

Muraglitazar Bristol-Myers Squibb/Merck

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Bristol-Myers Squibb and Merck & Co are co-developing muraglitazar, a dual peroxisome proliferator-activated receptor- α/γ agonist, for the potential treatment of type 2 diabetes and other metabolic disorders. In November 2004, approval was anticipated as early as mid-2005.

Introduction

Type 2 diabetes is a complex metabolic disorder that is characterized by hyperglycemia, insulin resistance and defects in insulin secretion. The disease is associated with older age, obesity, a family history of diabetes and physical inactivity. The prevalence of type 2 diabetes is increasing rapidly, and the World Health Organization warns that, unless appropriate action is taken, the number of sufferers will double to over 350 million individuals by the year 2030. Worryingly, it is estimated that only half of sufferers are diagnosed with the condition [www.who.int]. Therefore, prevention and treatment of type 2 diabetes mellitus represents a major clinical challenge. Although the pathophysiology of type 2 diabetes is not completely understood, over the past decade our understanding of fat and sugar metabolism has greatly improved, and evidence suggests that, besides altered glucose metabolism, abnormalities in fat metabolism also play a central role in the pathogenesis of this disease [579204], [579206], [579210].

The peroxisome proliferator-activated receptors (PPARs) are transcription factors belonging to the nuclear receptor superfamily. Three receptor isoforms have been cloned, namely PPAR α , γ and β/δ . Each subtype is expressed in a tissue-specific manner, and activity is exerted via binding to specific consensus DNA sequences, the peroxisome proliferator response elements (PPREs). PPARs are major regulators of lipid and glucose metabolism, and have been implicated in the regulation of insulin sensitivity and symptoms of obesity, as well as in the control of food intake. Thus, they have emerged as potential molecular targets for the treatment of human metabolic disorders. In particular, PPAR α (present in the liver, heart and, to a lesser extent, skeletal muscle) plays a significant role in the regulation of nutrient metabolism, including fatty acid oxidation, gluconeogenesis and amino acid metabolism. The modulation of PPAR α function could be important for the regulation of compensatory insulin secretion, which is suggested to be involved both in glucoregulation and liporegulation. Deregulation of PPAR α contributes to the pathogenesis of a variety of disease states, such as cardiac hypertrophy and hyperlipidemia [579213], [579216],

Originator Bristol-Myers Squibb Co

Licensee Merck & Co Inc

Status Pre-registration

Indications Metabolic disorder, Non-insulin-dependent diabetes

Actions Antihyperlipidemic agent, Hypoglycemic agent, Insulin sensitizer, PPAR α agonist, PPAR γ agonist

Synonym BMS-298585

Registry No: 331741-94-7

[579218], [579221], [579457], [579459]. PPAR γ is expressed in adipose tissue, lower intestine and cells involved in immunity. Activation of PPAR γ regulates glucose and lipid homeostasis, and triggers insulin sensitization [579216], [579218], [579458], [579461]. PPAR δ is expressed ubiquitously and has been found to be effective in controlling dyslipidemia and cardiovascular diseases [579216]. PPAR α agonists are used as potent hypolipidemic compounds, increasing plasma high-density lipoprotein (HDL)-cholesterol and reducing free fatty acids, triglycerides, low-density lipoprotein (LDL)-cholesterol and the number of small dense LDL particles. The use of PPAR γ activators in the treatment of type 2 diabetes is well established. However, several unwanted effects are associated to both treatments. In particular, weight gain, edema, mild anemia and possible increased risk of congestive heart failure often accompanies PPAR γ stimulation, while activation of PPAR α results in increased lipolysis and oxidation of fatty acids [579221], [579463], [579464], [579465].

Given the importance of simultaneously controlling glucose homeostasis, insulin sensitization and lipid metabolism in type 2 diabetes, activation of both PPAR α and γ subtypes should be beneficial. This goal was initially attempted by a combination of two selective agonists [579206], [579216], [579466], [587224], but a number of PPAR α/γ dual agonists have also recently appeared in the literature; KRP-297, tesaglitazar (AstraZeneca plc), DRF-4158 (Dr Reddys Research Foundation), ragaglitazar, GW-409544, LY-465608 (Eli Lilly & Co) and LY-510929 (Eli Lilly & Co/Ligand Pharmaceuticals Inc [579204]). This evaluation focuses on muraglitazar (BMS-298585), a PPAR α/γ dual agonist that is being developed by Bristol-Myers Squibb Co (BMS) in collaboration with Merck & Co Inc, for the oral treatment of type 2 diabetes [454850], [535305], [535435].

