

. Research and Development

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Main joint research activities

(1) Joint researches with domestic research organizations and companies

| Partners | Research subject | Schedule |
|--|--|-----------------|
| BF Research Institute | Basic research for development of medicines for dementia | Feb-97 - Feb-04 |
| New Energy & Industrial Technology Development Organization (NEDO) Project | Development of a support system for screening of pharmaceutical compounds (NEDO project) | Jul-99 - Mar-04 |
| Kagoshima University | Joint research on efficacy evaluation of anti-HIV drugs | Oct-97 - Mar-04 |
| RIKEN (The Institute of Physical and Chemical Research) | Research for physiological function of p51 oncogene, an original form of p53, and its application to medical treatment | Oct-00 - Mar-04 |
| 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 |
| Keio University | Research for human genome relating to hypertension and diabetic organopathy | Mar-02 - Feb-05 |
| RIKEN (The Institute of Physical and Chemical Research) | Research for human genome relating to osteoarthritis | Jul-02 - Mar-05 |
| Kirin Brewery | Licensing-in of the human antibody technology | Jul-03 - |

(2) Joint researches with overseas research organizations and companies

| Partner | Country | Research subject | Schedule |
|---|---------|--|-----------------|
| WHO | | Joint research on antimalarial drug discovery | Oct-99 - Oct-04 |
| Celera | U.S. | Joint research on human genome | Mar-00 - Feb-05 |
| Array BioPharma | U.S. | Joint research on lead compound synthesis | Jul-01 - Jul-04 |
| Gene Logic | U.S. | Data base of gene expression | Mar-02 - Mar-05 |
| Oxford University | 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-05 |
| Evotec NeuroSciences | Germany | Drug discovery alliance in Alzheimer's disease | Aug-03 - Jul-07 |

Recent Fruits of Takeda Research

(1) Discovery of a Novel Mechanism of Insulin Secretion through a Fatty Acid Receptor GPR40

Through orphan receptor and ligand research using genomic data, Takeda discovered a novel insulin secretion mechanism through free fatty acids, that promote insulin secretion by activating a receptor GPR40.

GPR40 was discovered as an orphan (without identified ligands) receptor in 1997, and last year it was found to express in the pancreas, having fatty acids as ligand. Takeda is the first body to have clarified the function of GPR40 as is mentioned above.

With these findings, new chemical entities that have specific action on GPR40 are expected to lead to the development of anti-diabetic drugs with novel mechanism of action, through controlling serum insulin level.

The above report appeared at advance online publication of "Nature" from February 24, 2003 and was published in the journal "Nature" on March 13 respectively.

(2) Discovery of a G protein-coupled Receptor Responsive to Bile Acids

Through orphan receptor and ligand research using genomic data, Takeda discovered that a novel G protein-coupled receptor, TGR5, was responsive to bile acids as a cell-surface receptor. The quantitative analysis for TGR5 mRNA showed that it was abundantly expressed in monocytes/macrophages, and treatment with bile acids was found to suppress the cytokine productions and phagocytosis. These findings suggest that TGR5 play a role in the immunosuppressive action of bile acids, and are expected to lead to the development of immunomodulatory drugs.

The above report appeared at online publication of "Journal of Biological Chemistry" from February 24, 2003 and was published in the printed journal on March 14.

Novel Orphan Ligands Identified by Takeda

| Ligands | Receptors | Expected target disease/area |
|------------------------------------|-----------|------------------------------|
| Prolactin-releasing peptide (PrRP) | hGR3 | Gynecology |
| Apelin | APJ | HIV infection |
| Galanin-like peptide (GALP) | GalR2 | Obesity |
| RF amide-Related Peptide(REFP) | OT7T022 | Gynecology |
| Metastin | OT7T175 | Gynecology |
| Neuropeptide W (NPW) | GPR7/GPR8 | Obesity |
| Neuropeptide B (NPB) | GPR7 | 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/15E | Gynecology |
| Bile acid | TGR5 | Immunology |
| Fatty acid | GPR40 | Diabetes |

Disease-specific Expression Profiles for Differentially Regulated Genes Identified by Takeda

