Drugs of the Future 2004, 29(8): 843-872

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Annual Update 2003/2004 - Treatment of Metabolic Disorders

As in previous months, the goal of this section is to present a balanced picture of the current status of therapies for metabolic disorders in the clinical stage, summarizing in a few pages the most important advances in this area over the last year or so. A table of oncolytic drugs for the treatment of bone cancer, osteosarcoma and cancer metastatic to the bone has been included at the end of this Annual Review.

Treatment of Metabolic Disorders by Condition

Condition	Phase	Drug	Source
Fracture	III	Chrysalin®	Chrysalis BioTechnology/OrthoLogic
	II	Ono-4819	Ono Pharmaceutical
	II	rhIGF-I/rhIGFBP-3	Insmed
	II	Trafermin[1]	Kaken
	I	Calcitonin (oral)[2]	Nobex
Gaucher's disease	I/II	Gene-activated glucocerebrosidase	Transkaryotic Therapies
	L-2003 (type 1)	Miglustat[3]	Actelion/Celltech Group
	III (type 3)	Miglustat[1,3]	Actelion/Celltech Group
Hyperammonemia	L-2003	Carglumic acid	Orphan Europe
Hyperphosphatemia	R-2004	Lanthanum carbonate[3]	Shire/Bayer
	II	Colestilan[1,3]	Mitsubishi Pharma
	II	Phosphate binder	ML Laboratories/Ineos Silicas
Hyperuricemia	Prereg.	Febuxostat[3]	Teijin/Ipsen/TAP Pharmaceutical
Lysosomal storage diseases	I	CDP-923	Celltech Group
	I	GENZ-112638	Genzyme
Mucopolysaccharidosis	III	Arylsulfatase B (recombinant human)	BioMarin
Mucopolysaccharidosis I	L-2003	Laronidase[3]	BioMarin/Genzyme
Mucopolysaccharidosis II (Hunter's syndrome)	III	Idursulfase	Transkaryotic Therapies/Genzyme
Niemann-Pick disease	III	Miglustat[1,3]	Actelion/Celltech Group
Obesity	III	Axokine®	Regeneron
	III	Rimonabant hydrochloride	Sanofi-Synthélabo
	II	AOD-9604	Metabolic Pharmaceuticals
	II	ATL-962	Alizyme/Takeda
	II	C-2735	Merck & Co.
	II	GI-181771	GlaxoSmithKline
	II	P-57	Phytopharm
	II	Pramlintide acetate[3]	Amylin
	I	APD-356	Arena
	I	C-2624	Merck & Co.
	I	C-5093	Merck & Co.
	I	Chromium picolinate/conjugated linoleic acid	Nutrition 21
	I	N-5984	Kyorin/Nisshin Pharma
	I	PEG-Axokine®	Regeneron/Nektar Therapeutics
	I	PYY3-36	Amylin/Nastech
	I	S-2367	Shionogi
	I	SLV-319	Solvay/Bristol-Myers Squibb
	I	SR-147778	Sanofi-Synthélabo
	I	T-71	Tularik
	Discontinued	SR-146131	Sanofi-Synthélabo
	Discontinued	SSR-125180	Sanofi-Synthélabo
Osteoporosis	Prereg.	Strontium ranelate[3]	Servier/Fujisawa
	III	ALX1-11[3]	NPS Pharmaceuticals/Nycomed
	III	Arzoxifene hydrochloride[3]	Lilly
	III	Lasofoxifene tartrate[3]	Ligand/Pfizer
	III	Minodronic acid[3]	Ono Pharmaceutical/Yamanouchi
	II/III	AMG-162	Amgen
	II	AAE-581	Novartis
	II	Apomine™	Ilex Oncology
	II	Calcitonin (oral)[2]	Emisphere/Novartis
	II	ED-71	Chugai
	II	Neridronate sodium[1]	Abiogen
	II	PSK-3471 (SERM-3471)	ProSkelia/Aventis Pharma
	II	Teriparatide (intranasal)[2,3]	Chugai/Daiichi Suntory

Continuation

Treatment of Metabolic Disorders by Condition

Condition	Phase	Drug	Source
Osteoporosis	I/II	AC-100	Acologix
	I/II	CP-533536	Pfizer/Atrix
	I	423557	GlaxoSmithKline
	I	BIM-44058	Ipsen/Teijin
	I	CHF-4227	Chiesi
	I	HF-0299	Hunter-Fleming
	I	Ostabolin-C™	Zelos Therapeutics
	I	SB-462795	GlaxoSmithKline
	I	Teriparatide (oral)[2,3]	Emisphere/Lilly
	I	Teriparatide (transdermal)[2,3]	Theratechnologies/Alza (Johnson & Johnson)
Osteoporosis (anorexia nervosa)	Prereg.	Norgestimate/ethinylestradiol[1]	Ortho-McNeil
Osteoporosis (in men)	I	Fispemifene	Hormos
Osteoporosis, postmenopausal	R-2003	Drospirenone/estradiol	Schering AG
	R-2003	Ibandronate sodium[1,3]	GlaxoSmithKline/Roche
	III	Bazedoxifene acetate[3]	Ligand/ Wyeth
	III	Bazedoxifene/conjugated estrogens	Ligand/Wyeth
	III	Zoledronic acid monohydrate[1,3]	Novartis
	II/III	Ospemifene[3]	Hormos
	I	Teriparatide (intranasal)[1]	Nastech
Paget's disease	III	Neridronate sodium[1]	Abiogen
	III	Zoledronic acid monohydrate[1,3]	Novartis
	I/II	Gallium maltolate	Titan
Phenylketonuria	I	Sapropterin dihydrochloride[3]	BioMarin
Pompe's disease	III	Recombinant human acid alpha-glucosidase[3]	Genzyme
Spinal fusion	I/II	Chrysalin®	Chrysalis BioTechnology/OrthoLogic
Tay-Sachs disease	III	Miglustat[1,3]	Actelion/Celltech Group

[1]Launched for another indication. [2]New formulation. [3]Monograph previously published in Drugs of the Future.

Treatment of Metabolic Disorders by Source

Source	Condition	Drug	Phase
Abiogen	Osteoporosis	Neridronate sodium[1]	II
	Paget's disease	Neridronate sodium[1]	III
Acologix	Osteoporosis	AC-100	I/II
Actelion	Gaucher's disease: type 1	Miglustat[3]	L-2003
	Gaucher's disease: type 3	Miglustat[1,3]	III
	Niemann-Pick disease	Miglustat[1,3]	III
	Tay-Sachs disease	Miglustat[1,3]	III
Alizyme	Obesity	ATL-962	II
Alza (Johnson & Johnson)	Osteoporosis	Teriparatide (transdermal)[2,3]	I
Amgen	Osteoporosis	AMG-162	II/III
Amylin	Obesity	Pramlintide acetate[3]	II
		PYY3-36	I
Arena	Obesity	APD-356	I
Atrix	Osteoporosis	CP-533536	I/II
Aventis Pharma	Osteoporosis	PSK-3471 (SERM-3471)	II
Bayer	Hyperphosphatemia	Lanthanum carbonate[3]	I
BioMarin	Mucopolysaccharidosis	Arylsulfatase B (recombinant human)	III
	Mucopolysaccharidosis I	Laronidase[3]	L-2003
	Phenylketonuria	Sapropterin dihydrochloride[3]	I
Bristol-Myers Squibb	Obesity	SLV-319	I
Celltech Group	Gaucher's disease: type 1	Miglustat[3]	L-2003
	Gaucher's disease: type 3	Miglustat[1,3]	III
	Lysosomal storage diseases	CDP-923	I
	Niemann-Pick disease	Miglustat[1,3]	III
	Tay-Sachs disease	Miglustat[1,3]	III
Chiesi	Osteoporosis	CHF-4227	I
Chrysalis BioTechnology	Fracture	Chrysalin®	III
	Spinal fusion	Chrysalin®	I/II
Chugai	Osteoporosis	ED-71	II
		Teriparatide (intranasal)[2,3]	II
Daiichi Suntory	Osteoporosis	Teriparatide (intranasal)[2,3]	II
Emisphere	Osteoporosis	Calcitonin (oral)[2]	II
		Teriparatide (oral)[2,3]	I
Fujisawa	Osteoporosis	Strontium ranelate[3]	II
Genzyme	Lysosomal storage diseases	GENZ-112638	I
	Mucopolysaccharidosis I	Laronidase[3]	L-2003
	Mucopolysaccharidosis II (Hunter's syndrome)	Idursulfase	III
	Pompe's disease	Recombinant human acid alpha-glucosidase[3]	III
GlaxoSmithKline	Obesity	GI-181771	II
	Osteoporosis	423557	I
		SB-462795	I
	Osteoporosis, postmenopausal	Ibandronate sodium[1,3]	R-2003
Hormos	Osteoporosis (in men)	Fispemifene	I
	Osteoporosis, postmenopausal	Ospemifene[3]	II/III
Hunter-Fleming	Osteoporosis	HF-0299	I
Ilex Oncology	Osteoporosis	Apomine™	II
Ineos Silicas	Hyperphosphatemia	Phosphate binder	II
Insmed	Fracture	rhIGF-I/rhIGFBP-3	II
Ipsen	Hyperuricemia	Febuxostat[3]	II
	Osteoporosis	BIM-44058	I
Kaken	Fracture	Trafermin[1]	II
Kyorin	Obesity	N-5984	I
Ligand	Osteoporosis	Lasofoxifene tartrate[3]	III
	Osteoporosis, postmenopausal	Bazedoxifene acetate[3]	III
		Bazedoxifene/conjugated estrogens	III
Lilly	Osteoporosis	Arzoxifene hydrochloride[3]	III
		Teriparatide (oral)[2,3]	I
Merck & Co.	Obesity	C-2624	I
		C-2735	II
		C-5093	I

Continuation

Treatment of Metabolic Disorders by Source

Source	Condition	Drug	Phase
Metabolic Pharmaceuticals	Obesity	AOD-9604	II
Mitsubishi Pharma	Hyperphosphatemia	Colestilan[1,3]	II
ML Laboratories	Hyperphosphatemia	Phosphate binder	II
Nastech	Obesity	PYY3-36	I
	Osteoporosis, postmenopausal	Teriparatide (intranasal)[1]	I
Nektar Therapeutics	Obesity	PEG-Axokine®	I
Nisshin Pharma	Obesity	N-5984	I
Nobex	Fracture	Calcitonin (oral)[2]	I
Novartis	Osteoporosis	AAE-581	II
		Calcitonin (oral)[2]	II
	Osteoporosis, postmenopausal	Zoledronic acid monohydrate[1,3]	III
	Paget's disease	Zoledronic acid monohydrate[1,3]	III
NPS Pharmaceuticals	Osteoporosis	ALX1-11[3]	III
Nutrition 21	Obesity	Chromium picolinate/conjugated linoleic acid	I
Nycomed	Osteoporosis	ALX1-11[3]	III
Ono Pharmaceutical	Fracture	Ono-4819	II
	Osteoporosis	Minodronic acid[3]	III
Orphan Europe	Hyperammonemia	Carglumic acid	L-2003
OrthoLogic	Fracture	Chrysalin®	III
	Spinal fusion	Chrysalin®	I/II
Ortho-McNeil	Osteoporosis (anorexia nervosa)	Norgestimate/ethinylestradiol[1]	Prereg.
Pfizer	Osteoporosis	CP-533536	I/II
		Lasofoxifene tartrate[3]	III
Phytopharm	Obesity	P-57	II
ProSkelia	Osteoporosis	PSK-3471 (SERM-3471)	II
Regeneron	Obesity	Axokine®	III
		PEG-Axokine®	I
Roche	Osteoporosis, postmenopausal	Ibandronate sodium[1,3]	R-2003
Sanofi-Synthélabo	Obesity	Rimonabant hydrochloride	III
		SR-146131	Discontinued
		SR-147778	I
		SSR-125180	Discontinued
Schering AG	Osteoporosis, postmenopausal	Drospirenone/estradiol	R-2003
Servier	Osteoporosis	Strontium ranelate[3]	Prereg.
Shionogi	Obesity	S-2367	I
Shire	Hyperphosphatemia	Lanthanum carbonate[3]	R-2004
Solvay	Obesity	SLV-319	I
Takeda	Obesity	ATL-962	II
TAP Pharmaceutical	Hyperuricemia	Febuxostat[3]	III
Teijin	Hyperuricemia	Febuxostat[3]	Prereg.
	Osteoporosis	BIM-44058	I
Theratechnologies	Osteoporosis	Teriparatide (transdermal)[2,3]	I
Titan	Paget's disease	Gallium maltolate	I/II
Transkaryotic Therapies	Gaucher's disease	Gene-activated glucocerebrosidase	I/II
	Mucopolysaccharidosis II (Hunter's syndrome)	Idursulfase	III
Tularik	Obesity	T-71	I
Wyeth	Osteoporosis, postmenopausal	Bazedoxifene acetate[3]	III
		Bazedoxifene/conjugated estrogens	III
Yamanouchi	Osteoporosis	Minodronic acid[3]	III
Zelos Therapeutics	Osteoporosis	Ostabolin-C™	I

[1]Launched for another indication. [2]New formulation. [3]Monograph previously published in Drugs of the Future.

Treatment of Metabolic Disorders

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423557

The calcium antagonist 423557, with potential in the treatment of osteoporosis, is in phase I clinical testing at GlaxoSmithKline.

AAE-581

Novartis has designed a new cathepsin K inhibitor, AAE-581, shown to inhibit enzyme activity in osteoclasts and thereby reduce collagen breakdown and bone resorption. Suitable for once-daily oral administration, the compound has demonstrated reductions in bone turnover and potential additional effects on bone formation in clinical trials in postmenopausal women. Phase IIb trials are planned for this year.