Synthesis and SAR

Muraglitazar is a non-thiazolidinedione, oxybenzylglycine PPAR α/γ dual agonist. The synthesis of muraglitazar and other analogs is detailed in WO-00121602, which describes 30 reaction schemes. In one example of the synthetic

route, muraglitazar was synthesized by reacting 4-hydroxybenzaldehyde and 5-methyl-2-phenyloxazole-4-ethanol in triphenylphosphine and diethylazodicarboxylate to yield the corresponding benzaldehyde intermediate, which was in turn reacted with 4-methoxy-*N*-benzylglycine ethyl ester and sodium triacetoxyborohydride. The ester group was removed by hydrolysis with sodium hydroxide to yield muraglitazar.

Preclinical Development

Binding studies with muraglitazar, based on a fluorescence polarization assay, demonstrated IC_{50} values of 0.42 and 0.14 μ M for PPAR α and PPAR γ , respectively. Muraglitazar did not, however, show any significant activity towards PPAR δ , or on a wide series of other nuclear hormone receptors [454098]. Potent agonistic activity at both PPAR α and PPAR γ was demonstrated in transiently transfected Hep-G2 and CV-1 cell lines, respectively, where the respective EC_{50} values of muraglitazar were 0.24 and 0.12 μ M [454098], [454181], [463529].

Muraglitazar was tested in hamsters fed a high-fat diet [454181], [463529]. This represents a highly predictive animal model for the treatment of human hyperlipidemia. In fact, unlike mice, these animals carry cholesterol in both HDL and LDL fractions, as do humans. Oral administration of muraglitazar led to *in vivo* PPAR α activation, as confirmed by the induction of the acyl CoA oxidase gene and suppression of the apoCIII gene in liver. This is in contrast to treatment with the PPAR γ agonist rosiglitazone, which did not cause induction of the acyl CoA oxidase gene. *In vivo*, PPAR γ activation was confirmed by the induction of lipoprotein lipase and aP2 genes in white adipose tissue. Administration of muraglitazar (10 mg/kg/day) for 4 weeks produced normalization of fasting plasma triglyceride (-81%), very low-density lipoprotein (VLDL)+LDL-cholesterol (-38%), free fatty acids (-60%) and fasting plasma glucose (-19%) levels. At a dose of 30 mg/kg/day, fasting plasma glucose was lowered by 41%. In addition, administration of muraglitazar (10 mg/kg/day) for 6 weeks in fed animals caused triglyceride lowering (-56%) and glucose lowering (-25%). At a dose of 30 mg/kg/day, these values were -61 and -53%, respectively [454181], [463529]. Similar results were demonstrated in C57BL/6 mice [463529].

The dual PPAR α/γ agonist activity of muraglitazar was also shown in *db/db* mice [454180]. In this study, muraglitazar (1 mg/kg/day) given for 7 days produced a reduction of plasma fasting glucose (-36%), insulin (-41%), triglyceride (-31%), and free fatty acid (-28%). The same dose for 14 days induced significant reduction of fed glucose (-46%), insulin (-35%), and triglyceride (-37%) plasma levels. In fasted animals, the ED_{50} values for normalization of glucose and triglyceride (compared with equivalent values in C57BL/6 mice) were 0.1 and 0.2 mg/kg/day, respectively. In fed animals the same ED_{50} values were 0.5 and 1.3 mg/kg/day for 14 days, respectively. Normalization of fasting plasma glucose, triglyceride and VLDL+LDL cholesterol were also seen in high fat/sucrose diet-fed mice after oral administration of muraglitazar.

In addition, studies with different models demonstrated that muraglitazar was able to normalize lipid content in the liver. This was because PPAR α activation enhanced lipid metabolism and lead to lipid lowering, which complements the insulin sensitizing antidiabetic effects of PPAR γ activation [454180], [454181].