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

Overview of project status (new compounds)

| Development code <generic name> | Drug Class | Indications or formulation | Country/ region | Stage of development |
|------------------------------------|---|--|--------------------|-------------------------|
| TAK-375 | Melatonin receptor agonist | Primary insomnia | Jpn | P-II |
| <ramelteon> | | | U.S. | P-III |
| | | | EU | P-III |
| | | Circadian rhythm sleep disorder (CRSD) | U.S. | P-II |
| TAK-559 | Insulin resistance-improving drug | Diabetes mellitus | Jpn | P-I |
| <Not decided yet> | | | U.S. | P-III |
| | | | EU | P-III |
| TAK-013 | LH-RH antagonist | Endometriosis, uterine fibroid | Jpn | P-I |
| <sufugolix> | | | U.S. | P-II |
| | | | EU | P-II |
| MCC-135 | Ca ⁺⁺ uptake enhancer/ Na ⁺ /Ca ⁺⁺ exchange system inhibitor | Chronic heart failure, myocardial infarction | U.S. | P-II |
| <caldaret> | | | EU | P-II |
| TAK-370 | Serotonin 5-HT ₄ receptor agonist | Gastro-esophageal reflux disease (GERD) | U.S. | P-II |
| <mosapride citrate> | | | | |
| TAK-475 | Squalene synthase inhibitor | Hyperlipemia | EU | P-II |
| <Not decided yet> | | | | |
| TAK-428 | Neurotrophic factor production accelerator | Diabetic neuropathy | U.S. | P-II |
| <Not decided yet> | | | EU | P-II |
| TAK-654 | Insulin resistance-improving drug | Diabetes mellitus | Jpn | P-I |
| <Not decided yet> | | | U.S. | P-II |
| | | | EU | P-II |
| TAK-802 | AchE inhibitor | Hypoactive bladder | Jpn | P-II |
| <Not decided yet> | | | | |

Overview of project status (additional indications / new formulations)

| Development code <generic name> Brand name (country/region) | Drug Class | Indications or formulation | Country/ region | Stage of development |
|---|-----------------------|---|--------------------|-------------------------|
| AG-1749 <lansoprazole> | Proton pump inhibitor | Symptomatic-GERD | Jpn | P-III |
| Takepron (Jpn , Asia) | | Injectable formulation | Jpn | P-III |
| Prevacid (U.S. , Asia) | | Injectable formulation | U.S. | Filed (Dec 02) |
| Ogast , Agopton , Lansox , etc. (EU) | | Smaller capsule | Jpn | Filed (Dec 02) |
| TAP-144-SR <leuprorelin acetate> | LH-RH agonist | 3-Month depot/premenopausal breast cancer | Jpn | P-II |
| Leuplin (Jpn) | | 6-month depot/prostate cancer | U.S./EU | P-II/III |
| Lupron Depot (U.S.) | | | | |
| Enantone etc. (EU , Asia) | | | | |

| Development code <generic name> Brand name (country/region) | Drug Class | Indications or formulation | Country/ region | Stage of development |
|--|--|--|--------------------|--|
| TCV-116 <candesartan cilexetil> Blopress (Jpn , EU , Asia) | Angiotensin II receptor antagonist | Chronic heart failure | Jpn | Filed (Dec 01) |
| Amias, Kenzen, etc. (EU) | | Diabetic nephropathy | Jpn | P-II |
| | | Fixed combination with diuretic | Jpn | Filed (Dec 02) |
| | | High dose | Jpn | P-III |
| | | Outcome study, DIRECT (Diabetic Retinopathy Candesartan Trial) | EU | P-III |
| AD-4833 <pioglitazone hydrochloride> Actos (Jpn , U.S., EU , Asia) | Insulin resistance-decreasing drug | Outcome study, PROACTIVE (PROspective pioglitAZone Clinical Trial In macroVascular Events) | EU | P-III |
| | | Monotherapy (30mg), High dose (45mg) for combination therapy 45mg tablet | EU | Approved (Aug 03) Approved (Sep 03) |
| | | Combination therapy (45mg) | U.S. | Filed (Jan 03) |
| | | Delay in progression of Atherosclerosis | U.S. | P-III |
| AO-128 <voglibose> Basen (Jpn , Asia) | α -glucosidase inhibitor | Impaired glucose tolerance (IGT) | Jpn | P-III |
| | | Fast disintegrating tablet | Jpn | Filed (Feb 03) |
| TAK-453-SR <morphine hydrochloride> | Morphine hydrochloride sustained release capsules | Cancerous pain | Jpn | P-III |
| MH-15E <morphine hydrochloride> | Morphine hydrochloride for extradural administration | Cancerous pain | Jpn | Filed (Jan 03) |
| NE-58095 <risedronate> | Bone resorption inhibitor | Once-a-week formulation | Jpn | P-III |

