Ⅹ. Pipeline

Development Activities

- ■ Compounds
- ■ Additional indications/formulations of compounds
- ■ Recent progress in stage
- ■ Discontinued project
- ■ Characteristics of projects
- ■ Other alliance projects
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(5) Development activities

■ US/EU/Jpn

Development code/product name <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
Feraheme® / Rienso® <ferumoxytol>	IV iron (injection)	Iron deficiency anaemia in adult patients with chronic kidney disease	EU	Approved (Jun 12)	In-license (AMAG)
Lotriga® <omega-3-acid ethyl esters 90>	EPA/DHA agent (oral)	Hyperlipidemia	Jpn	Approved (Sep 12)	In-license (Pronova)
Revestive® <teduglutide>	Glucagon-like peptide 2 analogue (injection)	Short bowel syndrome	EU	Approved (Sep 12)	In-license (NPS)
SGN-35 <brentuximab vedotin>	CD30 monoclonal antibody-drug conjugate (injection)	Relapsed or refractory Hodgkin lymphoma	EU Jpn	Filed (May 11) P-I/II	In-license (Seattle Genetics)
		Relapsed or refractory systemic anaplastic large cell lymphoma	EU Jpn	Filed (May 11) P-I/II	
		Relapsed cutaneous T-cell lymphoma	EU	P-III	
		Post-ASCT Hodgkin lymphoma	EU	P-III	
		Front line Hodgkin lymphoma	EU	P-I	
		Front line systemic anaplastic large cell lymphoma	EU	P-I	
SYR-322 <alogliptin>	DPP-4 inhibitor (oral)	Diabetes mellitus	US EU	FDA Complete Response Letter (Apr 12) Filed (May 12)	In-house
		Diabetes mellitus (Fixed-dose combination with Actos)	US EU	FDA Complete Response Letter (Apr 12) Filed (Jun 12)	
		Diabetes mellitus (Fixed-dose combination with metformin)	US EU	Filed (Nov 11) Filed (Jun 12)	
TAK-390MR <dexlansoprazole>	Proton pump inhibitor (oral)	Erosive esophagitis (healing and maintenance) and non-erosive gastro-esophageal reflux disease	EU Jpn	Filed (Mar 12) P-II	In-house
OMONTYS® <peginesatide>	Synthetic, peptide-based erythropoiesis-stimulating agent (injection)	Anemia due to chronic kidney disease in adult patients on dialysis	EU	Filed (Feb 12)	In-license (Affymax)
- <lurasidone hydrochloride>	Atypical antipsychotic agent (oral)	Schizophrenia	EU	Filed (Sep 12)	In-license (Dainippon Sumitomo)
		Bipolar disorder	EU	P-III	
Lu AA21004 <vortioxetine>	Multimodal anti-depressant (oral)	Major depressive disorder	US Jpn	Filed (Oct 12) P-III	In-license (Lundbeck)
		Generalized anxiety disorder	US	P-III	
ATL-962 <cetilistat>	Lipase inhibitor (oral)	Obesity	Jpn	Filed (Oct 12)	In-license (Norgine BV)*1
Contrave® <naltrexone SR /bupropion SR>	Mu-opioid receptor antagonist and dopamine/norepinephrine re-uptake inhibitor (oral)	Obesity	US	FDA Complete Response Letter (Jan 11)	In-license (Orexigen)
TAK-875 < - >	GPR40 agonist (Glucose-dependent insulin secretagogue) (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/injection)	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 Alizyme assigned ATL-962 (cetilistat) business to Norgine BV on 15 October, 2009