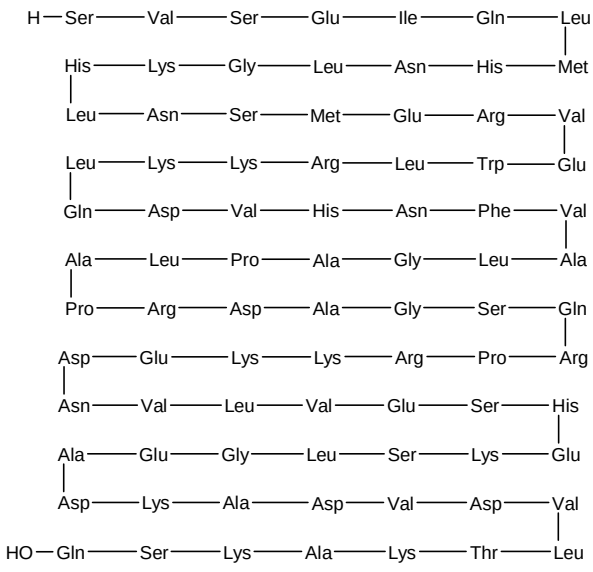
AC-100

AC-100 (Dentonin) is Acologix's lead drug candidate for the treatment of osteoporosis, fracture healing and dental tissue regeneration. A phase I clinical trial was successfully completed in healthy males and postmenopausal women administered doses of 50, 100, 200, 400 or 800 mg by s.c. injection. No safety issues were noted and the drug was well absorbed, giving blood levels proportional to the dose administered. No gender differences were observed. The company plans to begin a phase Ib/IIa trial in healthy postmenopausal women with low bone mass in the near future. AC-100 is a human-derived small peptide that has demonstrated potent bone anabolic and dental tissue formation activities *in vitro* and in animals. Synthetic peptide is reported to promote osteoblast differentiation and proliferation and bone matrix production, as well as mineralization, all key events in the formation of bone (1, 2). The company is seeking corporate partners for the development and marketing of AC-100 for systemic and local therapeutic indications.

1. *Acologix closes $40 million Series B financing.* Acologix Inc. Press Release 2004, May 3.

2. *Acologix completes phase I clinical trial of lead compound Dentonin.* Acologix Inc. Press Release 2003, April 30.

ALX1-11



ALX1-11 (rhPTH[1-84], Preos®) is NPS Pharmaceuticals' full-length human PTH drug candidate for the treatment of osteoporosis. The drug has completed a pivotal phase III trial and NDA filing with the FDA is expected later this year. NPS and Nycomed have signed a distribution and license agreement granting Nycomed rights to develop and market ALX1-11 in Europe, including the Commonwealth of Independent States (CIS) and Turkey. Nycomed will be responsible for European clinical devel-

opment, registration and marketing of ALX1-11. Nycomed plans to submit applications for regulatory approval of ALX1-11 in Europe following the NDA filing by NPS (1). ALX1-11 is also being tested in Europe in women using hormone replacement therapy in the POWER (Parathyroid Hormone for Osteoporotic Women on Estrogen Replacement) study. Furthermore, researchers at the University of California at San Francisco supervised the completion of a 2-year clinical study of ALX1-11 and alendronate (an antiresorption drug) used in combination or in sequence. Final results are anticipated sometime this year (2).

NPS recently reported encouraging preliminary results from a 2-year rat carcinogenicity study of ALX1-11. The study was initiated as a component of a standard toxicology package for submission with the NDA. Although complete toxicological, pathological and histopathological data continue to be compiled, an analysis of the available data indicates that there was no difference in the incidence of osteosarcoma seen in the low-dose and control arms of the study. A dose-related increase in the incidence of osteosarcoma occurred in the mid- and high-dose arms of the study, but at rates lower than those observed in published carcinogenicity studies using teriparatide, an *N*-terminal fragment of PTH. The bone-building effects of ALX1-11, as measured by increases in bone mineral density, bone mineral content and bone size, were confirmed. NPS continues to explore a lower frequency of bone lesions in the study compared to that seen in similar teriparatide studies. This finding may be due to the activation of a unique set of receptors that respond to the *C*-terminus of PTH, which is present in ALX1-11 but not in teriparatide. Based on this study, NPS believes it has identified a noncarcinogenic dose of ALX1-11 (3).

The TOP study was a multicenter, double-blind, randomized, placebo-controlled clinical trial that assessed the efficacy of NPS's recombinant parathyroid hormone in reducing the risk of vertebral fracture associated with osteoporosis. Approximately 2,600 postmenopausal women with osteoporosis were treated with placebo or ALX1-11 (100 μg s.c. once daily), together with daily supplements of calcium (700 mg) and vitamin D (400 IU), for 18 months. The rate of vertebral fractures during the study period was 3.4% with placebo and 1.4% with ALX1-11, a difference equivalent to a relative risk reduction of 59%. In the subgroup of patients with no previous fractures before inclusion in the study, ALX1-11 reduced the relative risk of fractures by 68%. The vertebral bone mineral density of patients treated with ALX1-11 increased by 7% compared with placebo. No significant differences were found in the incidence of adverse events in each study group. The most common adverse events were increases in the levels of calcium in serum and urine, followed by headache, nausea, dizziness and vomiting (4).

1. Nycomed to develop and market Preos in Europe. DailyDrugNews.com (Daily Essentials) April 23, 2004.

2. NPS Pharmaceuticals reports 2003 year-end R&D highlights. NPS Pharmaceuticals Press Release 2004, Feb 10.

3. *Encouraging preliminary results from rat carcinogenicity study of Preos.* DailyDrugNews.com (Daily Essentials) Nov 24, 2003.

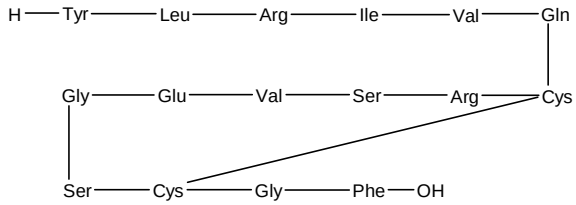
4. NPS announces positive phase III study results for Preos® in women with osteoporosis. NPS Pharmaceuticals Press Release 2004, March 30.

Original monograph – Drugs Fut 2000, 25(10): 1007.

AMG-162

AMG-162 (Amgen) is a fully human monoclonal antibody that specifically targets the receptor activator of nuclear factor-κB ligand (RANKL), a key mediator of the resorptive phase of bone remodeling. As a biological response modifier, AMG-162 potentially represents a unique therapy for osteoporosis and other disorders characterized by bone loss. The product is intended for twice-yearly administration by s.c. injection. Based on interim data from a phase II clinical study showing clinical benefits on bone endpoints, Amgen expects to begin phase III clinical evaluation of AMG-162 in osteoporosis this year. In addition, the company is studying AMG-162 for its ability to suppress bone loss in cancer patients with metastatic bone disease. Phase II trials for this indication are also expected to begin this year.

AOD-9604



Enrollment has been completed in Metabolic Pharmaceuticals' 300-patient phase IIb trial of the antiobesity drug AOD-9604, with over one-third of the patients finishing treatment. The last patient is expected to complete treatment in September 2004, and results are expected by late November 2004. Enrollment in the multicenter, randomized, double-blind, placebo-controlled trial in obese male and female patients began in November 2003. The patients are obese but otherwise healthy men and women aged 30-65. They are randomized to receive once-daily oral doses of either placebo, 1, 5, 10, 20 or 30 mg AOD-9604 as capsules for 12 weeks. The primary efficacy endpoints are the effect of AOD-9604 on body weight reduction and fat reduction measured from a CT scan. Secondary endpoints are other measures of obesity and perceived quality of life. Metabolic intends to seek a partner to assist in financing phase III trials for worldwide marketing approval. The AOD-9604 molecule, discovered by scientists at Monash

University, is a small, orally active peptide modeled on a part of the human growth hormone molecule. Daily dosing with AOD-9604 restores suppressed fat metabolism by mimicking the fat metabolic effects of growth hormone. Previous short-term clinical trials conducted on AOD-9604, with single doses and multiple doses for up to 1 week, indicated that the drug is orally active, well tolerated and shows the expected trends in weight loss (1-3).

1. *Enrollment under way for phase IIb obesity study of AOD-9604.* DailyDrugNews.com (Daily Essentials) Nov 11, 2003.

2. *Enrollment completed in phase IIb trial of AOD-9604 for obesity.* DailyDrugNews.com (Daily Essentials) June 8, 2004.

3. *Metabolic offers progress report.* DailyDrugNews.com (Daily Essentials) June 14, 2004.

APD-356

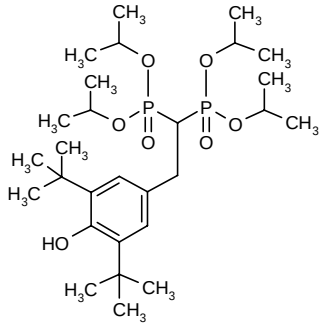
Following the successful completion of preclinical studies with APD-356, Arena's lead compound for obesity, a U.K.-based phase I trial was begun during the first quarter of 2004. APD-356 is a highly selective, orally available 5-HT_{2C} agonist that has been shown to reduce body weight and food intake in animal models of obesity. The double-blind, placebo-controlled, dose-escalation trial will evaluate the safety, tolerability and pharmacokinetic profile of single doses of APD-356 in 54 healthy, overweight volunteers. The study should be completed in the first half of 2004 and may lead to a larger, multiple-dose trial later in the year. The double-blind, placebo-controlled study would assess the safety of multiple doses of APD-356 and examine weight loss in healthy, overweight volunteers. A phase II trial in overweight and obese patients is anticipated for 2005. *In vivo* experiments showed that APD-356 selectively reduced fat mass in obese animals, while leaving lean body mass unchanged. Animals experienced a statistically significant decrease in total cholesterol, while HDL cholesterol increased. APD-356 is believed to act through regulation of satiety (1-3).

1. *APD-356 completes preclinical testing.* DailyDrugNews.com (Daily Essentials) Dec 19, 2003.

2. *APD-356 enters phase I trial for obesity.* DailyDrugNews.com (Daily Essentials) Feb 26, 2004.

3. Arena Pharmaceuticals reports Q1 R&D highlights. Arena Pharmaceuticals Press Release 2004, April 20.

Apomine™



Apomine™ is a bisphosphonate ester discovered at Ilex Oncology to act more like statins (increasing HMG-CoA reductase degradation) than bisphosphonate acids, mainly stimulating bone formation and increasing bone mineral content rather than inhibiting bone resorption. It is in phase II trials in postmenopausal women with osteoporosis.

Arylsulfatase B (Recombinant Human)

BioMarin recently completed the phase III trial of Aryplase™ (recombinant human arylsulfatase B), its investigational enzyme replacement therapy for the treatment of mucopolysaccharidosis VI (MPS VI, Maroteaux-Lamy syndrome). Following analysis of the data from the 6 clinical sites, results are expected to be reported in the second quarter of 2004. Pending positive results, the company plans to file simultaneous applications for approval in the U.S. and E.U. in the fourth quarter of 2004 (1-3).

Long-term data from phase I and II studies of Aryplase™ indicated that it is generally well tolerated and that patients continue to benefit from the treatment. An open-label phase II study enrolled 10 patients with MPS VI at 2 sites in the U.S. and Australia. Patients received Aryplase™ at a dose of 1.0 mg/kg. After 48 weeks of treatment with Aryplase™, endurance as measured by distance walked in 12 min improved by an average of 139% over baseline, representing an average incremental improvement of 56 m over the improvement observed after 24 weeks. Endurance, as measured by the number of stairs climbed in 3 min, increased by an average of 147% over baseline, representing an average incremental improvement of an additional 13 stairs over the improvement at 24 weeks. Urinary glycosaminoglycan (GAG) levels, another phase III secondary endpoint, were reduced by 76% on average after 48 weeks. This compares to a 71% reduction after 24 weeks. Sustained improvements were also observed in joint pain and stiffness, and variable improvements were observed in joint range of motion. Reduction in liver and spleen size was observed in all 5 patients with hepatosplenomegaly at baseline, and 4 of the 5 now have

liver volumes in the normal range. Pulmonary function improvements were observed in several patients, primarily between 24 and 48 weeks. A randomized, double-blind phase I study initially investigated doses of 0.2 and 1.0 mg/kg of Aryplase™ in 2 groups of 3 patients each. Following positive results after 24 weeks of treatment, all 6 patients continued to receive treatment at 1.0 mg/kg in an open-label extension study. Results after 96 weeks of treatment showed that endurance, as measured by the distance walked in 6 min, improved by an average of 96% over baseline. Gains in the 6-min walk test were maintained or improved from week 48 to week 96 for the 4 evaluable patients in the study at the 96-week time point. Urinary GAG levels were reduced by 75% on average after 96 weeks. Patients who initially received the lower dose experienced an incremental decrease in GAG levels after receiving treatment with the higher dose (4).

The company also reported positive results from its phase III trial of Aryplase™. The multicenter, double-blind, placebo-controlled trial was designed to evaluate the safety and efficacy of Aryplase™ for the treatment of MPS VI. The trial enrolled 39 patients aged 5-29 years at 6 sites in the U.S., Brazil, the U.K., Germany, France and Portugal. Patients were randomized to receive a weekly intravenous infusion of either Aryplase™ 1.0 mg/kg or placebo solution for 24 consecutive weeks. Patients receiving Aryplase™ demonstrated a statistically significant improvement in endurance compared to patients receiving placebo, as measured by the change relative to baseline in the distance walked in 12 min, the primary endpoint. The mean difference between patients receiving Aryplase™ and patients receiving placebo after 24 weeks was 92 m. Aryplase™ patients experienced a statistically significant reduction in GAGs excreted in the urine compared to patients receiving placebo. The average urinary GAG reduction in patients receiving Aryplase™ after 24 weeks was 75.5%. Aryplase™ patients also demonstrated an improvement in endurance compared to patients receiving placebo, as measured by the change relative to baseline in the number of stairs climbed per minute. Although not statistically significant, after 24 weeks, the average total improvement in the number of stairs climbed per minute in patients receiving Aryplase™ was approximately 6 compared to patients receiving placebo. Aryplase™ was generally safe and well tolerated. Following the 24-week double-blind trial, all patients who completed the study began receiving weekly infusions of Aryplase™ in an open-label extension study (5).

1. *BioMarin reports Q3 R&D highlights.* BioMarin Pharmaceutical Press Release 2003, Nov 4.

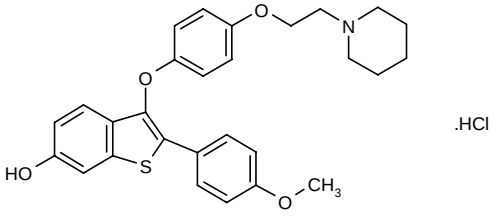
2. *BioMarin Pharmaceutical reports 2003 year-end R&D highlights.* BioMarin Pharmaceutical Press Release 2004, Feb 3.

3. *BioMarin Pharmaceutical reports Q1 R&D highlights.* BioMarin Pharmaceutical Press Release 2004, May 4.

4. *Positive long-term data obtained for Aryplase.* DailyDrugNews.com (Daily Essentials) Nov 10, 2003.

5. *Positive phase III results for Aryplase in MPS VI.* DailyDrugNews.com (Daily Essentials) June 7, 2004.

