

IX. Pipeline

Development Activities

- New compounds
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- Characteristics of projects
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- Clinical study protocol summaries
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Research Activities

- Main joint research activities
- Recent fruits of Takeda research
- Notes

[Progress in stage (Oct 2005 - Mar 2006)]

| Development code | Indications or formulations | Brand name (country/region) | Progress in stage |
|------------------|--|---|-------------------------|
| AD-4833 | Reduction of the risk of macrovascular events in patients with type 2 diabetes mellitus and pre-existing macrovascular disease | Actos (EU) | P-III Filed (Dec 05) |
| SYR-322 | Diabetes mellitus | < Not decided yet > (U.S., EU) | P-II P-III |
| ATL-962 | Obesity | < Not decided yet > (Jpn) | P-I P-II |
| TAK-390MR | Erosive esophagitis and non-erosive gastro-esophageal reflux disease | < Not decided yet > (Jpn) | P-I |
| SPI-0211 | Chronic idiopathic constipation | < AMITIZA™ > (U.S.) | Filed Approval (Jan 06) |
| AD-4833XT | Combination drug of Actos / Metformin XT | < ACTOplus met™ XR > (U.S.) | Filed (Mar 06) |
| NE-58095 | Paget's disease | < Benet > (Jpn) | P-II P-III |
| TAK-375 | Alzheimer's sleep / wake disturbance | < ROZEREM™ > (U.S.) | P-II |
| TAK-583 | Post-herpetic neuralgia | < Not decided yet > (U.S., EU) < Not decided yet > (Jpn) | P-I P-II P-I |
| SYR-322 | Diabetes mellitus | < Not decided yet > (Jpn) | P-I |

The lower part is a progress in stage after FY2005 3Q (Jan 2006) updates.

Development activities

New compounds

| Development code <generic name> | Drug Class | Indications | Country region | Stage | In-house / In-license | Note |
|---|--|--|-------------------|-------------------|---|--|
| SPI-0211 < lubiprostone > | Chloride channel opener | Chronic idiopathic constipation | U.S. | Approved (Jan 06) | In-license (Sucampo Pharmaceuticals Inc.) | Brand name: AMITIZA™(U.S.) Development is conducted by Sucampo Launched in U.S. (Apr 06) |
| | | Constipation-predominant Irritable Bowel Syndrome | U.S. | P-III | | |
| TAK-242 < Not decided yet > | TLR4 signal transduction inhibitor | Severe sepsis | Jpn | P-III | In-house | Fast Track |
| | | | U.S. | P-III | | |
| TAK-375 < ramelteon > | MT ₁ /MT ₂ receptor agonist | Insomnia | Jpn | P-III | In-house | Brand name: ROZEREM™ (U.S.) Launched in U.S. (Sep 05) |
| | | Alzheimer's sleep / wake disturbance | EU | P-III | | |
| | | Circadian rhythm sleep disorder (CRSD) | U.S. | P-II | | |
| TAK-475 < Not decided yet > | Squalene synthase inhibitor | Hyperlipidemia | U.S. | P-III | In-house | |
| | | | EU | P-III | | |
| | | | Jpn | P-I | | |
| TAK-390MR < Not decided yet > | Proton pump inhibitor | Erosive esophagitis and non-erosive gastro- esophageal reflux disease | U.S. | P-III | In-house | |
| | | | Jpn | P-I | | |
| BNP7787 < dimesna > | Chemotherapy supportive care drug | Prevention or reduction of neurotoxicity induced by anti cancer | U.S. | P-III | In-license (BioNumerik Pharmaceuticals, Inc) | Brand name: Tavocept(U.S.) Development is conducted by BioNumerik Fast Track |
| | | | Jpn | P-III | | |
| SYR-322 < Not decided yet > | DPPIV inhibitor | Diabetes mellitus | U.S. | P-III | In-house | |
| | | | EU | P-III | | |
| | | | Jpn | P-I | | |
| TAK-428 < Not decided yet > | Neurotrophic factor production accelerator | Diabetic neuropathy | U.S. | P-II | In-house | |
| | | | EU | P-II | | |
| | | | Jpn | P-II | | |
| TAK-654 < Not decided yet > | Insulin resistance-improving drug | Diabetes mellitus | U.S. | P-II | In-house | |
| | | | EU | P-II | | |
| | | | Jpn | P-II | | |
| TAK-536 < Not decided yet > | Angiotensin II receptor antagonist | Hypertension | U.S. | P-II | In-house | |
| | | | EU | P-II | | |
| TAK-715 < Not decided yet > | p38 MAPkinase inhibitor | Rheumatoid arthritis | U.S. | P-II | In-house | |
| | | | EU | P-II | | |
| | | | Jpn | P-I | | |
| TAK-583 < Not decided yet > | Neuropathic pain-improving drug | Post-herpetic neuralgia | U.S. | P-II | In-house | |
| | | | EU | P-II | | |
| | | | Jpn | P-I | | |
| LY333531 < ruboxistaurin > | PKCβ inhibitor | Diabetic maculopathy | Jpn | P-II | In-license (Eli Lilly) | Co-development |
| TAK-128 < Not decided yet > | Myelin formation accelerator | Diabetic neuropathy | U.S. | P-II | In-license (Mitsubishi Pharma Corporation) | Fast Track |
| | | | Jpn | P-II | | |
| R-851 < Not decided yet > | Immune response modifier | Human papillomavirus (HPV) infection | U.S. | P-II | In-license (3M) | Development is conducted by 3M |
| EMD72000 < matuzumab > | Humanized, monoclonal antibody (MAb) against the human EGFR | Gastric cancer, non-small cell lung cancer (NSLC), colorectal cancer | U.S. | P-II | In-license (Merck KGaA) | Co-development |
| | | | EU | P-II | | |
| | | | Jpn | P-I | | |
| ATL-962 < cetilistat > | Lipase inhibitor | Obesity | Jpn | P-II | In-license (Alizyme) | |

