

. Pipeline

Development Activities

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Research Activities

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Current progress in stage (First half in FY2006)

Development code	Indications or formulations	Brand name (country/region)	Progress in stage
AG-1749	Non-erosive reflux disease	Takepron [®] (Jpn)	Filed Approved (Jun 06)
AD-4833SU	Combination drug of Actos [®] / SU	Duetact [™] (U.S.)	Filed Approved (Jul 06)
AD-4833-536	Combination drug of Actos [®] / TAK-536	< Not decided yet > (U.S.)	P-III
TCV-116	Fixed combination with diuretic	Blopress, Amias, Kenzen (EU)	P-III
AF37702	Chronic kidney disease (CKD) / cancer-related anemia	Hematide [™] (U.S. , EU/ Jpn)	P-II / P-I
TAK-491	Hypertension	< Not decided yet > (U.S.,EU)	P-II
EMD72000	Gastric cancer, non-small cell lung cancer (NSLC), colorectal cancer	< Not decided yet > (Jpn)	P-II
AG-1749	Secondary eradication of Helicobacter pylori	Takepron [®] (Jpn)	Filed (Aug 06)
AD-4833MET	Combination drug of Actos [®] and metformin	Competact [™] (EU)	Filed Approved (Jul 06)
AG-1749-IV	Injectable formulation	Takepron [®] I.V.	Filed Approved (Oct 06)
TAK-583	Diabetic neuropathy	< Not decided yet > (U.S.,EU)	P-II

The lower part is a progress in stage after FY2006 1Q(July 2006) updates

Discontinuance (First half in FY2006)

Development code	Indications / Stage of development	Reason
TAK-715	Rheumatoid arthritis / P-II	This drug did not satisfy our criteria that are required to continue development
TAK-654	Diabetes mellitus / P-II	This drug did not satisfy our criteria that are required to continue development
TAK-128	Diabetic neuropathy / P-II	This drug did not show sufficient efficacy to support continuation of development activities.
TCV-116	Diabetic nephropathy / P-II	The results of Phase II study did not satisfy criteria of stage-up to Phase III even though TCV-116 showed efficacy and safety in improving proteinuria which is primary endpoint. Takeda terminated license agreement because the results of Phase III study did not show statistically significant effect of this drug in reducing the incidence of severe neuropathy which is primary endpoint.
BNP-7787	Prevention or reduction of neurotoxicity induced by anti cancer / P-III	The lower part is a change after FY2006 1Q (July 2006) updates.

The lower part is a change after FY2006 1Q (July 2006) updates.

