially enhancing the antitumor activity.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
BLB-750	Influenza vaccine	Prevention of pandemic influenza	cell culture influenza vaccine (H5N1) cell culture influenza vaccine (prototype)	cell culture influenza vaccine (H5N1) 1mL cell culture influenza vaccine (prototype) 1mL	Injection

[Mode of action / Supplemental]
BLB-750 is a cell culture-based pandemic influenza vaccine (H5N1 and prototype) to prevent infection in the case of a pandemic influenza. Obtaining the prototype approval will facilitate the registration of a vaccine in the event of a pandemic caused by an influenza strain other than H5N1.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-816	Hib vaccine	Prevention of infectious disease caused by Haemophilus influenza Type b (Hib)	-	Not decided yet	Injection

[Mode of action / Supplemental]
TAK-816 is a vaccine to prevent infection caused by Haemophilus Influenza Type b (Hib). Hib vaccine is developed by combining it with detoxified diphtheria toxin in order to increase immunogenicity, assuring the potential to induce the production of antibodies in infants. In September 2013, Takeda filed a New Drug Application to Japanese Ministry of Health, Labour and Welfare for the prevention of infectious disease caused by Hib

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	Mu-opioid receptor antagonist and dopamine/norepinephrine re-uptake inhibitor	Obesity	naltrexone SR /bupropion SR	CONTRAVE®	Oral

[Mode of action / Supplemental]
The two components of CONTRAVE act in a complementary manner in the central nervous system. The central pathways targeted by this treatment are involved in controlling the balance of food intake and metabolism, and regulating reward-based eating behavior. In clinical trials, CONTRAVE was shown to help obese patients initiate and sustain significant weight loss, improve important markers of cardiometabolic risk and increase the ability to control eating.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-875	GPR40 agonist	Diabetes mellitus	fasiglifam	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-875 is a novel, highly selective agonist of GPR40, one of the G-protein-coupled receptors that is expressed in pancreatic islet cells. Through its novel mechanism of action, TAK-875 has potential as a safe and effective treatment for type 2 diabetes by selectively improving glucose-dependent insulin secretion with a low risk of inducing hypoglycemia and pancreatic exhaustion, unlike sulfonylurea or glinides.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-700	Non-steroidal androgen synthesis inhibitor	Prostate cancer	orteronel	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-700 is an oral non-steroidal selective androgen synthesis inhibitor which targets 17,20 lyase, a key enzyme in the production of steroidal hormones. The 17,20 lyase enzyme is a key enzyme in the production of the common precursor molecules for male and female sex steroid hormones, which in men are synthesized in both the testes and the adrenal glands. This inhibitory activity makes TAK-700 a good candidate for development as a therapeutic agent for the treatment of castration-resistant prostate cancer where persistent extra-gonadal synthesis of androgens results in progression of PSA and metastases.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN9708	Proteasome inhibitor	Multiple myeloma, Relapsed or refractory primary (AL) amyloidosis, Solid tumors	ixazomib citrate	Not decided yet	Oral

[Mode of action / Supplemental]
MLN9708 is a proteasome inhibitor, which constitutes a unique approach to targeted therapy. Inhibition of the proteasome prevents the degradation of numerous regulatory proteins, affecting multiple signaling cascades within the cell. In vitro, non-clinical studies have shown that proteasome inhibition can be cytotoxic to a variety of cancer cell types.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN8237	Aurora A kinase inhibitor	Relapsed or refractory peripheral T-cell lymphoma, Diffuse large B-cell lymphoma, Non-small cell lung cancer, Small cell lung cancer, Gastroesophageal cancer, Head and neck cancer, Breast cancer, Ovarian cancer, Non-Hodgkin lymphoma, Solid tumors	alisertib	Not decided yet	Oral

[Mode of action / Supplemental]
MLN8237 is an oral highly-specific small molecule Aurora A kinase inhibitor. Both Aurora A kinase and Aurora B kinase play important roles in cell mitosis, but they have different distributions in the cell and different roles in the process of mitosis. Aurora A kinase is a serine/threonine kinase that exists in the centrosome and spindle poles and is known to play an important role in the formation of spindles at the time of mitosis.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
SYR-472	DPP-4 inhibitor	Diabetes mellitus	trelagliptin	Not decided yet	Oral

[Mode of action / Supplemental]
SYR-472 is a DPP-4 inhibitor, taken orally once weekly, that works by blocking Glucagon Like Peptide-1 (GLP-1) degradation to keep its concentration for a longer period of time. GLP-1, which is secreted within the digestive tract, stimulates pancreatic beta cells to increase the secretion of insulin, and GLP-1 has the potential to improve beta cell function itself.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-438	Potassium-competitive acid blocker	Acid-related diseases (GERD, Peptic ulcer, etc.)	vonoprazan	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-438 is a potassium-competitive acid blocker that suppresses gastric acid secretion by inhibiting the binding of potassium iron (K^+) to H^+, K^+-ATPase. It is anticipated to have a more potent inhibitory effect on gastric acid secretion, a faster onset of action, and a longer lasting effect than PPIs.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	VEGFR1-3, PDGFR, c-Kit inhibitor	Advanced non-squamous non-small cell lung cancer	motesanib diphosphate	Not decided yet	Oral