Development code/product name <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
MLN0002 <vedolizumab>	Humanized monoclonal antibody against α4β7 integrin (injection)	Ulcerative colitis	US EU Jpn	P-III P-III P-I	In-house
		Crohn's disease	US EU	P-III P-III	
MLN8237 <alisertib>	Aurora A kinase inhibitor (oral)	Relapsed or refractory peripheral T-cell lymphoma	US EU	P-III P-III	In-house
		Aggressive non-Hodgkin lymphoma, Acute myelogenous leukemia (AML), High-risk myelodysplastic syndrome (MDS), 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-491 <azilsartan medoxomil>	Angiotensin II receptor blocker (oral)	Hypertension (Fixed-dose combination with chlorthalidone)	EU	P-III	In-house
TAK-536 <azilsartan>	Angiotensin II receptor blocker (oral)	Hypertension (Fixed-dose combination with amlodipine besilate)	Jpn	P-III	In-house
TAK-438 < - >	Potassium-competitive acid blocker (oral)	Acid-related diseases (GERD, Peptic ulcer, etc.)	Jpn	P-III	In-house
TAK-375SL <ramelteon>	MT_1/MT_2 receptor agonist (sublingual)	Bipolar disorder	US	P-III	In-house
AMG 706 <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 < - >	Anti-angiopoietin peptibody (injection)	Ovarian cancer	Jpn	P-III	In-license (Amgen)
AMG 479 <ganitumab>	Human monoclonal antibody against human type 1 insulin-like growth factor receptor (IGF-1R) (injection)	Metastatic pancreas cancer	Jpn	P-III	In-license (Amgen)
Sovrima® <idebenone>	Mitochondria targeted anti-oxidant (oral)	Friedreich's ataxia	EU	P-III*2	In-license (Santhera)
		Duchenne muscular dystrophy	EU	P-III	
TAK-816 < - >	Hib vaccine (injection)	Prevention of infectious disease caused by Haemophilus influenza Type b (Hib)	Jpn	P-III	In-license (Novartis)
TAK-428 < - >	Neurotrophic factor production accelerator (oral)	Diabetic neuropathy	US EU	P-II P-II	In-house
TAK-385 < - >	LH-RH antagonist (oral)	Endometriosis, Uterine fibroids	Jpn	P-II	In-house
		Prostate Cancer	-	P-I	
- <veltuzumab>	CD20 monoclonal antibody (injection)	Rheumatoid arthritis	US EU	P-II P-II	In-license (Immunomedics)
TAK-361S < - >	Quadruple vaccine (injection)	Prevention of infectious disease caused by Diphtheria, Pertussis, Tetanus, Polio	Jpn	P-II	In-license (Japan Polio)
TAK-329 < - >	Glucokinase activator (oral)	Diabetes mellitus	-	P-I	In-house
TAK-448 < - >	Metastin analog (injection)	Prostate cancer	-	P-I	In-house
TAK-733 < - >	MEK inhibitor (oral)	Solid tumors	-	P-I	In-house

*2 Re-submission subject to data analysis

Development code /product name <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
TAK-960 < - >	PLK1 inhibitor (oral)	Solid tumors	-	P-I	In-house
TAK-441 < - >	Hedgehog signaling pathway inhibitor (oral)	Solid tumors	-	P-I	In-house
TAK-272 < - >	Direct renin inhibitor (oral)	Hypertension	-	P-I	In-house
TAK-259 < - >	α1D-adrenoceptor antagonist (oral)	Overactive bladder	-	P-I	In-house
TAK-357 < - >	Cognitive enhancer (oral)	Alzheimer's disease	-	P-I	In-house
TAK-063 < - >	PDE10A Inhibitor (oral)	Schizophrenia	-	P-I	In-house
MLN4924 < - >	NEDD 8 activating enzyme inhibitor (injection)	Advanced malignancies	-	P-I	In-house
MLN0128*3 **< - >**	mTORC1/2 inhibitor (oral)	Multiple myeloma, Waldenstrom's macroglobulinemia, Solid tumors	-	P-I	In-house
MLN1117*4 **< - >**	PI3Kα isoform inhibitor (oral)	Solid tumors	-	P-I	In-house
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 and generalized anxiety disorders	US Jpn	P-I *6 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)