Development activities

New compounds

Development code <generic name>	Drug Class	Indications	Country region	Stage	In-house / In-license	Note
SPI-0211 < lubiprostone >	Chloride channel opener	Constipation-predominant Irritable Bowel Syndrome	U.S.	P-III	In-license (Sucampo Pharmaceuticals Inc.)	Brand name : AMITIZATM™(U.S.) Development is conducted by Sucampo Launched in U.S. (Apr 06)
TAK-242 < Not decided yet >	TLR4 signal transduction inhibitor	Severe sepsis	Jpn	P-III		
			U.S.	P-III	In-house	Fast Track
			EU	P-III		
TAK-375 < ramelteon >	MT ₁ /MT ₂ receptor agonist	Insomnia	Jpn	P-III		
			EU	P-III	In-house	Brand name : ROZEREM™(U.S) Launched in U.S. (Sep 05)
		Alzheimer's sleep / wake disturbance	U.S.	P-II		
		Circadian rhythm sleep disorder (CRSD)	U.S.	P-II		
TAK-475 < Not decided yet >	Squalene synthase inhibitor	Hyperlipidemia	U.S.	P-III		
			EU	P-III	In-house	
			Jpn	P-I		
TAK-390MR < Not decided yet >	Proton pump inhibitor	Erosive esophagitis and non-erosive gastro-esophageal reflux disease	U.S.	P-III	In-house	
			Jpn	P-I		
SYR-322 < Not decided yet >	DPP-4 inhibitor	Diabetes mellitus	U.S.	P-III		
			EU	P-III	In-house	
			Jpn	P-I		
TAK-428 < Not decided yet >	Neurotrophic factor production accelerator	Diabetic neuropathy	U.S.	P-II	In-house	
			EU	P-II		
TAK-536 < azilsartan >	Angiotensin II receptor antagonist	Hypertension	U.S.	P-II		
			EU	P-II	In-house	
			Jpn	P-I		
AF37702 < Not decided yet >	Synthetic, peptide-based erythropoiesis-stimulating agent	Chronic kidney disease (CKD) / cancer-related anemia	U.S.	P-II		
			EU	P-II	In-license (Affymax)	Brand name: Hematide™(U.S.)
			Jpn	P-I		
TAK-583 < Not decided yet >	Neuropathic pain-improving drug	Post-herpetic neuralgia	U.S.	P-II		
			EU	P-II	In-house	
			Jpn	P-I		
		Diabetic neuropathy	U.S.	P-II		
			EU	P-II		
LY333531 < ruboxistaurin >	PKCβ inhibitor	Diabetic maculopathy	Jpn	P-II	In-license (Eli Lilly)	Co-development
R-851 < Not decided yet >	Immune response modifier	Human papillomavirus (HPV) infection	U.S.	P-II	In-license (3M)	Development is conducted by 3M
EMD72000 < matuzumab >	Humanized, monoclonal antibody (MAb) against the human EGFR	Gastric cancer, non-small cell lung cancer (NSLC), colorectal cancer	U.S.	P-II		
			EU	P-II	In-license (Merck KGaA)	Co-development
			Jpn	P-II		
ATL-962 < cetilistat >	Lipase inhibitor	Obesity	Jpn	P-II	In-license (Alizyme)	
TAK-491 < Not decided yet >	Angiotensin II receptor antagonist	Hypertension	U.S.	P-II	In-house	
			EU	P-II		

Additional indications / new formulations

Development code <generic name> Brand name (country/region)	Drug Class	Indications or formulations	Country/ region	Stage of development	In-house / In-license
TAP-144-SR < leuprorelin acetate > Leuplin (Jpn) Lupron Depot (U.S.) Enantone, etc. (EU , Asia)	LH-RH agonist	6-month depot/prostate cancer	EU (Germany) EU (Italy) EU (France)	Filed (Jun 05) Filed (Oct 05) Filed (Nov 05)	In-house
AG-1749 < lansoprazole > Takepron (Jpn , Asia) Prevacid (U.S. , Asia) Ogast , Agopton , Lansox , etc. (EU)	Proton pump inhibitor	Secondary eradication of Helicobacter pylori Injectable formulation	Jpn Jpn	Filed (Aug 06) Approved (Oct 06)	In-house
TCV-116 < candesartan cilexetil > Blipress (Jpn, EU, Asia) Amias, Kenzen, etc. (EU)	Angiotensin II receptor blocker	Fixed combination with diuretic High dose Outcome study, DIRECT (Diabetic RETinopathy Candesartan Trial)	Jpn EU Jpn EU	Filed (Dec 02) P-III P-III P-III	In-house
AD-4833 < pioglitazone hydrochloride > Actos (Jpn , U.S., EU , Asia)	Insulin resistance-improving drug	Combination drug of Actos / Metformin XT Combination drug of Actos / Metformin (Competact™) Combination drug of Actos / SU (Tandemact™) Reduction of the risk of macrovascular events in patients with type 2 diabetes mellitus and pre-existing macrovascular disease Delay in progression of Atherosclerosis Combination drug of Actos / TAK-536 Concomitant therapy with metformin	U.S. EU EU EU U.S. U.S. Jpn	Filed (Mar 06) Approved (Jul 06) Filed (Jul 05)* Filed (Dec 05) P-III P-III P-III	In-house
AO-128 < voglibose > Basen (Jpn , Asia)	-glucosidase inhibitor	Impaired glucose tolerance (IGT)	Jpn	P-III	In-house
NE-58095 < risedronate >	Bone resorption inhibitor	Once-a-week formulation Paget's disease	Jpn Jpn	Filed (Dec 04) P-III	In-license (Ajinomoto)

*Takeda received positive opinion from the Committee for Medicinal Products for Human Use ("CHMP") of the European Medicines Agency ("EMA"), recommending to grant a marketing authorization for Tandemact™ on October 18, 2006,

