

X. Pipeline

Development Activities

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Research Activities

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Development activities

■ New Compounds

Development code <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
SYR-322 <alogliptin>	DPP-4 inhibitor (oral)	Diabetes mellitus	US	Filed (Dec 07)	In-house
			Jpn	Filed (Sep 08)	
		Diabetes mellitus (Fixed-dose combination with ACTOS)	EU	P-III	
			US	Filed (Sep 08)	
			EU	P-III	
TAK-390MR <dexlansoprazole>	Proton pump inhibitor (oral)	Erosive esophagitis (healing and maintenance) and non-erosive gastro-esophageal reflux disease	US	Filed (Dec 07)	In-house
			Jpn	P-II	
TAK-375 <ramelteon>	MT ₁ /MT ₂ receptor agonist (oral)	Insomnia	EU	P-III <small>*Re-submission of a MAA is under consideration</small>	In-house
			Jpn	Filed (Feb 08)	
		Circadian rhythm sleep disorder (CRSD)	US	P-II	
Vectibix™ <panitumumab>	Fully human monoclonal antibody (MAb) against the human EGFR (injection)	Progressive and relapse cancer of the colon and rectum Head and neck cancer	Jpn	Filed (Jun 08)	In-license (Amgen)
			Jpn	P-III	
SNT-MC17 <idebenone>	Mitochondria targeted anti-oxidant (oral)	Friedreich's ataxia Duchenne muscular dystrophy	EU	Filed (Aug 07)	In-license (Santhera)
			EU	P-II	
TMX-67 <febuxostat>	Non-purine, selective xanthine oxidase inhibitor (oral)	Hyperuricemia in patients with chronic gout	US	Filed (Dec 04)	In-license (Teijin)
TAK-242 <resatorvid>	TLR4 signal transduction inhibitor (injection)	Severe sepsis	Jpn	P-III	In-house
			US	P-III	
			EU	P-III	
AMG706 <motesanib diphosphate>	VEGFR1-3 inhibitor (oral)	Progressive non-small cell lung cancer	US	P-III	In-license (Amgen)
			EU	P-III	
			Jpn	P-III	
TAK-491 <azilsartan medoxomil>	Angiotensin II receptor blocker (oral)	Hypertension	US	P-III	In-house
			EU	P-III	
Lu AA21004 <- - >	Serotonin Modulator & Stimulator (oral)	Mood and anxiety disorders	US	P-III	In-license (Lundbeck)
			EU	P-III	
			Jpn	P-I	
Hematide™ <- - >	Synthetic, peptide-based erythropoiesis-stimulating agent (injection)	Chronic kidney disease related anemia	US	P-III	In-license (Affymax)
			EU	P-III	
		Cancer related anemia	Jpn	P-I/II	
			-	P-I *Development suspended	
TAK-428 <- - >	Neurotrophic factor production accelerator (oral)	Diabetic neuropathy	US	P-II	In-house
			EU	P-II	
TAK-536 <azilsartan>	Angiotensin II receptor blocker (oral)	Hypertension	US	P-II	In-house
			EU	P-II	
			Jpn	P-II	
TAK-783 <- - >	T-cell function regulator (oral)	Rheumatoid arthritis	US	P-II	In-house
			EU	P-II	
			Jpn	P-I	
TAK-442 <- - >	Selective Factor Xa (FXa) inhibitor (oral)	Venous / arterial thromboembolism	US	P-II	In-house
			EU	P-II	
			Jpn	P-I	
TAK-379 <- - >	Insulin sensitizer (oral)	Diabetes mellitus	US	P-II	In-house
			EU	P-II	
			Jpn	P-I	

Development code <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
TAK-085 <->	EPA/DHA agent (oral)	Hypertriglyceridemia	Jpn	P-II	In-license (Pronova)
SYR-472 <->	DPP-4 inhibitor (oral)	Diabetes mellitus	US EU Jpn	P-II P-II P-I	In-house
MLN0518 <tandutinib>	Inhibitor of receptor kinases (FLT3, PDGFR, c-KIT) (oral)	Glioblastoma	US	P-II	In-house
MLN0002 <vedolizumab>	α 4 β 7 integrin inhibitor (injection)	Ulcerative colitis, Crohn's disease	US	P-II	In-house
ATL-962 <cetilistat>	Lipase inhibitor (oral)	Obesity	Jpn	P-II	In-license (Alizyme)
Lu AA24530 <->	Monoamine modulator (oral)	Mood and anxiety disorders	EU	P-II	In-license (Lundbeck)
AMG655 <->	Fully human monoclonal antibody agonist directed against DR5 (TRAIL-R2) (injection)	Progressive cancer	Jpn	P-I	In-license (Amgen)
TAK-100 <->	DPP-4 inhibitor (oral)	Diabetes mellitus	-	P-I	In-house
TAK-875 <->	Glucose-dependent insulin secretagogue (oral)	Diabetes mellitus	-	P-I	In-house
TAK-591 <->	Angiotensin II receptor blocker (oral)	Hypertension	-	P-I	In-house
TAK-700 <->	Sex hormone synthesis inhibitor (oral)	Prostate cancer	-	P-I	In-house
TAK-683 <->	GnRH modulator (injection)	Prostate cancer	-	P-I	In-house
TAK-448 <->	GnRH modulator (injection)	Prostate cancer	-	P-I	In-house
TAK-285 <->	HER2 inhibitor (oral)	Solid tumors	-	P-I	In-house
TAK-593	VEGFR, PDGFR inhibitor (oral)	Solid tumors	-	P-I	In-house
CBP501 <->	G2 checkpoint abrogator (injection)	Malignant mesothelioma, Lung cancer	-	P-I	In-license (CanBas)
TAK-385 <->	LH-RH receptor antagonist (oral)	Endometriosis, Uterus myoma	-	P-I	In-house
TAK-363 <->	Bladder hypersensitivity suppression (Suppression of micturition reflex) (oral)	Frequent urination, Urinary incontinence (Overactive bladder)	-	P-I	In-license (Toray)
MLN8237/8054 <->	Aurora A kinase inhibitor (oral)	Advanced malignancies	-	P-I	In-house
MLN4924 <->	Nedd 8 activating enzyme inhibitor (oral / injection)	Advanced malignancies	-	P-I	In-house