Arzoxifene Hydrochloride



The benzothiophene analogue arzoxifene hydrochloride (LY-353381.HCl) is a late-stage development candidate at Lilly for the treatment and prevention of osteoporosis and for reducing the risk of breast cancer. The compound is a member of the selective estrogen receptor modulator (SERM) family that exerts strong antagonist activity on estrogen receptors of the breast and endometrium, and agonist activity on bone and lipids.

Original monograph – Drugs Fut 1999, 24(6): 599.

ATL-962

Alizyme's ATL-962, an inhibitor of gastrointestinal lipases, is designed to cause weight loss by reducing the digestion and thus the absorption of fat from the diet. ATL-962 originated from an Alizyme-initiated collaborative drug discovery program involving Cambridge Discovery Chemistry, which was subsequently acquired by Millennium. Following the review of European phase IIb trial data, Takeda recently exercised its right to a license and development agreement with Alizyme and acquired an exclusive license to develop, manufacture and market ATL-962 in Japan for the treatment of obesity and associated conditions such as type 2 diabetes. The results reviewed by Takeda were from a multicenter, double-blind, randomized, placebo-controlled phase IIb trial in 372 clinically obese patients from 5 European countries which assessed the efficacy and safety of different doses of ATL-962 (60, 120 or 240 mg t.i.d.) for 12 weeks combined with a low-calorie diet. The trial met its primary endpoint of weight loss, demonstrating a statistically significant reduction in weight compared to placebo for the different treatment groups. The average body weight decrease achieved at the end of the treatment period was 2.06 kg with placebo and 3.32, 3.45 and 4.05 kg for 60, 120 and 240 mg of ATL-962, respectively. The levels of weight loss over 3 months were consistent with other approved obesity drugs of the same class. All doses of ATL-962 were well tolerated and mostly associated with mild adverse events, the most common of which were increased defecations, soft stools and abdominal pain. The prevalence of gastrointestinal adverse events was up to 90% lower than that reported for other drugs of this class (1, 2).

1. *Takeda exercises rights to ATL-962 for Japan.* DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

2. Bryson, A.M., Palmer, R.M.J., Kopelman, P. *Efficacy and tolerability of ATL-962, a lipase inhibitor, in obese patients.* Int J Obes 2004, 28(Suppl. 1): Abst T5:O2-003.

Axokine®

Axokine® is a modified form of the naturally occurring protein ciliary neurotrophic factor (CNTF) that is currently undergoing phase III evaluation for the treatment of obesity at Regeneron (1). The agent has a novel mechanism of action –inhibition of hunger signals that stimulate appetite. Regeneron is also developing a potentially more potent and longer acting pegylated version of Axokine® using technology from Nektar Therapeutics, which is currently in phase I clinical evaluation.

Treatment with Axokine® (1 μg/kg/day) was investigated in 1,968 nondiabetic overweight/obese patients in a multicenter, randomized, double-blind, placebo-controlled trial. In both active treatment (n=1,467) and placebo (n=501) groups, changes in body weight were correlated with changes in fasting plasma glucose, HbA1c levels, fasting plasma insulin and insulin resistance at 6 and 12 months. Differences between the groups were not significant. Subset analysis of this study indicated that Axokine® improves glycemic control in patients with impaired fasting glucose (n=164). Weight loss with Axokine® treatment was associated with reduced fasting plasma glucose and HbA1c content in these patients. Patients losing at least 5% of their baseline weight had a greater improvement in glycemic diagnosis than those losing less than 5% of their baseline weight (2, 3). The safety profile of Axokine® was also assessed in this trial. The study was completed by 66.7% of Axokine®-treated patients and 60.9% of placebo-treated patients, with most withdrawals caused by patient request, loss to follow-up and intolerable adverse events. The safety profile of Axokine® was favorable and the most common adverse events were injection-site reactions and nausea (4). The analysis of parameters such as hunger, fullness, preoccupation with food and food craving using visual analogue scales during the study period revealed that active weight loss induced by Axokine® was associated with appetite reduction (5) (see Table I).

Patients with type 2 diabetes were treated with placebo or Axokine® 0.5 or 1 μg/kg/day in a 12-week, multicenter, randomized trial. Of the 160 patients included, 97 were severely obese, and these patients lost significantly more weight with Axokine® 1 μg/kg/day than with placebo. More Axokine®-treated patients also had a response predictive of long-term weight loss (a loss of at least 4 kg by week 12) (6).

1. *Regeneron reports Q3 R&D highlights*. Regeneron Pharmaceuticals Press Release 2003, Oct 29.

2. Weinstein, S.P., Tardiff, B.E., Bays, H.E., Guler, H.-P., Aronne, L.J. *Weight loss with recombinant human variant ciliary neurotrophic factor (rhvCNTF [Axokine®]) improves glycemic control in overweight/obese subjects, especially in those with abnormal glycemic parameters at baseline*. 64th Annu Meet Sci Sess Am Diabetes Assoc (June 4-8, Orlando) 2004, Abst 2523-PO.

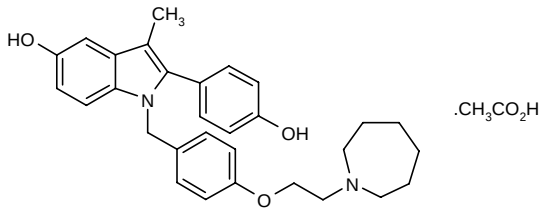
3. Weinstein, S.P., Tardiff, B.E., Anderson, J.W., Guler, H.-P., Weerasinghe, M.U. *Weight loss with recombinant human variant ciliary neurotrophic factor (rhvCNTF [Axokine®]) improves glycemic diagnosis in overweight/obese patients with impaired fasting glucose*. 64th Annu Meet Sci Sess Am Diabetes Assoc (June 4-8, Orlando) 2004, Abst 2524-PO.

4. Roberts, W., Kassner, S., Bianco, D., Tardiff, B., Guler, H.-P., Weinstein, S. *Safety and tolerability of recombinant human variant ciliary neurotrophic factor (rhvCNTF) for weight loss during a one-year clinical trial*. Int J Obes 2004, 28(Suppl. 1): Abst T5:P5b-035.

5. Tardiff, B., Guler, H.-P., Heymsfield, S., Weinstein, S. *Recombinant human variant ciliary neurotrophic factor (rhvCNTF) induces weight loss via appetite reduction*. Int J Obes 2004, 28(Suppl. 1): Abst T5:P5b-036.

6. Glicklich, A.S., Weinstein, S.P., Guler, H.-P., Grimes, I., Russell, T.L., Nadler, D., Hollander, P. *Treatment with recombinant human variant CNTF [rhvCNTF (Axokine®)] increases the likelihood of achieving early weight loss responder status in severely obese type 2 diabetic patients*. 64th Annu Meet Sci Sess Am Diabetes Assoc (June 4-8, Orlando) 2004, Abst 2511-PO.

Bazedoxifene Acetate



Bazedoxifene acetate (TSE-424) is a selective estrogen receptor modulator (SERM) in phase III trials at

Table I: Clinical studies of Axokine® (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Obesity	Randomized Double-blind Multicenter	Axokine®, 1.0 mg/kg/d s.c. x 1 y (n=1467) Placebo (n=501)	1968	Subcutaneous Axokine® showed a good safety profile and efficacy in decreasing body weight in overweight/obese patients through appetite reduction	4,5

Wyeth for the prevention and treatment of postmenopausal osteoporosis. Worldwide phase III studies in more than 9,000 women are designed to demonstrate that bazedoxifene will significantly reduce bone loss and prevent fractures. Regulatory submissions for the prevention of osteoporosis are planned in 2005. A combination of bazedoxifene and conjugated estrogens (Premarin®) is also in phase III clinical evaluation for the prevention of osteoporosis and the relief of vasomotor menopausal symptoms (1). Bazedoxifene was developed as part of a research and development collaboration between Ligand and the former Wyeth-Ayerst.

1. *Wyeth reviews R&D pipeline*. DailyDrugNews.com (Daily Essentials) June 7, 2004.

Original monograph – Drugs Fut 2002, 27(2): 117.

BIM-44058

BIM-44058 is an analogue of human parathyroid hormone-related hormone (hPTHrP1-34) reported to possess more potent bone anabolic activity but reduced calcium-mobilizing effects compared to PTH1-34. Designed at Ipsen for the treatment of osteoporosis and bone fractures, the compound was licensed last year to Teijin for Japan as part of a broad cross-licensing agreement. Phase I clinical trials are in progress at Ipsen.

C-2735/C-2624/C-5093

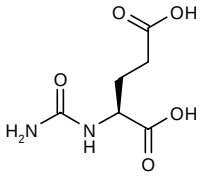
Merck & Co. has three potential antiobesity agents in clinical development: C-2735 and C-2624 in phase I and the more advanced C-5093 in phase II studies.

Calcitonin, Oral

Emisphere and Novartis are collaborating on the development of an oral formulation of salmon calcitonin (SMC-021) for the treatment of osteoporosis and related indications. Salmon calcitonin, currently available for administration by injection and as a nasal spray, has been shown to be effective in slowing bone loss and increasing bone density in the spine. Novartis is responsible for clinical development and commercialization and has completed phase IIa trials of a tablet formulation incorporating Emisphere technology, with phase IIb studies scheduled to commence later in the year.

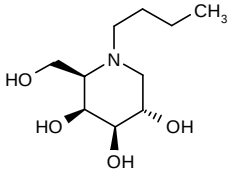
Nobex is also developing an oral formulation of calcitonin (NCT-025, Oratonin™) which in preclinical studies exhibited advantages in terms of bioavailability compared to other calcitonin products in development. Phase I trials are in progress and the company is targeting its oral product for vertebral fractures.

Carglumic Acid



Orphan Europe began marketing carglumic acid (Carbaglu®) in Europe last year for the treatment of hyperammonemia due to *N*-acetylglutamate synthase deficiency. It is a structural analogue of naturally occurring *N*-acetylglutamate and also activates the first enzyme in the urea cycle –carbamoylphosphate synthetase (carbamoyl-phosphate synthase)– and rapidly normalizes plasma ammonia levels in patients with *N*-acetylglutamate synthase deficiency.

CDP-923

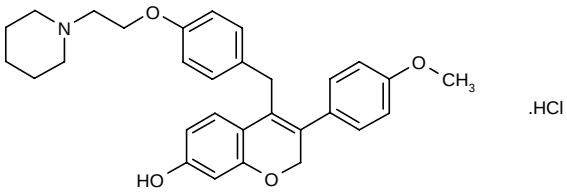


Late last year, Celltech Group completed its integration of Oxford GlycoSciences (OGS), which was acquired in May 2003. Among OGS's assets was CDP-923 (formerly OGT-923), a second-generation oral substrate reduction therapy for the treatment of certain lysosomal storage diseases, which is currently undergoing a multiple-dose phase I study in healthy volunteers designed to confirm preclinical findings that this compound lacks the gastrointestinal toxicity seen with the first-generation compound, miglustat. Celltech is now evaluating the best development plan for this compound for entry into pivotal phase II studies (1, 2).

1. *Celltech completes integration of OGS*. DailyDrugNews.com (Daily Essentials) Nov 24, 2003.

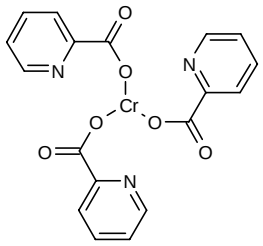
2. *Celltech reports 2003 year-end R&D highlights*. Celltech Group plc Press Release 2004, March 16.

CHF-4227

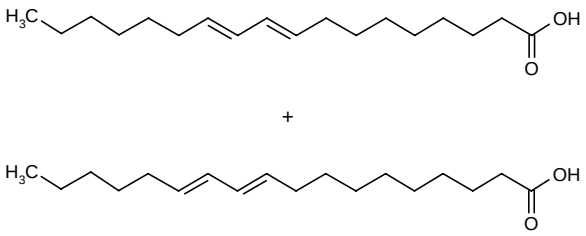


CHF-4227 is a new SERM from Chiesi for postmenopausal osteoporosis, with potentially greater beneficial effects on bone resorption and reduced side effects compared to lasofoxifene and raloxifene due to its improved estrogen agonist/antagonist profile. Phase I clinical trials have commenced.

Chromium Picolinate/ Conjugated Linoleic Acid



Chromium Picolinate



Conjugated Linoleic Acid

New research has shown that Nutrition 21's Zenergen™, a proprietary blend of chromium picolinate (Chromax®) and conjugated linoleic acid (Tonalin® CLA), may reduce fat and enhance weight loss. The *in vitro* and animal data suggest that Zenergen™ enhances carbohydrate metabolism and improves body composition. The animal data support the synergistic effects of the Zenergen™ formulation for weight loss, with benefits superior to those of each nutrient alone. A clinical trial is expected to conclude this year (1).

1. *Zenergen may reduce fat, enhance weight loss.* DailyDrugNews.com (Daily Essentials) Dec 29, 2003.

Chrysalin®

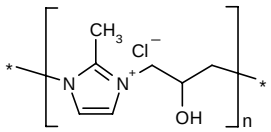
Chrysalis BioTechnology's lead product Chrysalin® (TP-508) is a 23-amino-acid synthetic peptide that represents a portion of the human enzyme thrombin. The drug interacts directly with selected thrombin receptors on cells involved in tissue repair, triggering the release of growth factors and other wound-healing signals, without affecting blood clotting. Chrysalin® is being evaluated in a phase III study for bone fracture healing under the direction of OrthoLogic, the company's commercial partner for orthopedic applications below the neck, and an NDA is expected to be filed in 2006. A phase I/II trial for fracture healing was completed and demonstrated that treated patients healed approximately 25-30% faster than controls, as seen with radiographic assessment. Phase I/II trials are also under way under OrthoLogic's direction for spinal fusion, while Chrysalis BioTechnology is directing its own phase II trials for chronic diabetic ulcers, with a pivotal trial being planned for the near future. In addition to the clinical programs, the drug is being studied in preclinical trials for cartilage repair, revascularization of ischemic heart tissue and dental bone repair. OrthoLogic has completed additional preclinical studies of Chrysalin® in a controlled-release PLGA matrix for a cartilage defect repair indication with positive results. The company intends to file an IND application for this indication and expects to initiate a human clinical trial before the end of 2004. Also, preclinical studies are expected to begin in the first half of this year to evaluate the use of Chrysalin® for ligament and tendon repair (1-3).

1. *Positive results for Chrysalin in preclinical dental bone formation study.* DailyDrugNews.com (Daily Essentials) Jan 23, 2004.