Characteristics of projects

{ New compounds }

Development code	Drug Class	Indications	Generic name	Brand name	Administration
SPI-0211	Chloride channel opener	Chronic idiopathic constipation, c-IBS	lubiprostone	AMITIZA™ (US)	oral administration
<p>This drug has new mechanism of action through chloride channel opener which causes an increase in intestinal fluid secretion for the treatment of chronic constipation and constipation-predominant Irritable Bowel Syndrome (c-IBS). Takeda has obtained the marketing right in the U.S. and Canada. An NDA for chronic idiopathic constipation which Sucampo filed was approved in January 2006. Promotional activities started in the US in April 2006.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-242	TLR4 signal transduction inhibitor	Severe sepsis	Not decided yet	Not decided yet	injection
<p>TAK-242 suppresses production of inflammatory mediators such as cytokine by inhibiting the signal transduction through Toll-like receptor 4 (TLR4) which is one of the receptors recognizing the bacterial components.</p> <p>Takeda was permitted to start global Phase III studies for severe sepsis patients by FDA and PMDA based on Phase I study results because TAK-242 shows strong suppressive effect of cytokine and safety. FDA granted TAK-242 fast track status (Jul 2005) for severe sepsis because, (1) severe sepsis is life-threatening disease, (2) TAK-242 may satisfy unmet medical needs as there are no drugs for severe sepsis patients.</p> <p>*TLR4: This receptor, that exists on surface of monocyte and macrophage, transmits activated signal into cell by sensing LPS (lipopolysaccharide)</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-375	MT ₁ /MT ₂ receptor agonist	Insomnia, Circadian rhythm sleep disorder (CRSD)	ramelteon	ROZEREM™(US)	oral administration
<p>This drug is highly specific to the MT₁/MT₂ receptor and induces sleep very akin to natural sleep. It has also been recognized that the drug has less adverse reactions which has not been designated as a controlled substance by US Drug Enforcement Administration (DEA). TAK-375 was approved in July 2005 and promotional activities started in September 2005.</p> <p>Takeda started Phase II study for studying efficacy for sleep/wake disturbance of Alzheimer's patients in the US based on the suggestion that there was relationship between abnormal activities including nocturnal awakening/roam in Alzheimer's patients and a reduction of nocturnal melatonin secretion.</p> <p>[Publications]</p> <p>Zammit G, Roth T, Erman M et al. Double-blind, placebo-controlled polysomnography and out patient trial to evaluate the efficacy and safety of Ramelteon in adult patients with chronic insomnia. Sleep, Vol 28, A 228, Abstract Supplement 2005</p> <p>Seiden D, Zee P, Weigand S et al. Double-blind, placebo-controlled outpatient clinical trial of Ramelteon for the treatment of chronic insomnia in an elderly population. Sleep, Vol 28, A 228, Abstract Supplement 2005</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-475	Squalene synthase inhibitor	Hyperlipidemia	Not decided yet	Not decided yet	oral administration
<p>This is an anti-hyperlipidemia drug having a new mechanism of action based on its squalene synthase inhibitory action. Based on the results of animal tests, it is expected that the drug has less possibility of developing rhabdomyolysis compared to HMG-CoA reductase inhibitors that currently offer the first-line therapy for this disease.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-390MR	Proton pump inhibitor	Erosive esophagitis and non-erosive gastro-esophageal reflux disease	Not decided yet	Not decided yet	oral administration
<p>The compound employs a new modified release technology on an enantiomer of lansoprazole that is a proton pump inhibitor originally developed by Takeda and is marketed by Takeda and its licensees in approximately 100 countries worldwide.</p> <p>TAP was permitted to start Phase III without conducting Phase II after consultation with FDA about TAK-390's development policy based on the results of Phase I study and abundant clinical evidence of lansoprazole. TAP is conducting Phase III studies in the U.S.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
SYR-322	DPP-4 inhibitor	Diabetes mellitus	Not decided yet	Not decided yet	oral administration
<p>DPPIV inhibitors, taken orally, work by blocking Glucagon Like Peptide-1(GLP-1) degradation to keep its concentration for a longer period of time. Therefore, DPPIV inhibitors are expected to be one of the new generation agents for diabetes treatment. Takeda is conducting Phase III studies in the US and EU, Phase I in Japan respectively.</p>					