[Mode of action / Supplemental]
Motesanib is an orally administered inhibitor targeting vascular endothelial growth factor (VEGF) receptor 1,2 and 3, platelet derived growth factor (PDGF) receptor and c-kit (Stem Cell Factor) receptors intending to inhibit angiogenesis and tumor growth.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AMG 386	Anti-angiopoietin peptibody	Ovarian cancer	trebananib	Not decided yet	Injection
[Mode of action / Supplemental] AMG 386 is a peptibody (Fc-peptide fusion protein) which binds to and inhibit Angiopoietin 1 and 2. Angiopoietins are known to be one of the cytokines which stimulate angiogenesis of vascular endothelial cells related to tumor growth and metastasis through different pathways from vascular endothelial growth factors. AMG386 inhibits vascular angiogenesis through binding to angiopoietins.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	Synthetic, peptide-based erythropoiesis-stimulating agent	Anaemia associated with chronic kidney disease in adult patients undergoing dialysis	peginesatide	OMONTYS® (US)	Injection
[Mode of action / Supplemental] OMONTYS, a synthetic, peptide-based erythropoiesis-stimulating agent (ESA), is designed to stimulate the production of red blood cells. As PEGylation allows maintenance of blood concentration, peginesatide is administratered once every four weeks either intravenously or subcutaneously. Serious cases of hypersensitivity reactions, including anaphylaxis, which can be life-threatening or fatal, were reported in the postmarketing setting in the US, leading to a voluntary recall of all lots of OMONTYS. An investigation into the root cause of the reactions was initiated and is ongoing.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
DENVax	Dengue vaccine	Prevention of dengue fever caused by dengue virus	-	Not decided yet	Injection
[Mode of action / Supplemental] DENVax is a live virus (attenuated tetravalent) vaccine, including the four serotypes of the dengue virus that cause disease in humans. The product is built on the backbone of the dengue type 2 virus, and in preclinical models stimulates both types of acquired immunity: humoral (antibody) and cell-mediated (T-cell) immune responses. In P-I and P-II clinical studies, DENVax induced immune responses to three or more of the dengue virus serotypes after two vaccinations with no safety concerns.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-385	LH-RH antagonist	Endometriosis, Uterine fibroids, Prostate cancer	relugolix	Not decided yet	Oral
[Mode of action / Supplemental] TAK-385 is a nonpeptidic oral LH-RH antagonist. It antagonizes LH-RH in the LH-RH receptor that exists in the anterior pituitary basophil (secretory cell), and lowers blood concentration of sex hormones by inhibiting secretion of LH and FSH caused by the stimulation of LH-RH. It is expected to become a treatment for sex hormone-dependent diseases such as endometriosis and uterine fibroids.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-361S	Quadruple vaccine	Prevention of infectious disease caused by Diphtheria, Pertussis, Tetanus, Polio	-	Not decided yet	Injection
[Mode of action / Supplemental] TAK-361S is a combined vaccine with a Diphtheria-Tetanus-acellular Pertussis (DTaP) vaccine and Sabin inactivated polio vaccine (sIPV). sIPV is an inactivated poliovirus vaccine (IPV) derived from the Sabin strains poliovirus (attenuated poliovirus). Compared to the inactive poliovirus vaccine produced from wild-type poliovirus that is used in many countries, sIPV does not require an advanced safe management site for its production.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Norovirus vaccine	Norovirus vaccine	Prevention of acute gastroenteritis (AGE) caused by norovirus	-	Not decided yet	Injection
[Mode of action / Supplemental] This product is the only clinical-stage vaccine against norovirus in the world, and has recently finished P-I/II trials that demonstrated a clinically relevant impact on the incidence of norovirus illness. The norovirus vaccine is administered by the intramuscular route.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-733	MEK inhibitor	Solid tumors	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-733 is a highly selective, allosteric, non-ATP competitive inhibitor of MEK kinase. MEK signaling plays an essential role in regulating both mitogenic and survival signals within tumor cells. This pathway is activated in 50 percent of human cancers, including colon, lung, breast, pancreas, melanoma, ovary and kidney. Inhibition of MEK by TAK-733 as a single agent and in combination with other drugs has a significant effect on the progression of tumor growth in pre-clinical models.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-272	Direct renin inhibitor	Hypertension	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-272 is a direct renin inhibitor (DRI), which is at the top of the enzymatic cascade of renin-angiotensin system (RAS). Non-clinical pharmacology studies have shown that TAK-272 selectively inhibited human renin and efficiently lowered blood pressure. Additionally TAK-272 has shown strong organ protective effects.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-063	PDE10A inhibitor	Schizophrenia	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-063 is a PDE10A inhibitor. An alternative approach to treating schizophrenia may be to selectively inhibit the enzyme PDE10A, thereby modulating the dopaminergic and glutamatergic second messenger pathways in the striatum. Inhibition of PDE10A in vivo has been reported to be associated with behavioral effects consistent with antipsychotic activity. Based on the potential effects of TAK-063 on striatal function, the initial nonclinical and clinical programs for TAK-063 are focused on the treatment of schizophrenia.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-137	AMPA receptor potentiator	Psychiatric disorders and neurological diseases	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-137 is an AMPA receptor (AMPA-R) potentiator. Glutamate is the major excitatory neurotransmitter in the brain and it produces its effects by binding to different receptors such as the AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid)-type glutamate receptor. In fact, AMPA receptors mediate most of the excitatory neurotransmission in the human central nervous system and also participate in processes thought to underlie memory and learning, and the formation of neural networks during brain development. Published preclinical and clinical data have suggested that positive modulation of AMPA receptors may be therapeutically effective in the treatment of various psychiatric disorders and neurological diseases. Of particular interest is the potential for AMPA-R potentiators to ameliorate cognitive deficits, a symptom known to accompany many CNS conditions.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
INV21	EV71 vaccine	Prevention of hand, foot and mouth disease caused by enterovirus 71	-	Not decided yet	Injection