*3 MLN0128 used to be INK128

*4 MLN1117 used to be INK1117

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

*6 To be prepared for P-III in the US

■ 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	Helicobacter pylori eradication by concomitant therapy with amoxicillin hydrate and either clarithromycin or metronidazole	Jpn Filed (Aug 12)	In-house
NE-58095 <risedronate> Benet® (Jpn)	Bone resorption inhibitor	Once-monthly formulation	Jpn Filed (Mar 12)	In-license (Ajinomoto)
AMITIZA® <lubiprostone>	Chloride channel activator	Opioid-Induced Constipation (OIC)	US Filed (Jul 12)	In-license (Sucampo)

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
VELCADE® **<bortezomib>**	Proteasome inhibitor	Front line MCL Relapsed diffuse large B cell lymphoma	US P-III US P-II	In-house
AD4833/TOMM40	Insulin sensitizer/ Biomarker assay	Alzheimer's disease prevention	US P-I EU P-I	In-license (Zinfandel)

■ Recent progress in stage **Progress in stage since release of FY2011 results (May 11, 2012)**

Development code	Indications	Country/Region	Progress in stage
Feraheme® / Rienso®	Iron deficiency anaemia in adult patients with chronic kidney disease	EU	Approved (Jun 12)
SYR-322	Diabetes mellitus	EU	Filed (May 12)
SYR-322	Diabetes mellitus (Fixed-dose combination with Actos)	EU	Filed (Jun 12)
SYR-322	Diabetes mellitus (Fixed-dose combination with metformin)	EU	Filed (Jun 12)
lubiprostone	Opioid-Induced Constipation (OIC)	US	Filed (Jul 12)
MLN9708	Multiple myeloma	US, EU	P-III
TAK-375SL	Bipolar disorder	US	P-III
TAK-357	Alzheimer's disease	-	P-I
TAK-063	Schizophrenia	-	P-I
MLN0264	Advanced gastrointestinal malignancies	-	P-I
ITI-214	Cognitive Impairment Associated with Schizophrenia	-	P-I
Lotriga®	Hyperlipidemia	Jpn	Approved (Sep 12)
teduglutide	Short bowel syndrome	EU	Approved (Sep 12)
AG-1749	Helicobacter pylori eradication by concomitant therapy with amoxicillin hydrate and either clarithromycin or metronidazole	Jpn	Filed (Aug 12)
lurasidone hydrochloride	Schizophrenia	EU	Filed (Sep 12)
Lu AA21004	Major depressive disorder	US	Filed (Oct 12)
ATL-962	Obesity	Jpn	Filed (Oct 12)
MLN9708	Relapsed or refractory primary (AL) amyloidosis	US, EU	P-III

Progress in stage since the announcement of FY2012 1Q results (July 30th, 2012) are listed under the bold dividing line

■ Discontinued projects **Discontinued since release of FY2011 results (May 11, 2012)**

Development code	Indications (Stage)	Reason
TAK-701	Advanced malignancies (P-I)	The decision to discontinue development was made because it no longer fits in the product development portofolio of Takeda
TAK-591	Hypertension (P-I)	As TAK-536 has been launched, there is no need to keep TAK-591
MLN0518	Glioblastoma (US P-II)	Clinical data from both single agent and a combination study did not warrant further development in glioblastoma
AMG 706	Advanced non-squamous non-small cell lung cancer (US, EU P-III)	MONET1 pivotal phase III trial did not meet its primary objective of demonstrating a statistically significant improvement in overall survival, and did not warrant further development in US and EU
AMG 706	Breast cancer (US P-I/II)	Currently, the focus of AMG 706 development is front line NSCLC in Japan and additional Asian countries
Vectibix®	Squamous cell carcinoma of head and neck (Jpn P-III)	The phase III study did not meet the primary endpoint of statistically significant improvement in overall survival. Amgen and Takeda do not plan an additional pivotal study

Projects discontinued since the announcement of FY2012 1Q results (July 30th, 2012) are listed under the bold dividing line