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 administration
<p>This 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 that of aldose reductase inhibitors and PKC inhibitors.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-536	Angiotensin II receptor blocker	Hypertension	Not decided yet	Not decided yet	oral administration
<p>According to preclinical trial, it is expected that this drug has insulin resistance improving effect and renal protective effect as well as anti-hypertensive effect.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AF37702	Synthetic, peptide-based erythropoiesis-stimulating agent	Chronic kidney disease (CKD) / cancer-related anemia	Not decided yet	Hematide	Injection
<p>Hematide, a synthetic, peptide-based erythropoiesis-stimulating agent (ESA), is designed to stimulate the production of red blood cells and is in Phase 2b clinical trials for anemia in dialysis, pre-dialysis and cancer chemotherapy patients.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-583	Neuropathic pain-improving drug	Post-herpetic neuralgia/ Diabetic neuropathy	Not decided yet	Not decided yet	oral administration
<p>This is a drug to improve neuropathic pain by suppressing neural disturbance. This drug's efficacy was verified in some neuropathic pain models. Takeda started Phase II study for diabetic neuropathy in the US and EU.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
LY333531	PKC β inhibitor	Diabetic maculopathy	ruboxistaurin	Not decided yet	oral administration
<p>This drug is PKC β Inhibitor. PKC (Protein kinase C) β, one of the enzymes known as adjusters of various cellular functions, becomes overactive under the hyperglycemic condition and is implicated in the underlying process of microvascular damages of angiogenesis and vascular flow disorder, leading to diabetic microvascular complications. It is expected that this drug prevents progression of diabetic retinopathy and neuropathy and improves symptom of patients by inhibiting PKC β. Takeda started Phase-II studies for diabetic maculopathy in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
R-851	Immune Response Modifier	Human papillomavirus (HPV) infection	Not decided yet	Not decided yet	topical administration
<p>The compound is part of the family of immune response modifier (IRM) molecules. IRMs act in a novel way to stimulate the human body's immune system to attack virus-infected cells and tumor cells. It is expected to be topical treatment for cervical high-risk human papillomavirus (HPV) infection and cervical dysplasia.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
EMD72000	Humanized, monoclonal antibody (MAb) against the human EGFR	Gastric cancer, non-small cell lung cancer(NSLC), colorectal cancer	matuzumab	Not decided yet	injection
<p>Matuzumab is a recombinant, humanized, monoclonal antibody (MAb) against the human EGFR (epidermal growth factor receptor), and it inhibits EGFR which is implicated in the development and progression of a number of human solid tumors. It currently is in Phase II clinical trials in patients with non-small cell lung, gastric and colorectal cancers in the US and EU. Takeda is conducting Phase II studies in patients with non-small cell lung cancer in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
ATL-962	Lipase inhibitor	Obesity	cetilistat	Not decided yet	oral administration
<p>This drug is gastro-intestinal lipases inhibitor. It is designed to cause weight loss by reducing the digestion and thus the absorption of fat from the diet. It is expected to be an effective treatment of obesity coupled with associated conditions, such as Type II diabetes. Takeda acquired an exclusive right of development and marketing of ALT-962 in Japan.</p> <p>According to the results of Phase IIb conducted by Alizyme in EU, Cetilistat (80mg and 120mg) caused statistically significant weight loss and reductions in HbA1c compared with placebo. No difference between the cetilistat groups and placebo group in treatment discontinuations due to gastro-intestinal adverse events, nor in the level of severe gastro-intestinal adverse events. Takeda is conducting Phase II studies for obesity in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-491	Angiotensin II receptor blocker	Hypertension	Not decided yet	Not decided yet	oral administration
<p>This drug is expected to show stronger anti-hypertensive action, and also to have superior profile in improving the insulin resistance and decreasing proteinuria, as compared to existing ARBs on the market. The anti-hypertensive drug with an function of improving insulin resistance will be clinically beneficial because many hypertension patients have diabetes mellitus.</p>					