Development code <generic name>	Drug Class (administration route)	Indications	Stage	In-house/ In-license
TAK-065 <->	Neuroregeneration enhancer (oral)	Alzheimer disease, Parkinson's disease	- P-I	In-house
TAK-438 <->	Potassium-competitive acid blocker (oral)	Acid-related diseases (GERD, Peptic ulcer disease, etc.)	- P-I	In-house
MLN0415 <->	IKK2 inhibitor (oral)	Inflammatory diseases	- P-I	In-house

■ Additional indications/new formulations

Development code <generic name> Brand name (country / region)	Drug Class	Indications or formulations	Stage	In-house / In-license
VELCADE® <bortezomib>	Proteasome inhibitor	First line multiple myeloma Follicular NHL Other tumors	US Approved (Jun 08) US P-III US P-II	In-house
AMITIZA® <lubiprostone>	Chloride channel opener	Opioid-Induced bowel dysfunction (OBD)	US P-III	In-license (Sucampo)
TAP-144-SR <leuprorelin acetate> Leuplin (Jpn) Lupron Depot (US) Enantone, etc. (EU, Asia)	LH-RH agonist	6-month depot/prostate cancer	EU (Austria) Approved (May 08) EU (Germany) Approved (Jul 08)	In-house
AG-1749 <lansoprazole> Takepron (Jpn, Asia) Prevacid (US, Asia) Ogast, Agopton, Lansox, etc. (EU)	Proton pump inhibitor	Risk reduction of NSAID-associated gastric ulcer	Jpn P-III	In-house
TCV-116 <candesartan cilexetil> Blopress (Jpn, EU, Asia) Amias, Kenzen, etc. (EU)	Angiotensin II receptor blocker	Fixed-dose combination with diuretic Fixed-dose combination with calcium channel blocker High dose Outcome study: DIRECT Diabetic RETinopathy Candesartan Trial	Jpn Filed (Mar 08) EU Filed (Jun 08) Jpn P-III Jpn P-III EU P-III	In-house
AD-4833 <pioglitazone> Actos (Jpn, US, EU, & Asia)	Insulin sensitizer	Combination drug of Actos / Metformin XR Delay in progression of Atherosclerosis Concomitant therapy with metformin Concomitant therapy with insulin Orally disintegrating tablets Fixed-dose combination with metformin	US Filed (Mar 06) US Filed (Aug 08) Jpn Filed (Jan 07) Jpn Filed (Jun 07) Jpn Filed (Sep 08) Jpn Filed (Oct 08)	In-house
AO-128 <voglibose> Basen (Jpn, Asia)	Alpha-glucosidase inhibitor	Prevention of onset of type 2 diabetes in patients with impaired glucose tolerance (IGT)	Jpn Filed (Dec 07)	In-house
KAD-1229 <mitiglinide> Glufast (Jpn)	Short-acting insulin secretagogue	Concomitant therapy with insulin sensitizer	Jpn Filed (Apr 07)	In-license (Kissei)
NE-58095 <risedronate> Benet (Jpn)	Bone resorption inhibitor	Paget's disease of bone	Jpn Approved (Jul 08)	In-license (Ajinomoto)

■ Recent progress in stage*

Development code	Indications	Country/Region	Progress in stage
VELCADE®	First line multiple myeloma	US	Approved (Jun 08)
TAP-144-SR	6-month depot/prostate cancer	EU (Austria)	Approved (May 08)
TAP-144-SR	6-month depot/prostate cancer	EU (Germany)	Approved (Jul 08)
NE-58095	Paget's disease of bone	Jpn	Approved (Jul 08)
TCV-116	Hypertension (Fixed-dose combination with diuretic)	EU	Filed (Jun 08)
Vectibix™	Progressive and relapse cancer of the colon and rectum	Jpn	Filed (Jun 08)
Lu AA21004	Mood and anxiety disorders	Jpn	P-I
TAK-448	Prostate cancer	-	P-I
SYR-322	Diabetes mellitus	Jpn	Filed (Sep 08)
SYR-322	Diabetes mellitus (Fixed-dose combination with Actos)	US	Filed (Sep 08)
AD-4833	Delay in progression of Atherosclerosis	US	Filed (Aug 08)
AD-4833	Diabetes mellitus (Orally Disintegrating tablets)	Jpn	Filed (Aug 08)
AD-4833	Diabetes mellitus (Fixed-dose combination with metformin)	Jpn	Filed (Oct 08)
TAK-379	Diabetes mellitus	US Jpn	P-II
TAK-593	VEGFR, PDGFR inhibitor	-	P-I

* Progress in stage since release of FY2007 Financial Results (May 9, 2008).