Progress in pipeline stage (Apr-Sep.2003)

| Development code | Indications or formulations | Brand name (country/region) | Progress of development stage |
|------------------|---|-----------------------------|-------------------------------|
| AD-4833 | Monotherapy (30mg), High dose (45mg) for combination therapy | Actos (EU) | Filed Approved (Aug 03) |
| AD-4833 | 45mg tablet | Actos (EU) | Filed Approved (Sep 03) |
| TAK-559 | Diabetes | undecided yet | P-II P-III |
| TAK-802 | Hypoactive bladder | undecided yet | P-II |
| TAK-654 | Diabetes | undecided yet | P-II |

Discontinuance of development (Apr-Sep.2003)

| Development code | Indications / Stage of development | Reason of discontinuation |
|------------------|------------------------------------|--|
| TAK-677 | P-II | Expected efficacy did not verified in Phase II studies. |
| TAK-637 | P-II | Based on the results of Ph-II studies and non-clinical studies, discontinuance of the development was decided from the risk/benefit viewpoint. |
| TAK-427 | P-II | Based on the results of Ph-II studies, discontinuance of the development was decided from the risk/benefit viewpoint. |

Stage of product pipeline in Japan, U.S. and EU

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|---|----------------------|----------|------------|-------|----------|
| TAK-375 | Melatonin receptor agonist Primary insomnia | | Japan | U.S. EU | | |
| | Circadian rhythm sleep disorder (CRSD) | | U.S. | | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | ramelteon | Original | | | | |
| <p>[Mechanism of action/description] (Melatonin receptor agonist) This drug is highly specific to the ML-1 receptor and induces sleep very akin to natural sleep in monkeys and cats. It has also been recognized that the drug has less adverse reactions such as movement disorder, disturbance of memory and drug dependence that are clinically relevant with the existing benzodiazepine hypnotic drugs. In the U.S., Phase III study for primary insomnia and Phase II study for CRSD are ongoing.</p> <p>[Publications] · International Journal of Neuropsychopharmacology (2000) 3, Sup.1 S214 · Japanese Journal of Pharmacology (2001) 85, Sup.I 257P</p> | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|--------------------------------------|----------------------|----------|------------|-------|----------|
| TAK-559 | Diabetes mellitus | Japan | | EU U.S. | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | Not decided yet | Original | | | | |
| <p>[Mechanism of action/description] (Insulin resistance-improving drug) This is an insulin resistance-improving drug with a non thiazolidinedion (TZD) structure. It controls blood glucose levels by improving the insulin resistance in liver and peripheral tissues. It is expected to have less possibility of unfavorable reactions such as body weight gain and edema compared to the TZD compounds.</p> | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|---|---|----------------------|------------|-----------|-------|----------|
| TAK-013 | LH-RH antagonist Endometriosis, uterine fibroid | Japan | U.S. EU | | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | sufugolix | Original | | | | |
| <p>[Mechanism of action/description] (LH-RH antagonist) This drug is an LH-RH antagonist that can be administered by oral route. It has a potent hormonal inhibitory action. It is expected to be a drug that is convenient for use in endometriosis and uterine fibroid. It is characterized by various points such as no induction of "flare up" that is clinically relevant with LH-RH agonists, fast onset of action and convenience of once-a-day administration.</p> | | | | | | |