Additional indications / new formulations

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

Characteristics of projects

{ New compounds}

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

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

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

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

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

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

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

| Development code | Drug Class | Indications | Generic name | Brand name | Administration |
|---|--|---------------------|-----------------|-----------------|---------------------|
| TAK-428 | Neurotrophic factor production accelerator | Diabetic neuropathy | Not decided yet | Not decided yet | oral administration |
| This is a new concept drug for diabetic neuropathy treatment. It repairs and regenerates the peripheral nerve tissues damaged by diabetes mellitus through increasing neurotrophic factors. It is expected to be a new treatment for diabetic neuropathy because of its different mechanism of actions from that of aldose reductase inhibitors and PKC inhibitors. | | | | | |

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

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

| Development code | Drug Class | Indications | Generic name | Brand name | Administration |
|---|--------------------------|----------------------|-----------------|-----------------|---------------------|
| TAK-715 | p38 MAP kinase inhibitor | Rheumatoid arthritis | Not decided yet | Not decided yet | oral administration |
| This drug is expected to improve symptoms and reduce joints destruction caused by rheumatoid arthritis by inhibiting p38 MAP kinase, leading to reduce production of TNF- α , IL-1, and IL-6. This drug is, unlike TNF- α inhibitors, low molecule entity, and therefore, can be administered orally. | | | | | |

| Development code | Drug Class | Indications | Generic name | Brand name | Administration |
|--|---------------------------------|-------------------------|-----------------|-----------------|---------------------|
| TAK-583 | Neuropathic pain-improving drug | Post-herpetic neuralgia | Not decided yet | Not decided yet | oral administration |
| This is a drug to improve neuropathic pain by suppressing neural disturbance. This drug's efficacy was verified in some neuropathic pain models. | | | | | |

| Development code | Drug Class | Indications | Generic name | Brand name | Administration |
|---|-----------------------|----------------------|---------------|-----------------|---------------------|
| LY333531 | PKC β inhibitor | Diabetic maculopathy | ruboxistaurin | Not decided yet | oral administration |
| This drug is PKC β Inhibitor. PKC (Protein kinase C) β , one of the enzymes known as adjusters of various cellular functions, becomes overactive under the hyperglycemic condition and is implicated in the underlying process of microvascular damages of angiogenesis and vascular flow disorder, leading to diabetic microvascular complications. It is expected that this drug prevents progression of diabetic retinopathy and neuropathy and improves symptom of patients by inhibiting PKC β . Eli Lilly is conducting Phase-III trials for diabetic neuropathy in the US. Takeda started Phase-II trial for diabetic maculopathy in Japan. Eli Lilly filed an NDA of diabetic retinopathy in the US (Feb 06). | | | | | |