Additional indications / new formulations

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAP-144-SR	LH-RH agonist	Prostate cancer, endometriosis premenopausal breast cancer	leuprorelin acetate	Leuplin (Japan), Lupron (U.S.), Enantone etc. (EU)	injection
<p>The 3-month depot formulation is a three month version of already available "Leuplin" of once-a-month dosing. The 4-month depot has already been marketed in the U.S. The 3-month depot formulation for prostate cancer was launched in Japan (Aug 02) and its application for breast cancer was approved in Japan (Aug 05). The 3-month depot formulation for breast cancer was approved in Germany (Jan 04). The 6-month depot formulation for an indication of prostate cancer was filed in Germany (Jun 05), Italy(Oct 05) and France (Nov 05).</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AG-1749	Proton pump inhibitor	peptic ulcer	lansoprazole	Takepron (Jpn), Prevacid (U.S.), etc	oral/injection
<p>This is a proton pump inhibitor having a potent inhibitory action on the gastric secretion. It suppresses the gastric acid secretion by inhibiting the proton pump within the gastric wall cells and exhibits the antiulcer action. The drug has already been launched as a therapeutic agent for peptic ulcers in approximately 100 countries worldwide.</p> <p>Injection is approved in the U.S. (May 04) and Japan (Oct 06) . An additional indication for NERD (Non-Erosive Reflux Disease) was approved in Japan (Jun 06). An additional indication for secondary eradication of Helicobacter pylori was filed in Japan (Aug 06).</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TCV-116	Angiotensin II receptor antagonist	Hypertension	candesartan cilexetil	Blopress (Jpn, EU), Atacand (U.S.), Amias (U.K.), Kenzen (Fr)	oral administration
<p>The drug lowers blood pressures by suppressing the effect of angiotensin II (A II), a hypertensive hormone, at the receptor level. It shows efficacy equivalent or superior to that of angiotensin converting enzyme (ACE) inhibitors which are widely in use. It has almost no adverse reaction of cough that is often reported with ACE inhibitors.</p> <p>The CHARM study showed that the drug was effective for heart failure. The indications of treatment for chronic heart failure to reduce the risk of death from cardiovascular causes were approved in EU (Nov 04), U.S. (Feb 05) and Japan (Oct 05). "DIRECT", outcome study, is being conducted in EU to investigate prevention/treatment efficacy on diabetic retinopathy. Fixed combination with diuretic was filed in Japan (Dec 02). Phase III studies of high dose is being conducted in Japan.</p> <p>[Publications]</p> <p>Christopher B Granger et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function intolerant to angiotensin-converting-enzyme inhibitors:the CHARM-Alternative trial. The LANCE vol.362 (9386) 6 Sep 2003 p772-776</p> <p>John JV McMurry et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting -enzyme inhibitors: the CHARM-Added trial. The LANCET Vol.362(9386) 6 Sep 2003 p767-771.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AD-4833	Insulin resistance-decreasing drug	Diabetes mellitus	pioglitazone hydrochloride	Actos (Japan, U.S., EU)	oral administration
<p>This is a drug that controls blood glucose levels by improving the sensitivity to insulin in the liver and peripheral tissues. The drug is taken only once daily. It does not exert action on normoglycemia and does not induce hypoglycemia.</p> <p>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 significantly reduces the combined risk of heart attacks, strokes and death by 16% in high risk patients with type 2 diabetes.</p> <p>CHICAGO and PERISCOPE are being conducted in the US in order to investigate the effect of Actos on reducing the risk of cardiovascular disease in the patients with type 2 diabetes.</p> <p>An NDA of the combination drug with conventional metformin was approved in the US (Aug 05 : ACTOplus met™) and it has been available since November 2005. It was also approved in EU (Jul 06 : Competact™). An extended release version of combination drug of ACTOplus met™ (ACTOplus met™ XR) was filed in March 2006.</p> <p>Indication of "Reduction of the risk of macrovascular events in patients with type 2 diabetes mellitus and pre-existing macrovascular disease" was filed in EU (Dec 06). An NDA of the combination drug with SU was approved in US (Jul 06: Duetact™). An application of that combination drug of Actos® and SU was submitted in EU (Jul 05 : Tamdemact™) and Takeda received positive opinion from The Committee for Medicinal Products for Human Use ("CHMP") of the EMEA(Oct 06)</p> <p>Phase III of concomitant therapy with metformin is being conducted in Japan.</p> <p>Goldberg RB, Kendall DM, Deeg MA. A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005 Jul;28(7):1547-54.</p> <p>Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitazone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AO-128	-glucosidase inhibitor	Diabetes mellitus	voglibose	Basen (Japan)	oral administration
<p>The drug inhibits the hydrolase (-glucosidase) for disaccharides that catalyzes decomposition of disaccharides into monosaccharides, thereby delaying the digestion and absorption of carbohydrates, resulting in improvement of postprandial hyperglycemia. The mechanism of action is different from those of other oral hypoglycemic drugs, therefore, this drug has less possibility of developing hypoglycemic symptoms.</p> <p>The drug is already available in the Japanese market as an improving agent for postprandial hyperglycemia in diabetes mellitus. Phase III clinical studies are being conducted with the intension of supplementing the indication of impaired glucose tolerance (suppression of development of insulin non-dependent diabetes mellitus).</p>					