[Mode of action / Supplemental]
INV21 is an inactivated whole virus particle formulated with aluminum hydroxide adjuvant, produced in Vero cells. The vaccine is based on a common strain of EV71 (the B2 sub-genogroup). In a P-I study in 36 healthy adults in Singapore, INV21 induced robust, neutralizing antibody responses against the EV71 virus in every individual. There were no safety concerns in the trial.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN4924	NEDD 8 activating enzyme inhibitor	Advanced malignancies	Not decided yet	Not decided yet	Injection

[Mode of action / Supplemental]
MLN4924 is a first-in-class small molecule inhibitor of a Millennium-discovered target, NEDD 8 activating enzyme (NAE). MLN4924 inhibits NAE, which controls key components of the ubiquitin proteasome pathway that are important for cancer cell growth and survival. In pre-clinical models, MLN4924 suppresses cancer cell growth leading to cell death. MLN4924 is currently being studied in patients with solid tumors and hematologic malignancies.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN0128	mTORC1/2 inhibitor	Multiple myeloma, Waldenstrom's macroglobulinemia, Solid tumors	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
MLN0128, a novel mTORC1/2 inhibitor, has generated encouraging data in multiple P-I studies and is expected to enter P-II studies in 2014.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN1117	PI3Kalpha isoform inhibitor	Solid tumors	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
MLN1117, a novel and selective inhibitor of the PI3Kalpha isoform, entered human clinical testing in September 2011. A P-I dose escalation study is underway to evaluate the safety, tolerability and pharmacokinetics of single-agent MLN1117 in patients with advanced solid malignancies who have tumors characterized by the presence of a PIK3CA mutation.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN0264	Antibody-drug conjugate targeting GCC	Advanced gastrointestinal malignancies	Not decided yet	Not decided yet	Injection

[Mode of action / Supplemental]
MLN0264 is a novel, first in class antibody drug conjugate (ADC) that selectively binds Guanylate Cyclase C (GCC) and kills GCC-expressing cells at sub-nanomolar concentrations. Its toxic payload, monomethyl auristatin E (MMAE; a very potent microtubulin inhibitor) is linked to a target specific monoclonal antibody, which was originated by Millennium, via a cleavable linker, utilizing proprietary technology licensed from Seattle Genetics.
GCC is a transmembrane receptor localized to the apical, but not the basolateral, membrane of epithelial tissues primarily in the colon. Malignant transformation results in loss of this anatomically privileged GCC expression profile and tumor, but not normal, tissue becomes accessible to systemically administered agents targeting GCC.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN2480	pan-Raf kinase inhibitor	Solid tumors	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
MLN2480 is a selective pan-Raf kinase inhibitor. The Raf kinases (A-Raf, B-Raf and C-Raf) are key regulators of cell proliferation and survival within the mitogen-activated protein kinase (MAPK) pathway. The MAPK pathway is frequently disregulated in human cancers, often via activating mutations of Ras or Raf. Following treatment with MLN2480, significant antitumor activity was observed in both tumor xenograft models that had B-Raf$^{V600E/D}$ mutations or were wild type for B-Raf. MLN2480 exhibited a promising preclinical profile and has potential to be a therapeutic agent for solid tumors.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MT203	GM-CSF monoclonal antibody	Rheumatoid arthritis	namilumab	Not decided yet	Injection

[Mode of action / Supplemental]
MT203 works by neutralizing GM-CSF (a fully human monoclonal antibody neutralizing Granulocyte macrophage colony-stimulating factor) signaling by binding the soluble cytokine. GM-CSF, a pro-inflammatory cytokine, has been shown to play a significant role in various autoimmune and inflammatory disease and supports development of MT203 for the treatment of rheumatoid arthritis (RA).

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Lu AA24530	Multimodal anti-depressant	Major depressive disorder, Generalized anxiety disorders	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
In pre-clinical studies, Lu AA24530 has demonstrated activities as a multi-modal enhancer with reuptake inhibition at monoamine transporters, and antagonist activity at 5-HT_3 and 5-HT_{2c} receptors. In vivo rat studies have demonstrated that treatment with Lu AA24530 leads to increases in acetylcholine, noradrenaline, dopamine and 5-HT levels in brain regions that play a key role in the regulation of mood.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AMG 403	Human monoclonal antibody against human Nerve Growth Factor (NGF)	Pain	fulranumab	Not decided yet	Injection

[Mode of action / Supplemental]
AMG 403 is a human monoclonal antibody that has the specific capacity to neutralize the biologic actions of human NGF. NGF has been shown to contribute to persistent pain in a variety of animal models of inflammatory and neuropathic pain, and is known to be elevated in the knee joints of humans with chronic arthritis and possibly other chronic painful conditions in humans.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
ITI-214	PDE1 inhibitor	Cognitive impairment associated with schizophrenia	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
ITI-214 potently inhibits the phosphodiesterase1 (PDE1) enzyme. The PDE1 inhibitor mechanism amplifies dopamine D1 receptor signaling in the prefrontal cortex of the brain, leading to improvement of cognition. This is unique compared to typical drugs for schizophrenia, most of which directly work on blocking dopamine receptors. PDE1 inhibitors including ITI-214 have been shown to enhance cognition in preclinical models.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-491	Angiotensin II receptor blocker	Hypertension	azilsartan medoxomil	EDARBI® (US, EU)	Oral

