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## Development activities

### New Compounds

Development code <generic name>	Drug Class (administration route)	Indications	Stage	In-house / In-license
<b>SPI-0211</b> < lubiprostone >	Chloride channel opener ( oral )	Constipation-predominant Irritable Bowel Syndrome	U.S. P-III	In-license. (Sucampo) P-III conducted by Sucampo
<b>TAK-242</b> < - >	TLR4 signal transduction inhibitor ( Injection )	Severe sepsis	Jpn P-III U.S. P-III EU P-III	In-house
<b>TAK-375</b> < ramelteon >	MT <sub>1</sub> /MT <sub>2</sub> receptor agonist ( oral )	Insomnia  Alzheimer's sleep / wake disturbance Circadian rhythm sleep disorder (CRSD)	Jpn P-III EU Filed (Mar 07) U.S. P-II U.S. P-II	In-house
<b>TAK-475</b> < - >	Squalene synthase inhibitor ( oral )	Hypercholesterolemia	U.S. P-III EU P-III Jpn P-II	In-house
<b>TAK-390MR</b> < - >	Proton pump inhibitor ( oral )	Erosive esophagitis and non-erosive gastro-esophageal reflux disease	U.S. P-III Jpn P-I	In-house
<b>SYR-322</b> < - >	DPP-4 inhibitor ( oral )	Diabetes mellitus	U.S. P-III EU P-III Jpn P-II	In-house
<b>TAK-428</b> < - >	Neurotrophic factor production accelerator ( oral )	Diabetic neuropathy	U.S. P-II EU P-II	In-house
<b>TAK-536</b> < azilsartan >	Angiotensin II receptor antagonist ( oral )	Hypertension	U.S. P-II EU P-II Jpn P-I	In-house
<b>AF37702</b> < - >	Synthetic, peptide-based erythropoiesis- stimulating agent ( Injection )	Chronic kidney disease (CKD) / cancer-related anemia	U.S. P-II EU P-II Jpn P-I / II	In-license (Affymax)
<b>TAK-583</b> < - >	Neuropathic pain-improving drug ( oral )	Post-herpetic neuralgia  Diabetic neuropathy	U.S. P-II EU P-II U.S. P-II EU P-II Jpn P-II	In-house
<b>LY333531</b> < ruboxistaurin >	PKC $\beta$ inhibitor ( oral )	Diabetic maculopathy	Jpn P-II	In-license (Eli Lilly)
<b>R-851</b> < - >	Immune response modifier (topical)	Human papillomavirus (HPV) infection	U.S. P-II	In-license (3M)
<b>EMD72000</b> < matuzumab >	Humanized, monoclonal antibody (MAb) against the human EGFR ( Injection )	Gastric cancer, non-small cell lung cancer (NSLC), colorectal cancer	U.S. P-II EU P-II Jpn P-II	In-license (Merck KGaA)
<b>ATL-962</b> < cetilistat >	Lipase inhibitor ( oral )	Obesity	Jpn P-II	In-license (Alizyme)
<b>TAK-491</b> < - >	Angiotensin II receptor antagonist ( oral )	Hypertension	U.S. P-II Jpn P-II	In-house

