

## IX. Pipeline

### Development Activities

- New compounds
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### Research Activities

- Main joint research activities
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### **[Progress in stage (Apr - Sep 2005)]**

Development code	Indications or formulations	Brand name (country/region)	Progress in stage
TAK-375	Insomnia	Rozerem (U.S.)	Filed Approved (Jul 05)
AD-4833SU	Combination drug of Actos / SU	<Not decided yet> (U.S.) <Not decided yet> (EU)	Filed (Jun 05) Filed (Jul 05)
TAP-144-SR	6-month depot	<Not decided yet> (Germany)	Filed (Jun 05)
SPI-0211	Constipation IBS	<Not decided yet> (U.S.)	P-II P-III
TAK-242	Severe sepsis	<Not decided yet> (Jpn, U.S., EU)	P-I P-III
AD-4833	Concomitant therapy with metformin	<Actos> ( Jpn)	P-III
SYR-322	Diabetes mellitus	<Not decided yet> (U.S.)	P-II
TAK-475	Hyperlipidemia	<Not decided yet> (Jpn)	P-I
TAP-144-SR	Premenopausal breast cancer	Leuplin SR injection kit 11 . 25 (Jpn)	Filed Approved (Aug 05)
AD-4833MET	Combination drug of Actos / Metformin	Actoplus Met (U.S.)	Filed Approved (Aug 05)
TAK-453-SR	Cancerous pain	Pacif capsules (Jpn)	Filed Approved (Sep 05)
TCV-116	Chronic heart failure	Blopress (Jpn)	Filed Approved (Oct 05)
TMR	Prevention of measles and rubella	Freeze-dried live attenuated measles and rubella combined vaccine Takeda	Filed Approved (Oct 05)
TAK-390MR	Erosive esophagitis and non-erosive gastro-esophageal reflux disease	<Not decided yet> (U.S.)	P-I P-III
R-851	Human papillomavirus (HPV) infection	<Not decided yet> (U.S.)	P-I P-II
TAK-128	Diabetic neuropathy	<Not decided yet> (Jpn)	P-I P-II
EMD72000	Gastric cancer, non-small cell lung cancer (NSLC), colorectal cancer	<Not decided yet> (Jpn, U.S., EU)	P-II in-licensed (Sep 05)

The lower part is a progress in stage after FY2005 1Q updates.

# Development activities

## New compounds

Development code <generic name>	Drug Class	Indications	Country region	Stage	In-house / In-license	Note
<b>SPL-0211</b> < lubiprostone >	Chloride channel opener	Chronic constipation Constipation-predominant Irritable Bowel Syndrome	U.S.	Filed (Mar 05)	In-license (Sucampo Pharmaceuticals Inc.)	Development is conducted by Sucampo
			U.S.	P-III		
<b>TAK-242</b> < Not decided yet >	TLR4 signal transduction inhibitor	Severe sepsis	Jpn	P-III	In-house	Fast Track
			U.S.	P-III		
<b>TAK-375</b> < ramelteon >	MT1/MT2 receptor agonist	Insomnia	Jpn	P-III	In-house	Brand name: Rozerem (U.S.) Launched in Sep 05
			EU	P-III		
<b>TAK-475</b> < Not decided yet >	Squalene synthase inhibitor	Hyperlipidemia	U.S.	P-II	In-house	
			EU	P-III		
<b>TAK-390MR</b> < Not decided yet >	Proton pump inhibitor	Erosive esophagitis and non-erosive gastro- esophageal reflux disease	Jpn	P-I	In-house	
			U.S.	P-III		
<b>BNP7787</b> < dimesna >	Chemotherapy supportive care drug	Prevention or reduction of neurotoxicity induced by anti cancer	U.S.	P-III	In-license (BioNumerik Pharmaceuticals, Inc)	Brand name: Tavocept (U.S.) Development is conducted by BioNumerik Fast Track
<b>TAK-428</b> < Not decided yet >	Neurotrophic factor production accelerato	Diabetic neuropathy	U.S.	P-II	In-house	
			EU	P-II		
<b>TAK-654</b> < Not decided yet >	Insulin resistance-improving drug	Diabetes mellitus	Jpn	P-II	In-house	
			U.S.	P-II		
<b>TAK-536</b> < Not decided yet >	Angiotensin II receptor antagonist	Hypertension	EU	P-II	In-house	
			U.S.	P-II		
<b>TAK-715</b> < Not decided yet >	p38 MAPkinase inhibitor	Rheumatoid arthritis	U.S.	P-II	In-house	
			EU	P-II		
<b>LY333531</b> < ruboxistaurin >	PKCβ inhibitor	Diabetic maculopathy	Jpn	P-II	In-license (Eli Lilly)	Co-development
<b>TAK-128</b> < Not decided yet >	Myelin formation accelerator	Diabetic neuropathy	U.S.	P-II	In-license (Mitsubishi Pharma Corporation)	Fast Track
			Jpn	P-II		
<b>SYR-322</b> < Not decided yet >	DPPIV inhibitor	Diabetes mellitus	U.S.	P-II	In-house	
<b>R-851</b> < Not decided yet >	Immune response modifier	Human papillomavirus (HPV) infection	U.S.	P-II	In-license (3M)	Development is conducted by 3M
<b>EMD72000</b> < matuzumab >	Humanized, monoclonal antibody (MAb) against the human EGFR	Gastric cancer, non-small cell lung cancer (NSLC), colorectal cancer	U.S.	P-II	In-license (Merck KGaA)	Co-development
			EU	P-II		
			Jpn	P-I		