[Mode of action / Supplemental]
TAK-491 is an angiotensin II receptor blocker, indicated for the treatment of hypertension, either alone or in combination with other antihypertensive agents. Pivotal P-III studies of monotherapy showed TAK-491 80mg was statistically superior to placebo and the highest approved doses of olmesartan medoxomil (40mg) and valsartan (320mg), in lowering both clinic and 24-hour mean blood pressure measurements.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	PDE-4 inhibitor	Chronic Obstructive Pulmonary Disease	roflumilast	DAXAS® (Ex. US) DALIRESP™, LIBERTEK® (EU)	Oral

[Mode of action / Supplemental]
DAXAS is a first-in-class, once-daily orally administered selective phosphodiesterase 4 (PDE4) inhibitor. It is a non-steroid, anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with COPD. The mechanism of action is the inhibition of PDE4, a major cyclic adenosine monophosphate (cAMP)-metabolising enzyme found in structural and inflammatory cells important to the pathogenesis of COPD. Inhibition of PDE4 increases intracellular cAMP and typically leads to an anti-inflammatory effect.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	Immunostimulant	Non-metastatic osteosarcoma	mifamurtide	MEPACT® (EU)	Injection

[Mode of action / Supplemental]
MEPACT is a first-in-class synthetic analog of muramyl dipeptide (MDP). MEPACT is a liposomal formulation specifically designed for in vivo targeting to macrophages by intravenous infusion.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TCV-116	Angiotensin II receptor blocker	Hypertension	candesartan cilexetil	BLOPRESS® (Jpn, EU, Asia), ATACAND® (US), AMIAS® (UK), KENZEN® (FRA), etc.	Oral

[Mode of action / Supplemental]
TCV-116 lowers blood pressure by suppressing the effect of angiotensin II, a hypertensive hormone, at the receptor level.

[Additional indications/formulations]

Development code	Drug Class	Indications or formulations	Generic name	Brand name	Administration
AG-1749	Proton pump inhibitor	Fixed-dose combination with low-dose aspirin	lansoprazole	TAKEPRON® (Jpn), PREVACID® (US), OGAST® (EU)	Oral/Injection

[Mode of action / Supplemental]
AG-1749 is a proton pump inhibitor having a potent inhibitory action on gastric secretion. It suppresses gastric acid secretion by inhibiting the proton pump within the gastric wall cells and exhibits an antiulcer action. The drug has already been launched as a therapeutic agent for peptic ulcers in approximately 90 countries worldwide.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-536	Angiotensin II receptor blocker	Hypertension	azilsartan	AZILVA® (Jpn)	Oral

[Mode of action / Supplemental]
The P-III trial in comparison with candesartan (BLOPRESS®) showed that TAK-536 was statistically superior to candesartan in lowering the change from baseline in sitting diastolic blood pressure, which was the primary endpoint. In addition, TAK-536 was also statistically superior to candesartan in lowering the change from baseline in sitting systolic blood pressure and in lowering the mean diastolic blood pressure and systolic blood pressure in 24 hours, daytime and night time measured by Ambulatory Blood Pressure Monitoring (ABPM), which were secondary endpoints. TAK-536 was safe and well tolerated, with the safety profile comparable to candesartan. A fixed dose combination of TAK-536 and amlodipine was filed in Japan in April 2013.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	IV iron	Iron deficiency anemia from all causes in patients who have a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used	ferumoxytol	RIENSO® (EU), FERAHEME® (Canada)	Injection

[Mode of action / Supplemental]
Treatment with RIENSO provides the following benefits: rapid repletion of iron stores in anemic patients; greater flexibility in the amount of iron that can be given to a patient in a single administration; fewer physician visits required for the administration of 1g of iron; and more rapid administration (IV vs. infusion) compared to existing formulations of IV iron. RIENSO was approved for iron deficiency anemia in adult patients with chronic kidney disease in the EU in June 2012, and is currently under review for iron deficiency anemia from all causes in patients who have a history of unsatisfactory oral iron therapy or in whom oral iron cannot be used. The product is also approved in Canada, where it is marketed by Takeda as FERAHEME, and in the US, where it is marketed by AMAG as FERAHEME.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAP-144-SR	LH-RH agonist	Prostate cancer, Premenopausal breast cancer (6-month formulation)	leuprorelin acetate	LEUPLIN® (Jpn), LUPRON DEPOT® (US), ENANTONE®, etc. (EU, Asia)	Injection

[Mode of action / Supplemental]
TAP-144-SR is a long-acting LH-RH agonist product, and is marketed in over 80 countries world-wide. It is a standard treatment of prostate cancer, and wth one injection it is possible to provide treatment from one to six months in the EU. A 3-month formulation was authorized in Japan for prostate cancer in August 2002 and for premenopausal breast cancer in August 2005. A 6-month formulation has been approved in the EU and has entered P-III in Japan.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-375SL	MT_1/MT_2 receptor agonist	Bipolar disorder	ramelteon	ROZEREM® (US, Jpn)	Sublingual

[Mode of action / Supplemental]
TAK-375SL is highly specific to the MT_1/MT_2 receptor. Abnormalities on circadian rhythms are prominent features of bipolar I disorder. Normalization or resynchronization of circadian rhythms with exogenous melatonin agonists is expected to become a treatment for either acute bipolar episodes or to prevent recurrence.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	Proteasome inhibitor	Front line mantle cell lymphoma, Relapsed diffuse large B-cell lymphoma	bortezomib	VELCADE®	Injection

[Mode of action / Supplemental]
VELCADE blocks the activity of proteasomes, which are enzymes found inside all human cells and necessary for their growth and survival. By inhibiting proteasomes activity, VELCADE causes a buildup of proteins, thereby inducing apoptosis/cell death. Proteasomes break down the resultant proteins which are created through the division and growth of cancer cells as well as other misfolded intracellular proteins. Proteasomes also break down the proteins that are responsible for angiogenesis and cell proliferation.