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

Region	Country	Development code / product name (stage)
Americas Ex. US	Brazil	SYR-322 (Filed Aug 11), TAK-491 (Filed Nov 11), SYR-322/metformin (Filed Jun 12), TAK-491/chlorthalidone (Filed Jun 12)
	Colombia	DAXAS*7 (Filed Aug 11), TAK-390MR (Filed Aug 12)
	Venezuela	DAXAS (Filed Jan 10)
Europe Ex. EU	Albania	DAXAS (Filed May 12)
	Kosovo	DAXAS (Approved May 12)
	Montenegro	DAXAS (Filed Jun 11)
	Switzerland	Rienso (Approved Sep 12), lurasidone hydrochloride (Filed Mar 12), SYR-322 (Filed Jul 12), SYR-322/metformin (Filed Jul 12), TAK-491 (Filed Aug 12), SYR-322/pioglitazone (Filed Aug 12), TAK-390MR (Filed Sep 12)
Russia/CIS	Armenia	DAXAS (Filed Jun 12)
	Uzbekistan	DAXAS (Approved Jun 12)
Asia Ex. Jpn	China	DAXAS (Filed Dec 11), SYR-322 (Filed Mar 12)
	Hong Kong	TAK-390MR (Approved Aug 12), TAK-491 (Filed Mar 12)
	Indonesia	DAXAS (Filed Sep 10), SYR-322 (Filed Jan 11), TAK-390MR (Filed Dec 11), TAK-491 (Filed Feb 12), TAK-491/chlorthalidone (Filed Jul 12)
	Philippines	TAK-491 (Filed Oct 11), TAK-390MR (Filed Nov 11), TCV-116*8/amlodipine besilate (Filed Jan 12)
	Singapore	DAXAS (Filed Aug 11)
	S. Korea	TAK-390MR (Approved Oct 12), SYR-322 (Filed Mar 12)
	Taiwan	SYR-322 (Filed Mar 11), TAK-491 (Filed Aug 11), TAK-390MR (Filed Sep 11), TAK-491/chlorthalidone (Filed May 12)
	Thailand	DAXAS (Filed Jan 11), TAK-390MR (Filed Aug 11), TAK-491 (Filed Sep 11), TAK-491/chlorthalidone (Filed Jun 12)
	Vietnam	DAXAS (Filed Dec 10)
Others	Australia	SYR-322 (Filed Aug 12)
	Botswana	DAXAS (Filed Dec 11)
	Egypt	DAXAS (Filed Jan 12)
	Isreal	DAXAS (Filed Aug 11)
	Mauritius	DAXAS (Filed Mar 11)
	Saudi Arabia	DAXAS (Filed May 12)
	South Africa	DAXAS (Filed Aug 09)
	Tanzania	DAXAS (Filed Sep 11)
	Uganda	DAXAS (Filed Apr 11)
	Zambia	DAXAS (Filed Feb 12)

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

*8 **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
Feraheme® / Rienso®	IV iron	Iron deficiency anaemia in adult patients with chronic kidney disease	ferumoxytol	Feraheme® (Canada) Rienso® (EU)	Injection

[Mode of action / Supplemental]
Treatment with Feraheme/Rienso® provides the following benefits: rapid repletion of iron stores in anaemic CKD 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. Ferumoxytol was approved in the EU in June 2012 as Rienso®, and is also approved in the US, where it is marketed by AMAG as Feraheme®.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-085	EPA/DHA agent	Hyperlipidemia	omega-3-acid ethyl esters 90	Lotriga® (Jpn)	Oral

[Mode of action / Supplemental]
TAK-085, marketed ex-Japan by Pronova, is a triglyceride lowering agent made from fish oil. It consists of purified EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). This drug was approved in Japan in September 2012 for the treatment of hyperlipidemia, and it is marketed for the indication of high triglyceridemia in the US and the indication of high triglyceridaemia and adjuvant treatment in secondary prevention after myocardial infarction in some countries in the EU such as Italy, Germany and the UK. The mechanism of action is yet to be fully clarified, however, it is thought to inhibit triglyceride synthesis in the liver.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Revestive®	Glucagon-like peptide 2 analogue	Short bowel syndrome	teduglutide	Revestive® (EU)	Injection