## 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
<b>AG-1749</b> <lansoprazole> Takepron (Jpn , Asia) Prevacid (U.S. , Asia) Ogast , Agopton , Lansox , etc. (EU)	Proton pump inhibitor	Injectable formulation  Symptomatic-GERD	Jpn  Jpn	Filed (Feb 04)  Filed (Sep 04)	In-house
<b>TAP-144-SR</b> <leuprorelin acetate> Leuplin (Jpn) Lupron Depot (U.S.) Enantone etc. (EU , Asia)	LH-RH agonist	3-Month depot/premenopausal breast cancer  6-month depot/prostate cancer	Jpn  EU (Germany)  U.S.	Approved (Aug 05)  Filed (Jun 05)  P-II/III	In-house
<b>TCV-116</b> <candesartan cilexetil> Blopress (Jpn, EU, Asia) Amias, Kenzen, etc. (EU)	Angiotensin II receptor antagonist	Chronic heart failure  Fixed combination with diuretic  High dose  Outcome study, DIRECT (Diabetic REtinopathy Candesartan Trial)  Diabetic nephropathy	Jpn  Jpn  Jpn  EU  Jpn	Approved (Oct 05)  Filed (Dec 02)  P-III  P-III  P-II	In-house
<b>AD-4833</b> <pioglitazone hydrochloride> Actos (Jpn , U.S., EU , Asia)	Insulin resistance-improving drug	Combination drug of Actos / Metformin    Combination drug of Actos / SU   Outcome study, PROactive (PROspective pioglitAzone Clinical Trial In macroVascular Events)  Delay in progression of Atherosclerosis  Concomitant therapy with metformin	U.S.  EU  U.S.  EU  EU  U.S.  Jpn	Approved (Aug 05)  Filed (Feb 05)  Filed (Jun 05)  Filed (Jul 05)  P-III  P-III  P-III	In-house
<b>AO-128</b> <voglibose> Basen (Jpn , Asia)	$\alpha$ -glucosidase inhibitor	Impaired glucose tolerance (IGT)	Jpn	P-III	In-house
<b>NE-58095</b> <risedronate>	Bone resorption inhibitor	Once-a-week formulation	Jpn	Filed (Dec 04)	In-licensed (Ajinomoto)
<b>TMR</b> <freeze-dried live attenuated measles and rubella combined vaccine> Freeze-dried live attenuated measles and rubella combined vaccine Takeda, (Japan)	Freeze-dried live attenuated measles and rubella combined vaccine	Prevention of measles and rubella	Jpn	Approved (Oct 05)	In-house
<b>TAK-453SR</b> <morphine hydrochloride> Pacif capsules(Japan)	Morphine hydrochloride sustained release capsules	Cancerous pain	Jpn	Approved (Sep 05)	In-house

