

## **X. Pipeline**

### **Development Activities**

- New compounds
- Additional indications/new formulations
- Characteristics of projects
- Other alliance projects
- Clinical study protocol summaries
- Outcome studies

### **Research Activities**

- Main joint research activities

## Development activities

### ■ New Compounds

Development code <generic name>	Drug Class (administration route)	Indications	Stage		In-house/ In-license
<b>SYR-322</b> <alogliptin>	DPP-4 inhibitor (oral)	Diabetes mellitus  Diabetes mellitus (Fixed-dose combination with Actos)	US	Filed (Dec 07)	In-house
			Jpn	Filed (Sep 08)	
			EU	P-III	
			US	Filed (Sep 08)	
			EU	P-III	
Jpn	P-I				
<b>TAK-390MR</b> <dexlansoprazole>	Proton pump inhibitor (oral)	Erosive esophagitis (healing and maintenance) and non-erosive gastro-esophageal reflux disease	US	Approved (Jan 09)	In-house
			Jpn	P-II	
<b>TMX-67</b> <febuxostat>	Non-purine, selective xanthine oxidase inhibitor (oral)	Hyperuricemia in patients with gout	US	Approved (Feb 09)	In-license (Teijin)
<b>TAK-375</b> <ramelteon>	MT <sub>1</sub> /MT <sub>2</sub> receptor agonist (oral)	Insomnia	Jpn	Filed (Feb 08)	In-house
			EU	P-III *Re-submission of MAA is under consideration	
<b>Vectibix®</b> <panitumumab>	Fully human monoclonal antibody (MAb) against the human EGFR (injection)	Progressive and relapse cancer of the colon and rectum	Jpn	Filed (Jun 08)	In-license (Amgen)
		Head and neck cancer	Jpn	P-III	
<b>SNT-MC17</b> <idebenone>	Mitochondria targeted anti-oxidant (oral)	Friedreich's ataxia	EU	P-III *Re-submission of MAA is under consideration	In-license (Santhera)
		Duchenne muscular dystrophy	EU	P-II	
<b>AMG706</b> <motesanib diphosphate>	VEGFR1-3 inhibitor (oral)	Progressive non-small cell lung cancer	US	P-III	In-license (Amgen)
			EU	P-III	
			Jpn	P-III	
<b>TAK-491</b> <azilsartan medoxomil>	Angiotensin II receptor blocker (oral)	Hypertension  Hypertension (Fixed-dose combination with Chlorthalidone)	US	P-III	In-house
			EU	P-III	
			US	P-III	
<b>MLN0002</b> <vedolizumab>	α4β7 integrin inhibitor (injection)	Ulcerative colitis, Crohn's disease	US	P-III	In-house
			EU	P-III	
<b>Lu AA21004</b> <- >	Serotonin modulator & stimulator (oral)	Mood and anxiety disorders	US	P-III	In-license (Lundbeck)
			EU	P-III	
			Jpn	P-I	
<b>Hematide™</b> <- >	Synthetic, peptide-based erythropoiesis-stimulating agent (injection)	Chronic kidney disease related anemia	US	P-III	In-license (Affymax)
		Chemotherapy-induced anemia	EU	P-III	
			Jpn	P-II/III	
			-	P-I *Development suspended	
<b>ATL-962</b> <cetilistat>	Lipase inhibitor (oral)	Obesity	Jpn	P-III	In-license (Alizyme)
<b>TAK-428</b> <- >	Neurotrophic factor production accelerator (oral)	Diabetic neuropathy	US	P-II	In-house
			EU	P-II	
<b>TAK-536</b> <azilsartan>	Angiotensin II receptor blocker (oral)	Hypertension	US	P-II	In-house
			EU	P-II	
			Jpn	P-II	
<b>TAK-783</b> <- >	T-cell function regulator (oral)	Rheumatoid arthritis	US	P-II	In-house
			EU	P-II	
			Jpn	P-I	
<b>TAK-442</b> <- >	Selective factor Xa (FXa) inhibitor (oral)	Venous / arterial thromboembolism	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
<b>TAK-085</b> < omega-3-acid ethyl esters 90 >	EPA/DHA agent (oral)	Hypertriglyceridemia	Jpn	P-II	In-license (Pronova)
<b>SYR-472</b> < - >	DPP-4 inhibitor (oral)	Diabetes mellitus	US EU Jpn	P-II P-II P-I	In-house
<b>MLN0518</b> <tandutinib>	Inhibitor of receptor kinases (FLT3, PDGFR, c-KIT) (oral)	Glioblastoma	US	P-II	In-house
<b>MLN8237</b> < - >	Aurora A kinase inhibitor (oral)	Aggressive NHL, Acute myelogenous leukemia (AML), High-risk myelodysplastic syndrome (MDS); Ovarian cancer	US EU	P-II P-II	In-house
<b>Lu AA24530</b> < - >	Monoamine modulator (oral)	Mood and anxiety disorders	EU Jpn	P-II P-I	In-license (Lundbeck)
<b>CBP501</b> < - >	Cell cycle dysregulator (injection)	Malignant pleural mesothelioma Lung cancer	US -	P-II P-I	In-license (CanBas)
<b>TAK-875</b> < - >	Glucose-dependent insulin secretagogue (oral)	Diabetes mellitus	Jpn US EU	P-II P-I P-I	In-house
<b>AMG655</b> < conatumumab >	Fully human monoclonal antibody agonist directed against DR5 (TRAIL-R2) (injection)	Progressive cancer	Jpn	P-I	In-license (Amgen)
<b>TAK-100</b> < - >	DPP-4 inhibitor (oral)	Diabetes mellitus	-	P-I	In-house
<b>TAK-591</b> < - >	Angiotensin II receptor blocker (oral)	Hypertension	-	P-I	In-house
<b>TAK-700</b> < - >	Sex hormone synthesis inhibitor (oral)	Prostate cancer	-	P-I	In-house
<b>TAK-683</b> < - >	GnRH modulator (injection)	Prostate cancer	-	P-I	In-house
<b>TAK-448</b> < - >	GnRH modulator (injection)	Prostate cancer	-	P-I	In-house
<b>TAK-285</b> < - >	HER2 inhibitor (oral)	Solid tumors	-	P-I	In-house
<b>TAK-593</b> < - >	VEGFR, PDGFR inhibitor (oral)	Solid tumors	-	P-I	In-house
<b>TAK-385</b> < - >	LH-RH receptor antagonist (oral)	Endometriosis, Uterus myoma	-	P-I	In-house
<b>TAK-701</b> < - >	HGF-antibody (injection)	Advanced malignancies	-	P-I	In-license (Galaxy Biotech)
<b>TAK-901</b> < - >	Aurora B kinase Inhibitor (injection)	Advanced malignancies	-	P-I	In-house