A subsequent study was conducted in severely diabetic *db/db* mice administered muraglitazar and the selective PPAR γ agonist rosiglitazone (both at 10 mg/kg/day) for 2 weeks. Fasting glucose was decreased by 51 and 30%, respectively. After an oral glucose challenge, the area under the glucose-response curve was decreased by 30 and 20%, respectively [541486]. In a parallel experiment on *db/db* mice [541486], muraglitazar (0.1 to 30 mg/kg/day for 4 weeks) induced a progressive, dose-dependent lowering of plasma triglycerides, free fatty acids, glucose and insulin. It should also be noted that treatment with muraglitazar (3 mg/kg/day) for 4 weeks normalized the level of plasma adiponectin, which was very low in *db/db* mice with respect to normal C57BL/6 mice (3.9 versus 20 μ g/ml). In addition, the compound was able to decrease corticosterone levels in a dose-dependent manner. Finally, a reduction in urine output from 12 to 1.9 ml was obtained after administration of 30 mg/kg/day of muraglitazar.

A study was conducted to verify whether muraglitazar was able to act directly upon macrophage foam cells, thereby retarding atherogenesis [542286]. Differentiating THP1 macrophage cells were treated for 24 h with 10 μ M of either muraglitazar or rosiglitazone *in vitro*. The results indicated that 10 μ M of muraglitazar induced the expression of multiple genes involved in reverse cholesterol transport, namely CD36 (3.8-fold), apoE (5.9-fold), liver X receptor (LXR) α/β (3.8-fold), and ATP-binding cassette transporter 1 (ABCA1) (2.8-fold). At the same concentration, rosiglitazone only weakly induced expression of CD36 (2.3-fold) and apoE (2.0-fold), and was not able to increase either LXR α/β or ABCA1 mRNA levels. When compared for their functional activities, muraglitazar increased cholesterol efflux from THP1 cells by 78%, while rosiglitazone increased it by only 35%. On the other hand, both compounds showed similar inhibitory potency (IC_{50} = 0.19 and 0.11 μ M for muraglitazar and rosiglitazone, respectively) upon secretion of monocyte chemoattractant protein 1 (which plays an important role in a number of inflammatory and immunological processes [587229]).

Metabolism and Pharmacokinetics

The permeability coefficient of muraglitazar in CaCo-2 cells is 211 nm/s at pH 5.5, which suggests that this compound is likely to be well absorbed in humans. The oral bioavailability of muraglitazar was 88, 79 and 18% in rats, monkeys and dogs, respectively [454098].

In pharmacokinetic studies, healthy individuals were randomly assigned to one of six sequential single-dose ascending groups (0.5, 1.5, 5, 25, 100 or 300 mg). Muraglitazar was rapidly absorbed, and T_{max} values were between 1 and 6 h. The mean half-life ranged from 19 to 27 h and proved to be consistent with once-daily dosing [542466]. These results were confirmed by a placebo-controlled trial of

muraglitazar (0.25, 5, 20 or 50 mg/day) and the PPAR γ agonist pioglitazone (45 mg/day) administered for 28 days to patients with type 2 diabetes. Muraglitazar was noted to have a half-life of between 18 and 30 h, and a T_{\max} of between 2.5 and 4 h, and dose-dependent increases in C_{\max} and AUC were noted [542450].

Muraglitazar proved to be a stronger inhibitor of CYP2C9 (IC_{50} value = 1.9 μ M) than CYP1A2, CYP2C19, CYP2D6 and CYP3A4 (IC_{50} > 10 μ M) [454098].

Toxicity

A two-year carcinogenicity study was conducted in rodents, and the incidence of tumors was found to be either species-specific or occurred at drug levels > 48-fold higher than the levels used to treat patients [572056].

Clinical Development

Phase II

A placebo- and active-controlled, multiple ascending-dose, 28-day study of once-daily oral muraglitazar (1.5, 5 or 20 mg/day) or pioglitazone (45 mg/day) was conducted in patients with type 2 diabetes (six to ten per group, randomly distributed) who had fasting serum glucose of 150 to 280 mg/dl and were given a standardized weight-maintaining diet. Seven plasma samples were collected within each 24-h period [541493], [544834]. The results indicate that muraglitazar dose-dependently improved 24-h mean glucose concentrations. In addition, a trend for reduction in fasting insulin was also observed. At a dose of \geq 5 mg, muraglitazar caused a larger decrease in 24-h mean glucose and fasting plasma glucose levels than pioglitazone at 45 mg (24-h mean glucose levels were -46, -76 and -100 mg/dl, and fasting glucose levels were -50, -101 and -95 mg/dl, following 45 mg of pioglitazone, and 5 and 20 mg of muraglitazar, respectively) [541493]. Muraglitazar was also able to dose-dependently decrease fasting triglyceride (-2, -27 and -51% with 1.5, 5 or 20 mg/day of muraglitazar, respectively, compared with -12% with 45 mg of pioglitazone). In addition, decreases in LDL cholesterol, total cholesterol, small-dense LDL, VLDL and increases in HDL cholesterol were observed. In general, the lipid-lowering profile of muraglitazar was better than that of pioglitazone [544834]. Results from a similar placebo-controlled trial of muraglitazar (0.25, 5, 20 or 50 mg/day), placebo or pioglitazone (45 mg/day) for 28 days in patients with type 2 diabetes confirmed these findings [542450].