2. *R&D highlights from the Rodman & Renshaw Techvest Healthcare Conference: Chrysalis BioTechnology.* DailyDrug News.com (Daily Essentials) Nov 21, 2003.

3. *OrthoLogic reports 2003 year-end R&D highlights.* OrthoLogic Press Release 2004, Jan 29.

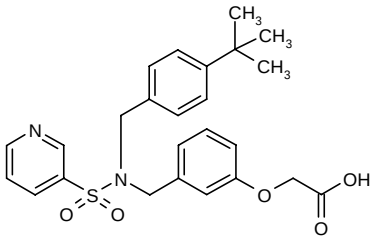
Colestilan



Colestilan (colestimide, Cholebine®), a nonabsorbable anion exchange resin, was first introduced in Japan in 1999 for the treatment of hypercholesterolemia by the former Tokyo Tanabe (now Mitsubishi Pharma) and Yamanouchi. In addition to cholesterol, the compound binds phosphate in the intestine and increases its excretion, leading to improvement in hyperphosphatemia in patients on hemodialysis. Phase II trials are under way in the U.S. and the E.U. for hyperphosphatemia.

Original monograph – Drugs Fut 1993, 18(1): 15.

CP-533536

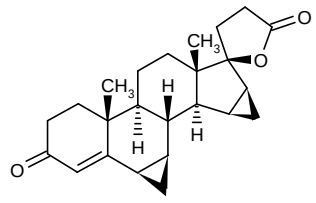


CP-533536 is a potent and selective prostaglandin EP_2 receptor agonist with potential for inducing new bone formation and fracture healing, currently in early clinical testing at Pfizer for the treatment of osteoporosis.

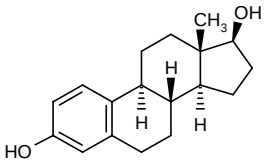
Pfizer has completed the initial phase of clinical testing of CP-533536 formulated in Atrix's Atrigel® sustained-release drug delivery system, and is advancing the product into additional clinical testing. CP-533536 is the first compound to advance into clinical trials under a broad strategic alliance between Atrix and Pfizer under which Pfizer evaluates certain compounds in its development pipeline using Atrix's unique drug delivery systems. The agreement, signed in August 2000, grants Atrix manufacturing rights and royalties on resulting commercialized products. The Atrigel® drug delivery system consists of biodegradable polymers dissolved in biocompatible carriers. The liquid product forms an implant when administered into tissue sites. There, the encapsulated drug is released from the implant in a controlled manner as the polymer matrix biodegrades. The Atrigel® system can deliver small molecules, peptides or proteins over a time period ranging from days to months (1).

1. *Pfizer advances Atrigel product into further clinical testing.* DailyDrugNews.com (Daily Essentials) Jan 13, 2004.

Drospirenone/Estradiol



Drospirenone

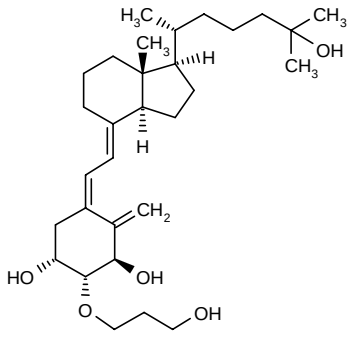


Estradiol

Schering AG expects to gain approval in 2004 for its hormone replacement therapy (HRT) Angeliq® (drospirenone/estradiol) in the U.S. and to launch it in Europe. Angeliq® has already been approved in Europe, but Schering halted its roll-out due to health fears over HRT in the wake of the Women's Health Initiative (WHI) study. A European launch is expected to take place in the second half of 2004. In the U.S., where the FDA initially rejected Angeliq® in 2002, a launch is anticipated for 2005 (1). The product is indicated for the treatment of menopausal symptoms and the prevention of osteoporosis in postmenopausal women.

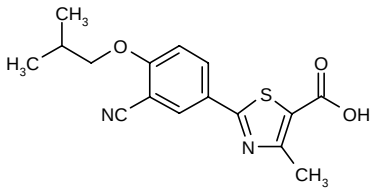
1. *Schering plans introduction of new drugs in coming years.* DailyDrugNews.com (Daily Essentials) March 11, 2004.

ED-71



ED-71 is a vitamin D analogue synthesized at Chugai that reportedly acts preferentially on bone to increase bone mass without causing hypercalcemia, by both inhibiting bone resorption and enhancing bone formation. It is currently in phase II clinical development as a potential new drug for osteoporosis.

Febuxostat



Development work on febuxostat (TMX-67), a selective xanthine oxidase/xanthine dehydrogenase inhibitor, continued during the year, culminating in Teijin filing for regulatory approval in Japan in April for use in the treatment of gout and hyperuricemia. Licensees Ipsen and TAP Pharmaceutical are conducting phase III trials in Europe and the U.S., respectively (1, 2).

A multicenter, double-blind, randomized clinical trial determined the safety profile and the effects of febuxostat in the treatment of gout. A total of 136 male and 17 female patients with gout were randomized to receive placebo or

Table II: Clinical studies of febuxostat (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Gout	Randomized Double-blind	Febuxostat, 40 mg o.d. + Colchicine x 2 wks → Febuxostat, 40 mg o.d. x 2 wks Febuxostat, 80 mg o.d. + Colchicine x 2 wks → Febuxostat, 80 mg o.d. x 2 wks Febuxostat, 120 mg o.d. + Colchicine x 2 wks → Febuxostat, 120 mg o.d. x 2 wks Placebo + Colchicine x 2 wks → Placebo x 2 wks	153	Febuxostat alone or combined with colchicine was well tolerated and more effective than placebo in reducing serum urate levels in patients with gout	3
Gout, Hyperuricemia	Randomized Double-blind	Febuxostat, 10 mg o.d. x 8 wks (n=32) Febuxostat, 10 mg o.d. x 2 wks → 20 mg o.d. x 6 wks (n=32) Febuxostat, 10 mg o.d. x 2 wks → 40 mg o.d. x 6 wks (n=32) Placebo (n=32)	128	Febuxostat at daily doses of up to 40 mg was well tolerated and reduced serum uric acid levels in patients with gout or hyperuricemia	4

febuxostat (40, 80 or 120 mg) once daily for 4 weeks. The serum urate levels of the patients, measured at the end of the study, showed significant reductions compared to baseline with all febuxostat dose levels. The average reductions achieved with each study treatment were 2% with placebo and 37%, 44% and 59%, respectively, with 40, 80 and 120 mg of febuxostat. The percentages of patients who achieved serum urate levels below 6 mg/dl in these study groups were, respectively, 0%, 56%, 76% and 94%. Most patients completed the study, and the incidence of adverse events was similar with febuxostat (54%) and placebo (50%). Most adverse events were mild and self-limiting, and the most common were diarrhea, pain, back pain, headache and arthralgia (3). These results and those from the following study are summarized in Table II.

Another multicenter, double-blind, randomized, placebo-controlled clinical trial evaluated the efficacy and tolerability of febuxostat in 128 Japanese patients with gout or hyperuricemia, defined as baseline serum uric acid levels of 8.0 mg/dl or greater. Thirty-two patients were randomized to receive placebo for 6 weeks, while a total of 96 patients were first treated with febuxostat 10 mg once daily for 2 weeks and then 10, 20 or 40 mg once daily for another 6 weeks. Compared with placebo, the drug significantly reduced the serum uric acid levels of the patients. The effects induced by febuxostat increased with dose, and the drug was equally effective in patients with gout and hyperuricemia. Febuxostat was well tolerated, and the most common adverse events were gout flare, common cold syndrome and increases in the levels of C-reactive protein, creatine phosphokinase and alanine aminotransferase; most adverse events were mild and transient, and only 3% of the patients withdrew from the study due to adverse events (4).

A recently completed clinical trial evaluated the effects of renal impairment on the safety, pharmacokinetics and pharmacodynamics of febuxostat. Thirty-one male and female subjects with normal renal function or mild, moderate or severe renal impairment received a daily oral dose of 80 mg of febuxostat for 7 days. Blood samples collected during the first 24 h after the end of the treatment revealed that renal impairment had no significant effects on the pharmacokinetic and pharmacodynamic profile of febuxostat. The drug was equally well tolerated in all study groups. Most adverse events were mild or transient, and the most common were diarrhea, headache, abdominal pain and ecchymosis associated with venipuncture (5).

1. *Consolidated financial statements – Summary*. Teijin Web Site May 6, 2004.

2. *Broad crosslicensing agreement between Ipsen and Teijin.* DailyDrugNews.com (Daily Essentials) 2003, July 9.

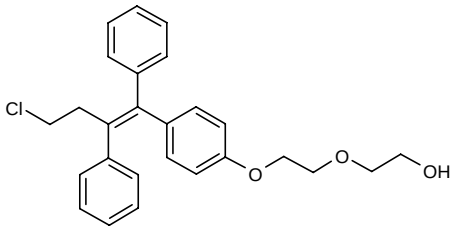
3. Becker, M.A., Schumacher, H. Jr., Wortmann, R.L., Joseph-Dridge, N., Lademacher, C. *A safety and efficacy clinical trial of a novel non-purine selective inhibitor of xanthine oxidase, febuxostat in subjects with gout*. Ann Rheum Dis 2004, 63(Suppl. 1): Abst OP0007.

4. Kamatani, N., Fujimori, S., Hada, T., Hosoya, T., Kato, R., Matsuzawa, Y., Ueda, T. *Phase II dose-response clinical trial using febuxostat (TMX-67), a novel-type xanthine oxidase/xanthine dehydrogenase inhibitor, for gout and hyperuricemia*. 67th Annu Sci Meet Amer Coll Rheumatol/38th Annu Sci Meet Assoc Rheumatol Health Profess (Oct 23-28, Orlando) 2003, Abst 1349.

5. Swan, S., Khosravan, R., Mayer, M.D. et al. *Effect of renal impairment on pharmacokinetics, pharmacodynamics, and safety of febuxostat (TMX-67), a novel non-purine selective inhibitor of xanthine oxidase.* 67th Annu Sci Meet Amer Coll Rheumatol/38th Annu Sci Meet Assoc Rheumatol Health Profess (Oct 23-28, Orlando) 2003, Abst 1348.

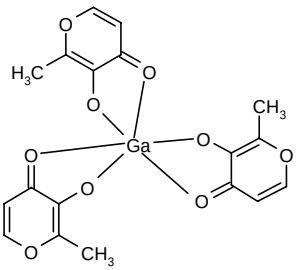
Original monograph – Drugs Fut 2001, 26(1): 32.

Fispemifene



Hormos has discovered a novel SERM –fispemifene– for male osteoporosis. Although the compound binds to estrogen receptors, it is practically hormonally inactive *in vivo*. It is therefore expected to prevent bone loss without affecting male genital organs. Phase I trials are under way.

Gallium Maltolate



Titan is conducting early-stage clinical trials of oral gallium maltolate in several types of cancer (bladder and prostate cancer, multiple myeloma and refractory lymphoma), and it may also have therapeutic potential in bone diseases such as Paget's disease (1).

The pharmacokinetics of gallium maltolate were assessed in 12 patients with primary hyperparathyroidism or an advanced form of Paget's disease. These subjects received a single dose of 200, 400 or 600 mg of gallium maltolate followed 14 days later by 3 consecutive daily doses of the drug. The levels of gallium ion in serum increased dose-dependently, while other parameters such as apparent clearance, half-life or terminal-phase apparent volume of distribution were similar at all dose levels. Peak concentrations similar to those required to inhibit bone resorption *in vivo* were found in patients receiving the 600-mg dose of gallium maltolate, therefore suggesting that these serum concentrations might have therapeutic effects. The drug also appeared to have a good safety profile, as no deaths were reported and only one serious adverse event (an episode of congestive heart failure) was considered to be possibly related to the treatment. Additional studies are needed to determine the potential benefits of gallium maltolate in the treatment of metabolic bone diseases (2, 3).

1. *Titan reports fourth quarter and year end 2003 results.* Titan Pharmaceuticals Press Release 2004, March 11.

2. Lum, B.L., Gottlieb, A., Altman, R., Sayre, P.H., Valone, F. *Pharmacokinetics of oral gallium maltolate administered in a single or multiple dose schedule in patients with Paget's disease of bone or primary hyperparathyroidism: A pilot study.* 25th Annu Meet Amer Soc BoneMiner Res (Sept 19-23, Minneapolis) 2003, Abst M404.

3. *Oral gallium formulation reported to reach therapeutic serum levels in Paget's disease.* DailyDrugNews.com (Daily Essentials) Oct 3, 2003.

Gene-Activated Glucocerebrosidase

Transkaryotic Therapies has initiated a clinical trial to evaluate the safety and clinical activity of gene-activated glucocerebrosidase (GA-GCB), its enzyme replacement therapy for the treatment of Gaucher's disease. Twelve patients with type 1 Gaucher's disease will receive treatment for 9 months. The trial is expected to be completed in 2005. GA-GCB is a human glucocerebrosidase product developed using TKT's proprietary gene activation technology. The company intends to seek a partner for the GA-GCB product (1).

1. *GA-GCB enters clinical trial for Gaucher's disease.* DailyDrugNews.com (Daily Essentials) April 29, 2004.

GENZ-112638

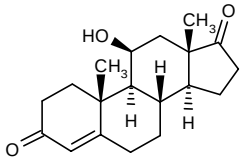
A phase I clinical trial of GENZ-112638 (Genzyme), a small-molecule substrate inhibitor for the oral treatment of lysosomal storage disorders, began enrolling patients recently (1).

1. *Genzyme reports financial results for first quarter*. Genzyme Corp. Press Release April 15, 2004.

GI-181771

The cholecystokinin CCK_1 receptor agonist GI-181771 is undergoing phase I clinical evaluation at GlaxoSmithKline for obesity and gallstone prophylaxis.

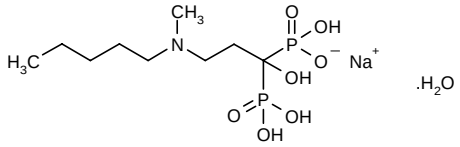
HF-0299



HF-0299 is an endogenous steroid end product synthesized in the human adrenal cortex with the ability to pro-

mote bone formation and increase bone strength at doses not associated with steroidal hormonal effects. The compound therefore appears to hold promise for the treatment of osteoporosis in both men and women. Hunter-Fleming has completed a single-dose phase I study and expects to begin a multiple-dose phase I trial this year.