Development code <generic name>	Drug Class (administration route)	Indications	Stage	In-house/ In-license
MLN4924 <->	Nedd 8 activating enzyme inhibitor (oral / injection)	Advanced malignancies	- P-I	In-house
MLN9708	Proteasome inhibitor (oral / injection)	Advanced malignancies	- P-I	In-house
TAK-065 <->	Neuroregeneration enhancer (oral)	Alzheimer disease, Parkinson's disease	- P-I	In-house
TAK-937 <->	Cerebroprotective agent (Injection)	Acute stroke	- P-I	In-house
TAK-438 <->	Potassium-competitive acid blocker (oral)	Acid-related diseases (GERD, Peptic ulcer, 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
TAP-144-SR <leuprorelin acetate> Leuplin (Jpn) 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	Secondary eradication of Helicobacter pylori (Single pack of three drugs) Prevention of onset of low dose aspirin related gastric ulcer Risk reduction of NSAID-related gastric ulcer	Jpn Filed (Mar 09) Jpn Filed (Mar 09) Jpn P-III	In-house
TCV-116 <candesartan cilexetil> Blopess (Jpn, EU, Asia) Amias, Kenzen, etc. (EU)	Angiotensin II receptor blocker	Fixed-dose combination with hydrochlorothiazide Fixed-dose combination with hydrochlorothiazide (high dose) Fixed-dose combination with amlodipine besylate High dose	Jpn Approved (Jan 09) EU Filed (Jun 08) Jpn Filed (Mar 09) Jpn P-III	In-house
AD-4833 <pioglitazone> Actos (Jpn, US, EU, & Asia)	Insulin sensitizer	Concomitant therapy with biguanides Concomitant therapy with insulin Fixed-dose combination with extended-release metformin Delay in progression of Atherosclerosis Orally disintegrating tablets Fixed-dose combination with metformin Fixed-dose combination with glimepiride	Jpn Approved (Dec 08) Jpn Approved (Mar 09) US Filed (Mar 06) EU Filed (Oct 08) US Filed (Aug 08) Jpn Filed (Sep 08) Jpn Filed (Oct 08) Jpn P-III	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
VELCADE® <bortezomib>	Proteasome inhibitor	First line multiple myeloma Follicular NHL First line MCL	US Approved (Jun 08) US P-III US P-III	In-house
NE-58095 <risedronate> Benet (Jpn)	Bone resorption inhibitor	Paget's disease of bone	Jpn Approved (Jul 08)	In-license (Ajinomoto)
KAD-1229 <mitigliinide> Glufast (Jpn)	Short-acting insulin secretagogue	Concomitant therapy with thiazolidinediones	Jpn Approved (Fed 09)	In-license (Kissei)
AMITIZA® <lubiprostone>	Chloride channel opener	Opioid-Induced bowel dysfunction (OBD)	US P-III	In-license (Sucampo)