## Characteristics of projects

### { New compounds }

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>SPI-0211</b>	Chloride channel opener	Chronic constipation, c-IBS	lubiprostone	Not decided yet	oral administration
<p>This drug has new mechanism of action as 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. Sucampo filed an NDA for chronic idiopathic constipation on March 2005.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-242</b>	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 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 because 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
<b>TAK-375</b>	MT <sub>1</sub> /MT <sub>2</sub> receptor agonist	Insomnia, Circadian rhythm sleep disorder (CRSD)	ramelteon	Rozerem	oral administration
<p>This drug is highly specific to the MT<sub>1</sub>/MT<sub>2</sub> 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 and promotion activities started in September 2005.</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
<b>TAK-475</b>	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. 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
<b>TAK-390MR</b>	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.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>BNP7787</b>	Chemotherapy supportive care drug	Prevention or reduction of neurotoxicity induced by anti cancer	dimesna	Tavocept	injection
<p>This drug is a chemotherapy supportive care drug to prevent or mitigate neuropathy including the numbness, pain and loss of feeling in hands and feet, which is often caused by Taxane and Platinum, which are standards antitumor drugs for advanced lung cancer and relapsed advanced breast cancer.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-428</b>	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.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-654</b>	Insulin resistance-improving drug	Diabetes mellitus	Not decided yet	Not decided yet	oral administration
<p>This is an insulin resistance-improving drug with a non-thiazolidinedione (TZD) structure. It controls blood glucose by improving the insulin resistance in liver and peripheral tissues. It is expected to have less possibility of unfavorable reactions such as weight gain and edema, compared to the TZD compounds.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-536</b>	Angiotensin II receptor antagonist	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
<b>TAK-715</b>	p38 MAP kinase inhibitor	Rheumatoid arthritis	Not decided yet	Not decided yet	oral administration
<p>This drug is expected to improve symptoms and reduce joints destruction caused by rheumatoid arthritis by inhibiting p38 MAP kinase, leading to reduce production of TNF-<math>\alpha</math>, IL-1, and IL-6. This drug is, unlike TNF-<math>\alpha</math> inhibitors, low molecule entity, and therefore, can be administered orally.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>LY333531</b>	PKC $\beta$ inhibitor	Diabetic maculopathy	ruboxistaurin	Not decided yet	oral administration
<p>This drug is PKC <math>\beta</math> Inhibitor. PKC (Protein kinase C) <math>\beta</math>, 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 <math>\beta</math>. Eli Lilly is conducting Phase-III trials for diabetic neuropathy in the US. Takeda started Phase-II trial for diabetic maculopathy in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-128</b>	Myelin formation accelerator	Diabetic neuropathy	Not decided yet	Not decided yet	oral administration
<p>This is a drug for diabetic neuropathy that has a new mechanisms of action. It is expected to improve function of neurotransmitter by accelerating myelin formation that can restore or regenerate peripheral nerve system damaged by diabetes mellitus. This drug is expected to be treatment for severe case or radical drug for diabetic neuropathy because of its function of restoring or regenerating peripheral nerve system. FDA granted fast track status in September 2005. Phase II study was started in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>SYR-322</b>	DPPIV 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.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>R-851</b>	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
<b>EMD72000</b>	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. Phase II for non-small cell lung cancer is prepared to start in Japan.</p>					

## Additional indications / new formulations

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. Injection is approved in the U.S. (May 04) and filed in Japan (Feb 04) . Smaller capsule was approved in Japan (Jan 04). Symptomatic GERD was filed in Japan (Sep 04).</p>					

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 was filed in EU (Jun 05).</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 (E)	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. The CHARM study showed that the drug was effective for heart failure. The indications of treatment for chronic heart failure was approved in EU (Nov 04), U.S. (Feb 05) and Japan (Oct 05). Fixed combination with diuretic was filed in Japan (Dec 02). Phase III of high dose is conducted in Japan. "DIRECT", outcome study, is being conducted in EU to investigate prevention/treatment efficacy on diabetic retinopathy. Clinical trial is being conducted about diabetic nephropathy 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
<b>AD-4833</b>	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>NDA's of the combination drug with metformin were approved in the US (Aug 05 : Actoplus Met™) and it was filed in EU (Feb 05) respectively. Actoplus Met was available in 1 November. NDA's of the combination drug with SU were filed in US (Jun 05) and in EU (Jul 05). Landmark data from the PROactive Study, presented at the 41st meeting of the European Association for the Study of Diabetes (EASD) in Athens 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>Phase III of concomitant therapy with metformin is 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
<b>AO-128</b>	-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), and an additional formulation of fast disintegrating tablet was approved in Japan (Feb 04).</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.

<b>TAK-220</b>	<b>In-house</b>	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

<b>TRM-1</b>	<b>Licensed from:</b> Human Genome Sciences, Inc.	<b>Agreed</b> Aug.2002
		<b>Stage</b> Under preparation for clinical trials (Japan) <b>Territory</b> Japan
A complete human antibody relevant to TRIAL-R1 discovered by Human Genome Sciences, Inc. This compound suppressed the growth of human breast, colon and uterine cancers in animal model.		
<b>ATL-962</b>	<b>Licensed from:</b> Alizyme	<b>Agreed</b> Jan. 2004
		<b>Stage</b> P-I (Japan) <b>Territory</b> Japan
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 effective treatment of obesity coupled with its associated conditions, such as Type II diabetes. Alizyme conducted Phase-II trials in EU. Takeda acquired an exclusive right of development and marketing of ALT-962 in Japan.		
<b>Actos / Fortamet</b>	<b>Agreement with :</b> Andrx	<b>Agreed</b> Jan. 2004
		<b>Stage</b> Under preparation for clinical trials <b>Territory</b> World
This is a combination product of Actos and Fortamet (metformin extended release). Andrx has developed a formulation of the combination product of Actos and Fortamet. Takeda will be responsible for clinical development activities and NDA submission. The combination product will be manufactured by Andrx, and exclusive marketing rights worldwide will be held by Takeda. Fortamet was approved in the US (Apr 04).		
<b>TAK-363</b>	<b>Agreement with :</b> Toray	<b>Agreed</b> Mar. 2005
		<b>Stage</b> P-I (U.S.) <b>Territory:</b> 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.		
<b>Omacor</b>	<b>Licensed from:</b> Pronova	<b>Agreed</b> Nov. 2005
		<b>Stage</b> Under preparation for clinical trials (J <b>Territory</b> Japan
This drug 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 hightriglyceridaemia in the US and the indication of hightriglyceridaemia and adjuvant treatment in secondary prevention after myocardial infarction in EU.		