Ibandronate Sodium



Ibandronate sodium is a highly potent, third-generation, nitrogen-containing bisphosphonate. GlaxoSmithKline and Roche are codeveloping ibandronate, currently available in over 50 countries as Bondronat® for the treatment of hypercalcemia of malignancy, for osteoporosis in all countries except Japan. In May 2003, a once-daily formulation of the bisphosphonate was approved in the U.S. under the brand name Boniva™ for the treatment and prevention of osteoporosis in postmenopausal women. More recently, it was approved for this same indication by regulatory authorities in Europe, where it is known under the brand name Bonviva™. The European Commission has also approved the use of oral and intravenous ibandronate sodium (Bondronat®) for the prevention of skeletal events in patients with breast cancer and bone metastases. Clinical trials demonstrated a significant reduction in skeletal-related events and significant, rapid and sustained pain relief over the 2-year study. A supplemental NDA was filed with the FDA in May for a novel, once-monthly oral formulation of ibandronate sodium for the treatment and prevention of postmenopausal osteoporosis. This more convenient once-monthly formulation will also be filed in Europe later this year. Regulatory filings are also expected this year for a quarterly i.v. dosing regimen (1-7).

The ongoing MOBILE (Monthly Oral Ibandronate in Ladies) study is the first phase III clinical trial to evaluate the efficacy and safety of once-monthly ibandronate in the management of osteoporosis in postmenopausal women. An interim analysis conducted after 1 year of treatment revealed that all ibandronate regimens (100 mg p.o., 50 mg p.o. on 2 consecutive days, and 150 mg p.o.) administered once monthly were at least as effective as a regimen of 2.5 mg p.o. once daily in increasing the bone mineral density of postmenopausal women. The final results of the MOBILE study will be obtained when the subjects have received treatment for 2 years (2).

Intravenous bisphosphonate administration, which avoids the upper gastrointestinal tolerability concerns associated with oral regimens, may be of considerable value for many patients with osteoporosis, such as elderly and institutionalized patients, because it ensures full treatment compliance, but the i.v. route has to be used with caution since acute renal failure has been observed following the i.v. administration of several bisphosphonates and prolonged i.v. infusions can also be potentially associated with thrombotic complications and infections. Bisphosphonate dosing by i.v. injection could provide a convenient alternative to i.v. infusion that would be suitable for use in the primary care setting and would avoid many of the complications associated with prolonged infusions. This option is viable with the highly potent, nitrogen-containing bisphosphonates such as ibandronate, which, unlike other lower potency bisphosphonates, can be administered as an i.v. injection of only a few milligrams in regimens with extended between-dose intervals. The data obtained with ibandronate, using both oral administration and i.v. injection, for the treatment and prevention of postmenopausal osteoporosis were recently reviewed (8).

1. *New European approval for Bondronat.* DailyDrugNews.com (Daily Essentials) Nov 6, 2003.

2. *Once monthly ibandronate found effective in the management of osteoporosis.* DailyDrugNews.com (Daily Essentials) Jan 20, 2004.

3. *GlaxoSmithKline reports 2003 year-end R&D highlights.* GlaxoSmithKline Press Release 2004, Feb 12.

4. *sNDA filed for once-monthly oral formulation of Boniva.* DailyDrugNews.com (Daily Essentials) May 28, 2004.

5. *GlaxoSmithKline reports Q1 R&D highlights.* GlaxoSmithKline Press Release 2004, April 29.

6. *Roche reports Q1 R&D highlights.* Roche Press Release 2004, April 21.

7. *Roche reports 2003 year-end R&D highlights.* Roche Press Release 2004, Feb 4.

8. Adami, S., Viapiana, O. *Ibandronate: New option in the treatment of osteoporosis.* Drugs Today 2003, 39(11): 877.

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Idursulfase

Transkaryotic Therapies and Genzyme are collaborating on the development of idursulfase (iduronate-2-sulfatase, I2S) as an enzyme replacement therapy for Hunter's syndrome, or mucopolysaccharidosis type II (MPS II). Idursulfase is a human iduronate-2-sulfatase produced by genetic engineering technology, designed to replace an enzyme that is deficient in patients with Hunter's syndrome, thereby either stopping or reversing disease progression. The product has orphan drug status in both the U.S. and Europe. Under their agreement, Genzyme will commercialize idursulfase in certain Asia/Pacific territories. In September 2003, TKT began enrolling patients in the pivotal AIM (Assessment of I2S in MPS II) study following data from a phase I/II clinical trial showing improvements in a variety of clinical measures, and enrollment was completed earlier this year. The 12-month, randomized, double-blind, placebo-controlled AIM study is designed to evaluate safety and efficacy of weekly and every-other-week infusions of idursulfase, administered at a dose of 0.5 mg/kg. Ninety-six Hunter's syndrome patients will receive a total of 52 infusions of either idursulfase, idursulfase alternating with placebo, or placebo. The primary efficacy endpoint is a single composite variable which combines two clinical measurements: forced vital capacity as a measure of respiratory function and the 6-min walk test as a measure of functional capacity. Other efficacy endpoints include measurements of joint range of motion and combined liver and spleen size. The trial is being conducted at 9 sites around the world. Topline data are expected in the second quarter of 2005, with submissions for marketing approval in the U.S. and Europe anticipated to follow during the second half of 2005. The inclusion of patients from Japan, brought about with the help of TKT's Japanese partner Genzyme, may help fulfill some requirements for Japanese approval (1-3).

1. *Transkaryotic Therapies reports Q3 R&D highlights*. Transkaryotic Therapies Press Release 2003, Oct 29.

2. *Enrollment extended in AIM study of I2S in Hunter syndrome.* DailyDrugNews.com (Daily Essentials) Feb 25, 2004.

3. *TKT completes patient enrollment in pivotal Hunter syndrome clinical trial.* Transkaryotic Therapies Press Release 2004, March 5.

Lanthanum Carbonate

Shire has developed lanthanum carbonate (Fosrenol™), a noncalcium, nonaluminum phosphate binder for hyperphosphatemia in end-stage renal disease patients, under license from AnorMED. The product received its first approval in Sweden early this year and Sweden will now act as reference member state for Europe-wide approval. Lanthanum carbonate binds to dietary phosphate in the gastrointestinal tract, rendering the complex unable to pass through the intestinal lining into the bloodstream, instead being eliminated from the body. Overall phosphate absorption from the diet is therefore decreased significantly. In clinical studies, it lowered serum phosphate levels within 8 weeks, which was maintained in some patients for 36 months or more. A recently published 12-month study in new dialysis patients showed that treatment with lanthanum carbonate led towards normalization of pre-existing bone disease compared to patients treated with calcium carbonate. The product has also been submitted for regulatory approval in the U.S. and Canada; an approvable letter was issued by the FDA last year. Shire recently outlicensed the rights to develop, market and sell lanthanum carbonate in Japan, where phase I development has been completed, to Bayer Yakuhin (1-3).

A randomized, double-blind, placebo-controlled study determined the effects of doses of 225, 675, 1350 and 2250 mg/day of lanthanum carbonate in 145 hemodialysis patients with hyperphosphatemia, and found that the drug dose-dependently reduced serum phosphate levels. The maximum effects were found with 1350 and 2250 mg/day, which resulted in average reductions of 0.95 and 1.1 mg/dl, respectively, after 6 weeks of treatment. This was associated with an increase in the percentage of phosphorus-controlled patients, which was 40% among patients treated with the two highest dose levels. The incidence of drug-related adverse events was similar to placebo (44% *vs.* 39%). The authors concluded that lanthanum carbonate doses higher than 675 mg/day were effective in reducing serum phosphorus levels in patients with hyperphosphatemia (4). Forty of these patients were enrolled in an open-label extension trial where they received lanthanum carbonate at an initial dose of 300 mg/day, later titrated to doses ranging from 300 to 2250 mg/day, as required to achieve serum phosphorus control. After an average of 6-48 months of treatment, 95% of patients reported adverse events, but most of these (66%) were mild. The most common adverse events at least possibly related to the drug were diarrhea (17%), nausea (17%), vomiting (14%) and anorexia (14%). Only 26 serious adverse events were reported, and none of

Table III: Clinical studies of lanthanum carbonate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Failure, renal (chronic), Hemodialysis	Randomized Double-blind	Lanthanum carbonate, 225 mg p.o. o.d. x 6 wks (n=28) Lanthanum carbonate, 675 mg p.o. o.d. x 6 wks (n=29) Lanthanum carbonate, 1350 mg p.o. o.d. x 6 wks (n=30) Lanthanum carbonate, 2259 mg p.o. o.d. x 6 wks (n=26) Placebo (n=32)	145	Lanthanum carbonate at doses higher than 675 mg was significantly more effective than placebo in reducing serum phosphorus levels in hemodialysis patients with chronic renal failure	4
Failure, renal (chronic), Hemodialysis	Open	Lanthanum carbonate, 300 [later titrated to 300-2250] mg p.o. o.d. x 6.48 [mean] mo	40	Lanthanum carbonate 300-2250 mg/d was safe and effective in maintaining clinically acceptable serum phosphorus levels in patients with chronic renal failure for long periods of time. No serious drug-related adverse events were seen	5
Failure, renal	Open	Lanthanum carbonate, 1500-3000 mg p.o. o.d. x 12 mo (n=333) Calcium carbonate o.d. x 6 mo → Lanthanum carbonate, 1500-3000 mg p.o. o.d. x 6 mo (n=185)	518	Lanthanum carbonate was effective and well tolerated in the treatment of hyperphosphatemia associated with chronic renal failure. Compared to calcium carbonate, it was associated with a lower incidence of hypercalcemia	6
Failure, renal (chronic), Hemodialysis	Randomized Open Multicenter	Lanthanum carbonate, 375-3000 mg p.o. o.d. x 2 y (n=647) Baseline therapies (n=642)	1289	Compared to standard therapies, lanthanum carbonate was equally effective in reducing serum phosphorus levels in patients with chronic renal failure and was associated with a lower incidence of adverse events	7

these were considered to be drug-related. No evidence of lanthanum accumulation was found (5). The results from these and the following studies are depicted in Table III.

In another open-label extension study, 518 hemodialysis patients previously treated with lanthanum carbonate or calcium carbonate for 6 months received 1500-3000 mg/day lanthanum carbonate for another 6 months. At the end of the study, both treatments resulted in similar mean serum phosphorus levels. The incidence of hypercalcemia was 20.2% after receiving calcium carbonate for 6 months, but this decreased to 2.7% after switching to 6 months of lanthanum carbonate. Lanthanum carbonate was well tolerated and the incidence of serious adverse events was low in both study groups (6).

An ongoing multicenter, open-label clinical trial is assessing the long-term efficacy and safety of lanthanum carbonate (375-3000 mg/day) and other therapies (sevelamer hydrochloride or calcium and aluminum salts) in 1,289 patients with chronic renal failure and baseline serum phosphorus levels higher than 5.9 mg/dl. An interim analysis was conducted after an average exposure of 422.2 days to standard therapies and 304.1 days to lanthanum carbonate. Both study groups showed similar reductions in serum phosphorus levels, but patients treated with lanthanum carbonate reported a better safety profile. This drug showed a lower incidence of serious adverse events (51.0% *vs.* 65.4%), hypercalcemia (3.4% *vs.* 10.4%), diarrhea (19.8% *vs.* 27.4%), abdominal pain (14.1% *vs.* 20.9%) and dyspepsia (8.2% *vs.* 14.8%), together with a lower mortality rate (5.1% *vs.* 12.0%) (7).

1. *Fosrenol receives approval in Sweden.* DailyDrugNews.com (Daily Essentials) 2004, March 26.

2. *AnorMED expands Fosrenol licensing agreement*. DailyDrugNews.com (Daily Essentials) 2004, Jan 21.

3. *Bayer acquires Fosrenol rights in Japan*. DailyDrugNews.com (Daily Essentials) 2003, Dec 12.

4. Finn, W., Joy, M., Webster, I., Gill, M *Lanthanum carbonate (Fosrenol™) causes significant reductions in serum phosphorus and Ca x P product in a dose-ranging, placebo-controlled study*. Nephrol Dial Transplant 2003, 18(Suppl. 4): Abst W437.

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6. Hutchison, A., Webster, I., Gill, M, Schmieder, R. *Safety and tolerability of lanthanum carbonate in haemodialysis patients: A 12-month study*. Nephrol Dial Transplant 2003, 18(Suppl. 4): Abst W432.

7. Finn, W.F., Joy, M.S., Webster, I., Gill, M. *A long-term (2-year) assessment of the safety and efficacy of lanthanum carbonate (Fosrenol™), a non-calcium, non-aluminium phosphate binder for the treatment of hyperphosphataemia*. Nephrol Dial Transplant 2003, 18(Suppl. 4): Abst W438.

Original monograph – Drugs Fut 2003, 28(3): 224.

Laronidase

An enzyme replacement therapy for the treatment of mucopolysaccharidosis I (MPS I), laronidase (alronidase) is a recombinant form of the enzyme alpha-L-iduronidase jointly developed by BioMarin and Genzyme and launched last year as Aldurazyme® in the U.S. and the E.U. It has also been approved in a number of other markets, including Canada, Norway, Iceland, Israel and the Czech Republic, and applications are pending in Australia, New Zealand, Korea, Russia and Bulgaria (1-4).

1. *BioMarin reports Q3 R&D highlights*. BioMarin Pharmaceutical Press Release 2003, Nov 4.

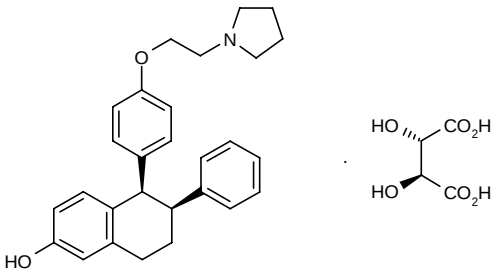
2. *BioMarin Pharmaceutical reports 2003 year-end R&D highlights*. BioMarin Pharmaceutical Press Release 2004, Feb 3,

3. *Canadian approval of Aldurazyme for MPS I*. DailyDrugNews.com (Daily Essentials) June 11, 2004.

4. *BioMarin Pharmaceutical reports Q1 R&D highlights*. BioMarin Pharmaceutical Press Release 2004, May 4.

Original monograph – Drugs Fut 2003, 28(5): 432.

Lasofoxifene Tartrate



Advanced-stage clinical studies are continuing at Pfizer with the SERM lasofoxifene tartrate for the treatment of osteoporosis (1-3). This compound was discovered as part of a collaboration with Ligand.