A phase II trial (study 006) tested multiple doses of muraglitazar and pioglitazone in 1477 drug-naive patients, and demonstrated that patients who achieved glycemic control with 5 mg of muraglitazar maintained levels below the American Diabetes Association hemoglobin (HbA_{1c}) target of < 7% for up to two years [571507], [572056].

Phase III

Several phase III trials involving > 4500 patients with type 2 diabetes were underway at the time of publication [571507]. One open-label trial (study-018) involving 449 drug-naive patients demonstrated that muraglitazar (2.5 or 5 mg, or 5 mg open label) reduced HbA_{1c} levels by approximately 8.1, 7.9 and 10.6% to 6.97, 6.66 and 7.98%, respectively. In study

021, muraglitazar (2.5 or 5 mg) in combination with sulfonylurea was tested in 583 patients inadequately controlled on sulfonylurea. HbA_{1c} levels were reduced from approximately 8 and 8.2% to 6.95 and 6.96%, respectively. Muraglitazar (2.5 or 5 mg) was also tested in combination with metformin in 652 patients inadequately controlled on metformin (study 022). HbA_{1c} levels decreased from approximately 8% to 7.08 and 6.84%, respectively. In study 025, 5 mg of muraglitazar versus 30 mg of pioglitazone was tested in 1159 patients inadequately controlled by treatment with metformin. In both monotherapy and combination trials, 5 mg of muraglitazar reduced triglyceride levels by 26 to 19% from baseline and increased HDL-cholesterol by 14 to 16% from baseline, with no change in LDL-cholesterol [572056].

Side Effects and Contraindications

No serious adverse effects were observed when muraglitazar was administered at doses of \leq 20 mg/day to type 2 diabetic patients who had fasting serum glucose levels of 150 to 280 mg/dl and were given a standardized weight-maintaining diet [541493], [544834]. Similarly, in a placebo-controlled, sequential, ascending single-dose study, muraglitazar was well tolerated and did not show any serious adverse effect in healthy individuals at single doses up to 300 mg [542466]. In another placebo-controlled trial of muraglitazar (0.25, 5, 20 or 50 mg/day) in type 2 diabetes patients, the drug was well tolerated, with no unexpected adverse events or discontinuations noted. However, two cases of edema were reported at the highest dose [542450], and interim analysis of phase III data confirmed that, comparable with other PPAR agonists, muraglitazar treatment resulted in dose-related increases in weight gain, mild-to-moderate peripheral edema and fluid retention that may lead to, or exacerbate, congestive heart failure [571507].

Patent Summary

Two patents by Bristol-Myers Squibb Co, WO-01021602 (published in March 2001) and US-06414002 (published in July 2002) report a detailed synthesis of muraglitazar and its analogs, which are indicated as modulators of blood glucose, triglyceride, insulin and non-esterified fatty acid levels. In addition, many patents report the effects related to the use of a dual PPAR α/γ ligand in combination with other drugs. In particular, WO-2003084572 (published in October 2003 by Sankyo Co Ltd) describes a combination with an acyl-CoA:cholesterol acyltransferase inhibitor for preventing or treating atherosclerosis and related pathologies. WO-02051441 (published in July 2002 by Sankyo Co Ltd) describes combination with a diuretic such as furosemide, to prevent increase of heart weight and edema. WO-2004017896 (published in March 2004 by Merck & Co Inc) describes a combination of a dual PPAR α/γ agonist and an angiotensin II type I receptor antagonist for the treatment of hypertension and type 2 diabetes. Finally, WO-03088962 (published in October 2003 by Merck & Co Inc) describes the combination of a dual PPAR α/γ agonist with a second drug, chosen among different classes of compounds involved in cholesterol regulation.