## Additional indications/new formulations

Development code <generic name> Brand name (country/region)	Drug Class	Indications or formulations	Stage	In-house / In-license
<b>TAP-144-SR</b> < leuprorelin acetate > Leuplin (Jpn) Lupron Depot (U.S.) Enantone, etc. (EU , Asia)	LH-RH agonist	6-month depot/prostate cancer	EU (Ger) Filed (Jun 05) EU (Ita) Filed (Oct 05) EU (Fra) Filed (Nov 05)	In-house
<b>AG-1749</b> < lansoprazole > Takepron (Jpn , Asia) Prevacid (U.S. , Asia) Ogast , Agopton , Lansox , etc. (EU)	Proton pump inhibitor	Secondary eradication of Helicobacter pylori NSAID-induced ulcer	Jpn Filed (Aug 06) Jpn P-III	In-house
<b>TCV-116</b> < candesartan cilexetil > Blopess (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 P-III EU P-III Jpn P-III EU P-III	In-house
<b>AD-4833</b> < pioglitazone hydrochloride > Actos (Jpn, U.S., EU, Asia)	Insulin resistance-improving drug	Combination drug of Actos / Metformin XT Reduction of the risk of macrovascular events in patients with type 2 diabetes mellitus and pre-existing macrovascular disease (PROactive) Delay in progression of Atherosclerosis Combination drug of Actos / TAK-536 Concomitant therapy with metformin Concomitant therapy with insuline	US Filed (Mar 06) The results from PROactive study were added into the labelings, EU (Jan 07), U.S. (Feb 07) U.S. P-III U.S. P-III Jpn Filed (Jan 07) Jpn P-III	In-house
<b>AO-128</b> < voglibose > Basen (Jpn, Asia)	α-glucosidase inhibitor	Impaired glucose tolerance (IGT)	Jpn P-III	In-house
<b>NE-58095</b> < risedronate > Benet (Jpn)	Bone resorption inhibitor	Once-a-week formulation Paget's disease	Jpn Approved (Apr 07) Jpn P-III	In-license (Ajinomoto)

### Recent progress in stage (since October 2006)

Development code	Indications or formulations	Brand name (country/region)	Progress in stage
TAK-475	Hypercholesterolemia	< not decided yet > (Jpn)	P-I P-II
AD-4833	Combination drug of Actos / SU	Tandemact (EU)	Filed Approved
AD-4833	Concomitant therapy with metformin and SU	Actos (EU)	Filed Approved
AD-4833	Concomitant therapy with metformin	Actos (Jpn)	P-III Filed
TAK-375	Insomnia	Rozerem (EU)	P-III Filed
SYR-322	Diabetes mellitus	< not decided yet > (Jpn)	P- P-
TAK-583	Diabetic neuropathy	< not decided yet > (Jpn)	P- P-
AG-1749	NSAID-induced ulcer	< not decided yet > (Jpn)	P-III started
NE-58095	Once-a-week formulation	Benet (Jpn)	Filed Approved
AD-4833	Reduction of the risk of macrovascular events in patients with type 2 diabetes mellitus and pre-existing macrovascular disease (PROactive)	Actos (U.S., EU)	The results from PROactive study were added into the labelings.
AD-4833	Concomitant therapy with insuline	Actos (Jpn)	P-III started

The lower part shows progresses in stage after FY2006 3Q (Jan 2007) updates.

## Characteristics of projects

### [ New compounds ]

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>SPI-0211</b>	Chloride channel opener	Chronic idiopathic constipation, c-IBS	lubiprostone	AMITIZA® (US)	oral
<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, the promotional activities started in the US in April 2006. Sucampo is now conducting the phase III studies for a c-IBS indication.</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 studies for severe sepsis patients by the U.S. FDA and the Japanese PMDA based on Phase I study results which showed TAK-242's strong suppressive efficacy on cytokine and the safety. The 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 that can be used for broad range of 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), etc.	ramelteon	ROZEREM™ (US)	oral
<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 and it has not been designated as a controlled substance by the 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
<b>TAK-475</b>	Squalene synthase inhibitor	Hypercholesterolemia	Not decided yet	Not decided yet	oral
<p>This is an anti-hypercholesterolemia drug having a new mechanism of action based on its squalene synthase inhibitory action. The concomitant therapy with existing treatments such as HMG-CoA reductase inhibitors, fibrates may lead to show efficacy as well as TAK-475 monotherapy. 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. The product is in phase III in the U.S. and EU, and in phase II in Japan.</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
<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., and Takeda is conducting phase I studies in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>SYR-322</b>	DPP-4 inhibitor	Diabetes mellitus	Not decided yet	Not decided yet	oral
DPP-4 inhibitors, taken orally, work by blocking Glucagon Like Peptide-1(GLP-1) degradation to keep its concentration for a longer period of time. Therefore, DPP-4 inhibitors are expected to be one of the new generation agents for diabetes treatment. GLP-1 stimulates pancreatic beta cells to increase the secretion of insulin, and GLP-1 has the potential to improve beta cell function itself. Takeda is conducting Phase III studies in the US and EU, Phase II in Japan respectively.					