## 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.

### Example: Clinical study protocol

Compound	Study title	Stage	Study description
TAK-128	A Phase 2, Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Study to Evaluate the Efficacy and Safety of Three Doses of TAK-128 in Subjects with Mild to Moderate Diabetic Neuropathy	P-II	To determine whether TAK-128 is safe, or if it can improve or slow the progression
TAK-242	A Multicenter, Double-Blind, Placebo-Controlled Study To Evaluate The Efficacy And Safety Of TAK-242 In Adults With Severe Sepsis	P-III	This drug is being developed to treat severe sepsis with septic shock and/or respiratory failure. The primary purpose of this study is to identify the optimal dosing regimen and to demonstrate that TAK-242 reduces 28-day all-cause mortality in subject with severe sepsis.
TAK-475	Effect of TAK-475 or placebo on blood cholesterol levels in subjects with elevated cholesterol	P-III	The purpose is to determine if patients with elevated cholesterol, but not taking any other lipid medication, could lower their cholesterol with administration of TAK-475. This study will evaluate the efficacy and safety of TAK-475 compared to placebo in subjects with primary hypercholesterolemia. Subjects who have signed the informed consent will undergo necessary evaluations to determine eligibility for a dietary run-in phase. Subjects who meet randomization criteria will enter treatment with one of the following randomized treatment: TAK-475 or placebo.

## 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. Endpoints are heart attack, stroke, below-knee amputation and cardiovascular events.		
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 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.</p> <p>PROactive (PROspective PioglitAzone Clinical Trial In MacroVascular Events) was a randomised, double blind, placebo-controlled outcome study to determine the effects of ACTOS on mortality and morbidity associated with cardiovascular disease progression in more than 5,000 high risk patients with type 2 diabetes when added to standard of care treatment. Standard of care included the routine use of anti-hypertensives such as ACE inhibitors and beta blockers; glucose lowering agents such as metformin, sulphonylureas and insulin; antiplatelet drugs such as aspirin, and lipid-modifying medicines such as statins and fibrates.</p> <p>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>		

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><u>CHARM-Alternative: (Candesartan vs Placebo)</u> 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&lt;0.0004).</p> <p><u>CHARM-Added: (Candesartan + conventional therapy vs. Conventional therapy)</u> 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 of 15% (p=0.011) .</p> <p><u>CHARM-Preserved: (Candesartan vs. Placebo)</u> 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 is planned to revealed in 2007. DIRECT consists of following three separate clinical studies in one programme.</p> <ol style="list-style-type: none"> <li>1.Type 1 diabetic patients without retinopathy for primary prevention.</li> <li>2.Type 1 diabetic patients with retinopathy for secondary prevention.</li> <li>3.Type 2 diabetic patients with retinopathy for secondary prevention.</li> </ol> <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
Biomolecular Engineering Research Institute	Research for application of biomolecular functions	Jun-01 - Mar-06
Shin Nippon Biomedical Laboratories	Research for toxico-genomics	Jan-02 - Jan-06
RIKEN (The Institute of Physical and Chemical Research)	Analysis of SNPs related to pioglitazone-induced edema	Feb-03 - Mar-06
Keio University	Target discovery for molecules differentiating neuronal stem cells to neurons	Apr-03 - Mar-06
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-06

### (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 - Mar-06
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	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

## 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)	OT7T022	Gynecology
Metastin	OT7T175	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
Neuromedin U	FM3/TGR1	Hypertension
EG-VEGF	ZAQ/ISE	Gynecology
Bile acid	TGR5	Immunology
Fatty acid	GPR40	Diabetes
$\beta$ -alanine	TGR7	Neuropathic pain

### Disease-specific Expression Profiles for Differentially Regulated Genes

Gene discovered	Expected target disease
CLCA1	Respiratory diseases
LLPL	Atherosclerosis