

## Product Development

# Trying to beat PPAR

By Susan Schaeffer  
Staff Writer

Since entering the market in 1999, the PPAR gamma agonists Avandia rosiglitazone from GlaxoSmithKline plc and Actos pioglitazone from Eli Lilly and Co. and Takeda Chemical Industries Ltd. have created a blockbuster class of diabetes therapeutics — even though both are known to cause serious side effects. Thus, with their eyes on a roughly \$3 billion market occupied by two compounds whose clinical profiles leave room for improvement, a large number of biotech and pharma companies are racing to bring out the next generation of PPAR modulators.

Peroxisome proliferation activated receptors are ligand-activated transcription factors that regulate cellular and physiological metabolism. PPAR gamma is the target of the marketed glitazones, which lower blood glucose and are used to treat Type II diabetes. Another subtype, PPAR alpha, is the target of marketed fibrate drugs, which are used to lower triglycerides and raise HDL cholesterol. A third subtype, PPAR delta, is believed to play a role in cholesterol transport and in raising HDL cholesterol (see "PPAR Comparison," A2).

Both Avandia and Actos are insulin sensitizers that belong to the thiazolidinedione class of PPAR gamma full agonists. In 2003, GlaxoSmithKline (LSE:GSK; GSK, London, U.K.) reported \$1.6 billion in total sales for Avandia and Avandamet, which is a combination of Avandia and metformin. U.S. sales of Avandia and Avandamet were \$1.3 billion in 2003. Takeda (Osaka, Japan) reported \$1.4 billion in U.S. sales of Actos for its fiscal year ended March 31, 2004, while LLY (Indianapolis, Ind.) reported \$431.2 million in Actos sales for 2003.

Labels for both drugs carry a warning of the risk of cardiac

failure and other cardiac effects due to edema, and both are known to cause weight gain and decreased hematocrit.

In addition, both compounds have had mixed effects on lipid metabolism, which is often abnormal in diabetics. Actos lowers triglycerides and raises HDL cholesterol but is neutral with regard to LDL. Avandia raises LDL and HDL. In clinical trials, its effect on triglycerides was variable.

With clear room for improvement, no fewer than 10 biotech and pharma companies are moving their next-generation PPAR modulators through development — including dual agonists, pan agonists and partial antagonists (see "PPAR Pipeline," page 3).

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**'The paradox is that the greater the weight gain, the better the drugs work.'**

— Ralph DeFronzo  
of U of Texas

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### Make it a double

Several companies are betting that an insulin sensitizer that also improves lipid metabolism would have an advantage. The dual agonists seek to do just that by adding alpha activity.

Muraglitazar from Bristol-Myers Squibb Co. and Galida tesaglitazar from AstraZeneca plc (LSE:AZN; AZN) are dual PPAR alpha and gamma agonists in Phase III trials. In April, BMY (Princeton, N.J.) partnered with Merck & Co. Inc. (MRK, Whitehouse Station, N.J.) to develop and market muraglitazar to treat blood glucose and lipid abnormalities in patients with Type II diabetes. AZN (London, U.K.) is developing Galida to reduce cardiovascular events by treating insulin resistance in both Type II diabetes and metabolic syndrome.

Neither company would discuss the specifics of their trials, but Ralph DeFronzo, chief of the diabetes division at the University of Texas Health Science Center in San Antonio and an investigator in the muraglitazar trials, said that the dual agonists

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## PPAR comparison

The three PPAR subtypes — alpha, gamma and delta — have different patterns of tissue expression and distinct functions. Therefore, modulating different PPAR subtypes has different effects on glucose and lipid metabolism.

Subtype	Tissue	Function	Effect of modulators on			
			Glucose	LDL-C	HDL-C	Triglycerides
Alpha	Liver, kidney, heart, muscle	Lipid metabolism	None	Lowers	Raises	Lowers
Delta	Broad distribution	Cholesterol transport	None	Lowers	Raises	Lowers
Gamma	Adipose	Glucose homeostasis, fat cell differentiation	Lowers	Raises	Raises	Variable

as a class are demonstrating some benefits over the marketed drugs.