(Progress since release of FY2008 1Q results (July 31, 2008) are listed under the bold dividing line.)

■ Discontinued project*

Development code	Indications (Stage)	Reason
TAK-583	Post-herpetic neuralgia (PHN) (P-II) Painful diabetic neuropathy (PDN) (P-II) Diabetic peripheral neuropathy (DPN) (P-II)	Proof of concept was not demonstrated in P-II studies in US/EU.
TAK-851	Human papillomavirus (HPV) infection (P-II)	Results of P-II study in US did not meet its predefined efficacy endpoints.
IY-81149	Acid-related diseases (GERD, Peptic ulcer disease, etc) (P-II)	Results of P-II study in US did not meet its predefined endpoints.
GVAX	Prostate cancer (P-III)	Program was held based on the results of a previously unplanned futility analysis which indicated that the trial had low chance of meeting its predefined primary endpoints of an improvement of survival.

* Discontinued since release of FY2007 Financial Results (May 9, 2008).

(Discontinuation since release of FY2008 1Q results (July 31, 2008) are listed under the bold dividing line.)

■ Characteristics of projects
[New compounds]

Development code	Drug Class	Indications	Generic name	Brand name	Administration
SYR-322	DPP-4 inhibitor	Diabetes mellitus	Alogliptin	Not decided yet	Oral
<p>DPP-4 inhibitors, taken orally, work by blocking Glucagon Like Peptide-1 (GLP-1) degradation to maintain 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 submitted a New Drug Application for SYR-322 in the U.S. in Dec 07, in Japan in Sep 08, and for a fixed-dose combination with Actos in the U.S. in Sep 08, and is conducting Phase III studies in the E.U. respectively.</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	Dexlansoprazole	Not decided yet	Oral
<p>This compound employs a new modified release technology on an enantiomer of lansoprazole, which is a proton pump inhibitor originally developed by Takeda and is marketed by Takeda and its licensees in approximately 90 countries worldwide. Takeda submitted a New Drug Application for TAK-390MR in Dec 07 in the U.S. and is conducting Phase II study in Japan.</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), etc.	Ramelteon	ROZEREM™ (U.S.)	Oral
<p>This drug is highly specific to the MT₁/MT₂ receptor and induces a 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 U.S. Drug Enforcement Administration (DEA). TAK-375 was approved in Jul 05 and promotional activities started in Sep 05. Takeda submitted a New Drug Application for Ramelteon in Feb 08 in Japan. TGRD (EU) decided to withdraw the original application in the E.U. in Sep 08, because it concluded that a marketing authorization for ramelteon could be better supported at an early date by submission of new data via a new MAA.</p> <p>[Publications] 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 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
Vectibix™ (AMG954)	Fully human monoclonal antibody (MAb) against the Human EGFR	Progressed and relapse cancer of the colon and rectum Head and neck cancer	Panitumumab	Vectibix™	Injection
<p>Vectibix™ was approved in the U.S. in Sep 06, and the E.U. in Dec 07. It is indicated as a monotherapy for the treatment of EGFR-expressing, metastatic colorectal carcinoma (mCRC) with disease progression on or following fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens. It is a recombinant, human 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. The U.S. sales of this product in 2007 was \$170MM, and in 1-2Q of 2008 was \$57MM. (according to Financial Statements of Amgen Inc.)</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
SNT-MC17	Mitochondria targeted anti-oxidant	Friedreich's ataxia, Duchenne muscular dystrophy	Idebenone	Not decided yet	Oral
<p>Santhera started the clinical development of Idebenone for treatment of Friedreich's Ataxia, which results from impaired energy production in mitochondria, the cells' energy production centers, and elevated oxidative stress. It was found that the neurological and cardiac outcome were improved by Idebenone, and Santhera filed a marketing authorization application for SNT-MC17 for Friedreich's Ataxia to EMEA. In Aug 07, Santhera and Takeda extended their European marketing collaboration for SNT-MC17 into Duchenne muscular dystrophy, and a phase II study is now being conducted in Europe.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TMX-67	Non-purine, selective xanthine oxidase inhibitor	Hyperuricemia in patients with chronic gout	Febuxostat	Not decided yet	Oral

TMX-67 is an oral, once daily, potent non-purine selective inhibitor of xanthine oxidase which causes gout. The former joint venture, TAP received its second approvable letter from the FDA in Aug 08 for its New Drug Application submitted in Dec 04. After consulting with the FDA, TAP conducted a new 6-month comparative study with allopurinol, and Takeda submitted the additional data on July 18, 2008.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-242	TLR4 signal transduction inhibitor	Severe sepsis	Resatorvid	Not decided yet	Injection

TAK-242 suppresses production of inflammatory mediators such as cytokines by inhibiting the signal transduction through Toll-like receptor 4 (TLR4) which is one of the receptors that recognizes bacterial components.