Development code	Drug Class	Indications or formulations	Generic name	Brand name	Administration
AD-4833/TOMM40	Insulin sensitizer/ Biomarker assay	Delay of onset of mild cognitive impairment due to Alzheimer's disease	-	-	Oral

[Mode of action / Supplemental]
The TOMM40 biomarker, discovered by Zinfandel, is being developed to identify older adults at high risk of developing mild cognitive impairment due to Alzheimer's disease within the subsequent five years. In August 2013, Takeda and Zinfandel initiated a global P-III clinical trial (TOMMORROW Trial) investigating a genetic based biomarker risk assignment algorithm utilizing TOMM40 to predict risk of mild cognitive impairment (MCI) due to Alzheimer's disease (AD) within a five year period. The TOMMORROW trial will also evaluate the efficacy of the investigational low dose AD-4833 (pioglitazone) in delaying the onset of MCI due to AD in cognitively normal individuals at high risk as determined by the risk assignment algorithm

Development code	Drug Class	Indications or formulations	Generic name	Brand name	Administration
-	Chloride channel activator	Liquid formulation	lubiprostone	AMITIZA® (US)	Oral
[Mode of action / Supplemental] Amitiza has a novel mechanism of action as a chloride channel activator, which causes an increase in intestinal fluid, and thereby increasing the passage of the stool and improving symptoms associated with chronic idiopathic constipation.					

■ Other alliance projects

TAK-799/TRM-1	Licensed from: Human Genome Sciences, Inc.	Agreed:	Aug 2002	
		Stage:	Under preparation for clinical trials (Japan)	Territory: Japan
A complete human antibody relevant to TRAIL-R1 discovered by Human Genome Sciences, Inc. HGS is conducting P-II studies for multiple myeloma and non-squamous non-small cell lung cancer in the US.				

Kanda HPV vaccine	Licensed from: The Japan Health Sciences Foundation	Agreed:	October 2010	
		Stage:	Under preparation for clinical trials	Territory : Worldwide
Kanda human papillomavirus (HPV) vaccine has the potential to be effective against all high-risk HPV that are highly likely to cause cervical cancer. Since the coverage of high-risk HPV by conventional vaccines is not yet sufficient, Kanda HPV has the potential to become a universal vaccine. So far, it has been confirmed that the Kanda HPV vaccine has neutralizing activity against six variations of high-risk HPV that are often identified in cervical cancer patients.				

ITI-214	Licensed from: Intra-Cellular Therapies, Inc.	Agreed:	February 2011	
		Stage:	ITI-214 has commenced Phase 1, and other assets are under preparation for clinical trials	Territory : Worldwide
Phosphodiesterase type 1 (PDE1) inhibitors discovered by Intra-Cellular Therapies for the treatment of cognitive impairment associated with schizophrenia. It has been shown that orally available, small molecule inhibitors of PDE1 restore dopamine signaling in neurons and enhance cognition in preclinical models. These compounds have potential to be treatments for a variety of psychiatric and neurological diseases.				

Fomepizole	Licensed from: Paladin Labs Inc.	Agreed:	May 2011	
		Stage:	Under preparation for clinical trials	Territory : Japan
Fomepizole is an alcohol dehydrogenase inhibitor. By inhibiting alcohol dehydrogenase, the ethylene glycol- or methanol-metabolizing enzyme, the drug controls the metabolization of the two substances, thereby preventing the production of poison-causing toxic metabolites. Based on its high affinity with alcohol dehydrogenase, fomepizole is used as standard treatment for ethylene glycol and methanol poisonings.				

■ Clinical study protocol summaries

All clinical study protocol summaries are disclosed on the English-language web-site (http://www.takeda.com/c-t/) and all clinical study protocol information in the Japanese-language is disclosed on the Japanese-language web-site (http://www.takeda.co.jp/c-t/).

We anticipate that this disclosure assure transparency of information on the clinical trials for the benefit of healthcare professionals, their patients and other stakeholders, which we believe will contribute to the appropriate use of Takeda's products worldwide.