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

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

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

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

Additional indications / new formulations

| Development code | Drug Class | Indications | Generic name | Brand name | Administration |
|--|-----------------------|--------------|--------------|--|----------------|
| AG-1749 | Proton pump inhibitor | peptic ulcer | lansoprazole | Takepron (Jpn), Prevacid (U.S.), etc | oral/injection |
| <p>This is a proton pump inhibitor having a potent inhibitory action on the gastric secretion. It suppresses the gastric acid secretion by inhibiting the proton pump within the gastric wall cells and exhibits the antiulcer action. The drug has already been launched as a therapeutic agent for peptic ulcers in approximately 100 countries worldwide.</p> <p>Injection is approved in the U.S. (May 04) and filed in Japan (Feb 04) . Symptomatic GERD was filed in Japan (Sep 04).</p> | | | | | |

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

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

| Development code | Drug Class | Indications | Generic name | Brand name | Administration |
|--|------------------------------------|-------------------|----------------------------|----------------------------|---------------------|
| AD-4833 | Insulin resistance-decreasing drug | Diabetes mellitus | pioglitazone hydrochloride | Actos (Japan, U.S., EU) | oral administration |
| <p>This is a drug that controls blood glucose levels by improving the sensitivity to insulin in the liver and peripheral tissues. The drug is taken only once daily. It does not exert action on normoglycemia and does not induce hypoglycemia.</p> <p>Landmark data from the PROactive Study, presented at the 41st meeting of the European Association for the Study of Diabetes (EASD) in Athens (Sep. 05) demonstrated that Actos significantly reduces the combined risk of heart attacks, strokes and death by 16% in high risk patients with type 2 diabetes.</p> <p>CHICAGO and PERISCOPE are being conducted in the US in order to investigate the effect of Actos on reducing the risk of cardiovascular disease in the patients with type 2 diabetes.</p> <p>An NDA of the combination drug with conventional metformin was approved in the US (Aug 05 : ACTOplus metTM) and it has been available since November 2005. It was also filed in EU (Feb 05). An extended release version of combination drug of ACTOplus metTM (Brandname: ACTOplus metTM XR) was filed in March 2006.</p> <p>Indication of "Reduction of the risk of macrovascular events in patients with type 2 diabetes mellitus and pre-existing macrovascular disease" was filed in EU (Dec 06). NDAs of the combination drug with SU were filed in US (Jun 05) and in EU (Jul 05) respectively.</p> <p>Phase III of concomitant therapy with metformin is being conducted in Japan.</p> <p>Goldberg RB, Kendall DM, Deeg MA, A comparison of lipid and glycemic effects of pioglitazone and rosiglitazone in patients with type 2 diabetes and dyslipidemia. Diabetes Care. 2005 Jul;28(7):1547-54.</p> <p>Dormandy JA, Charbonnel B, Eckland DJ, et al. Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. Lancet. 2005 Oct 8;366(9493):1279-89.</p> | | | | | |

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

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

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

Other alliance projects

| | | | |
|--|--|---|------------------------|
| TRM-1 | Licensed from: Human Genome Sciences, Inc. | Agreed Aug.2002 | |
| | | Stage Under preparation for clinical trials (Japan) | Territory Japan |
| A complete human antibody relevant to TRAIL-R1 discovered by Human Genome Sciences, Inc. This compound suppressed the growth of human breast, colon and uterine cancers in animal model. | | | |