The FDA granted TAK-242 fast track status (Jul 2005) for severe sepsis because, (1) severe sepsis is life-threatening condition, (2) TAK-242 is likely to satisfy unmet medical needs as there is no existing drug that can be used for a broad range of severe sepsis patients. Following an initial analysis of a Phase III study conducted in the U.S., the E.U. and Japan, it was determined to conduct the Phase III study again, which is now on-going.

Note: TLR4 exists on the surface of immunocytes, such as monocytes and macrophages. They recognize LPS (lipopolysaccharide) and transmit activated signals into the cells.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AMG706	VEGFR1-3 inhibitor	Progressive non-small cell lung cancer	Motesanib diphosphate	Not decided yet	Oral

AMG706 is an oral, multi-kinase inhibitor targeting vascular endothelial growth factor (VEGF), platelet derived growth factor (PDGF) and c-kit receptors intending to inhibit angiogenesis and tumor growth. The on-going international Phase III study is based on combination therapy with carboplatin and paclitaxel under the indications of metastatic non-small cell lung cancer (NSCLC).

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-491	Angiotensin II receptor blocker	Hypertension	Azilsartan medoxomil	Not decided yet	Oral

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 III studies in the U.S. and the E.U.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Lu AA21004	Serotonin Modulator & Stimulator	Mood and anxiety disorders	Not decided yet	Not decided yet	Oral

Agreement for co-development and co-commercialization of Lu AA21004 and Lu AA24530 in U.S. and Japan was signed in September 2007.

Phase II study (POC) finished in September 2007 which showed that in comparison to placebo, Lu AA 21004 has a superior efficacy and an excellent safety profile. Compared with currently approved antidepressants, preclinical models have demonstrated that the compounds have the potential to address important unmet needs for patients in terms of both fast onset of effect and increased efficacy.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Hematide™	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 a once every four weeks administration is now being applied in the clinical studies. Affymax started phase III studies for anemia in dialysis and pre-dialysis in the U.S. in Oct 07. Takeda and Affymax agreed to suspend co-development of Hematide to treat chemotherapy-induced anemia.