■ Outcome studies

SYR-322 (1)

Study title	EXAMINE (EXamination of cArdiovascular outcoMes: alogliptIN vs. standard of carE)		
Outline	A Multicenter, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate Cardiovascular Outcomes Following Treatment with Alogliptin in Addition to Standard of Care in Subjects with Type 2 Diabetes and Acute Coronary Syndrome		
Place	918 locations globally	**Total population**	5,384 patients
Status	The EXAMINE CV safety outcomes trial met its primary endpoint of non-inferiority compared to placebo in addition to standard of care showing that alogliptin does not increase CV risk in Type 2 diabetes patients at high-risk for MACE due to recent ACS. The EXAMINE trial primary endpoint occurred at similar rates in the alogliptin and placebo groups (in 11.3% of patients vs. 11.8% of patients during a median follow-up period of 18 months; hazard ratio, 0.96; one-sided repeated CI, 1.16). The principal secondary safety endpoint was the primary composite with the addition of hospitalization for unstable angina that required coronary revascularization within 24 hours of hospital admission. Testing of the secondary composite endpoint of CV death, myocardial infarction, stroke and unstable angina with urgent revascularization showed no difference in rates on alogliptin versus placebo (12.7% vs. 13.4%, hazard ratio, 0.95, one-sided repeated CI bound, 1.14). Other secondary endpoints included CV death alone and death from any cause. CV death, occurred in 112 patients treated with alogliptin (4.1%) and 130 patients treated with placebo (4.9%) for a hazard ratio of 0.85 (95% confidence limits [CL] of 0.66 to 1.10, p = 0.21). All cause mortality (death from any cause) occurred in 153 patients treated with alogliptin (5.7%) and 173 patients treated with placebo (6.5%) for a hazard ratio of 0.88 (95% CL of 0.71 to 1.09, p = 0.23). Overall, rates of death from any cause and CV death were not statistically significant different between alogliptin and placebo groups. Additional safety end points included angioedema, hypoglycemia, pancreatitis, malignancy, and results of laboratory testing. Rates of hypoglycemia, malignancy, pancreatitis, dialysis, and serum aminotransferase elevations were similar for the alogliptin and placebo groups. No events of pancreatic cancer were reported during the trial. The alogliptin and placebo groups did not differ significantly with regard to rates of serious adverse events (33.6% and 35.5%, respectively, p = 0.14).		

AD-4833 (1)

Study title	PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events)		
Outline	This is a study to investigate the preventive effects on the progression of macrovascular disease in type 2 diabetes patients. AD-4833 or placebo will be added to conventional oral anti-diabetic drugs for comparative purpose. Primary endpoints are cardiovascular events (death, heart attack, stroke, and below-knee amputation).		
Place	19 countries in Europe	**Total population**	5,238 patients
Status	Landmark data from the PROactive Study, presented at the 41st meeting of the European Association for the Study of Diabetes (EASD) in Athens (Sep 05) demonstrated that ACTOS® (pioglitazone HCl) significantly reduces the combined risk of heart attacks, strokes and death by 16% in high risk patients with type 2 diabetes. This study focused on two key endpoints: a primary combination endpoint of seven different macrovascular events of varying clinical importance; and a principal secondary combination endpoint of life-threatening events including death, heart attack and stroke. The study results were published in The Lancet in October 2005. The primary endpoint was reduced by 10% but had not reached statistical significance by study end (P=0.095). The principal secondary endpoint of life-threatening events showed that pioglitazone significantly reduced the risk of heart attacks, strokes and death by 16% (P=0.027). Results of new analyses found that ACTOS (pioglitazone HCl) significantly reduced the risk of recurrent stroke in high-risk patients with type 2 diabetes at the World Congress of Cardiology in Barcelona. According to the results, there were statistically significant benefits of ACTOS in patients who had suffered a prior stroke. The incidence of recurrent stroke was reduced by 47 percent (P=0.008) and the combined risk of death, MI or stroke was reduced by 28 percent (P<0.05). There was no effect of ACTOS on subsequent strokes in patients who had never experienced a stroke.		

AD-4833 (2)

Study title	CHICAGO (Carotid intima-media tHICkness in Atherosclerosis using pioGlitazOne)		
Outline	CHICAGO is the largest and longest study to examine the effects of ACTOS on measures of the atherosclerotic disease process in patients with type 2 diabetes, by carotid intima-media thickness, or CIMT, that is defined as the thickness of the inner lining of a patient's carotid, or neck artery.		
Place	US	**Total population**	462 patients
Status	Results from the clinical trial, CHICAGO were part of a late-breaker presentation at the American Heart Association's Scientific Sessions 2006. The study results were published in the JAMA (the Journal of the American Medical Association) in November 2006. The analysis demonstrated a statistically significant relative reduction in the progression of CIMT with ACTOS. According to the results, patients in the ACTOS arm showed a -0.001 mm change in arterial thickness from baseline versus an increase of 0.012 mm in the glimepiride arm, a total difference of 0.013 mm between the two arms (P=0.017). The results also showed a highly significant relative change in the maximum CIMT values, commonly considered a more indicative measure of overall treatment impact. The glimepiride-treated group showed a 0.026 increase, compared to a 0.002 increase in the ACTOS-treated group, resulting in a treatment difference of 0.024 (P=0.008). ACTOS provided significantly better glycemic control based on reductions in A1c levels, which in the ACTOS-treated group decreased by 0.33 percent versus the glimepiride group that saw a decrease of 0.01 percent, resulting in a -0.32 percent (P=0.002) difference between the two arms. Adjudicated cardiac events, composite endpoints of non-fatal myocardial infarction (MI), non-fatal stroke and death, showed no events in the ACTOS arm (n=230) and 2 events in the glimepiride arm (n=228). ACTOS decreased triglyceride levels by 13.5 percent versus an increase of 2.1 percent with glimepiride (P=0.001), and increased HDL-C levels by 12.8 percent versus a decrease of 1.1 percent with glimepiride (P=0.001). Both treatment arms increased in LDL-C levels: 5.8 percent with ACTOS compared to 1 percent with glimepiride (P=0.12).		