■ Recent progress in stage\*

Development code	Indications	Country/Region	Progress in stage
<b>TAK-390MR</b>	Erosive esophagitis (healing and maintenance) and non-erosive gastro-esophageal reflux disease	US	Approved (Jan 09)
<b>TCV-116</b>	Hypertension (Fixed-dose combination with hydrochlorothiazide)	Jpn	Approved (Jan 09)
<b>AD-4833</b>	Diabetes mellitus (Concomitant therapy with biguanides)	Jpn	Approved (Dec 08)
<b>AD-4833</b>	Diabetes mellitus (Fixed-dose combination with extended -release metformin)	EU	Filed (Oct 08)
<b>MLN0002</b>	Ulcerative colitis, Crohn's disease	US EU	P-III P-III
<b>ATL-962</b>	Obesity	Jpn	P-III
<b>TAK-875</b>	Diabetes mellitus	Jpn	P-II
<b>CBP501</b>	Malignant pleural mesothelioma	US	P-II
<b>SYR-322</b>	Diabetes mellitus (Fixed-dose combination with Actos)	Jpn	P-I
<b>Lu AA24530</b>	Mood and anxiety disorders	Jpn	P-I
<b>TMX-67</b>	Hyperuricemia in patients with gout	US	Approved(Feb 09)
<b>KAD-1229</b>	Diabetes mellitus(Concomitant therapy with thiazolidinediones)	Jpn	Approved(Feb 09)
<b>AD-4833</b>	Diabetes mellitus(Concomitant therapy with insulin)	Jpn	Approved(Mar 09)
<b>TCV-116</b>	Hypertension(Fixed-dose combination with amlodipine besylate)	Jpn	Filed(Mar 09)
<b>AG-1749</b>	Prevention of Onset of low dose aspirin related gastric ulcer	Jpn	Filed(Mar 09)
<b>AG-1749</b>	Treatment of secondary eradication of Helicobacter pylori(Single pack of three drugs)	Jpn	Filed(Mar 09)
<b>TAK-491</b>	Hypertension (Fixed-dose combination with Chlorthalidone)	US	P-III
<b>MLN8237</b>	Aggressive NHL, Acute myelogenous leukemia (AML), High-risk myelodysplastic syndrome (MDS), Ovarian cancer	US EU	P-II P-II
<b>TAK-701</b>	Advanced malignancies	-	P-I
<b>TAK-901</b>	Advanced malignancies	-	P-I
<b>MLN9708</b>	Advanced malignancies	-	P-I
<b>TAK-937</b>	Acute stroke	-	P-I