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

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 U.S. and the E.U.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-536	Angiotensin II receptor blocker	Hypertension	Azilsartan	Not decided yet	Oral
<p>Based on the results of preclinical trials, it is expected that this drug has an insulin resistance improving effect and renal protective effect as well as an anti-hypertensive effect.</p> <p>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., the E.U. and Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-783	T-cell function regulator	Rheumatoid arthritis	Not decided yet	Not decided yet	Oral
<p>Based on non-clinical data, this drug is expected to correct autoimmune reaction by Th1 lymph cell, which is supposed to be a cause of RA.</p> <p>As this drug acts on the cause of RA and may have wider safety allowance than immune depression agents, it is expected to have potential to be effective for the cases in which MTX (first-line standard therapy) is not effective. Phase II studies are being conducted in the U.S. and the E.U. in 2007 and Phase I study in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-442	Selective Factor Xa (FXa) inhibitor	Venous / arterial thromboembolism	Not decided yet	Not decided yet	Oral
<p>This drug is an orally selective and directly competitive inhibitor of activated Factor Xa (FXa) as Factor Xa plays a critical role in the blood coagulation cascade, inhibition of FXa is expected to result in interruption of either venous or arterial thromboembolism. Now, Takeda is conducting Phase II study in the U.S. and Phase I study in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-379	Insulin sensitizer	Diabetes mellitus	Not decided yet	Not decided yet	Oral
<p>This drug is an oral diabetic agent categorized as insulin sensitizer same as Actos, and is being developed to further enhance the diabetic franchise.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-085	EPA/DHA agent	Hypertriglyceridemia	Not decided yet	Not decided yet	Oral
<p>TAK-085 (Omacor) that is marketed by Pronova is a 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 the E.U. Takeda is currently conducting Phase II study in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
SYR-472	DPP-4 inhibitor	Diabetes mellitus	Not decided yet	Not decided yet	Oral
<p>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 of 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 II studies in the U.S and E.U. and Phase I studies in Japan.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN0518	Inhibitor of receptor kinases (FLT3, PDGFR, c-KIT)	Glioblastoma	Tandutinib	Not decided yet	Oral
<p>MLN0518 is an oral small molecule multi-kinase (RTF FLT3, PDGFR and c-KIT) inhibitor, which suppresses growth of cancer cells effectively by inhibiting multiple kinases related to growth of cells. MLN0518 passes the blood brain barrier and concentrates in the brain at high levels. In vitro studies show substantial activity in glioblastoma in combination with Avastin.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN0002	$\alpha 4\beta 7$ integrin inhibitor	Ulcerative colitis, Crohn's disease	Vedolizumab	Not decided yet	Injection
<p>MLN0002 is a humanized antibody that selectively binds to $\alpha 4\beta 7$ integrin, which is predominantly found in the gastro-intestinal tract. Integrins are a type of cell surface protein, that's main roles are cellular binding to the extra cellular matrix and signal transduction from the extra cellular matrix.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
ATL-962	Lipase inhibitor	Obesity	Cetilistat	Not decided yet	Oral
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. According to the results of Phase IIb conducted by Alizyme in the E.U., 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.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Lu AA24530	Monoamine modulator	Mood and anxiety disorders	Not decided yet	Not decided yet	Oral
An agreement for co-development and co-commercialization of Lu AA21004 and Lu AA24530 in U.S. and Japan was signed in Sep 07. Phase II study started in October 2007 in Europe by Lundbeck. Compared with currently approved antidepressants, preclinical models have demonstrated that the compounds have the potential to address important unmet needs for patients in terms of both fast onset of effect and increased efficacy.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AMG655	Fully human monoclonal antibody agonist directed against DR5 (TRAIL-R2)	Progressive cancer	Not decided yet	Not decided yet	Injection
AMG 655 is a fully human monoclonal antibody agonist directed against DR5 (TRAIL-2) receptor and is designed to activate caspases and induces apoptosis in sensitive tumor cells.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-100	DPP-4 inhibitor	Diabetes mellitus	Not decided yet	Not decided yet	Oral
This drug is a DPP-4 inhibitors and being developed to further enhance the diabetic franchise					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-875	Glucose-dependent insulin secretagogue	Diabetes mellitus	Not decided yet	Not decided yet	Oral
This drug is a glucose-dependent insulin secretagogue and is being developed to further enhance the diabetic franchise.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-591	Angiotensin II receptor blocker	Hypertension	Not decided yet	Not decided yet	Oral
This drug is an Angiotensin II receptor blocker under development to further enhance the area of cardiovascular disease. Takeda will seek ways to differentiate itself in clinical stage.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-700	Sex hormone synthesis inhibitor	Prostate cancer	Not decided yet	Not decided yet	Oral
TAK-700 has a mechanism of action to inhibit the biosynthesis of sex hormone synthesis and expected as a new hormone drug for hormone therapy of prostate cancer.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-683	GnRH modulator	Prostate cancer	Not decided yet	Not decided yet	Injection
TAK-683 adjusts the secretion of GnRH and reduces testosterone rapidly and strongly. This is thought to have a new mechanism of action to suppress the sex hormones for treatment medication of prostate cancer.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-448	GnRH modulator	Prostate cancer	Not decided yet	Not decided yet	Injection
TAK-448 adjusts the secretion of GnRH and reduces testosterone rapidly and strongly. This is thought to have a new mechanism of action to suppress the sex hormones for treatment medication of prostate cancer.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-285	HER2 inhibitor	Solid tumor	Not decided yet	Not decided yet	Oral
TAK-285 is a low molecular tyrosine kinase inhibitor which inhibits the HER2 of growth factor receptor inhibitors in cancer. The strength of its antitumor effect is confirmed in the non-clinical pharmacology studies and this product is expected as a best in class HER2 inhibitor.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-593	VEGFR, PDGFR inhibitor	Solid tumor	Not decided yet	Not decided yet	Oral
TAK-593 is a novel small molecule selective inhibitor of the tyrosine kinases for the vascular endothelial growth factor (VEGF) and platelet derived growth factor (PDGF) receptor families. Signaling of VEGF and PDGF receptors play a crucial role in tumor angiogenesis which is necessary for solid tumor growth and metastasis. TAK-593 uniquely shows potent pseudo-irreversibility against VEGF2 and PDGF β .					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
CBP501	G2 checkpoint abrogator	Malignant mesothelioma, Lung cancer	Not decided yet	Not decided yet	Injection
CBP501 has a mechanism of action to 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 to be 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 the DNA of cancer cells.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-385	LH-RH receptor antagonist	Endometriosis, Uterus myoma	Not decided yet	Not decided yet	Oral
TAK-385 is an oral LH-RH receptor antagonist, and rapidly reduces sex hormone concentrations in the blood after administration.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-363	Bladder hypersensitivity suppression (Suppression of micturition reflex)	Frequent urination, Urinary incontinence (Overactive bladder)	Not decided yet	Not decided yet	Oral
This is a drug for frequent urination/urinary incontinence (overactive bladder). 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. Study results to date indicate that TAK-363 does not have an anticholinergic action and is expected to have better efficacy and lesser side effects than anticholinergic products currently on the market.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN8237/8054	Aurora A kinase inhibitor	Advanced malignancies	Not decided yet	Not decided yet	Oral
MLN8237/8054 is a selective inhibitor of the activity of the Aurora A kinase which is necessary for cell division.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN4924	Nedd 8 activating enzyme inhibitor	Advanced malignancies	Not decided yet	Not decided yet	Oral/Injection
MLN4924 inhibits Nedd 8 Activating Enzyme (NAE) which plays an important role in the ubiquitin - proteasome cascade and suppresses growth of cancer cells. This drug has the potential to be administered orally as well as intravenously.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-065	Neuroregeneration enhancer	Alzheimer disease, Parkinson's disease	Not decided yet	Not decided yet	Oral
Based on the neurogenerative enhancing effect of this compound, it is anticipated that it will inhibit the progress of neurodegeneration and promote the recovery of neurofunction. With the number of patients with Alzheimer's Disease expected to increase in proportion with the aging of the population and with the development of new drugs for the treatment of Alzheimer's Disease, the potential market in this field is forecast to reach 400 billion yen by the year 2020. Parkinson's disease is another disease with no effective treatment, and it is expected that an effective treatment may be possible based on a therapy with a neuroregenerative effect to suppress the disease's progress and to assist with the recovery of neurofunction.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-438	Potassium-competitive acid blocker	Acid-related diseases (GERD, Peptic ulcer disease, etc)	Not decided yet	Not decided yet	Oral
TAK-438 is a potassium-competitive acid blocker with a mechanism of action to inhibit H ⁺ , K ⁺ -ATPase in a reversible and K ⁺ -competitive fashion, which is final step of acid secretion in gastric glands and different from ordinary proton pump inhibitors (PPIs). Based on the result of nonclinical study, TAK-438 showed more potent inhibitory effect of acid secretion than PPIs and showed a stronger and long-lasting effect than PPIs. Therefore, TAK-438 is expected, compared to PPIs, it can be assumed that TAK-438 has a clinically stronger efficacy than PPIs.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
MLN0415	IKK2 inhibitor	Inflammatory diseases	Not decided yet	Not decided yet	Oral
MLN0415 is being targeted for rheumatoid arthritis, multiple sclerosis, chronic obstructive pulmonary disease, and inflammatory bowel disease. IKK activates NF- κ B which is known to play an important role in inflammatory diseases by inhibiting IKK. MLN0415 is expected to suppress the onset and exacerbation of inflammation.					