AD-4833 (3)

Study title	PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation)		
Outline	PERISCOPE is the first clinical trial to examine the effects of an oral antidiabetic medication on the development of coronary atherosclerosis in patients with type 2 diabetes using IVUS technology.		
Place	US, Canada, Latin America	**Total population**	543 patients
Status	The PERISCOPE trial was presented as a late breaker at the 57th Annual Scientific Session of the American College of Cardiology in Chicago in 2008. This trial demonstrated that ACTOS slows progression and reductions in atheroma volume which is a marker of coronary atherosclerosis. This trial adds to the body of cardiovascular data for ACTOS. ACTOS studies, conducted over the past 10 years in more than 16,000 patients, including short- and long-term trials, as well as prospective and observational studies, have shown no evidence that ACTOS is associated with an increased risk of heart attack, stroke, or death. The study results were published in the JAMA (the Journal of the American Medical Association) in March 2008. The analysis demonstrated a statistically significant difference in percent change in coronary artery atheroma volume in favor of ACTOS treatment compared to glimepiride treatment. The data showed that patients treated with glimepiride, a sulfonylurea and commonly used diabetes medication, exhibited progression of coronary atherosclerosis. In contrast, the ACTOS arm showed no progression of coronary atherosclerosis over the 18-month period from the initial baseline measurement Cardiovascular safety data was collected by looking at macrovascular events and episodes of congestive heart failure (CHF). The number of episodes of a common cardiovascular endpoint of cardiovascular mortality, non-fatal MI, or non-fatal stroke was 6 (2.2%) in glimepiride patients and 5 (1.9%) in ACTOS-treated patients. The number of hospitalizations due to CHF were equivalent in both arms. In the ACTOS-treated group, more patients were experienced a bone fracture than in glimepiride-treated group and in glimepiride there could be seen more patients with hypoglycemia and angina than in the ACTOS-treated group.		

TCV-116 (1)

Study title	CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality)		
Outline	This study was conducted to evaluate the clinical benefits of candesartan in patients with heart failure.		
Place	Around 26 countries	**Total population**	7,601 patients
Status	Data presented at the European Society of Cardiology (ESC) annual meeting in August 2003 demonstrated that candesartan could reduce both cardiovascular deaths as well as hospital admissions for heart failure, across a broad spectrum of patients with chronic heart failure. CHARM consists of following three studies. **CHARM-Alternative**: (Candesartan vs. Placebo) Patients: LVEF *40% or lower, intolerance to ACE-I In patients who were not taking ACE-inhibitors due to previous intolerance, candesartan significantly reduced the risk of cardiovascular death or hospital admissions for chronic heart failure, with an overall risk reduction of 23% ($p<0.0004$). **CHARM-Added**: (Candesartan + conventional therapy vs. Conventional therapy) Patients: LVEF 40% or lower In patients that were prescribed conventional therapy for chronic heart failure including an ACE inhibitor, candesartan demonstrated additional mortality and morbidity benefits. Candesartan significantly reduced the risk of cardiovascular death or hospital admissions for chronic heart failure by 15% (P=0.011) . **CHARM-Preserved**: (Candesartan vs. Placebo) Patients: LVEF higher than 40% The results showed that 11% risk reduction in favor of candesartan (P=0.118). There was also a significant 40% reduction in the number of patients diagnosed with new onset diabetes (47 vs. 77; P=0.005). Pooled analysis of the three studies showed that candesartan provided a significant reduction in cardiovascular death (P=0.012) and also demonstrated a positive trend in the overall reduction in all cause mortality (P=0.055). Interestingly, it also demonstrated a significant 22% reduction in onset of new diabetes, with 163 new cases of diabetes on candesartan compared with 202 on placebo. *LVEF: Left Ventricular Ejection Fraction. LVEF is a clinical indicator to evaluate degree of heart failure (Normal 60%-70%) *Cardiovascular death: death of stroke, myocardial infarction		

TCV-116 (2)

Study title	DIRECT (DIabetic REtinopathy Candesartan Trial)		
Outline	The world's first large scale clinical study to investigate prevention/treatment efficacy on diabetic retinopathy (candesartan vs. placebo)		
Place	30 countries	**Total population**	5,231 patients
Status	Data from the DIRECT Programme, the first large-scale study programme assessing the effect of treatment with an angiotensin receptor blocker (ARB) on the incidence and progression of diabetic eye complications, was presented at the European Association of the Study of Diabetes (EASD) congress in Rome in September 2008. The data show a strong trend in favour of treatment with candesartan 32mg in reducing the incidence of diabetic retinopathy in Type 1 diabetes patients, although not statistically significant, and a significant increase in regression of diabetic retinopathy in Type 2 diabetes patients. Study 1 'DIRECT-Prevent 1' (n=1,421) studied the effect of candesartan on the incidence of retinopathy (primary endpoint) in normotensive, normoalbuminuric Type 1 diabetes patients. In Type 1 patients with no signs of diabetic retinopathy at baseline, candesartan caused an 18% reduction in the incidence of diabetic retinopathy as measured by 2-step change on the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale (primary endpoint, p=0.0508), but a 35% reduction for 3-step change (post-hoc analysis, p=0.003). Study 2 'DIRECT-Protect 1' (n=1,905) studied the effect of candesartan on the progression of retinopathy (primary endpoint) in normotensive, normoalbuminuric Type 1 diabetes patients already affected by retinopathy. In the Type 1 diabetic patients with retinopathy at baseline there were no differences in the results in progression of retinopathy between the two treatment groups (p=0.85). Study 3 'DIRECT-Protect 2' (n=1,905) studied the effect of candesartan on the progression of retinopathy (primary endpoint) in normoalbuminuric, normotensive or treated hypertensive, Type 2 diabetes patients with retinopathy. Treatment with candesartan also reduced the risk of progression of retinopathy by 13% over placebo in Type 2 diabetes patients, primary endpoint, p=0.2. However, in these Type 2 diabetes patients with relatively early signs of diabetic retinopathy, candesartan increased the probability of regression of retinopathy by 34% compared with placebo (pre-defined secondary endpoint, p=0.009).		