Note: We disclose information about projects in Phase II or later stage basically. However, we also disclose information about projects in earlier stage if the information of the projects was released in scientific congresses.

TAK-220	In-house	Presented at: The 10th Conference on Retroviruses and Opportunistic Infections (Feb. 2003)			
		Stage: Phase -I (U.S.)			
<p>This is a CCR5 antagonist which can be administered orally. It selectively inhibits an invasion of HIV on immune cells (macrophage, activated T-cell). It is expected to be a promising novel candidate as anti-HIV drug because of different mechanism of action as compared to existing anti HIV drugs such as reverse transcriptase inhibitors and protease inhibitors.</p>					

Other alliance projects

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 Phase II study for multiple myeloma in the U.S.			

TAK-363	Agreement with : Toray	Agreed Mar. 2005	
		Stage P-I (U.S.)	Territory: World except for Japan
This is a drug for frequent urination/urinary incontinence. Currently, these symptoms are treated with anticholinergic agents which are known to have side effects such as dry mouth, constant urge to urinate and constipation. Based on the findings to date, TAK-363 does not have anticholinergic actions and is expected to have better efficacy and lesser side effects. Therefore, it can be a treatment option with new mechanism of action for frequent urination and urinary incontinence, contributing to improvement of the QOL of the patients.			

TAK-085	Licensed from: Pronova	Agreed Nov. 2005	
		Stage Under preparation for clinical trials (Japan)	Territory Japan
TAK-085 (Omacor™) that is marketed by Pronova is TG lowering agent made from fish oil. It consists of purified EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid). It is marketed for the indication of high triglyceridaemia in the U.S. and the indication of high triglyceridaemia and adjuvant treatment in secondary prevention after myocardial infarction in EU.			

HuL2G7	Licensed from: Galaxy Biotech, LLC	Agreed Jul. 2006	
		Stage Under preparation for clinical trials	Territory World
HuL2G7 is a recombinant, humanized antibody that blocks the activity of human HGF, a growth factor believed to mediate proliferation, metastasis, anti-apoptosis and neoangiogenesis of many types of tumors. Takeda has received exclusive worldwide rights to develop, manufacture and market the HuL2G7 antibody.			

XEN401	Licensed from: Xenon Pharmaceuticals Inc.	Agreed Sep. 2006	
		Stage Under preparation for clinical trials	Territory Japan and certain Asian countries
XEN401 is a novel chemical entity with tractable synthesis, oral bioavailability, favorable pharmacological properties, and potential broad analgesic utilities including the treatment of both neuropathic and inflammatory pain.			

Clinical study protocol summaries

Takeda has started disclosure of its clinical trials information in the web-site since July 1, 2005.

All clinical study protocol summaries are disclosed in English web-site (<http://www.takeda.co.jp/english/ct/index.html>) and clinical study protocol information in Japan is disclosed in Japanese web-site (<http://www.takeda.co.jp/ct/index.html>.)

We expect that this disclosure assure the transparency of the information on the clinical trials for the healthcare profession, the patients and other related persons, which we believe will contribute to appropriate use of Takeda's products worldwide.