\* Progress in stage since release of FY2008 2Q results (Nov 4, 2008).

Progress since release of FY2008 3Q results (February 3, 2009) are listed under the bold dividing line.

■ **Discontinued project\***

<b>Development code</b>	<b>Indications (Stage)</b>	<b>Reason</b>
<b>TCV-116</b>	Prevention of onset and progression of diabetic retinopathy (P-III)	With the result of DIRECT Programme which shows no statistically significant difference in the primary endpoints, we decided not to pursue this indication.
<b>TAK-242</b>	Severe sepsis(P-III)	Following a thorough review of development strategy, we have concluded that the profile of this drug does not meet the criteria to support continuation of further development activities.
<b>TAK-379</b>	Diabetes mellitus(P-II)	Following a thorough review of development strategy, we have concluded that the profile of this drug does not meet the criteria to support continuation of further development activities.
<b>TAK-375</b>	Circadian rhythm sleep disorder(CRSD) (P-II)	In consideration of future marketability, we decided to discontinue further development activities.
<b>TAK-363</b>	Frequent urination, Urinary incontinence(P-I)	Following a comprehensive review of development project, it was determined that this drug does not meet the internal criteria to proceed with further development activities.
<b>MLN8054</b>	Advanced malignancies(P-I)	Following the results of P-I studies and based on development prioritization, development was discontinued

\* Discontinued since release of FY2008 2Q results (Nov 4, 2008).

Discontinuation since release of FY2008 3Q results (February 3, 2009) 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

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.

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	KAPIDEX™	Oral

KAPIDEX, taken once-daily, employs a new modified release technology on an enantiomer of lansoprazole, which is originally developed by Takeda and is marketed by Takeda and its licensees in approximately 90 countries worldwide. KAPIDEX is the first proton pump inhibitor with a Dual Delayed Release™ formulation designed to provide two separate releases of medication.

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	ULORIC®	Oral

TMX-67 is an oral, once daily, potent non-purine selective inhibitor of xanthine oxidase which causes gout. This drug lowers the level of uric acid in the blood of hyperuricemic patients with gout, with clinical data supporting its safety and efficacy. In addition, TMX-67's safety profile does not require dose adjustment for patients with mild-to-moderate renal or hepatic impairment.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-375	MT <sub>1</sub> /MT <sub>2</sub> receptor agonist	Insomnia	Ramelteon	ROZEREM™ (U.S.)	Oral

This drug is highly specific to the MT<sub>1</sub>/MT<sub>2</sub> 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).

Development code	Drug Class	Indications	Generic name	Brand name	Administration
Vectibix™	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

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. 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.

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

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.

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.

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, in the non-clinical studies, as compared to existing ARBs on the market.

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

MLN0002 is a humanized antibody that selectively binds to  $\alpha 4\beta 7$  integrin, which inhibits the binding between  $\alpha 4\beta 7$  integrin and MAdCAM-1 (mucosal adhesion molecule 1) existing mainly in the intestinal mucosa. Integrins are a type of cell surface protein, its main roles are cellular binding to the extracellular matrix and signal transduction from the extracellular matrix. In the Phase II studies (POC) involving 400 patients with ulcerative colitis and Crohn's disease, the rate of mucosal healing and the rate of remission of symptoms including diarrhea frequently observed in patients with inflammatory bowel disease were significantly higher in the treatment group than in the placebo administration group. In these studies, the safety profile was also evaluated with satisfactory results.