TCV-116 (3)

Study title	CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)		
Outline	Large scale clinical study of high-risk hypertensive patients in Japan		
Place	Japan	**Total population**	4,728 patients
Status	This is the first large-scale outcome study in Japan comparing BLOPRESS®, (generic name: candesartan cilexetil), angiotensin receptor blocker and amlodipine, a calcium antagonist, both of which are the most frequently prescribed medicines in Japan in each class. In the study, the incidences of cardiovascular (CV) events in 4,728 Japanese patients with high-risk hypertension were compared in the two treatment groups for 3 years or longer. BLOPRESS reduced all-cause mortality by 15% compared with amlodipine, although this difference was not statistically significant. In obese patients with hypertension, in particular, BLOPRESS significantly reduced all-cause mortality by 49% compared to amlodipine (P=0.045). <Secondary endpoint> BLOPRESS significantly reduced new onset of diabetes by 36% compared to amlodipine (P=0.030). Stratified analysis revealed that this effect was conspicuous, particularly in obese patients with higher body mass index.		

TCV-116 (4)

Study title	HIJ-CREATE (The Heart Institute of Japan-Candesartan Randomized trial for Evaluation in Coronary Artery Disease)		
Outline	Large-scaled outcome study with coronary artery disease patients with hypertension		
Place	Japan	**Total population**	2,049 patients
Status	During the American Heart Association's Scientific Session 2007, held at Orlando, Miami, the results of the HIJ-CREATE study ("CREATE study") were presented in late-breaking clinical trials session. This is a large-scaled outcome study with coronary artery disease patients with hypertension in Japan, comparing the reduction of incidence of major adverse cardiovascular events ("MACE") between therapy with BLOPRESS and that with non-ARB standard therapy, and the total number of patients is 2,049. ・Reduction of incidence of MACE in patients with impaired renal function BLOPRESS showed 21% reduction in incidence of MACE as compared to the non-ARB standard therapy. (P=0.039) ・The new onset rates of diabetes mellitus The new onset rate with BLOPRESS and non-ARB standard therapy are 1.1% and 2.9% respectively. (P=0.027)		

Research Activities

■ Main joint research activities

(1) Joint researches with domestic research organizations and companies

Partner	Research subject	Schedule
Kirin Brewery Company Ltd. (Now Kyowa Hakko Kirin Ltd.)	Licensing-in of the human antibody technology	2003/7-
Kyoto University	Research collaboration for basic and clinical research project of discovering treatments for obesity and schizophrenia based on CNS control	2011/1-2016/3
Osaka University	Joint research on development of platform for practical application and commercialization of nano-particle vaccines	2012/2-2015/1

(2) Joint research with overseas research organizations and companies

Partner	Country	Research subject	Schedule
Oxford Centre for Diabetes, Endocrinology and Metabolism	UK	Partnership with Oxford Diabetes Centre	2002/4-
XOMA Ltd.	US	Joint research on discovery, development and production technologies of monoclonal antibody	2006/11-
Alnylam Pharmaceuticals, Inc.	US	Collaboration for Discovery and Development of RNAi Therapeutics	2008/5-2013/5
Seattle Genetics	US	Research collaboration on Antibody-Drug Conjugate	2009/3-
CellCentric	UK	Exclusive licensing of one of the CellCentric's epigenetics projects for the development and commercialization in oncology field	2010/2-
BC Cancer Agency	Canada	Research collaboration for discovery of novel candidate targets for cancer treatment	2010/3-
University College London	UK	Research collaboration on development of novel cancer treatment	2010/3-2014/3
Sage Bionetworks	US	Research collaboration on discovering effective therapeutic targets for Central Nervous System (CNS) disease	2010/11-2014/11
Florida Hospital, Sanford-Burnham Medical Research Institute	US	Research collaboration to target obesity	2010/12-2015/2
Zinfandel Pharmaceuticals	US	Licensing Agreement for Alzheimer's Disease Biomarker TOMM40 for the risk of Alzheimer's disease	2010/12-
Samyang Corporation	S. Korea	Joint research on novel DDS platform technology for RNAi therapeutics	2011/4-2014/3
Structural Genomics Consortium	Canada	Participation in consortium to advance basic research on selected drug targets based on three-dimensional structures of human proteins	2011/7-2015/6 *Takeda joined 2012/4
BC Cancer Agency	Canada	Research collaboration to explore new drug targets based on gene analysis	2012/8-2015/7
Advinus Therapeutics	India	Discovery collaboration focused on novel targets for major therapeutic areas, including Inflammation, CNS, and Metabolic diseases	2012/10-2015/9
Resolve Therapeutics	US	Collaboration to develop compounds for the treatment of Systemic Lupus Erythematosus (SLE)	2013/2-
Tri-Institutional Therapeutics Discovery Institute	US	Collaboration of academic institutions and industry to more effectively develop innovative treatments and therapies	2013/10 -2016/9