[Mode of action / Supplemental]
Teduglutide is a once-daily subcutaneous treatment for Short Bowel Syndrome (SBS). It is a novel, recombinant analogue of human glucagon-like peptide 2 (GLP-2), a protein involved in the rehabilitation of the intestinal lining. Revestive® has received orphan drug designation as SBS is a rare disease affecting less than 10,000 patients in Europe, and was approved as a first in class treatment in September 2012. NPS Pharmaceuticals holds the marketing rights in the US, Canada, Mexico and Isreal, with Takeda holding the rights in all other regions. (NPS filed in the US in 2011 with the brand name GATTEX)

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 systemic anaplastic large cell lymphoma, Relapsed cutaneous T-cell lymphoma	brentuximab vedotin	ADCETRIS® (EU)	Injection

[Mode of action / Supplemental]
Brentuximab vedotin (ADCETRIS) 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
SYR-322	DPP-4 inhibitor	Diabetes mellitus	alogliptin	NESINA®(Jpn)	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. Alogliptin was approved in Japan in April 2010, and clinical/registration activities are currently ongoing to support the approval of alogliptin globally.

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

[Mode of action / Supplemental]
DEXILANT, which was originally developed by Takeda and is marketed by Takeda in the US, Canada and Mexico, is taken once-daily, and employs a new modified release technology on an enantiomer of lansoprazole. DEXILANT 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
-	Synthetic, peptide-based erythropoiesis-stimulating agent	Anemia due to chronic kidney disease in adult patients on dialysis	peginesatide	OMONTYS® (US)	Injection

[Mode of action / Supplemental]
Peginesatide, 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. Peginesatide is approved in the US and filed in the EU for the treatment of anemia due to Chronic Kidney Disease in adult patients on dialysis.

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, Takeda filed a MAA in the EU.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Lu AA21004	Multimodal anti-depressant	Major depressive disorder, Generalized anxiety disorder	vortioxetine	Not decided yet	Oral

[Mode of action / Supplemental]
In vitro studies indicate that Lu AA21004 is a 5-HT3 and 5-HT7 receptor antagonist, 5-HT1B receptor partial agonist, 5-HT1A receptor agonist and inhibitor of the 5-HT transporter serotonin transporter (SERT). 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.. Lu AA21004 has demonstrated a low drug-drug interaction potential. It is extensively metabolized in the liver and the absorption of Lu AA21004 is independent of food intake. In October 2012, Takeda filed a NDA in the US for the treatment of Major Depressive Disorder.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
ATL-962	Lipase inhibitor	Obesity	cetilistat	Not decided yet	Oral

[Mode of action / Supplemental]
ATL-962 is a gastro-intestinal lipase inhibitor. It is designed to decrease weight by reducing the digestion and thus the absorption of fat from the diet. According to the results of P-II conducted by Alizyme, cetilistat (80mg and 120mg) caused statistically significant weight loss and reductions in HbA1c compared with placebo. Treatment discontinuations due to gastro-intestinal adverse events in the cetilistat groups were lower than those in the orlistat groups. In October 2012, Takeda filed a NDA to the Japanese Ministry of Health, Labor and Welfare.

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 (Glucose-dependent insulin secretagogue)	Diabetes mellitus	Not decided yet	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, different from sulfonylurea agents 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 a selective, non-steroidal 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/Injection