“With gamma, you get lower glucose,” he said. “If you add alpha, what you can expect is lowered LDL and triglycerides and raised HDL. And what you see is about 20% lower LDL, 35-40% lower triglycerides, and 10-20% higher HDL.”

DeFronzo added that the dual PPARs are much more potent than the marketed drugs, although they still cause weight gain and edema. However, he argued that the importance of these side effects has been overemphasized.

According to DeFronzo, the weight gain seen with PPAR gamma is “only a cosmetic problem.” In fact, he said, “the paradox is that the greater the weight gain, the better the drugs work. The question is, does the weight gain make things worse? On the contrary, it shows the drugs are working. So you have to come up with more innovative ways to manage the weight gain.”

DeFronzo said that most of the weight gain comes in the first six months of treatment and can be managed through a combination of diet, slowly titrating the dose, and combining the drugs with metformin.

Edema, meanwhile, is part and parcel of the powerful anti-atherogenic effects seen when a compound binds PPAR alpha receptors on vessels, according to DeFronzo.

“When you bind PPAR alpha, nitric oxide is released. NO stops the atherosclerotic process and causes vasodilation, which lowers blood pressure — which is good. When NO is released, the kidneys are signaled to hold on to salt and water. About 5% of people will retain extra. A little bit of edema doesn't hurt anybody. I view it as a way to tell the drug is working.”

According to DeFronzo, congestive heart failure as a result of edema is very uncommon and usually seen in patients who also are on insulin. “In most cases,” he said, “you are preventing CHF because of the vasodilation.”

Some researchers believe that adding alpha activity may add new side effects, especially since MRK and Kyorin Pharmaceutical Co. Ltd. (Tokyo, Japan) stopped Phase III development of their MK-767 PPAR alpha and gamma agonist in 2003, citing cases of a rare form of malignant tumor in long-term safety trials in mice.

But DeFronzo said that the dual agonists do not pose the same risk of tumors in humans. “It is known to happen with all the drugs in mice and rats, and it is known not to happen in humans,” he said.

AZN would not say specifically whether it saw such tumors in mice treated with Galida. But company spokesperson Emily Denney told BioCentury that, after completing its Phase IIb program in more than 1,000 patients and its two-year carcinogenicity studies, AZN is “confident in its safety and efficacy profile” and is moving forward with its Phase III program.

### Or a triple

GSK and Plexxikon Inc. (Berkeley, Calif.) are going one step further with their pan agonists, which add not only alpha but also delta activity, with the idea of compounding the improvement in lipid metabolism.

GSK's 677954 is in Phase II testing. The company has not disclosed data from human trials, but spokesperson Rick Koenig said that in obese rhesus monkeys, the compound showed a greater than 30% reduction in blood glucose and insulin, greater than 20% reduction in LDL cholesterol, and increases in HDL cholesterol, without weight gain or fluid retention.

Plexxikon's PLX204 has completed several preclinical studies and will enter the clinic in a European pharmacokinetic study in healthy volunteers this summer. The only data the company has disclosed are from a study in the Zucker diabetic fatty (ZDF) rat model of Type II diabetes. In that study, PLX204 lowered glucose and hemoglobin A1c (HbA1c) levels more than 50% compared to placebo, lowered triglycer-

ides four times more than placebo, and raised HDL cholesterol more than 25% compared to placebo without causing significant weight gain.

Edema was not studied in that trial. However, President and CEO Kathleen Sereda Glaub said the company has not seen heart weight gain in preclinical studies conducted since the ZDF study.

The company expects to submit an IND in the fourth quarter to begin a U.S. Phase I/IIa trial of PLX204 to treat Type II diabetes.