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

Phase II study (POC) finished in Sep 07 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. As PEGylation allows maintenance of blood concentration, once every four weeks administration is now being applied in the clinical studies.

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 II conducted by Alizyme, Cetilistat (80mg and 120mg) caused statistically significant weight loss and reductions in HbA1c compared with placebo. Treatment discontinuations due to gastro-intestinal adverse events in the cetilistat groups are lower than those in the orlistat groups.

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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TAK-536	Angiotensin II receptor blocker	Hypertension	Azilsartan	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.

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

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. 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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-442</b>	Selective Factor Xa (FXa) inhibitor	Venous / arterial thromboembolism	Not decided yet	Not decided yet	Oral

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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-085</b>	EPA/DHA agent	Hypertriglyceridemia	omega-3-acid ethyl esters 90	Not decided yet	Oral

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. The mechanism of action is yet to be fully disclosed, however, it is expected to inhibit triglyceride synthesis in the liver.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>SYR-472</b>	DPP-4 inhibitor	Diabetes mellitus	Not decided yet	Not decided yet	Oral

This drug is 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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>MLN0518</b>	Inhibitor of receptor kinases (FLT3, PDGFR, c-KIT)	Glioblastoma	Tandutinib	Not decided yet	Oral

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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>MLN8237</b>	Aurora A kinase inhibitor	Aggressive NHL, Acute myelogenous leukemia (AML), High-risk myelodysplastic syndrome (MDS); Ovarian cancer	Not decided yet	Not decided yet	Oral

MLN8237 is an oral highly-specific small molecule Aurora A kinase inhibitor. Both Aurora A kinase and Aurora B kinase play important roles in cell mitosis, but they have different distributions in the cell and different roles in the process of mitosis. Aurora A kinase is a serine/threonine kinase that exists in the centrosome and spindle poles and is known to play an important role in the formation of spindles at the time of mitosis.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>Lu AA24530</b>	Monoamine modulator	Mood and anxiety disorders	Not decided yet	Not decided yet	Oral

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
<b>CBP501</b>	Cell cycle dysregulator	Malignant pleural mesothelioma, Lung cancer	Not decided yet	Not decided yet	Injection

Many forms of cancer therapy seek to destroy neoplastic cells by inducing DNA damage. In the presence of a DNA lesion, the damage sensor ATR becomes active. ATR initiates the G2 checkpoint, arresting cell cycle progression until the DNA repair machinery can repair the lesion. After repair is complete, the cell cycle machinery is free to initiate nuclear division. Disruption of the DNA damage-dependent mitotic checkpoint can enhance the effectiveness of cancer therapies. Millennium in collaboration with CanBas Limited, is developing CBP501. CBP501 interferes with the ability of cells to arrest in the context of DNA damage, which can have fatal consequences for dividing cells.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-875</b>	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
AMG655	Fully human monoclonal antibody agonist directed against DR5 (TRAIL-R2)	Progressive cancer	Conatumumab	Not decided yet	Injection

AMG655 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-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. While existing therapies for this indication target testosterone production in the testes, it is also secreted by cells in the adrenal cortex. Testosterone is synthesized in the mitochondrial membrane of adrenal cells by a series of enzymes including seventeen twenty lyase.

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 growth factor receptor, HER2. 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 PDGFβ.