[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
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 antibody that selectively binds to α4β7 integrin, which inhibits the binding between α4β7 integrin and MAdCAM-1(mucosal adhesion molecule 1) existing mainly in the intestinal mucosa. Integrins are a type of cell surface protein; their main roles are cellular binding to the extracellular matrix and signal transduction from the extracellular matrix. In the P-II studies (POC) involving 400 patients with ulcerative colitis and Crohn's disease, the rate of mucosal healing and the rate of remission of symptoms including diarrhea frequently observed in patients with inflammatory bowel disease were significantly higher in the treatment group than in the placebo administration group. In these studies, the safety profile was also evaluated with satisfactory results.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN8237	Aurora A kinase inhibitor	Relapsed or refractory peripheral T-cell Lymphoma, Non Hodgkin lymphoma, Acute myelogenous leukemia (AML), High-risk myelodysplastic syndrome (MDS), Ovarian cancer, 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 spindlesat 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-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 EDARBI 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
TAK-536	Angiotensin II receptor blocker	Hypertension	azilsartan	AZILVA® (Jpn)	Oral

[Mode of action / Supplemental]
The P-III trial in comparison with Blopress showed TAK-536 was statistically superior to Blopress 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 Blopress 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 Blopress.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-438	Potassium-competitive acid blocker	Acid-related diseases (GERD, Peptic ulcer, etc.)	Not decided yet	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
TAK-375SL	MT_1/MT_2 receptor agonist	Bipolar disorder	ramelteon	-	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 episodes or to prevent recurrence.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AMG 706	VEGFR1-3, PDGFR, c-Kit inhibitor	Advanced non-squamous non-small cell lung cancer	motesanib diphosphate	Not decided yet	Oral

[Mode of action / Supplemental]
AMG 706 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	Not decided yet	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
AMG 479	Human monoclonal antibody against human type 1 insulin-like growth factor receptor (IGF-1R)	Metastatic pancreas cancer	ganitumab	Not decided yet	Injection

[Mode of action / Supplemental]
AMG 479 is a human monoclonal antibody antagonist of insulin like growth factor receptor type 1 (IGF-1R). The signaling, which is created by ligand's binding to IGF-1R, stimulates cell survival pathway, and leads to tumor growth and survival. AMG479 inhibits the binding of IGF-1 to its receptor (IGF-1R), and thus, it is considered to suppress the tumor cell growth and invasion.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	Mitochondria targeted anti-oxidant	Friedreich's ataxia, Duchenne muscular dystrophy	idebenone	Sovrima®	Oral

[Mode of action / Supplemental]
Idebenone is a small molecule optimized to facilitate the transport of electrons within mitochondria, which is necessary for the production of cellular energy. Santhera is conducting the clinical development of idebenone for the treatment of Friedreich's Ataxia, which results from impaired energy production in mitochondria, the cells' energy production centers, and elevated oxidative stress. It was found that the neurological and cardiac outcome was improved by idebenone.

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

[Mode of action / Supplemental]
TAK-816 is a vaccine to prevent infection caused by Haemophilus Influenzae 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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-428	Neurotrophic factor production accelerator	Diabetic neuropathy	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-428 is a new concept drug for diabetic neuropathy treatment. It repairs and regenerates the peripheral nerve tissues damaged by diabetes mellitus through increasing neurotrophic factors. It is expected to be a new treatment for diabetic neuropathy because of its different mechanism of actions from those of aldose reductase inhibitors and PKC inhibitors.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-385	LH-RH antagonist	Endometriosis, Uterine fibroids, Prostate cancer	Not decided yet	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
-	CD20 monoclonal antibody	Rheumatoid arthritis	veltuzumab	Not decided yet	Injection

[Mode of action / Supplemental]
Veltuzumab is a humanized monoclonal antibody targeting CD20 receptors on B lymphocytes. Veltuzumab is subcutaneously administered, and is intended as an add-on to methotrexate (MTX) for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severe active RA who have had an inadequate response to MTX alone or MTX in combination with TNF inhibitors. The current clinical study is aiming for second and third line setting.