Stage of product pipeline in Japan, U.S. and EU

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|--------------------------------------|---------------------------------|------------|-----------|-------|----------|
| MCC-135 | CHF and myocardial infarction | | EU U.S. | | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | Not decided yet | In-licensed (Mitsubishi Pharma) | | | | |
| [Mechanism of action/description] (Ca ⁺⁺ intake promotion/Na ⁺ /Ca ⁺⁺ exchange system inhibitor) This drug exhibits heart dilating disorder-improving effect and cardiac muscle-protecting (inhibiting necrosis of heart muscle) by the promoting action of Ca ion intake in the myoplasmic reticulum of the cardiac muscle cells as well as by the inhibiting action of Na-Ca ion exchange system. It is expected to be a drug for treatment of cardiac diseases having a new mechanism of action. | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|---|-------------------------|----------|-----------|-------|----------|
| TAK-370 | Gastro-esophageal reflux disease (GERD) | | U.S. | | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | Mosapride citrate | In-licensed (Dainippon) | | | | |
| [Mechanism of action/description] (Gastroprokinetic drug) This is a gastroprokinetic drug that enhances gastrointestinal motility by acting on serotonin 5-HT ₄ receptor selectively. It has less adverse reactions such as development of extrapyramidal symptoms and lactation abnormality, which are often reported with conventional drugs of that class, as well as less possibility of adverse effect on heart (prolongation (heartburn, nausea and vomiting) associated with chronic gastritis. Takeda has been granted a world-wide right of development and marketing excluding Japan, China, Taiwan and Korea. | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|--------------------------------------|----------------------|----------|-----------|-------|----------|
| TAK-475 | Hyperlipemia | | EU | | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | Not decided yet | Original | | | | |
| [Mechanism of action/description] (Squalene synthase inhibitor) This is an anti-hyperlipidemic drug having a new mechanism of action based on its squalene synthase inhibitory action. It is expected that the drug has less possibility of developing rhabdomyolysis compared to HMG-CoA reductase inhibitors that currently offer the first-line therapy for this disease. | | | | | | |

Stage of product pipeline in Japan, U.S. and EU

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|--------------------------------------|----------------------|------------|-----------|-------|----------|
| TAK-428 | Diabetic neuropathy | | EU U.S. | | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | Not decided yet | Original | | | | |
| <p>[Mechanism of action/description] (Neurotrophic factor production accelerator) This is a diabetic neuropathy treatment drug of a new concept that increasing neurotrophic factors repair and regenerate the peripheral nerve tissues damaged by diabetes mellitus.</p> | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|--------------------------------------|----------------------|----------|-----------|-------|----------|
| TAK-654 | Diabetes mellitus | Japan | US EU | | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | Not decided yet | Original | | | | |
| <p>[Mechanism of action/description] (Insulin resistance-improving drug) This is an insulin resistance-improving drug with a non-thiazolidinedione (TZD) structure. It controls blood glucose by improving the insulin resistance in liver and peripheral tissues. It is expected to have less possibility of unfavorable reactions such as weight gain and edema, compared to the TZD compounds.</p> | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|---|--------------------------------------|----------------------|----------|-----------|-------|----------|
| TAK-802 | AchE inhibitor Hypoactive bladder | | Japan | | | |
| [Product name] | Not decided yet | [Dosage form] Tablet | | | | |
| [Generic name] | Not decided yet | Original | | | | |
| <p>[Mechanism of action/description] (AChE inhibitor) This drug improves urinary disturbance through increasing contraction of detrusor muscle in voiding phase by inhibiting AchE. It is expected to have superior urinary voiding efficiency without deterioration of storage function of bladder due to its weak contraction in detrusor muscle in storage phase and urethra sphincter. These contractions are always problem in other AchE inhibitors.</p> | | | | | | |