Outcome studies

AD-4833

Study title		PROactive(PROspective pioglitAzon 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, below-knee amputation).		
Place	15 countries in Europe	Total population	5,238 patients
Status	<p>Landmark data from the PROactive Study, presented at the 41st meeting of the European Association for the Study of Diabetes (EASD) in Athens (Sep. 2005) 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.</p> <p>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).</p> <p>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.</p>		

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	<p>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.</p> <p>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).</p> <p>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) .</p> <p>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).</p> <p>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.</p> <p>*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</p>		

TCV-116 (2)

Study title		DIRECT (DIabetic REtinopathy Candesartan Trial)	
Outline	The world's first large scale study to investigate prevention/treatment efficacy on diabetic retinopathy (candesartan vs. placebo)		
Place	30 countries	Registered population	5,238 patients
Status	<p>The randomization of patients to DIRECT was completed in Feb.2004. The results are planned to be announced in 2007. DIRECT consists of following three separate clinical studies in one programme.</p> <ol style="list-style-type: none"> 1.Type 1 diabetic patients without retinopathy for primary prevention. 2.Type 1 diabetic patients with retinopathy for secondary prevention. 3.Type 2 diabetic patients with retinopathy for secondary prevention. <p>Each study of programme will investigate the effect of candesartan in diabetic, normotensive, normoalbuminuric patients.</p>		

Research Activities

Main joint research activities

(1) Joint researches with domestic research organizations and companies

Partners	Research subject	Schedule
Kirin Brewery	Licensing-in of the human antibody technology	Jul-03 -
Kyoto University	Kyoto Cell / Biodynamic Simulation	Oct-03 - Mar-08
Osaka University	Development of novel diagnostics of lifestyle-related diseases by novel secretory factors	Apr-04 - Mar-07

(2) Joint researches with overseas research organizations and companies

Partner	Country	Research subject	Schedule
Array BioPharma	U.S.	Joint research on lead compound synthesis	Jul-01 -
Gene Logic	U.S.	Data base of gene expression (extended target disease since Mar-03)	Mar-02 - Dec-06
Oxford Centre for Diabetes Endocrinology and Metabolism	U.K.	Partnership with Oxford Diabetes Centre	Apr-02 - Mar-07
Beth Israel Deaconess Medical Center (Harvard Medical School)	U.S.	Joint research on drug discovery related to diabetes and obesity	Jul-02 - Jul-07
Evotec NeuroSciences	Germany	Drug discovery alliance in Alzheimer's disease	Aug-03 - Jul-07
Lexicon Genetics Incorporated	U.S.	Joint research on drug target of hypertension	Jul-04 - Jul-07
Paradigm Therapeutics	U.K.	Drug discovery alliance in CNS disease	Jul-05 - Jun-08
XOMA Ltd	U.S.	Joint research on discovery, development and production technologies of monoclonal antibody	Nov-06 -

Recent fruits of Takeda research

Novel Orphan Ligands Identified by Takeda

Ligands	Receptors	Expected target disease/area
Prolactin-releasing peptide (PrRP)	hGR3	Gynecology
Apelin	APJ	Cancer
Galanin-like peptide (GALP)	GalR2	Obesity
RF amide-Related Peptide(REFP)	OT7/T022	Gynecology
Metastin	OT7/T175	Gynecology
Neuropeptide W (NPW)/Neuropeptide B (NPB)	GPR7/GPR8	Obesity
QRFP	AQ27	Obesity

Novel Orphan Receptors (Ligands are known) Identified by Takeda

Ligands	Receptors	Expected target disease/area
Melanin Concentrating Hormone (MCH)	SLC-1	Obesity
Urotensin	SENr(GPR14)	Cardiovascular disorders
Neurodynin U	FM3/TGR1	Hypertension
EG-VEGF	ZAQ/ISE	Gynecology
Bile acid	TGR5	Immunology
Fatty acid	GPR40	Diabetes
β -alanine	TGR7	Neuropathic pain

Disease-specific Expression Profiles for Differentially Regulated Genes

Identified by Takeda

Gene discovered	Expected target disease
CLCA1	Respiratory diseases
LLPL	Atherosclerosis