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
<b>TAK-701</b>	HGF-antibody	Advanced malignancies	Not decided yet	Not decided yet	Injection
Tumor formation and progression correlate with increased signaling through the hepatocyte growth factor ligand to the type six receptor tyrosine kinase, MET. Signaling through these kinases has been implicated in cancer cell growth and survival, tumor migration and angiogenesis. In preclinical studies, TAK-701 has been shown to bind to the ligand inhibit binding of the ligand to the MET receptors.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-901</b>	Aurora B kinase inhibitor	Advanced malignancies	Not decided yet	Not decided yet	Injection
During cell division, Aurora kinase B is thought to play a central role in controlling the proper progression of cells through mitosis by regulating the attachment of the spindles to kinetochores, and the accurate segregation of sister chromatids to each daughter cell. Aurora kinase B is also thought to function in the separation of daughter cells during cytokinesis. The Aurora kinase genes are over-expressed and amplified in a variety of cancers. The dysregulation of the Aurora kinases and their essential roles in cell division make them attractive targets for therapeutic intervention of human cancers. In preclinical studies, TAK-901 has been shown to bind and potentially inhibit Aurora B.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>MLN4924</b>	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
<b>MLN9708</b>	Proteasome inhibitor	Advanced malignancies	Not decided yet	Not decided yet	Oral/Injection
Proteasome inhibition constitutes a unique approach to targeted therapy. Inhibition of the proteasome prevents the degradation of numerous regulatory proteins, affecting multiple signaling cascades within the cell. In vitro, non-clinical studies have shown that proteasome inhibition can be cytotoxic to a variety of cancer cell types.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-065</b>	Neuroregeneration enhancer	Alzheimer's 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
<b>TAK-937</b>	Cerebroprotective agent	Acute stroke	Not decided yet	Not decided yet	Injection
TAK-937 is a cerebroprotective agent which is designed to treat the acute stroke. Unlike the existing products which suppress the ischemic neuronal cell death through a single mechanism of action, this compound has various mechanisms such as suppressing neuroexcitatory, preventing production of inflammatory cytokine and inducing hypothermia, and inhibits the progression of the brain tissue damage caused by hypo-perfusion. Hence, this compound is expected to have an efficacy in the clinical trials, and higher efficacy is also expected in combination with thrombolytic agent.					

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>TAK-438</b>	Potassium-competitive acid blocker	Acid-related diseases (GERD, Peptic ulcer, etc)	Not decided yet	Not decided yet	Oral
TAK-438 is a potassium-competitive acid blocker with a mechanism of action to inhibit H <sup>+</sup> , K <sup>+</sup> -ATPase in a reversible and K <sup>+</sup> -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
<b>MLN0415</b>	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-κB 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
TAP-144-SR	LH-RH agonist	Prostate cancer, Endometriosis, Premenopausal breast cancer	Leuprorelin acetate	Leuplin (Jpn), Lupron (U.S.), Enantone, etc. (E.U., Asia)	Injection

Successful development of drug deliverly 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 of 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, Asia), 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 90 countries worldwide.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
TCV-II6	Angiotensin II receptor blocker	Hypertension	Candesartan cilexetil	Blopress (Jpn, E.U., Asia), 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 08. 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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AD-4833	Insulin sensitizer	Diabetes mellitus	Pioglitazone	Actos (Jpn, 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<sup>®</sup> 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<sup>®</sup> (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<sup>®</sup> (pioglitazone HCl) slows progression and reductions in atheroma volume which is a marker of coronary atherosclerosis.

Combination dosage forms	Actos + metformin	Actos +SU	Actos + SYR-322	Orally disintegrating tablets
Jpn	Filed (Oct 08)	P-III	P-I	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 > Filed (Oct 08) < Competact prolonged-release >	Approved (Jan 07) < Tamdemact >	P-III	—————

Development code	Drug Class	Indications	Generic name	Brand name	Administration
AO-128	Alpha-glucosidase inhibitor	Diabetes mellitus	Voglibose	Basen (Jpn, Asia)	Oral

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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>VELCADE®</b>	Proteasome inhibitor	First line multiple myeloma, Follicular NHL First line MCL	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 are responsible for angiogenesis and cell proliferation.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>NE-58095</b>	Bone resorption inhibitor	Paget's disease of bone	Risedronate	Benet (Jpn)	Oral

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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>KAD-1229</b>	Short-acting insulin secretagogue	Concomitant therapy with insulin sensitizer	Mitiglinide	Glufast (Jpn)	Oral

By selectively binding to sulfonylurea receptors (SUR1) of pancreatic  $\beta$ -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.