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
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 those of aldose reductase inhibitors and PKC inhibitors. Takeda is conducting Phase II studies in the US and EU.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-536</b>	Angiotensin II receptor blocker	Hypertension	azilsartan	Not decided yet	oral
According to preclinical trials, it is expected that this drug has insulin resistance improving effect and renal protective effect as well as anti-hypertensive effect. Takeda is conducting phase III studies of a fixed combination dosage form of TAK-536/Actos, while the single dosage form is in phase II in the U.S. and EU and phase I in Japan respectively.					

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

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-538</b>	Neuropathic pain-improving drug	Post-herpetic neuralgia/ Diabetic neuropathy	Not decided yet	Not decided yet	oral
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.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>LY333531</b>	PKC $\beta$ inhibitor	Diabetic maculopathy	ruboxistaurin	Not decided yet	oral
This drug is PKC $\beta$ Inhibitor. PKC (Protein kinase C) $\beta$ , 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 $\beta$ . Takeda signed a joint development/co-marketing agreement with Eli Lilly on December 18, 2003. Takeda started Phase-II studies for diabetic maculopathy in Japan.					

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
<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. Phase II studies are being conducted in the U.S.</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. 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
<b>ATL-962</b>	Lipase inhibitor	Obesity	cetilistat	Not decided yet	oral
<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 2 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
<b>TAK-491</b>	Angiotensin II receptor blocker	Hypertension	Not decided yet	Not decided yet	oral
<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 a function of improving insulin resistance will be clinically beneficial because many hypertension patients have diabetes mellitus. Takeda is conducting phase II studies in the U.S. and EU.</p>					

**[ Additional indications/new formulations ]**

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAP-144-SR</b>	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
<b>AG-1749</b>	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), while the phase III studies are conducted for NSAIDs-induced ulcers.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TCV-116</b>	Angiotensin II receptor antagonist	Hypertension	candesartan cilexetil	Blopress (Jpn, EU), Atacand (U.S.), Amias (U.K.), Kenzen (Fr), etc.	oral
<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 are being conducted in Japan.</p> <p>[Publications]            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 LANCET vol.362 (9386) 6 Sep 20            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

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.

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.

Combination dosage forms	Actos + metformin	Actos + metformin XR	Actos + SU	Actos + TAK-536
U.S.	Approved ( Aug 05) <ACTOplus met>	Filed (Mar 06) <ACTOplus met XR>	Approved (Jul 06) <Duetact>	Phase III
EU	Approved (Jul 06) <Competact>	---	Approved (Jan 07) <Tandemact>	---

[Publications]

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.

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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AO-128	-glucosidase inhibitor	Diabetes mellitus	voglibose	Basen (Japan)	oral

The drug inhibits the hydrolase ( $\alpha$ -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.

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 for an additional indication of impaired glucose tolerance (suppression of development of insulin non-dependent diabetes mellitus).

**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.)
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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.

## Other alliance projects

<b>TRM-1</b>	<b>Licensed from:</b> <b>Human Genome Sciences, Inc.</b>	<b>Agreed:</b>	Aug. 2002	<b>Territory : Japan</b>
		<b>Stage:</b>	Under preparation for clinical trials (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.				

<b>TAK-363</b>	<b>Agreement with :</b> <b>Toray</b>	<b>Agreed:</b>	Mar. 2005	<b>Territory : Worldwide except Japan</b>
		<b>Stage:</b>	P-I (U.S.)	
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>TAK-085</b>	<b>Licensed from:</b> <b>Pronova</b>	<b>Agreed:</b>	Nov. 2005	<b>Territory : Japan</b>
		<b>Stage:</b>	P-I (Jpn)	
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.				