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

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

| | | | |
|--|----------------------------------|---|------------------------|
| Hematide | Licensed from: Affymax | Agreed Feb. 2006 | |
| | | Stage Under preparation for clinical trials (Japan) | Territory Japan |
| Hematide, a synthetic peptide-based next-generation erythropoiesis-stimulating agent (ESA), is designed to stimulate the production of red blood cells. It is currently being evaluated in four Phase 2 clinical trials in the United States and Europe to treat anemia in chronic kidney disease (CKD) and cancer patients. Takeda holds an exclusive right of development and commercialization in Japan. Takeda is responsible for all development and commercialization costs in Japan, and Affymax is responsible for the manufacture and supply of drug substance to Takeda. Takeda then will manufacture the final commercial product for use in Japan. | | | |

Clinical study protocol summaries

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

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

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

Example: Clinical study protocol

| Compound | Study title | Stage | Study description |
|----------|---|-----------|--|
| TAK-375 | A study of the safety of Ramelteon in subjects with moderate to severe Chronic Obstructive Pulmonary Disease. | Phase IV | This study will evaluate the safety of ramelteon, a newly approved insomnia medication, in patients with chronic obstructive pulmonary disease(COPD). Patients will complete five study visits, three of which will require overnight stays in sleep clinic. |
| TAK-322 | Placebo-controlled study of SYR-322 in the treatment of type 2 diabetes | Phase III | To evaluate efficacy and safety of SYR-322 compared to placebo. |
| TAK-475 | Effect of TAK-475 and simvastatin alone or in combination on blood cholesterol levels. | Phase III | The purpose of this study is to evaluate the difference in efficacy and safety of TAK-475 and simvastatin compared to placebo when administrated together or alone in subjects with primary hypercholesterolemia. Subjects who have signed the informed consent will undergo necessary evaluations to determine eligibility for a dietary run-in periods. Subjects who meet randomized treatment groups:TAK-475 together with simvastatin, TAK-475 alone, simvastatin alone, or placebo. |

Outcome studies

AD-4833

| Study title | PROactive(PROspective pioglitAzon Clinical Trial In macroVascular Events) | | |
|-------------|---|------------------|----------------|
| Outline | This is a study to investigate the preventive effects on the progression of macrovascular disease in type 2 diabetes patients. AD-4833 or placebo will be added to conventional oral anti-diabetic drugs for comparative purpose. Primary endpoints are cardiovascular events(death, heart attack, stroke, below-knee amputation). | | |
| Place | 15 countries in Europe | Total population | 5,238 patients |
| Status | <p>Landmark data from the PROactive Study, presented at the 41st meeting of the European Association for the Study of Diabetes (EASD) in Athens demonstrated that ACTOS® (pioglitazone HCl) significantly reduces the combined risk of heart attacks, strokes and death by 16% in high risk patients with type 2 diabetes.</p> <p>PROactive (PROspective PioglitAzone Clinical Trial In MacroVascular Events) was a randomised, double blind, placebo-controlled outcome study to determine the effects of ACTOS on mortality and morbidity associated with cardiovascular disease progression in more than 5,000 high risk patients with type 2 diabetes when added to standard of care treatment. Standard of care included the routine use of anti-hypertensives such as ACE inhibitors and beta blockers; glucose lowering agents such as metformin, sulphonylureas and insulin; antiplatelet drugs such as aspirin, and lipid-modifying medicines such as statins and fibrates.</p> <p>This study focused on two key endpoints: a primary combination endpoint of seven different macrovascular events of varying clinical importance; and a principal secondary combination endpoint of life-threatening events including death, heart attack and stroke.</p> <p>The primary endpoint was reduced by 10% but had not reached statistical significance by study end (p=0.095). The principal secondary endpoint of life-threatening events showed that pioglitazone significantly reduced the risk of heart attacks, strokes and death by 16% (p=0.027).</p> | | |