Current Opinion

Muraglitazar was discovered and developed by Bristol-Myers Squibb as a part of an intensive internal research

program to deliver innovative medicines for patients with type 2 diabetes, and the present collaboration with Merck is expected to realize the full potential of this compound. Muraglitazar has proven to have beneficial effects on plasma glucose and lipid regulation, both in preclinical and clinical studies. The superior results often seen with muraglitazar when compared with pioglitazone or rosiglitazone seem to confirm the hypothesis that a dual PPAR α/γ agonist should provide additional benefits on glucose and/or lipid control, relative to a single PPAR subtype-selective agent.

Besides its capability to improve glucose homeostasis and to prevent adipogenesis, muraglitazar has also demonstrated anti-inflammatory, anti-atherosclerosis and antihypertensive activities. In addition, it restored normal levels of both adiponectin and corticosterone, which adds significant value to its profile. Adiponectin is a collagen-like circulating protein secreted by adipocytes that is proposed to mediate obesity-related resistance to insulin, and its low levels are predictive of future development of diabetes. Though the mechanism of regulation of plasma adiponectin levels is not completely understood, transcriptional activation of the adiponectin gene via PPAR γ was described [579467], [579468], [579469], [579473], [579474]. As far as the role of corticosterone is concerned, it has been well documented that diabetes, as well as fasting, is characterized by elevated glucocorticoids. A study aiming to verify if higher levels of corticosterone are necessary for hypothalamic responses to fasting and diabetes has been reported. The results indicated that a rise in corticosterone is necessary, but not sufficient, to reduce hypothalamic proopiomelanocortin (an anorexigenic neuropeptide) mRNA. By contrast, elevated plasma levels of corticosterone are both necessary and sufficient for the induction of hypothalamic agouti-related protein (an orexigenic neuropeptide) mRNA both in fasting and diabetes [587658]. In addition, a relationship between cholesterol level and decreased osteoblast activity, as well as neuropathic complications in diabetic individuals was proposed [587231], [587233].

Positive experimental data reported for PPAR α/γ dual agonists, in comparison with selective PPAR γ and PPAR α agonist, have encouraged several companies to conduct research in this area. Representative examples comprise structurally different compounds, including a series containing LY-929 (Ligand Pharmaceuticals Inc/ Eli Lilly & Co), which proved to be equipotent at both receptor subtypes *in vitro* and had an ED₅₀ value of 0.004 mg/kg for glucose normalization in Zucker diabetic fatty rats [579204]. Other interesting compounds from the same collaboration include series containing both a phenoxyisobutyric acid residue and a substituted 2-phenyl-5-methylloxazole moiety, which are characteristic of PPAR α and PPAR γ ligands, respectively [587234], [587237]. Researchers at GlaxoSmithKline reported a series of α -alkoxy- β -phenylpropanoic acid derivatives containing a phenyloxadiazole as lipophilic group. One of the significant terms in this series had EC₅₀ values of 0.013 and 0.004 μ M, for PPAR α and PPAR γ , respectively [419773]. GW-409544 was synthesized in the same laboratories and was structurally related to the selective PPAR γ ligand farglitazar (GlaxoSmithKline plc), but demonstrated *in vitro* EC₅₀ of

0.002 and 0.0002 μ M, for PPAR α and PPAR γ , respectively [480939]. The α -alkoxy- β -phenylpropanoic acid motif has been exploited by several other research groups and led to the discovery, amongst others, of tesaglitazar (AstraZeneca plc; presently in phase III clinical trials) [442540], [587243] and ragaglitazar (previously in development by Novo Nordisk A/S) [588268]. Representative PPAR α/γ agonists also exist in the thiazolidinedione series, including KRP-297, the first dual agonist to be reported in the literature [587365], and Merck & Co Inc has reported another series of thiazolidinedione derivatives that showed good oral antidiabetic activity in preclinical models [484817]. Another moiety that is often found in dual PPAR α/γ ligands is the chromane-2-carboxylic acid [587368]. The amide BVT-142 is under investigation by Biovitrum AB [472881], while Novartis Institutes for Biomedical Research Inc is investigating LBM-642, which was shown to be more efficacious in lipid lowering than fenofibrate in a first proof-of-concept trial. Proof-of-concept data in diabetes are expected in mid-2005 [581315]. An anomaly is ertiprotafib [587372], an insulin sensitizer developed for treatment of type 2 diabetes, which probably acts *in vivo* by multiple independent mechanisms, including protein tyrosine phosphatase-1 β inhibition and dual PPAR α/γ agonism. The compound proved able to robustly increase insulin sensitivity in both mouse and rat models of insulin resistance. As well as its effects on hyperglycemia and hyperinsulinemia, ertiprotafib dramatically reduced both serum triglyceride and free fatty acid levels in the same models [587372].