Development code	Drug Class	Indications	Generic name	Brand name	Administration
<b>AMITIZA®</b>	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, and thereby increasing the passage of the stool and improving symptoms associated with chronic idiopathic constipation. In clinical trials, 60 percent of patients who used AMITIZA experienced a spontaneous bowel movement within the first 24 hours. It improved signs and symptoms related to chronic constipation, including abdominal bloating, discomfort, stool consistency and straining. Additionally, these symptomatic improvements lasted over the 6 to 12 month treatment period.

## ■ Other alliance projects

<b>TAK-799/TRM-1</b>	<b>Licensed from:</b> Human Genome Sciences, Inc.	<b>Agreed:</b>	Aug 2002		
		<b>Stage:</b>	Under preparation for clinical trials	<b>Territory: Japan</b> (Japan)	

A complete human antibody relevant to TRAIL-R1 discovered by Human Genome Sciences, Inc. HGS is conducting Phase II studies for multiple myeloma and non-squamous non-small cell lung cancer in the U.S.

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

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>TAK-361S</b>	<b>Licensed from:</b> Japan Poliomyelitis Research Institute	<b>Agreed:</b>	April 2008		
		<b>Stage:</b>	Under preparation for clinical trials	<b>Territory : Worldwide</b>	

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.

## ■ 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 05) demonstrated that ACTOS® (pioglitazone HCl) significantly reduces the combined risk of heart attacks, strokes and death by 16% in high risk patients with type 2 diabetes. This study focused on two key endpoints: a primary combination endpoint of seven different macrovascular events of varying clinical importance; and a principal secondary combination endpoint of life-threatening events including death, heart attack and stroke.</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>		

AD-4833 (3)

<b>Study title</b>	<b>PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation)</b>		
<b>Outline</b>	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.		
<b>Place</b>	U.S., Canada, Latin America	<b>Total population</b>	543 patients
<b>Status</b>	<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)

<b>Study title</b>	<b>CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality)</b>		
<b>Outline</b>	This study was conducted to evaluate the clinical benefits of candesartan in patients with heart failure.		
<b>Place</b>	Around 26 countries	<b>Total population</b>	7,601 patients
<b>Status</b>	<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 clinical study to investigate prevention/treatment efficacy on diabetic retinopathy (candesartan vs. placebo)		
<b>Place</b>	30 countries	<b>Total population</b>	5,231 patients
<b>Status</b>	<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.</p> <p>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.</p> <p>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.</p> <p>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)

<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<sup>®</sup>, (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<sup>®</sup> reduced all-cause mortality by 15% compared with Amlodipine, although this difference was not statistically significant. In obese patients with hypertension, in particular, Blopress<sup>®</sup> significantly reduced all-cause mortality by 49% compared to Amlodipine (P=0.045). &lt;Secondary endpoint&gt;</p> <p>Blopress<sup>®</sup> 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)

<b>Study title</b>	<b>HIJ-CREATE (The Heart Institute of Japan-Candesartan Randomized trial for Evaluation in Coronary Artery Disease)</b>		
<b>Outline</b>	Large-scaled outcome study with coronary artery disease patients with hypertension		
<b>Place</b>	Japan	<b>Total population</b>	2,049 patients
<b>Status</b>	<p>During the American Heart Association's Scientific Session 2007, held at Orlando, Miami, the results of the HIJ-CREATE study ("CREATE study") were presented in late-breaking clinical trials session.</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<sup>®</sup>), 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"> <li>• Reduction of incidence of MACE in patients with impaired renal function</li> </ul> <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"> <li>• The new onset rates of diabetes mellitus</li> </ul> <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
Kirin Brewery Company Ltd. (Now Kyowa Hakko Kirin Ltd.)	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-
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-
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
Seattle Genetics	U.S.	Research collaboration on Antibody-Drug Conjugate	2009/3-

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