[Additional indications/new formulations]

Development code	Drug Class	Indications	Generic name	Brand name	Administration
VELCADE[®]	Proteasome inhibitor	First line multiple myeloma, Follicular NHL, Other tumors	Bortezomib	VELCADE [®]	Injection
VELCADE blocks the activity of proteasomes, which are enzymes found inside all human cells and necessary for their growth and survival. By inhibiting proteasomes activity, VELCADE causes a buildup of proteins, thereby inducing apoptosis/cell death. Proteasomes break down the resultant proteins which are created through the division and growth of cancer cells as well as other misfolded intracellular proteins. Proteasomes also break down the proteins that's inhibit are responsible for angiogenesis and cell proliferation.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AMITIZA[®]	Chloride channel opener	Opioid-induced bowel dysfunction	Lubiprostone	AMITIZA [®] (U.S.)	Oral
This drug has a novel mechanism of action as a chloride channel opener, which causes an increase in intestinal fluid. Takeda has obtained the marketing rights in the U.S. and Canada. An NDA for chronic idiopathic constipation was filed by Sucampo and approved in January 2006, with promotional activities starting in the U.S. in April 2006. Sucampo obtained FDA approval for IBS-C in April 2008, and is now conducting phase III studies for opioid-induced bowel dysfunction.					

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. (E.U.)	Injection
Successful development of drug delivery system (DDS) now allows for long-acting LH-RH agonist product. With one injection it is possible to provide treatment from one to four months in the E.U. TAP-144-SR is marketed in approximately 80 countries world-wide and is the standard for treatment in prostate cancer. A 6-month formulation for prostate cancer was authorized in Austria in May 08 and in Germany in Jul 08. A 3-month formulation was authorized in Japan for prostate cancer in Aug 02 and for premenopausal breast cancer in Aug 05.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AG-1749	Proton pump inhibitor	Risk reduction of NSAID-associated gastric ulcer	Lansoprazole	Takepron (Jpn), Prevacid (U.S.), etc	Oral/Injection
This is a proton pump inhibitor having a potent inhibitory action on gastric secretion. It suppresses gastric acid secretion by inhibiting the proton pump within the gastric wall cells and exhibits an antiulcer action. The drug has already been launched as a therapeutic agent for peptic ulcers in approximately 100 countries worldwide. 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 risk reduction of NSAID-associated gastric ulcers.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TCV-116	Angiotensin II receptor blocker	Hypertension	Candesartan cilexetil	Blopress (Jpn, E.U.), Atacand (U.S.), Amias (U.K.), Kenzen (Fr), etc.	Oral

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 the treatment of heart failure. The indications of treatment for chronic heart failure to reduce the risk of death and hospitalization from cardiovascular causes were approved in U.S. (Feb 05), chronic heart failure to reduce the risk of death in E.U. (Nov 04) and chronic heart failure in Japan (Oct 05).

Data from the DIRECT Programme was presented at the European Association of the Study of Diabetes (EASD) congress in Rome in Sep 2008. The data show a strong trend in favour of treatment with candesartan 32mg in reducing the incidence of diabetic retinopathy in Type 1 diabetes patients, although not statistically significant, and a significant increase in regression of diabetic retinopathy in Type 2 diabetes patients.

In Japan, Takeda submitted a New Drug Application for a fixed-dose combination tablet with a diuretic in Mar 08, and is now conducting a Phase III study for a fixed-dose combination tablet with a calcium channel blocker and for a high dose.

[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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AD-4833	Insulin sensitizer	Diabetes mellitus	Pioglitazone	Actos (Japan, U.S., E.U.)	Oral

This is a drug that controls blood glucose levels by improving 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.