Though dual PPAR α/γ activators seem to have a favorable ADME (absorption, distribution, metabolism, excretion) profile compared with the selective PPAR ligands, several concerns have arisen during preclinical and clinical studies and many compounds were subsequently withdrawn. In particular, amongst those previously mentioned, ragaglitazar was discontinued due to observations of bladder tumors in rodents [478168], [478217]. The same fate followed KRP-297, which was discontinued in November 2003 since it caused the insurgence of a rare form of malignant tumors in mice [514245]. On this basis, although the majority of biological data reported so far indicate that muraglitazar is a promising candidate for the treatment of type 2 diabetes, some caution is required. In fact, several questions still arise on the application of dual PPAR α/γ agonists for the treatment of diabetes and other metabolic diseases, as recently commented in exhaustive reviews [579204], [579480]. One of the main concerns refers to the suggestion that modulation, rather than activation, of PPAR activity might be the most effective strategy for treating metabolic disorders, as this will improve glucose homeostasis while preventing adipogenesis. In this respect, the definition of the correct PPAR α/γ ratio could be difficult, since several variables could play a role, for example, the tissue distribution of the receptor subtypes and the potentially active drug metabolites, which could have different potencies at the two PPARs and generate new side effects, with respect to the parent compounds. Finally, it remains to be seen how a dual PPAR α/γ agonist compares to a so called 'pan-agonist', which is also able to interact with the PPAR δ subtype. Though this subtype has been poorly

investigated and its functional role is still unclear, its involvement in fertility, cancer and the nervous system has been suggested. In addition, the positive role of PPAR δ agonists in hyperlipidemia, atherosclerosis, obesity, cholesterol efflux, energy expenditure in muscles and inflammation has been highlighted [579481], [587374]. Selective PPAR δ agonists are currently being evaluated in clinical studies. Attention has been drawn to the presence in omnivorous diets of phytanic acid, which could have an impact on mitochondrial biogenesis and insulin sensitivity as it is able to activate PPAR δ [587375]. Finally, a few worrying side effects such as edema and weight gain have

been recorded for muraglitazar, as has already been observed with other PPAR α/γ dual agonists. However, no clear evidence has been given until now that they are dependent on PPAR activation. Therefore, if all the questions posed above have a positive answer, muraglitazar could become a useful treatment for type 2 diabetes.

Commercial Opinion

In February 2005, Credit Suisse First Boston estimated annual sales of muraglitazar of US \$21 million in 2006, and predicted that this would increase to US \$162.2 million by 2010 [588299].

Licensing

Merck & Co Inc

In April 2004, BMS and Merck & Co Inc entered into a global collaborative agreement for muraglitazar. BMS was to receive a US \$100 million upfront payment and US \$275 million in additional payments based upon the achievement of certain regulatory milestones. BMS and Merck were to jointly develop the clinical and marketing strategy for muraglitazar and share equally in future development and commercialization costs. Both companies were to co-promote the product on a global basis, and Merck was to receive payments based on net sales levels. In April 2004, Merck & Co Inc received development and commercialization rights for a back-up compound to [535435].

Development history

In November 2004, BMS and Merck anticipated approval of muraglitazar as early as mid-2005 [537619]. An NDA was submitted in December 2004 [577532]. Bristol-Myers Squibb Co, in collaboration with Merck & Co Inc, is developing a follow-on compound from muraglitazar. By November 2004, phase I trials of the follow-on compound were underway [486672], [572056] and several additional backup compounds were under investigation [486672].