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	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) which has never been approved, even as a single vaccine, anywhere in the world. Compared to the inactive poliovirus vaccine produced from wild-type poliovirus that is used in many countries except Japan, sIPV does not require an advanced safe management site for its production.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-329	Glucokinase activator	Diabetes mellitus	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]
TAK-329 is a glucokinase activator being developed for treatment of diabetes. It is expected to have a hypoglycemic action by enhancing both glucose uptake in the liver and insulin secretion from the pancreas. Glucokinase is one of the enzymes which are essential when converting ingested glucose into the energy that is necessary for organisms. It also adjusts insulin secretion in pancreatic beta-cells according to the glucose level.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-448	Metastin analog	Prostate cancer	Not decided yet	Not decided yet	Injection

[Mode of action / Supplemental]

TAK-448 is postulated to be a metastin analog and agonist of the GPR54 receptor on upstream hypothalamic neurons. Activation of the GPR54 receptor is hypothesized to lead to the transmission of a signal that stimulates downstream neurons to increase the secretion of gonadotropin release hormones. Continued stimulation of the GPR54 receptor is thought to result in the desensitization of receptor transduction, which is anticipated to result in a complete cessation of the signaling pathway, inhibiting testosterone production.

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-960	PLK1 inhibitor	Solid tumors	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]

TAK-960 is a potent, selective PLK1 (Polo-like kinase-1) inhibitor with anti-proliferative activities in a broad range of cancer cell lines. It has been reported that PLK1 is overexpressed in various human cancers and its overexpression is associated with poor prognosis. TAK-960 has potent anti-tumor activities in various xenograft models including one with MDR (multiple drug resistance)-expressing tumors by oral administration.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-441	Hedgehog signaling pathway inhibitor	Solid tumors	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]

TAK-441 selectively binds to Smoothened, a transmembrane activator of the hedgehog signaling pathway, and inhibits this pathway. Activation of the hedgehog pathway is linked to tumorigenesis. In addition, over-expression of hedgehog ligands has been detected in various tumors. TAK-441 has demonstrated antitumor activity in mouse tumor models in a dose-dependent manner. Therefore, TAK-441 has a potential to be a novel therapeutic agent for various solid tumors.

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-259	α1D-adrenoceptor antagonist	Overactive bladder	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]

TAK-259 is a novel, orally available, highly potent and selective antagonist of human α1D-adrenoceptor and is being developed for the treatment of overactive bladder (OAB). There is a need for a therapy that can provide desired efficacy with no or minimal antimuscarinic or cardiovascular side effects, and TAK-259 is expected to provide better efficacy as well as safety over the currently available OAB treatments as demonstrated in non-clinical studies.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-357	Cognitive enhancer	Alzheimer's disease	Not decided yet	Not decided yet	Oral

[Mode of action / Supplemental]

Cognitive enhancer TAK-357 is a new molecular entity that is being developed for the treatment of cognitive dysfunction associated with AD. The results of nonclinical studies indicate that TAK-357 has beneficial effects on indicators of neuronal viability in vitro, and that daily oral treatment of genetically modified mice with the compound reduces the deficits that occur in hippocampal and cortical glucose utilization and in the performance of a Novel Object Recognition task in this animal model of AD. The mechanism through which TAK-357 exerts these activities is under investigation.

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
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 Phase I studies and is expected to enter Phase 2 studies in 2012.

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 Phase 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 (is a fully human monoclonal antibody neutralising 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 moderate to severe rheumatoid arthritis (RA). Preclinical studies support the further investigation of MT203 in RA, and MT203 is currently in clinical Phase I development

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Lu AA24530	Multimodal anti-depressant	Major depressive and 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]
AMG403 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, and is very selective for the PDE1 enzyme relative to other PDE enzymes. As a result, it does not significantly affect the activity of other enzymes, receptors or ion channels.
PDE enzymes inactivate important brain signaling molecules such as cyclic AMP and cyclic GMP. PDE1 inhibitors block this inactivation resulting in an increase in signaling activity in certain neurotransmitter pathways. Intra-Cellular Therapies has shown that orally available, small molecule inhibitors of PDE1 restore dopamine signaling in neurons and enhance cognition in preclinical models.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	PDE-4 inhibitor	COPD	roflumilast	DAXAS®, (global) 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. This mechanism of action and the selectivity also apply to roflumilast-N-oxide, which is the major active metabolite of roflumilast.
In clinical trials, roflumilast reduced exacerbations in patients with severe to very severe COPD independent of underlying treatment with long-acting bronchodilators or inhaled corticosteroids (ICS) and improved lung function (forced expiratory volume in one second [FEV1]) in a broad patient population.
Roflumilast was first approved in the EU in July 2010. In the US, roflumilast was approved in February 2011 and is marketed by Forest Laboratories under the brand name Daliresp™.