Stage of product pipeline in Japan, U.S. and EU

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|---|---|----------|----------|-----------|-------|--------------|
| AG-1749 | Proton pump inhibitor Peptic ulcers | | | | | |
| (New dosage form) | | | | | | |
| (Additional indication) | Symptomatic GERD | | | Japan | | |
| | Fast disintegrating tablet | | | | | U.S/EU/Japan |
| (New dosage form) | Injection | | | Japan | U.S. | |
| | Smaller capsule | | | | Japan | |
| [Product name] | Takepron (Jpn), Prevacid (U.S.), Zoton (U.K.) | | | | | |
| [Generic name] | Lansoprazole | Original | | | | |
| [Mechanism of action/description] | | | | | | |
| (Proton pump inhibitor) | | | | | | |
| 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 put on the markets as a therapeutic agent for peptic ulcers in more than 90 countries of the world. Injection is filed in the U.S. and is under development (Phase III) in Japan, and the clinical trials for the treatment of symptomatic GERD are at Phase III stage. | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|--|--------------------------------|----------|-----------|-------|----------|
| TAP-144-SR | LH-RH agonist | | | | | U.S. |
| 3M,6M DPS | 3-Month depot formulation (Breast Cancer) | | Japan | | | |
| (New dosage form) | 6-Month depot formulation (Prostate Cancer) | | | U.S./EU | | EU |
| [Product name] | Leuplin (Japan), Lupron (U.S.), Enantone etc. (EU) | [Dosage form] Injection | | | | |
| [Generic name] | Leuprorelin acetate | Original | | | | |
| [Mechanism of action/description] | | | | | | |
| (LH-RH agonist) | | | | | | |
| This is the 3-month depot formulation of already available "Leuplin" of once-a-month dosing. This formulation has already been put on the market abroad, and the 4-month depot has already been marketed in the U.S. The 3-month depot formulation for prostate cancer was launched in Japan in August 2002 and its application for breast cancer is under phase III clinical trials. In the U.S. and EU, the 6-month depot formulation for prostate cancer is under phase II/III studies. | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|---|---|-----------------------------|----------|-----------|-------|----------|
| TCV-116 | Angiotensin II receptor antagonist | | | | | |
| (Additional indications) | (1) Chronic heart failure (CHF) | | | | Japan | |
| | (2) Diabetic nephropathy | | | EU | | |
| | (3) Fixed combination with diuretic | | Japan | | Japan | U.S./EU |
| | (4) High dose | | | Japan | | |
| | (5) Diabetic RETinopathy Candesartan Trial(DIRECT) | | | EU | | |
| [Product name] | Blopress (Jpn, EU), Atacand (U.S.), Amias (U.K.), Kenzen (Fr) | [Dosage form] Tablet | | | | |
| [Generic name] | Candesartan cilexetil | Original | | | | |
| [Mechanism of action/description] | | | | | | |
| (Angiotensin receptor antagonist) | | | | | | |
| The drug lowers blood pressures by suppressing the effect of angiotensin (A), 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. It is expected that the drug would be also effective for heart failure, diabetic retinopathy and nephropathy. Clinical evaluation for additional application of these indications are now going on. Outcome study "DIRECT" is being conducted in EU to invest prevention/treatment efficacy on diabetic retinopathy. | | | | | | |
| [Publications] | | | | | | |
| · Journal of Human Hypertension (1997) 11, Suppl. 2 | | | | | | |
| · J. Clin. Therap. Medicines (1996) 12, 2613-2661 | | | | | | |

Stage of product pipeline in Japan, U.S. and EU

| Development code | Indications/action or classification | Phase | Phase | Phase | Filed | Launched |
|---|--|----------------------|-------|-------|-------|----------|
| AD-4833 | Insulin resistance-decreasing drug | | | | | |
| (Additional indication) | (1) PROspective pioglitAzone Clinical Trial In macroVascular Events (PROactive) | | | EU | | |
| | (2) Monotherapy | | | | | EU |
| | (3) Delay in progression of Atherosclerosis | | | U.S. | | |
| | (4) Combination therapy (45mg) | | | | U.S. | EU |
| [Product name] | Actos (Japan), Actos (U.S., EU) | [Dosage form] Tablet | | | | |
| [Generic name] | Pioglitazone hydrochloride | Original | | | | |
| <p>[Mechanism of action/description] (Insulin resistance-improving drug)</p> <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. In Japan, the concomitant therapy with α-glucosidase was approved in Jun. 2002. An outcome study (PROactive) is ongoing with the targeted number of patients already having been enrolled.</p> <p>Approval for type 2 diabetes mellitus: Japan (99/09/22), U.S. (99/07/15), EU (00/10/13)</p> <p>[Publications]</p> <ul style="list-style-type: none"> · JAP. J. CLI. MED.(1997), 74(5), 162-296 · JAP. J. CLI. MED.(1997), 74(6), 165-311 | | | | | | |

| Development code | Indications/action or classification | Phase | Phase | Phase | Filed | Launched |
|---|--|----------------------|-------|-------|-------|----------|
| AO-128 | α-glucosidase inhibitor | | | | | |
| (Additional indication) | Impaired glucose tolerance (IGT) | | | Japan | | |
| | Fast disintegrating tablet | | | | Japan | |
| [Product name] | Basen (Japan) | [Dosage form] Tablet | | | | |
| [Generic name] | Voglibose | Original | | | | |
| <p>[Mechanism of action/description] (α-glucosidase inhibitor)</p> <p>The drug inhibits the hydrolase (α-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 going on with the intension of supplementing the indication of glucose tolerance abnormality (suppression of development of insulin non-dependent diabetes mellitus), and an additional formulation of fast disintegrating tablet was filed and under review.</p> | | | | | | |