Developer	Country	Status	Indication	Date	Reference
Bristol-Myers Squibb Co	US	Pre-registration	Non-insulin-dependent diabetes	23-DEC-04	577532
Merck & Co Inc	US	Pre-registration	Non-insulin-dependent diabetes	23-DEC-04	577532
Bristol-Myers Squibb Co	US	Discovery	Metabolic disorder	12-FEB-04	525071

Literature classifications

Biology

Study Type	Effect Studied	Experimental Model	Result	Reference
<i>In vitro</i>	Activity.	Binding studies based on a fluorescence polarization assay.	Muraglitazar demonstrated IC ₅₀ values of 0.42 and 0.14 μ M for PPAR α and PPAR γ , respectively.	454098
<i>In vivo</i>	Efficacy.	Hamsters fed a high-fat diet and treated with muraglitazar (10 or 30 mg/kg/day for 6 weeks).	At 10 mg/kg/day muraglitazar caused lowering of triglyceride (-56%) and glucose (-25%) in robust fed animals. At 30 mg/kg/day, triglyceride and glucose values were -61 and -53%, respectively.	454181
<i>In vivo</i>	Efficacy.	Mice fed a high-fat/sucrose diet orally administered muraglitazar (1 mg/kg/day) for 14 days.	Normalization of fasting plasma glucose, triglyceride and VLDL+LDL cholesterol was observed.	454180
<i>In vitro</i>	Activity.	Differentiating THP1 macrophage cells treated for 24 h with 10 μ M of either muraglitazar or rosiglitazone.	Muraglitazar induced the expression of multiple genes involved in reverse cholesterol transport, while rosiglitazone was either much weaker or inactive in this regard.	542286
<i>In vivo</i>	Activity.	<i>Db/db</i> mice treated muraglitazar (with 3 mg/kg/day) or 4 weeks.	Muraglitazar normalized adiponectin levels and induced a decrease in corticosterone levels.	541486

Metabolism

Study Type	Effect Studied	Model Used	Result	Reference
<i>In vivo</i>	Bioavailability.	Rats, monkeys and dogs.	The oral bioavailability of muraglitazar was 88, 79 and 18% in rats, monkeys and dogs, respectively.	454098
<i>In vivo</i>	Pharmacokinetics.	Healthy individuals were randomly assigned to one of six sequential, dose-ascending muraglitazar groups (0.5, 1.5, 5, 25, 100 and 300 mg).	Muraglitazar was rapidly absorbed and demonstrated T _{max} values from 1 to 6 h. The mean half-life ranged from 19 to 27 h and proved to be consistent with once-daily dosing.	542466

Clinical

Effect Studied	Model Used	Result	Reference
Efficacy.	Type 2 diabetes patients with a fasting serum glucose level of 150 to 280 mg/dl on a standardized weight-maintaining diet and were administered either muraglitazar, pioglitazone or placebo once daily for 28 days.	Muraglitazar improved 24-h mean glucose concentrations in a dose-dependent manner and reduced fasting insulin levels. Muraglitazar at a dose of ≥ 5 mg produced a greater decrease in 24-h mean glucose and fasting plasma glucose levels than pioglitazone at 45 mg.	541493
Efficacy.	Type 2 diabetes patients with a fasting serum glucose level of 150 to 280 mg/dl on a standardized weight maintaining diet and administered either muraglitazar, pioglitazone or placebo.	Muraglitazar was able to decrease fasting triglyceride in a dose-dependent manner and the lipid-lowering profile of muraglitazar was superior than that for pioglitazone.	544834
Safety.	A placebo-controlled, sequential, ascending single-dose study in healthy individuals.	Muraglitazar was well tolerated and did not show any serious adverse effect at single doses up to 300 mg.	542466
Safety and tolerability.	A placebo-controlled trial in type 2 diabetes patients.	Muraglitazar (0.25, 5, 20 or 50 mg/day) was generally well tolerated. However, two cases of edema were reported at the highest dose.	542450
Safety.	A phase III, placebo-controlled trial in treatment-naive type 2 diabetic patients.	Preliminary data indicate dose-related increases in weight gain, mild-to-moderate peripheral edema, and fluid retention.	571507

Associated patent

Title Oxa- and thiazole derivatives useful as antidiabetic and antiobesity agents.

Assignee Bristol-Myers Squibb Co

Publication WO-00121602 29-MAR-01

Priority US-19990155400 22-SEP-99

Inventors Cheng PTW, Devasthale P, Jeon YT, Chen S, Zhang H.

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535305 **Bristol-Myers Squibb and Merck announce global development and commercialization alliance for muraglitazar, a novel compound for diabetes.** Bristol-Myers Squibb Company *PRESS RELEASE* 2004 April 28

535435 **Merck & Co enters alliance for BMS's diabetes drug muraglitazar.** Merck & Co Inc *PRESS RELEASE* 2004 April 28

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