At the American Heart Association's Scientific Sessions 2006, data showing that ACTOS[®] (pioglitazone HCl) halted the progression of atherosclerosis as measured by carotid intima-media thickness (CIMT) in patients with type 2 diabetes were presented.

At the American College of Cardiology Annual Scientific Session 2008, data were presented that demonstrated that ACTOS[®] (pioglitazone HCl) slows progression and reductions in atheroma volume which is a marker of coronary atherosclerosis.

Takeda submitted a New Drug Application for an additional indication of delay in progression of atherosclerosis in the U.S. (Aug 08), orally disintegrating tablets (Sep 08) and fixed dose combination with metformin in Japan (Oct 08).

Combination dosage forms	Actos + metformin	Actos +SU	Actos + SYR-322	Orally disintegrating tablets
Jpn	Filed (Oct 08)	—————	—————	Filed (Sep 08)
U.S.	Approved (Aug 05) < Actoplus met > Filed (Mar 06) < Actoplus met XR >	Approved (Jul 06) < Duetact >	Filed (Sep 08)	—————
E.U	Approved (Jul 06) < Competact >	Approved (Jan 07) < Tamdemact >	P-III	—————

[Publications]

Goldberg RB, Kendall DM, Deeg MA, A comparison of lipid and glyceemic 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	Alpha-glucosidase inhibitor	Diabetes mellitus	Voglibose	Basen (Japan)	Oral
<p>This 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 that of other oral hypoglycemic drugs, leading to the belief that this drug has less potential for inducing hypoglycemic symptoms. This drug is already available in the Japanese market as an improving agent for postprandial hyperglycemia in diabetes mellitus. A supplemental New Drug Application for an additional indication of impaired glucose tolerance (suppression of development of insulin non-dependent diabetes mellitus) was submitted in Dec 07.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
KAD-1229	Short-acting insulin secretagogue	Concomitant therapy with insulin sensitizer	Mitiglinide	Glufast (Jpn)	Oral
<p>By selectively binding to sulfonylurea receptors (SUR1) of pancreatic β-cells, KAD-1229 promotes insulin secretion thereby expressing its anti-diabetic effect. It demonstrates effects promptly after dosing as compared with conventional insulin secretagogues, so it brings insulin secretion closer to its natural patterns and improves postprandial hyperglycemia. Because of its short duration of action, Glufast is less likely to trigger hypoglycemia. An application was filed for an additional indication of concomitant therapy with an insulin-resistance improving drug in Apr 07.</p>					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
NE-58095	Bone resorption inhibitor	Paget's disease of bone	Risedronate	Benet (Jpn)	Oral
<p>NE-58095 suppresses bone metabolism by inhibiting the function of osteoclast and suppressing bone resorption. Risedronate is a first-line treatment in the U.S. and E.U. for diseases with increased bone metabolism, such as Paget's disease of bone.</p>					

Takeda begins disclosure of its development projects in phase I stage starting updates this time, aiming to ensure the transparency of corporate management through promoting the information disclosure.

■ Other alliance projects

TAK-799/TRM-1	Licensed from: Human Genome Sciences, Inc.	Agreed:	Aug 2002		
		Stage:	Under preparation for clinical trials (Japan)	Territory: Japan	
<p>A complete human antibody relevant to TRAIL-R1 discovered by Human Genome Sciences, Inc. HGS is conducting Phase II studies for multiple myeloma in the U.S.</p>					

TAK-701/HuL2G7	Licensed from: Galaxy Biotech, LLC	Agreed:	Jul 2006		
		Stage:	Under preparation for clinical trials	Territory: Worldwide	
<p>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.</p>					

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

TAK-361S	Licensed from: Japan Poliomyelitis Research Institute	Agreed:	April 2008		
		Stage:	Under preparation for clinical trials	Territory : Worldwide	
<p>Takeda will develop a "quadruple vaccine" including Sabin-IPV which is a combination of the combined diphtheria, tetanus, and acellular pertussis vaccine (DTaP) that has already been developed and marketed by Takeda. Sabin-IPV is an only inactivated poliovirus vaccine by attenuated strain, and the production process of Sabin-IPV offers better safety than those of the virulent strain-derived inactivated one. Based on these profiles, WHO expect the early development of Sabin-IPV.</p>					

■ Clinical study protocol summaries

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

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

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

■ Outcome studies

AD-4833 (1)

Study title	PROactive (PROspective 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, and below-knee amputation).		
Place	19 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).</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>		

AD-4833 (3)