The results of a phase II study indicate that lasofoxifene can safely prevent bone loss in postmenopausal women. The study included 394 healthy postmenopausal women between the ages of 50 and 74 years who were treated for 1 year with lasofoxifene 0.017, 0.05, 0.15 or 0.5 mg/day or placebo. At the end of the study, all doses of lasofoxifene were associated with significant increases in lumbar spine bone mineral density compared to placebo. Most patients treated with lasofoxifene (75%) experienced increases in bone mineral density at the lumbar spine. In addition, biochemical markers of bone metabolism were significantly reduced with lasofoxifene at 6 months, as was LDL cholesterol. The most common adverse events were vasodilatation, leg cramps and leukorrhea. Thus, lasofoxifene demonstrated potential for use in postmenopausal women at low doses (4).

1. *Pfizer reports Q3 R&D highlights*. Pfizer Press Release 2003, Oct 22.

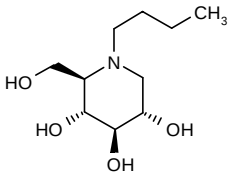
2. *Ligand reports Q4 R&D highlights*. Ligand Pharmaceuticals Press Release 2004, March 3.

3. *Pfizer reports 2003 year-end R&D highlights*. Pfizer Press Release 2004, Jan 22.

4. Bolognese, M.A., Weiss, S.R., Ettinger, M.P., Moffett, A.H., Lee, A. *Lasofoxifene: A next generation selective estrogen receptor modulator (SERM) for the prevention of bone loss in postmenopausal women*. Osteoporosis Int 2004, 15(Suppl. 1): Abst OC19.

Original monograph – Drugs Fut 1998, 23(10): 1066.

Miglustat



Actelion launched miglustat (Zavesca®) as the first oral treatment for type 1 Gaucher's disease in the spring of 2003 in the U.K. and later in Germany, followed by a number of other European markets. The product was approved by the FDA in mid-2003 and launched in the U.S. early this year. It was also approved in Israel in 2003 and in Canada in March 2004. Miglustat is a substrate reduction therapy designed to reduce the production of the glycosphingolipid substrate, stored in excess amounts in Gaucher's patients, to a level that can be effectively cleared by the naturally occurring enzyme glucocerebrosidase. In two clinical studies, miglustat significantly reduced liver and spleen volumes and increased platelet and hemoglobin levels in patients who were either treatment-naïve or who had discontinued enzyme replacement therapy for at least 3 months. In a third study, miglustat maintained the hematological and organ volume benefits in patients who had previously been on long-term enzyme replacement therapy. Actelion licensed miglustat from Oxford GlycoSciences, now part of Celltech Group. Actelion is the worldwide license holder for miglustat, excluding Israel, where it is licensed to Teva. Based on preclinical evidence supporting the use of miglustat in other related lipid storage diseases, phase III trials in late-onset Tay-Sachs, type 3 Gaucher's and Niemann-Pick type C disease are being conducted. The first results of a 1-year, 30-patient, open-label, controlled study in late-onset Tay-Sachs disease should be available by the end of 2004. The therapy has orphan drug status in the E.U. and the U.S. (1-6).

1. *Preclinical and clinical development efforts at Actelion*. DailyDrugNews.com (Daily Essentials) Nov 5, 2003.

2. *Celltech completes integration of OGS*. DailyDrugNews.com (Daily Essentials) Nov 24, 2003.

3. *Actelion reports Q3 R&D highlights*. Actelion Press Release 2003, Oct 28.

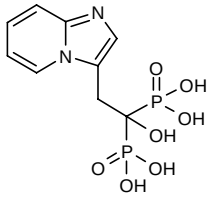
4. *Zavesca launched in U.S.* DailyDrugNews.com (Daily Essentials) Jan 9, 2004.

5. *Actelion reports Q1 R&D highlights*. Actelion Press Release 2004, April 27.

6. *Actelion and Celltech modify Zavesca license agreement*. DailyDrugNews.com (Daily Essentials) June 21, 2004.

Original monograph – Drugs Fut 2003, 28(3): 229.

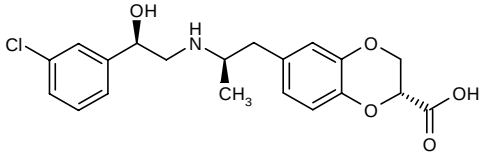
Minodronic Acid



Ono Pharmaceutical and Yamanouchi are conducting phase III clinical studies in Japan with the potent bisphosphonate minodronic acid (Ono-5920, YM-529, Onobis®) for the treatment of osteoporosis. The compound is highly effective in preventing bone resorption and increasing bone mineral density and is associated with less gastrointestinal side effects than available drugs.

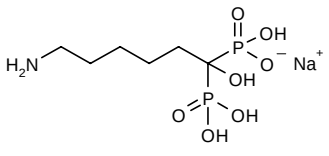
Original monograph – Drugs Fut 2002, 27(10): 935.

N-5984



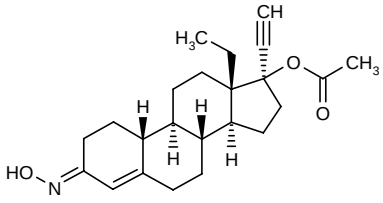
The potent and selective β_3-adrenoceptor agonist N-5984 is being codeveloped by Kyorin and Nisshin Pharma for obesity and diabetes. N-5984 is reported to reduce plasma glucose, insulin, triglycerides and free fatty acids, as well as to improve glucose tolerance, and it is presently in phase I clinical testing.

Neridronate Sodium

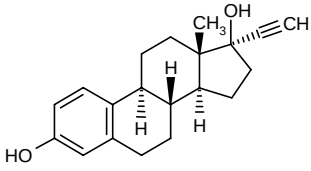


Neridronate sodium (Nerixia®) was introduced in Italy by Abiogen in 2002 as the first treatment for osteogenesis imperfecta, a metabolic condition characterized by extreme bone fragility. The company continues to study the drug for use in other related indications, with phase III trials under way in Paget's disease and phase II trials in osteoporosis.

Norgestimate/Ethinylestradiol



Norgestimate

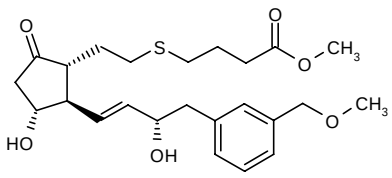


Ethinylestradiol

In September of last year, Ortho-McNeil announced the filing of an NDA with the U.S. FDA seeking clearance for use of the company's Ortho Tri-Cyclen® (norgestimate/ethinylestradiol) tablets for increasing bone mineral density in adolescents with anorexia nervosa. Currently, there is no approved treatment for the osteoporosis that is often seen in these subjects (1). At present, Ortho Tri-Cyclen® is marketed for preventing pregnancy and for the treatment of acne vulgaris in females.

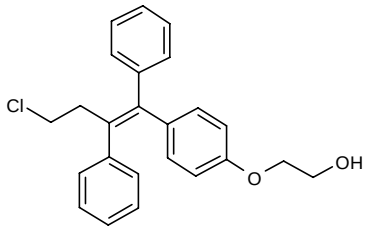
1. *New Drug Application submitted to FDA for Ortho Tri-Cyclen®*. Ortho-McNeil Pharmaceutical Press Release Sept 25, 2003.

Ono-4819



The prostaglandin EP_4 receptor agonist Ono-4819 (Ono Pharmaceutical) has marked bone-forming activity and is in phase II clinical development in Japan for vertebral fracture healing in patients with osteoporosis.

Ospemifene



Ospemifene (FC-1271a), a new SERM in phase II/III development at Hormos for postmenopausal osteoporosis and postmenopausal urogenital atrophy, has been found to decrease markers of bone resorption and formation in a study in healthy postmenopausal women. Biochemical markers of bone turnover were studied in 159 women (mean age of 57-58 years) treated for 3 months with doses of 30, 60 or 90 mg or placebo in the randomized, double-blind trial. Significant and dose-dependent reductions in urinary *N*-terminal crosslinking telopeptides of type I collagen were seen with ospemifene (6.1%, 9.4% and 12.9%, respectively), as well as a significant decrease in urinary *C*-terminal crosslinking telopeptides of type I collagen with ospemifene 90 mg (4.8%). These markers were increased in the placebo group. Reductions in markers of bone formation were also dose-dependent. In the 30-, 60- and 90-mg groups, procollagen type I N-propeptide decreased by 1.8%, 9.8% and 15.3%, respectively, procollagen type I C-propeptide decreased by 2.6%, 12% and 11.9%, respectively, and bone-specific alkaline phosphatase decreased by 0.7%, 1.9% and 2.6%, respectively. The highest doses had the greatest effect on bone turnover markers, the levels of which began to return to baseline values 2-4 weeks after treatment discontinuation (1).

1. Komi, J., Heikkinen, J., Rutanen, E.M., Halonen, K., Lammintausta, R., Yikorkala, O. *Effects of ospemifene, a novel SERM, on biochemical markers of bone turnover in healthy postmenopausal women*. Gynecol Endocrinol 2004, 18(3): 152.

Original monograph – Drugs Fut 2004, 29(2): 38.

Ostabolin-C™

Zelos Therapeutics has commenced clinical trials of Ostabolin-C™, a novel parathyroid hormone (PTH) analogue for the treatment of osteoporosis. The Canadian study will enroll 40 healthy volunteers aged 40-75 years. Each week 1 cohort of volunteers will receive a single s.c. injection of either Ostabolin-C™ or placebo. The Ostabolin-C™ dose in each subsequent cohort will be escalated until the fifth cohort has been treated. The phase Ia study will be followed immediately by a phase Ib trial wherein volunteers in each of the 5 cohorts will receive daily injections for a 1-week period. Subjects will be monitored for safety, serum levels of Ostabolin-C™, and serum markers of bone formation and resorption. Ostabolin-C™ is a 31-amino-acid cyclic PTH analogue designed to have enhanced stability and therapeutic properties in the treatment of osteoporosis as compared to PTH and other PTH analogues. Ostabolin-C™ has the same or improved bone formation efficacy as seen with first-generation PTH analogues but, based on animal studies, does not stimulate calcium release. The compound originated from research in the Parathyroid Hormone Project within the National Research Council of Canada (NRC) and was subsequently licensed to Zelos (1).

Ostabolin-C™ is being studied in several different formulations for two indications. The injectable form is in phase I trials for osteoporosis. A pulmonary formulation, in preclinical trials, is also being evaluated for osteoporosis, with phase I trials expected in the first quarter of 2006. Ostabolin-C™ is also being studied in preclinical trials as a topical agent for psoriasis. The product demonstrated efficacy in a psoriasis animal model, and proof of concept was demonstrated in humans with psoriasis. The projected clinical start date for the topical PTH is late 2004 (2).

1. *Ostabolin-C enters clinical trials*. DailyDrugNews.com (Daily Essentials) March 12, 2004.

2. *R&D highlights from the 3rd Annual Global Biotech Forum for Investing & Partnering: Zelos*. DailyDrugNews.com (Daily Essentials) April 30, 2004.

P-57

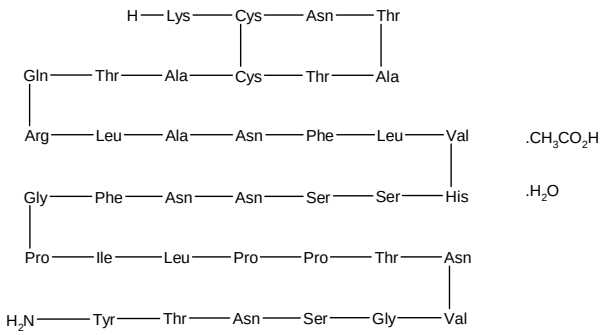
P-57 is a plant extract in development at Phytopharm for meal replacement for the dietary control of obesity. The compound has been shown to reduce both carbohydrate and fat intake, substantially reduce caloric intake in man and reduce body fat. P-57 is in phase IIa trials, and a reformulation of the compound is in progress (1).

1. *R&D highlights from the 3rd Annual Global Biotech Forum for Investing & Partnering: Phytopharm*. DailyDrugNews.com (Daily Essentials) April 27, 2004.

Phosphate Binder

ML Laboratories and Ineos Silicas are codeveloping a phosphate binder for the treatment of hyperphosphatemia in kidney failure patients. A phase I study in healthy volunteers has been completed and showed that the anion exchange compound was tolerated at doses sufficient for significantly reducing phosphate absorption from the diet. Patients are currently being recruited for a phase II trial.

Pramlintide Acetate



Amylin is in the process of seeking regulatory approval for pramlintide acetate (Symlin®) for the treatment of type 1 and insulin-using type 2 diabetes, and is also developing the compound for the treatment of obesity (AC-137). Pramlintide is a synthetic version of the human hormone amylin and the first member of a new class of drugs known as amylinomimetics, or amylin receptor agonists.

During the first quarter of this year, the company initiated the first phase II study for pramlintide in the treatment of obesity. The dose-escalation study for this program, which recently completed enrollment, is designed to evaluate the safety and tolerability of rising doses of pramlintide in approximately 200 obese subjects with and without diabetes (1, 2).

1. *Amylin reports Q1 R&D highlights*. Amylin Pharmaceuticals Press Release 2004, April 28.

2. *Enrollment completed in phase II obesity study of AC-137*. DailyDrugNews.com (Daily Essentials) April 1, 2004.

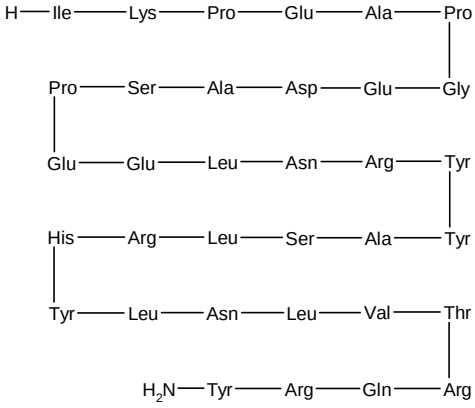
Original monograph – Drugs Fut 2001, 26(5): 444.

PSK-3471 (SERM-3471)

This new designer estrogen is one of a new generation of SERMs for the prevention and treatment of osteoporosis. ProSkelia, an independent company spun off from Aventis Pharma in 2002 that focuses on bone diseases and hormone disorders, is conducting phase IIa clinical studies and partner Aventis Pharma has an option to license the drug at the end of this stage of development (1).

1. *ProSkelia announces phase IIa clinical study for selective estrogen receptor modulator PSK 3471*. Proskelia SAS Press Release 2004, Jan 26.

PYY3-36



Two pharmaceutical companies are developing peptide YY3-36 (PYY3-36) for the treatment of obesity. PYY3-36 is a high-affinity neuropeptide Y_2 receptor agonist synthesized by endocrine cells in the gut and which reduces appetite and food intake through the modulation of appetite circuits in the hypothalamus.