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 (Fr), etc.	Oral

[Mode of action / Supplemental]
TCV-116 lowers blood pressure by suppressing the effect of angiotensin II (A 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	Helicobacter pylori eradication by concomitant therapy with amoxicillin hydrate and either clarithromycin or metronidazole	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 or formulations	Generic name	Brand name	Administration
NE-58095	Bone resorption inhibitor	Once-monthly formulation	risedronate	Benet® (Jpn)	Oral
[Mode of action / Supplemental] Benet inhibits bone resorption by suppressing the function of osteoclastic cells. The once-monthly formulation is expected to enhance the convenience of administration for patients compared to a once-daily or a once-weekly formulation.					

Development code	Drug Class	Indications or formulations	Generic name	Brand name	Administration
-	Chloride channel activator	Opioid-Induced Constipation (OIC)	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.					

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 (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. With 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 Aug 02 and for premenopausal breast cancer in Aug 05. A 6-month formulation was approved in EU and has entered P-III in Japan.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
-	Proteasome inhibitor	Front line MCL, 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
AD4833/TOMM40	Insulin sensitizer/ Biomarker assay	Alzheimer's disease prevention	pioglitazone	-	Oral
[Mode of action / Supplemental] The TOMM40 biomarker, discovered by Zinfandel, is being developed to identify older adults at high risk of developing Alzheimer's disease within the subsequent five years. Takeda and Zinfandel will attempt to prospectively validate the TOMM40 biomarker as a test of individual risk, and will study pioglitazone in connection with the TOMM40 biomarker and Alzheimer's disease.					

■ 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-002	**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

Takeda has been disclosing information on its clinical trials on its web site since July 1, 2005.

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

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. 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 candesartan cilexetil (tradename in Japan: Blopress®), an angiotensin receptor blocker ("ARB"), 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 CNS-acting drugs for obesity and schizophrenia	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-
LG Life Sciences	S. Korea	Joint collaboration on anti-obesity drugs	2007/3-2012/8
Alnylam Pharmaceuticals, Inc.	US	Collaboration for Discovery and Development of RNAi Therapeutics	2008/5-
Seattle Genetics	US	Research collaboration on Antibody-Drug Conjugate	2009/3-
University of Washington	US	Joint collaboration on anti-obesity drugs	2009/3-2013/3
CellCentric	UK	Exclusive licensing of one of the CellCentric's epigenetics projects for the development and commercialization in oncology field	2010/2-
Dimerix	Australia	Research collaboration on searching of GPCR for development of products	2010/3-
The BC Cancer Agency	Canada	Research collaboration for discovery of novel candidate targets for cancer treatment	2010/3-2013/3
University College London	UK	Research collaboration on development of novel cancer treatment	2010/3-2014/3
University College London	UK	Research collaboration in ophthalmologic disease	2010/3-2013/3
Metabolex, Inc.	US	Research collaboration on evaluation and validation of protein targets for development of biological products	2010/4-
Envoy Therapeutics Inc.	US	Research collaboration on discovering new drug targets for schizophrenia with Envoy's "bacTRAP®" technology	2010/10-
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	2010/12-2012/12
Zinfandel Pharmaceuticals	US	Licensing Agreement for Alzheimer's Disease Biomarker TOMM40 for the risk of Alzheimer's disease	2010/12-
Heptares Therapeutics	UK	Drug discovery collaboration focused on GPCR linked to CNS disorders	2011/4-2013/3
Samyang Corporation	S. Korea	Joint research on novel DDS platform technology for RNAi therapeutics	2011/4-2013/3
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
The 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