Study title	PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation)		
Outline	PERISCOPE is the first clinical trial to examine the effects of an oral antidiabetic medication on the development of coronary atherosclerosis in patients with type 2 diabetes using IVUS technology.		
Place	U.S., Canada, Latin America	Total population	543 patients
Status	<p>The PERISCOPE trial was presented as a late breaker at the 57th Annual Scientific Session of the American College of Cardiology in Chicago. This trial demonstrated that ACTOS slows progression and reductions in atheroma volume which is a marker of coronary atherosclerosis. This trial adds to the body of cardiovascular data for ACTOS. ACTOS studies, conducted over the past 10 years in more than 16,000 patients, including short- and long-term trials, as well as prospective and observational studies, have shown no evidence that ACTOS is associated with an increased risk of heart attack, stroke, or death.</p> <p>The analysis demonstrated a statistically significant difference in percent change in coronary artery atheroma volume in favor of ACTOS treatment compared to glimepiride treatment. The data showed that patients treated with glimepiride, a sulfonylurea and commonly used diabetes medication, exhibited progression of coronary atherosclerosis. In contrast, the ACTOS arm showed no progression of coronary atherosclerosis over the 18-month period from the initial baseline measurement</p> <p>Cardiovascular safety data was collected by looking at macrovascular events and episodes of congestive heart failure (CHF). The number of episodes of a common cardiovascular endpoint of cardiovascular mortality, non-fatal MI, or non-fatal stroke was 6 (2.2%) in glimepiride patients and 5 (1.9%) in ACTOS-treated patients. The number of hospitalizations due to CHF were equivalent in both arms. In the ACTOS-treated group, more patients were experienced a bone fracture than in glimepiride-treated group and in glimepiride there could be seen more patients with hypoglycemia and angina than in the ACTOS-treated group.</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). 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 clinical study to investigate prevention/treatment efficacy on diabetic retinopathy (candesartan vs. placebo)		
Place	30 countries	Total population	5,231 patients
Status	<p>Data from the DIRECT Programme, the first large-scale study programme assessing the effect of treatment with an angiotensin receptor blocker (ARB) on the incidence and progression of diabetic eye complications, was presented at the European Association of the Study of Diabetes (EASD) congress in Rome in September 2008. The data show a strong trend in favour of treatment with candesartan 32mg in reducing the incidence of diabetic retinopathy in Type 1 diabetes patients, although not statistically significant, and a significant increase in regression of diabetic retinopathy in Type 2 diabetes patients.</p> <p>Study 1 'DIRECT-Prevent 1' (n=1,421) studied the effect of candesartan on the incidence of retinopathy (primary endpoint) in normotensive, normoalbuminuric Type 1 diabetes patients. In Type 1 patients with no signs of diabetic retinopathy at baseline, candesartan caused an 18% reduction in the incidence of diabetic retinopathy as measured by 2-step change on the Early Treatment of Diabetic Retinopathy Study (ETDRS) scale (primary endpoint, p=0.0508), but a 35% reduction for 3-step change (post-hoc analysis, p=0.003).</p> <p>Study 2 'DIRECT-Protect 1' (n=1,905) studied the effect of candesartan on the progression of retinopathy (primary endpoint) in normotensive, normoalbuminuric Type 1 diabetes patients already affected by retinopathy. In the Type 1 diabetic patients with retinopathy at baseline there were no differences in the results in progression of retinopathy between the two treatment groups (p=0.85).</p> <p>Study 3 'DIRECT-Protect 2' (n=1,905) studied the effect of candesartan on the progression of retinopathy (primary endpoint) in normoalbuminuric, normotensive or treated hypertensive, Type 2 diabetes patients with retinopathy. Treatment with candesartan also reduced the risk of progression of retinopathy by 13% over placebo in Type 2 diabetes patients, primary endpoint, p=0.2. However, in these Type 2 diabetes patients with relatively early signs of diabetic retinopathy, candesartan increased the probability of regression of retinopathy by 34% compared with placebo (pre-defined secondary endpoint, p=0.009).</p>		

TCV-116 (3)

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

TCV-116 (4)

Study title	HIJ-CREATE (The Heart Institute of Japan-Candesartan Randomized trial for Evaluation in Coronary Artery Disease)		
Outline	Large-scaled outcome study with coronary artery disease patients with hypertension		
Place	Japan	Total population	2,049 patients
Status	<p>During the American Heart Association's Scientific Session 2007, held at Orlando, Miami, the results of the HIJ-CREATE^[1] study ("CREATE study") were presented in late-breaking clinical trials session.</p> <p>This is a large-scaled outcome study with coronary artery disease patients with hypertension in Japan, comparing the reduction of incidence of major adverse cardiovascular events ("MACE") between therapy with candesartan cilexetil (tradename in Japan: Blopress[®]), an angiotensin receptor blocker ("ARB"), and that with non-ARB standard therapy, and the total number of patients is 2,049.</p> <ul style="list-style-type: none"> Reduction of incidence of MACE in patients with impaired renal function <p>Blopress showed 21% reduction in incidence of MACE as compared to the non-ARB standard therapy. (P=0.039)</p> <ul style="list-style-type: none"> The new onset rates of diabetes mellitus <p>The new onset rate with Blopress and non-ARB standard therapy are 1.1% and 2.9% respectively. (P=0.027)</p>		

Research Activities

■ Main joint research activities

(1) Joint researches with domestic research organizations and companies

Partner	Research subject	Schedule
Kyowa Hakko Kirin	Licensing-in of the human antibody technology	2003/7-

(2) Joint research 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	U.S.	Joint collaboration on diabetes and obesity field	2002/7-
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
Archemix Corp.	U.S.	Collaboration for Discovery and Development of Aptamer Therapeutics	2007/6-
Alnylam Pharmaceuticals, Inc.	U.S.	Collaboration for Discovery and Development of RNAi Therapeutics	2008/5-2013/5

(*) Roche and Arius Research Inc. announced that the two companies have signed a definitive agreement for Roche to acquire Arius on July 23, 2008.