<b>HuL2G7</b>	<b>Licensed from:</b> <b>Galaxy Biotech, LLC</b>	<b>Agreed:</b>	Jul. 2006	<b>Territory : Worldwide</b>
		<b>Stage:</b>	Under preparation for clinical trials	
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.				

<b>XEN401</b>	<b>Licensed from:</b> <b>Xenon Pharmaceuticals Inc.</b>	<b>Agreed:</b>	Sep. 2006	<b>Territory : Japan and certain Asian countries</b>
		<b>Stage:</b>	Under preparation for clinical trials	
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.				

<b>CBP501</b>	<b>Agreement with:</b> <b>CanBas Co., Ltd.</b>	<b>Agreed:</b>	Mar. 2007	<b>Territory : Worldwide (joint development and co-promotion in the US)</b>
		<b>Stage:</b>	P-I (U.S.)	
CBP501 has a mechanism of action to selectively abrogate the G2 checkpoint, which is used by cancer cells to determine if a cell is progressing correctly through replication within the cell cycle. CBP501 is expected as a potential cancer treatment with lesser influence on normal cells, when being used as concomitant therapy with chemotherapy anti-cancer drugs which will lead to promoting the damages to DNA of cancer cells.				

## 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 (1)

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&lt;0.05).</p> <p>There was no effect of ACTOS on subsequent strokes in patients who had never experienced a stroke.</p>		

### 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	U.S.	Total population	462 patients
Status	<p>Results from the clinical trial, CHICAGO were part of a late-breaker presentation at the American Heart Association's Scientific Sessions 2006.</p> <p>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).</p> <p>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.</p> <p>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).</p> <p>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).</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><b>CHARM-Alternative:</b> (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&lt;0.0004).</p> <p><b>CHARM-Added:</b> (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><b>CHARM-Preserved:</b> (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)

<b>Study title</b>	<b>DIRECT (DIabetic REtinopathy Candesartan Trial)</b>		
<b>Outline</b>	The world's first large scale study to investigate prevention/treatment efficacy on diabetic retinopathy (candesartan vs. placebo)		
<b>Place</b>	30 countries	<b>Total population</b>	5,238 patients
<b>Status</b>	<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"> <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>		

## TCV-116 (3)

<b>Study title</b>	<b>CASE-J (Candesartan Antihypertensive Survival Evaluation in Japan)</b>		
<b>Outline</b>	Large-scale clinical study of high-risk hypertensive patients in Japan		
<b>Place</b>	Japan	<b>Total population</b>	4,728 patients
<b>Status</b>	<p>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.</p> <p>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). &lt;Secondary endpoint&gt;</p> <p>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.</p>		

## Research Activities

### Main joint research activities

#### (1) Joint researches with domestic research organizations and companies

Partner	Research subject	Schedule
Kirin Brewery	Licensing-in of the human antibody technology	2003/7 ~
Osaka University	Development of novel diagnostics of lifestyle-related diseases by novel secretory factors	2004/4 ~ 2008/3

#### (2) Joint researches with overseas research organizations and companies

Partner	Country	Research subject	Schedule
Oxford Centre for Diabetes Endocrinology and Metabolism	U.K.	Partnership with Oxford Diabetes Centre	2002/4 ~ 2008/3
Beth Israel Deaconess Medical Center (Harvard Medical School)	U.S.	Joint research on drug discovery related to diabetes and obesity	2002/7 ~ 2007/7
Evotec NeuroSciences	Germany	Drug discovery alliance in Alzheimer's disease	2003/8 ~ 2007/7
Lexicon Genetics Incorporated	U.S.	Joint research on drug target of hypertension	2004/7 ~ 2007/7
Arius Research Inc.	Canada	Joint research agreement on functional antibodies in cancer field	2006/4 ~ 2009/3
XOMA Ltd.	U.S.	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 ~ 2011/3