Amylin has initiated a phase I clinical study with AC-162352 (human PYY3-36) for the treatment of obesity. The dose-escalating safety study will enroll up to 80 healthy volunteers. In December 2002, Curis licensed patents covering the use of PYY to Amylin for the *in vivo* treatment of metabolic diseases, including diabetes and obesity. Administration of PYY to humans has been shown to suppress appetite and reduce food intake. Under the licensing agreement, Curis receives an upfront licensing fee, milestone cash payments and a royalty on sales. Amylin is solely responsible for development and clinical testing of the PYY compound. Curis retains rights to other PYY patent applications that relate to the use of PYY to transform stem cells into insulin-producing cells and other types of specialized cells (1-4).

Nastech also recently commenced an in-clinic, parallel, multiple-dose, randomized, double-blind, placebo-controlled, dose-sequencing phase Ic study for its PYY3-36 nasal spray. The study will randomize 36 normal healthy subjects aged 18-65 years with a body mass index of 30-40 kg/m^2 to receive 3 daily administrations of various dose sequences of PYY3-36 or placebo over 8 consecutive days. The study aims to determine how many times a day PYY3-36 needs to be administered to achieve optimal weight loss results. Inter- and intrasubject variability and gender effects on appetite scores, caloric reduction and duration, pharmacokinetics and safety will all also be evaluated. This should be the final study before initiation of phase II weight loss studies in 2004. Results from a phase Ia nasal absorption and tolerance study in healthy subjects indicated that intranasal administration results in concentrations of PYY3-36 that equal or even exceed normal postmeal levels. A double-blind, randomized, placebo-controlled, crossover phase Ib dose-ranging study commenced in January 2004 in

overweight adult male and female subjects with a body mass index of 27-40 kg/m^2 to determine the optimal dose of PYY3-36 based on an assessment of appetite and food intake for the 24 h following intranasal administration. PYY3-36 reduced appetite by 5-19% (evaluated using visual analogue scores) and the 24-h total caloric intake by 4-15%. All adverse events were mild or moderate and resolved without treatment; these included throat dryness, nausea, headache, sore throat, lethargy and dizziness (5-8).

1. *Amylin reports Q3 R&D highlights*. Amylin Pharmaceuticals Press Release 2003, Nov 4.

2. *Amylin files IND for PYY compound for obesity*. DailyDrugNews.com (Daily Essentials) Jan 14, 2004.

3. *Amylin PYY obesity drug candidate enters phase I safety study*. DailyDrugNews.com (Daily Essentials) April 1, 2004.

4. *Amylin reports Q1 R&D highlights*. Amylin Pharmaceuticals Press Release 2004, April 28.

5. *Nastech begins a clinical trial with intranasal PYY in overweight adults*. DailyDrugNews.com (Daily Essentials) Jan 23, 2004.

6. *Nastech's intranasal PYY3-36 spray tested in phase Ic study for obesity*. DailyDrugNews.com (Daily Essentials) Feb 26, 2004.

7. *Nastech initiates dose-range finding calorie reduction study using PYY obesity drug nasal spray: Inter- and intra-subject variability of pharmacokinetic and pharmacodynamic parameters (duration of appetite suppression and calorie reduction) to be assessed*. Nastech Pharmaceutical Press Release 2004, Jan 20.

8. *Nastech reports positive PYY obesity and apomorphine sexual dysfunction clinical trial data*. Nastech Pharmaceutical Press Release 2004, March 10.

Additional References

Park, A. et al. *Intranasal administration of peptide YY3-36: A phase 1 dose ranging and safety study in healthy human subjects*. 86th Annu Meet Endocr Soc (June 16-19, New Orleans) 2004, Abst P1-346.

Park, A. et al. *Nasal peptide YY3-36 : Phase 1 dose ranging and safety study in healthy subjects*. Int J Obes 2004, 28(Suppl. 1): Abst T7d:P7d-037.

Recombinant Human Acid Alpha-Glucosidase

Pivotal clinical trials are under way at Genzyme for Myozyme™, the company's recombinant human acid alpha-glucosidase (rhGAA), in children under 3 years of age with the infantile-onset form of Pompe's disease. Genzyme also plans to conduct clinical studies of the enzyme replacement therapy in older children and adults with Pompe's disease once supplies of the product become available.

Original monograph – Drugs Fut 2003, 28(6): 538.

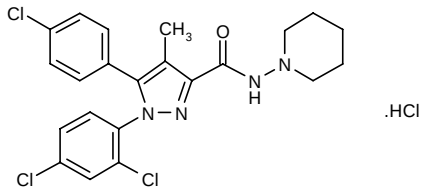
rhIGF-I/rhIGFBP-3

Insmed's rhIGF-I/rhIGFBP-3 (SomatoKine®) is a proprietary delivery composition of insulin-like growth factor-I (IGF-I) administered as a once-daily subcutaneous injection to restore IGF-I levels to more normal ranges in metabolic and anabolic disorders where IGF deficiency exists. A pivotal phase III trial is under way for the treatment of growth hormone insensitivity syndrome (GHIS), phase II studies for diabetes and severe burn injury, and a phase II trial in elderly female patients with recent hip fracture has been completed. In recovery from hip fractures, administration of the product has demonstrated significant improvement in functional recovery and bone mineral density (1, 2).

1. *SomatoKine granted orphan drug designation for extreme insulin resistance*. DailyDrugNews.com (Daily Essentials) Dec 18, 2003.

2. *University of Rochester to study rhIGF-I/rhIGFBP-3 for myotonic dystrophy*. DailyDrugNews.com (Daily Essentials) Jan 12, 2004.

Rimonabant Hydrochloride



Sanofi-Synthélabo recently reported very positive results from phase III trials with its potential blockbuster drug rimonabant hydrochloride (SR-141716, Acomplia™) for the treatment of obesity and smoking cessation. The rimonabant phase III program for smoking cessation and in obese, dyslipidemic patients is scheduled to be completed by the end of this year (1, 2). Rimonabant is the first potent and selective central cannabinoid CB_1 receptor antagonist.

RIO-Lipids is a multinational, multicenter, double-blind, placebo-controlled 1-year treatment study conducted in 1,036 overweight/obese dyslipidemic patients who were randomly assigned to receive a once-daily dose of rimonabant 20 mg, rimonabant 5 mg or placebo. Treatment with rimonabant 20 mg significantly reduced body weight, waist circumference and plasma triglyceride levels, increased HDL cholesterol levels and improved plasma insulin and glucose levels. Rimonabant 20 mg also reduced the prevalence of patients meeting the NCEP-ATP III criteria for the presence of metabolic syndrome from 52.9% to 25.8%.

Table IV: Clinical studies of rimonabant hydrochloride (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Obesity	Randomized Double-blind Multicenter	Rimonabant, 5 mg o.d. + Mild hypocaloric diet x 16 wks Rimonabant, 10 mg o.d. + Mild hypocaloric diet x 16 wks Rimonabant, 20 mg o.d. + Mild hypocaloric diet x 16 wks Placebo + Mild hypocaloric diet x 16 wks	287	Rimonabant dose-dependently reduced body weight and waist circumference of patients with obesity	6

These findings indicate that rimonabant could be useful for the treatment of cardiovascular diseases in high-risk abdominally obese patients (3-5).

A total of 287 subjects with a body mass index of 29-41 were included in a randomized clinical trial that determined the effects of rimonabant on body weight and waist circumference. Each patient was given a mild hypocaloric diet together with placebo or rimonabant (5, 10 or 20 mg) once daily for 16 weeks. Rimonabant dose-dependently reduced both body weight and waist circumference. Body weight reduction was significantly greater compared to placebo for all rimonabant doses, whereas only the highest dose of rimonabant was significantly more effective than placebo in reducing waist circumference. All study treatments were well tolerated (6) (see Table IV).

1. *Sanofi-Synthélabo reports 2003 year-end R&D highlights*. Sanofi-Synthélabo Press Release 2004, Feb 16.

2. *Sanofi-Synthélabo reports Q1 R&D highlights*. Sanofi-Synthélabo Press Release 2004, April 22.

3. Després, J.-P. *Selective cannabinoid receptor antagonism and its role in the management of obesity/metabolic syndrome*. Metab Syndr Type II Diabetes Atheroscler Congr (May 19-23, Marrakesh) 2004, Abst LL-18.

4. Després, J.-P. *Selective cannabinoid receptor antagonism and its role in the management of obesity/metabolic syndrome*. Metab Syndr Type II Diabetes Atheroscler Congr (May 19-23, Marrakesh) 2004, Abst P-42.

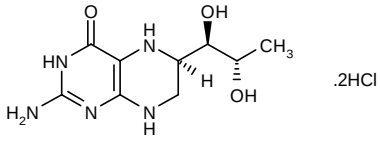
5. Despres, J.-P., Golay, A., Sjöstrom, L. *Weight loss in overweight/obese dyslipidemia subjects treated with rimonabant: The RIO-Lipids trial*. Int J Obes 2004, 28(Suppl. 1): Abst T5:O2-005.

6. Abu-Lebdeh, H., Geohas, J., Brazg, R., Block, M., Noveck, R., Free, R., Jensen, M. *The selective CB1-receptor antagonist rimonabant reduces body weight and waist circumference in obese subjects*. Int J Obes 2004, 28(Suppl. 1): Abst T5:O2-001.

S-2367

A centrally acting antiobesity agent, Shionogi's S-2367 both reduces appetite and increases energy expenditure. Phase I trials in the U.S. are in progress.

Sapropterin Dihydrochloride



BioMarin has brought together a phenylketonuria (PKU) advisory board comprised of experts in PKU and other metabolic diseases to help guide and participate in BioMarin's PKU product development programs. The company is evaluating two approaches to address the full spectrum of mild to severe PKU patients: sapropterin dihydrochloride (dapropterin dihydrochloride, Phenoptin™), an oral synthetic form of the naturally occurring enzyme cofactor tetrahydrobiopterin (6R-BH4) for mild to moderate patients, and phenylase, an enzyme replacement therapy for more severe patients. In the first quarter of this year, BioMarin commenced evaluation of sapropterin in PKU patients. Several published clinical studies suggest that it can effectively reduce blood phenylalanine levels in PKU patients. This reduction in blood phenylalanine levels will be an important efficacy measurement for the PKU clinical development programs. BioMarin has filed for orphan drug status for sapropterin. The company has also entered into a manufacturing partnership with Merck Eprova AG, a subsidiary of Merck KGaA, which specializes in the manufacturing of pterin- and folate-derived pharmaceuticals similar to sapropterin. Merck Eprova has also developed proprietary technology to lower the cost of production and prolong stability of sapropterin (1).

The first pilot trial will enroll 20 PKU patients aged over 8 years. The open-label study will evaluate PKU patient responsiveness to the enzyme cofactor 6R-BH4. The aim is to define the 6R-BH4 screening method that will be used to identify the population of PKU patients that will most likely respond in future clinical trials to sapropterin. The study is expected to conclude in the second quarter of 2004. Sapropterin has the potential to reduce high neurotoxic phenylalanine levels, addressing the underlying cause of the acute and chronic symptoms of PKU. BioMarin anticipates commencing at least one additional clinical trial in PKU by the end of 2004 (2-4).

1. *Expert advisory board to guide BioMarin's PKU programs*. DailyDrugNews.com (Daily Essentials) Feb 4, 2004.

2. *BioMarin initiates PKU clinical program*. DailyDrugNews.com (Daily Essentials) Feb 25, 2004.

3. *BioMarin Pharmaceutical reports 2003 year-end R&D highlights*. BioMarin Pharmaceutical Press Release 2004, Feb 3.

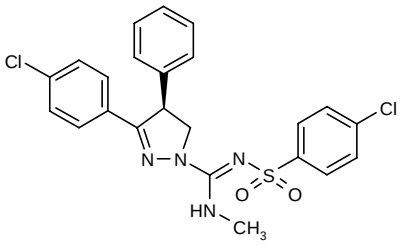
4. *BioMarin Pharmaceutical reports Q1 R&D highlights*. BioMarin Pharmaceutical Press Release 2004, May 4.

Original monograph – Drugs Fut 1991, 16(1): 30.

SB-462795

SB-462795 is a new cathepsin K inhibitor undergoing early clinical development at GlaxoSmithKline as a potential new therapy for osteoporosis and osteoarthritis.

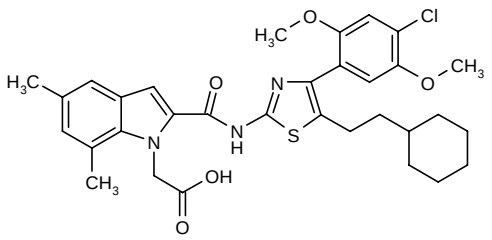
SLV-319



Bristol-Myers Squibb and Solvay have entered into a worldwide agreement for the Solvay compound SLV-319, which is in phase I development for the potential treatment of obesity and other metabolic disorders. SLV-319 belongs to a novel class of agents called cannabinoid type 1 (CB_1) antagonists. Clinical and preclinical studies involving this class of drug have shown that blocking the CB_1 receptor results in reduced food intake. The parties will jointly develop and commercialize SLV-319 on a global basis (1).

1. *BMS and Solvay to codevelop SLV-319*. DailyDrugNews.com (Daily Essentials) May 19, 2004.

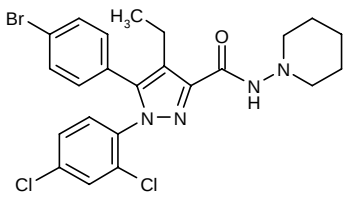
SR-146131/SSR-125180



SR-146131

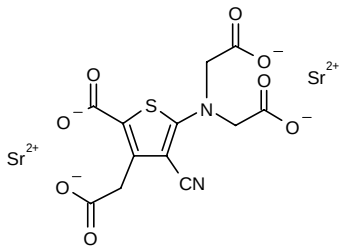
The development of these two Sanofi-Synthélabo compounds has been discontinued. Both SR-146131 and SSR-125180 (a backup compound to SR-146131) were cholecystokinin CCK_1 receptor agonists with potential utility in obesity that had reached phase I clinical development.

SR-147778



A novel cannabinoid CB_1 receptor antagonist from Sanofi-Synthélabo, SR-147778 is a backup compound to rimonabant (see above) and is being studied in phase I clinical trials for its potential as a novel obesity therapy.