| Development code | Indications/action or classification | Phase I | Phase II | Phase III | Filed | Launched |
|--|---|-----------------------|----------|-----------|-------|----------|
| TAK-453-SR | Morphine hydrochloride sustained release capsule | | | | | |
| | Cancerous pain | | | Japan | | |
| [Product name] | Not decided yet | [Dosage form] Capsule | | | | |
| [Generic name] | Morphine hydrochloride | | | | | |
| <p>[Mechanism of action/description]</p> <p>This is a small-sized sustained release capsule of once-a-day administration used for treatment of various types of cancers associated with agonizing pain.</p> | | | | | | |

Pre-clinical/Phase-I projects already announced as exceptional cases

| | | |
|---|-----------------|--|
| TAK-165 | Original | Presented at: |
| | | The 93rd American Association for Cancer Research (Apr.2002) |
| Stage Phase-I (Japan, U.S., EU) | | |
| Description | | |
| This is a novel anti-cancer agent discovered by Takeda. TAK-165 suppresses the growth of HER2 positive cell by inhibition of HER2 tyrosine kinase in vivo. The agent also demonstrates anti-tumor activity against HER2 over-expressing xenograft models. | | |
| TAK-165 was assigned as fast-track product by the U.S. FDA in March 2002, for treatment of metastatic breast cancers that are either refractory to Herceptin treatment or where the patients are not eligible for that treatment. | | |

| | | |
|---|---|------------------------------|
| TAK-201 | Licensed from: Meiji Milk Products Co., Ltd. | Agreed Nov. 2000 |
| | | Stage Phase-I (Japan) |
| Description | | |
| This substance acts directly onto immunocytes (T cells) to prevent allergic response in patients of cryptomeria pollinosis. | | |

| | | |
|---|---|---------------------------------|
| TAK-128 | Licensed from: Mitsubishi Pharma | Agreed Feb. 2001 |
| | | Stage Phase-I (U.S., EU) |
| Description | | |
| Unlike ARI, TAK-128 enhances nerve regeneration and has prolonged effect against diabetic nerve damage. | | |

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

| | | |
|--|---------------------------------------|--|
| TRM-1 | Licensed from: Human Genome | Agreed Aug., 2002 |
| | | Stage Under preparation for clinical trials (Japan) |
| Description | | |
| A complete human antibody relevant to TRIAL-R1 discovered Human Genome Sciences, Inc. It was shown in animal | | |

Outcome studies

TCV-116 (1)

| | | | |
|----------------------|--|------------------------------|----------------|
| Study title | CHARM (Candesartan in Heart failure Assessment of Reduction in Mortality) | | |
| Brief outline | This is a comparative study vs. placebo on the mortality/ hospitalization ratio in patients with heart failure. | | |
| Place | Around 26 countries | Registered population | 7,601 patients |
| Status | 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. | | |

TCV-116 (2)

| | | | |
|----------------------|--|--------------------------|----------------|
| Study title | DIRECT (DIabetic RETinopathy Candesartan Trial) | | |
| Brief outline | The world's first large scale study to investigate prevention/treatment efficacy on diabetic retinopathy (D.B.T. vs. | | |
| Place | 26 countries | Target population | 4,500 patients |
| Status | On-going. The result is expected to be available in 2005. | | |

AD-4833

| | | | |
|----------------------|--|--------------------------|----------------|
| Study title | PROactive(PROspective pioglitAzon Clinical Trial In macroVascular Events) | | |
| Brief outline | This is a study to investigate the preventive effects on the progression of macrovascular disease in type 2 diabetes patients. AD-4833 or placebo will be added to conventional oral anti-diabetic drugs for comparative purpose. Endpoints are heart attack, stroke, below-knee amputation and cardiovascular events. | | |
| Place | 15 countries in Europe | Target population | 5,000 patients |
| Status | Patients recruitment completed. The result is expected to be available in 2005. | | |