TCV-116 (1)

| Study title | CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality) | | |
|-------------|---|------------------|----------------|
| Outline | This study was conducted to evaluate the clinical benefits of candesartan in patients with heart failure. | | |
| Place | Around 26 countries | Total population | 7,601 patients |
| Status | <p>Data presented at the European Society of Cardiology (ESC) annual meeting in August 2003 demonstrated that candesartan could reduce both cardiovascular deaths as well as hospital admissions for heart failure, across a broad spectrum of patients with chronic heart failure. CHARM consists of following three studies.</p> <p><u>CHARM-Alternative: (Candesartan vs Placebo)</u> Patients: LVEF *40% or lower, intolerance to ACE-I In patients who were not taking ACE-inhibitors due to previous intolerance, candesartan significantly reduced the risk of cardiovascular death or hospital admissions for chronic heart failure, with an overall risk reduction of 23% (p<0.0004).</p> <p><u>CHARM-Added: (Candesartan + conventional therapy vs. Conventional therapy)</u> Patients: LVEF 40% or lower In patients that were prescribed conventional therapy for chronic heart failure including an ACE inhibitor, candesartan demonstrated additional mortality and morbidity benefits. Candesartan significantly reduced the risk of cardiovascular death or hospital admissions for chronic heart failure by 15% (p=0.011) .</p> <p><u>CHARM-Preserved: (Candesartan vs. Placebo)</u> Patients: LVEF higher than 40% The results showed that 11% risk reduction in favor of candesartan (p=0.118). There was also a significant 40% reduction in the number of patients diagnosed with new onset diabetes (47 vs. 77; p=0.005).</p> <p>Pooled analysis of the three studies showed that candesartan provided a significant reduction in cardiovascular death (p=0.012) and also demonstrated a positive trend in the overall reduction in all cause mortality (p=0.055). Interestingly, it also demonstrated a significant 22% reduction in onset of new diabetes, with 163 new cases of diabetes on candesartan compared with 202 on placebo.</p> <p>*LVEF:Left Ventricular Ejection Fraction. LVEF is a clinical indicator to evaluate degree of heart failure (Normal 60-70%) *Cardiovascular death: death of stroke, myocardial infarction</p> | | |

TCV-116 (2)

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

Research Activities

Main joint research activities

(1) Joint researches with domestic research organizations and companies

| Partners | Research subject | Schedule |
|---|---|-----------------|
| Biomolecular Engineering Research Institute | Research for application of biomolecular functions | Jun-01 - Mar-06 |
| Shin Nippon Biomedical Laboratories | Research for toxico-genomics | Jan-02 - Jan-06 |
| RIKEN (The Institute of Physical and Chemical Research) | Analysis of SNPs related to pioglitazone-induced edema | Feb-03 - Mar-06 |
| Keio University | Target discovery for molecules differentiating neuronal stem cells to neurons | Apr-03 - Mar-06 |
| Kirin Brewery | Licensing-in of the human antibody technology | Jul-03 - |
| Kyoto University | Kyoto Cell / Biodynamic Simulation | Oct-03 - Mar-08 |
| Osaka University | Development of novel diagnostics of lifestyle-related diseases by novel secretory factors | Apr-04 - Mar-07 |

(2) Joint researches with overseas research organizations and companies

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

Recent fruits of Takeda research

Novel Orphan Ligands Identified by Takeda

| Ligands | Receptors | Expected target disease/area |
|---|-----------|------------------------------|
| Prolactin-releasing peptide (PrRP) | hGR3 | Gynecology |
| Apelin | APJ | Cancer |
| Galanin-like peptide (GALP) | GalR2 | Obesity |
| RF amide-Related Peptide(REFP) | OT7T022 | Gynecology |
| Metastin | OT7T175 | Gynecology |
| Neuropeptide W (NPW)/Neuropeptide B (NPB) | GPR7/GPR8 | Obesity |
| QRFP | AQ27 | Obesity |

Novel Orphan Receptors (Ligands are known) Identified by Takeda

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

Disease-specific Expression Profiles for Differentially Regulated Genes

Identified by Takeda

| Gene discovered | Expected target disease |
|-----------------|-------------------------|
| CLCA1 | Respiratory diseases |
| LLPL | Atherosclerosis |

Notes

- December 2005, Takeda acquired all rights and information about a novel target which was validated by the collaboration with Evotec Neurosciences (Germany).
- March 2006, Takeda acquired an exclusive right of LG474, a target for drug discovery in cardiovascular field, which was discovered by Lexicon (Texas,USA)
- March 2006, Takeda acquired an exclusive access to certain number of functional mouse monoclonal antibodies developed by Arius (Canada).