Strontium Ranelate



Servier's strontium ranelate (ranelic acid distrontium salt, Protelos®, Osseor®) recently received a favorable opinion from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMEA) for the treatment of postmenopausal osteoporosis to reduce the risk of vertebral and hip fractures (1, 2). This compound promotes bone formation by stimulating osteoblasts and reduces bone resorption by decreasing osteoclasts. Servier has licensed strontium ranelate to Fujisawa (FK-481) for Japan, where it is presently undergoing phase II clinical evaluation.

Not one of the currently available medications has, so far, unequivocally demonstrated its ability to fully prevent the occurrence of new vertebral or peripheral osteoporotic fractures once osteoporosis is established. Therefore, several new therapies are currently under development to optimize the risk/benefit ratio of osteoporosis treatment. Strontium ranelate is composed of an organic moiety (ranelic acid) and two atoms of stable nonradioactive strontium. *In vitro*, strontium ranelate increases collagen and noncollagenic protein synthesis by mature osteoblast-enriched cells. The effects of strontium ranelate on bone formation were confirmed by its ability to enhance preosteoblastic cell replication. The stimulation by strontium ranelate of the replication of osteoprogenitor

cell and collagen, as well as noncollagenic protein, synthesis in osteoblasts provides substantial evidence to categorize strontium ranelate as a bone-forming agent. In the isolated rat osteoclast assay, preincubation of bone slices with strontium ranelate induced concentration-dependent inhibition of the bone-resorbing activity of osteoclasts. Strontium ranelate also concentration-dependently inhibited, in a chicken bone marrow culture, the expression of both carbonic anhydrase II and the α-subunit of the vitronectin receptor. These findings showing that strontium ranelate significantly affects bone resorption due to a direct and/or matrix-mediated inhibition of osteoclast activity, and also inhibits osteoclast differentiation, are compatible with the profile of an antiresorptive drug. In normal rats, administration of strontium ranelate induces an improvement in the mechanical properties of the humerus and/or the lumbar vertebra, associated with a commensurate increase in bone dimension, shaft and volume. Strontium ranelate was administered to 160 early postmenopausal women in a 24-month, double-blind, placebo-controlled, randomized study. Daily oral doses of 125 mg, 500 mg and 1 g of strontium ranelate were compared with placebo. At the conclusion of the study, the percent variation in lumbar-adjusted bone mineral density from baseline was significantly different in the group receiving 1 g/day of strontium ranelate compared with placebo (+1.41% *vs*. –0.98%). Increase in total hip and neck bone mineral density averaged, respectively, 3.2% and 2.5%. Strontium ranelate does not induce any significant adverse reactions compared with those observed in women receiving a placebo for the same duration. In a double-blind, placebo-controlled phase II study, the effect of strontium ranelate in postmenopausal women with vertebral osteoporotic fractures was assessed. Daily doses of 500 mg, 1 g and 2 g of strontium ranelate or placebo were given to 353 Caucasian women with osteoporosis. At the conclusion of this 2-year study, the annual increase in lumbar-adjusted bone mineral density of the group receiving 2 g of strontium ranelate was +2.97%, which was significantly different compared with placebo. A significant increase in bone alkaline phosphatase and, over a 6-month period, a significant decrease in urinary pyridium crosslinks (NTX) were evident. During the second year of treatment, the dose of 2 g was associated with a 44% reduction in the number of patients experiencing a new vertebral deformity. Bone histomorphometry showed no mineralization defects. The same percentage of withdrawals due to adverse effects was observed for patients receiving placebo and for those receiving 2 g of strontium ranelate. The compound was further investigated in a large phase III program that included two extensive trials for the treatment of severe osteoporosis, one assessing the effects of strontium ranelate on the risk of vertebral fractures (SOTI) and the other evaluating its effects on peripheral (nonspinal) fractures (TROPOS). The primary analysis of the SOTI (Spinal Osteoporosis Therapeutic Intervention) study, evaluating the effect of 2 g of strontium ranelate on vertebral fracture rates, revealed a 41% reduction in the relative risk of experiencing a first new vertebral fracture with strontium ranelate compared with placebo, throughout the 3-year study. The TROPOS study revealed a significant reduction in the relative risk of experiencing a first nonvertebral fracture in the group treated with strontium ranelate compared with placebo, throughout the 3-year study in the intent-to-treat population. A 41% reduction in the relative risk of experiencing a hip fracture was demonstrated in the per-protocol population. Overall, these results imply that strontium ranelate is an effective and safe treatment for vertebral and nonvertebral osteoporosis, with a unique mode of action (3).

The SOTI study was a multicenter, double-blind, randomized, placebo-controlled clinical trial that evaluated the potential efficacy of strontium ranelate in the treatment of osteoporosis. A total of 1,649 postmenopausal women at least 50 years of age with 1 or more fractures confirmed by spinal radiography and a lumbar spine bone mineral density of 0.84 g/cm^2 or less received placebo or strontium ranelate (2 g/day p.o.) for 3 years. All subjects received supplements of up to 1000 mg of calcium and 400-800 IU of vitamin D every day. Compared with placebo, strontium ranelate reduced the risk of new vertebral fractures by 49% after 1 year of treatment and by 41% during the entire study period. The percentage of patients with symptomatic vertebral fractures during the study was 11.3% with strontium ranelate and 17.4% with placebo. Strontium ranelate was also associated with a lower incidence of back pain (17.7% *vs*. 21.3%) and increases in the bone mineral density at the spine, femoral neck and total hip (14.4%, 8.3% and 9.8%, respectively, compared to placebo). Both treatments were associated with a high compliance (83% with strontium ranelate and 85% with placebo) and similar rates of adverse events, serious adverse events and discontinuations due to events. The most common gastrointestinal adverse events were diarrhea (6.1% with strontium ranelate and 3.6% with placebo) and gastritis (3.6% *vs*. 5.5%) (4) (see Table V).

A study of strontium ranelate in subjects aged 74 years and older has shown that the risk of hip fracture is reduced in older postmenopausal women. In the study, 1,977 patients were given strontium ranelate or placebo. The relative risk of hip fracture in the intent-to-treat population was 0.64 with strontium ranelate compared to controls, representing a significant reduction over 3 years (5).

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Table V: Clinical studies of strontium ranelate (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Osteoporosis, postmenopausal	Randomized Double-blind Multicenter	Strontium ranelate, 2 g p.o. o.d. + Calcium, 1000 mg/d + Vitamin D, 400-800 IU/d x 3 y (n=719) Placebo + Calcium, 1000 mg/d + Vitamin D, 400-800 IU/d (n=723)	1649	Strontium ranelate was well tolerated and more effective than placebo in reducing back pain and the risk of new vertebral fractures, increasing bone mineral density at the spine, femoral neck and total hip and improving quality of life for issues specifically related to osteoporosis, in postmenopausal women with osteoporosis	4

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T-71

Tularik has advanced T-71, an oral drug candidate for the treatment of obesity, into the clinic. A randomized, double-blind, placebo-controlled phase I trial will evaluate the safety and pharmacokinetics of single doses of T-71 in overweight to obese healthy adult volunteers in the U.K. The effect of T-71 on appetite, satiety and other markers of activity will also be measured. A multiple-ascending-dose study in overweight to obese healthy volunteers will follow. T-71 acts on an undisclosed central nervous system target and has demonstrated the ability to reduce appetite and increase metabolic rate. In preclinical studies, T-71 was also shown to decrease insulin and lipid levels (1-3).

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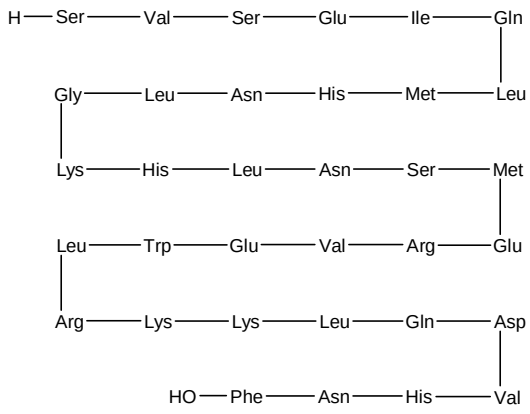
Teriparatide



The recombinant human PTH fragment teriparatide (PTH1-34) is currently available from Lilly, as Forteo® in the U.S. and Forsteo® in the E.U. and certain other countries, for s.c. injection for the treatment of osteoporosis in postmenopausal women who are at high risk of fracture. Teriparatide acts in a novel way on the bone remodeling process so that new bone is generated and added to the skeleton faster than old bone is broken down (1). Teriparatide is also the subject of a collaborative agreement with Emisphere, whereby oral formulations of the product are being prepared using Emisphere's eligen™ technology. Clinical testing is under way.

Moreover, teriparatide is in development for intranasal administration in the treatment of osteoporosis by Nastech, and by Chugai under license from Daiichi Suntory Pharma (SUN-E3001, CHS-13340).

Nastech, recently commenced a phase I trial to evaluate intranasal administration of its PTH1-34 in healthy subjects. The study is designed to determine nasal

absorption and safety of the investigational PTH1-34 nasal spray formulation *versus* the subcutaneous injection currently approved for the treatment of postmenopausal osteoporosis (2). In May 2003, Chugai's intranasal recombinant PTH1-34 CHS-13340 entered phase II trials in Japan as a potential osteoporosis therapy (3).

A transdermal formulation of teriparatide (ThPTH, TH-0229) is being developed by Theratechnologies in collaboration with Alza (Johnson & Johnson) for the treatment of osteoporosis. Preliminary results from a phase I study showed that delivery of ThPTH using Alza's Macroflux® technology allows for rapid delivery of PTH, good bioavailability, biological activity of PTH and a good safety profile. The first-in-human study was designed to obtain information on safety and to determine the pharmacokinetic and pharmacodynamic profile of Macroflux®-PTH patch delivery. The overall objectives were to confirm the proof of concept previously established in animals and to define the conditions for further development. In a crossover design, a total of 20 female subjects received both a single application of a 2 cm^2 Macroflux®-PTH patch and a subcutaneous injection of commercially available PTH (Forteo®) at a clinically effective dose. Preliminary results indicate that the Macroflux®-PTH patch delivered PTH, as measured by ELISA, at blood levels in the range of those obtained with subcutaneous administration. After adjusting for glomerular filtration, the calculated glomerular filtrate urinary cyclic AMP (cAMP) concentration increased markedly within 2 h for both routes of administration. Changes were also observed for both routes of administration in other markers of PTH biological activity, such as serum calcium. There were no serious adverse events reported for the Macroflux®-PTH treatment group. Full analysis of the data is currently under way. Theratechnologies plans to advance into calibration studies aimed at achieving bioequivalence with subcutaneous injection (4, 5).

1. *Roll-out of Forsteo across E.U.* DailyDrugNews.com (Daily Essentials) Nov 6, 2003.

2. *Phase I trial evaluates intranasal PTH1-34*. DailyDrugNews.com (Daily Essentials) May 5, 2004.

3. *Chugai Pharmaceutical reports 2003 year-end R&D highlights*. Chugai Pharmaceutical Web Site 2004, Feb 13.

4. *Dosing starts in phase I study of transdermal PTH*. DailyDrugNews.com (Daily Essentials) Dec 29, 2003.

5. *ThPTH successfully tested in first-in-man study*. DailyDrugNews.com (Daily Essentials) May 5, 2004.

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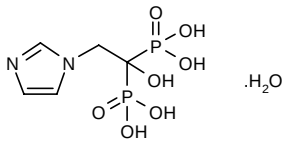
Trafermin

Kaken markets trafermin (Fiblast®, KCB-1), a human recombinant form of basic fibroblast growth factor (bFGF) licensed from Scios, in Japan as a spray formulation for the treatment of intractable skin ulcers. Presently, phase II development is ongoing for the treatment of bone fractures, periodontitis and diabetic ulcers.

Zoledronic Acid Monohydrate



A bisphosphonate inhibitor of osteoclastic bone resorption, zoledronic acid monohydrate (Zometa®) is marketed by Novartis for the treatment of hypercalcemia of malignancy and for use in patients with multiple myeloma and bone metastases from solid tumors. Zoledronic acid (ZOL-446) is also being evaluated in phase III clinical trials for use in postmenopausal osteoporosis and Paget's disease.

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Annual Update 2003/2004 - Treatment of Bone Cancers

According to the National Cancer Institute classification, the group of musculoskeletal cancers covers cancer of the bone, cartilage, fat, muscle, blood vessels or other connective or supportive tissue (1). Musculoskeletal cancer can be divided into two main groups: bone cancer and soft tissue sarcoma. Primary bone cancer and soft tissue sarcoma are uncommon types of cancer, accounting for less than 1% of new cases of cancer diagnosed each year in the U.S. (2). More commonly, tumors from other organs, such as the breasts, lungs and prostate, metastasize to the bone. Osteosarcoma is the most common type of bone cancer and develops in growing bones; Ewing's sarcoma, another form of bone cancer, appears to arise in immature nerve tissue in bone marrow. Osteosarcoma and Ewing's sarcoma occur more frequently in children and adolescents.

In the table that follows, drugs under active development for bone cancer and cancer metastatic to the bone are shown. Drugs for soft tissue sarcoma will be covered in the annual update on musculoskeletal drugs, and drugs for Kaposi's sarcoma (a cancer originated in blood vessels) will be reviewed in the AIDS annual update (*Source: Prous Science Integrity®*).

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1. NCI web site (www.cancer.gov)

2. Cancer statistics 2004 (American Cancer Society)

Itziar Escudero

Treatment of Bone Cancers

Condition	Phase	Drug	Target	Source
Cancer metastatic to bone	R-2003	Ibandronate sodium		Roche
	II	AMG-162	RANKL	Amgen
	II	Anti-PTHrP MAb	PTHrP	Chugai
	II	Imatinib mesilate[1]	PDGFR α and β, KIT, ABL1 and ABL2	National Cancer Institute
	I	Alpharadin		Algeta
Ewing's sarcoma	II	Exatecan mesilate	DNA topoisomerase I	Daiichi Pharmaceutical/ EORTC
	II	Imatinib mesilate[1]	PDGFR α and β, KIT, ABL1 and ABL2	National Cancer Institute
Osteosarcoma	III	MTP-PE		IDM (Immuno-Designed Molecules)
	II	L-Alanosine	AMP	Salmedix
	I	Octreotide acetate[1]	Growth hormone	National Cancer Institute

[1]Launched for another indication. EORTC: European Organization for Research and Treatment of Cancer; AMP: Adenosine monophosphate; PDGFR: Platelet-derived growth factor receptor; PKB: Protein kinase B; EGFR: Epidermal growth factor receptor; RANKL: Receptor activator of nuclear factor-κB ligand; PTHrP: Parathyroid hormone-related protein/peptide.