Besides adding alpha and delta activity, Glaub noted that PLX204 does not belong to the same chemical class as Actos and Avandia, which may account for some of the difference in clinical profiles. The compound was discovered using Plexxikon's scaffold-based drug discovery technology, which starts by screening a core library of scaffolds against a family of targets and uses successive rounds of co-crystallization and chemistry to identify and optimize leads.

It also is known that PLX204 only partially agonizes PPAR gamma, which is believed to affect the compound's clinical profile versus the full agonists.

### In a bind

The third group of next-generation PPAR modulators are seeking to mitigate or eliminate the side effects of the glitazones by changing the way their compounds bind PPAR gamma, thus activating and inactivating different sets of genes.

Metabolex Inc.'s MBX-102 is a partial PPAR gamma agonist/antagonist in Phase II testing. According to Thomas Gustafson, vice president of biology, “full agonists lock the receptor into a totally active conformation. A partial agonist/antagonist can bind the receptor and compete with endogenous ligand. This causes different sets of genes to be activated or inactivated.”

While it is not clearly understood what genes MBX-102 turns on and off,

## PPAR pipeline

Selected PPAR modulators in development to treat Type II diabetes. (A) An undisclosed backup compound is entering Phase II studies.

Company	Compound	MOA	Status	Milestone
Bristol-Myers/Merck	Muraglitazar (A)	PPAR gamma and alpha agonist	Ph III	Submit NDA in 9-12 mos
AstraZeneca	Galida tesaglitazar	PPAR gamma and alpha agonist	Ph III	Submit NDA and MAA in 2006
GlaxoSmithKline	677954	PPAR gamma, alpha and delta agonist	Ph II	Submit NDA in 2008
Metabolex	MBX-102	PPAR gamma partial agonist/antagonist	Ph II	Data IQ05
Tularik	T131	PPAR gamma selective modulator	Ph II	NA
Eli Lilly/Ligand	LY818	PPAR gamma and alpha partial agonist	Ph II	Begin Ph III 2004
Eli Lilly/Ligand	LY929	PPAR gamma and alpha agonist	Ph I	NA
Plexikon	PLX204	PPAR gamma, alpha and delta agonist	Preclin	Submit IND 4Q04
CareX	2 undisclosed	PPAR gamma partial agonists	Preclin	Begin Ph I 2Q05

the company believes that differences in the activation of genes are what give the compound its different clinical profile.

MBX-102 is a single enantiomer of halofenate, which MRK developed through Phase III studies as a lipid-lowering therapeutic. According to Harold Van Wart, Metabolex president and CEO, halofenate showed excellent lipid and glucose lowering, but no edema and little weight gain.

However, because halofenate's lipid lowering effect was merely comparable to a marketed fibrate, and the compound had a low incidence of GI side effects, MRK decided it wasn't commercializable. Metabolex has determined that one isomer was responsible for glucose and lipid lowering, and the other, which inhibits COX-1, was responsible for the GI side effects. MBX-102 is halofenate minus the unwanted isomer.

Van Wart said that MRK's data, plus preclinical studies of MBX-102, support glucose and lipid effects comparable to or better than the marketed drugs, with minuscule potential for weight gain or edema.

The ongoing Phase II trial is enrolling 198 patients with Type II diabetes who are using insulin but whose fasting blood glucose is not well controlled. "Since the marketed compounds show the greatest weight gain and edema in patients on insulin, we view our trial as the most stringent situation," said Van Wart. Metabolex (Hayward, Calif.) expects data in the first quarter of 2005.

CareX SA also is working on partial agonists, with two unnamed compounds in preclinical development. According to CareX (Strasbourg, France), both Avandia and Actos cause PPAR gamma to recruit the co-factor TIF-2, and the PPAR-gamma/TIF-2 complex is associated with adipocyte formation. CareX's compounds are designed to avoid recruitment of TIF-2.

"If you don't recruit TIF-2, you don't get adipocyte differentiation and you don't get weight gain," CEO Geoffrey Race said. "Therefore, the challenge is to achieve that while still achieving the same level of insulin sensitization."

According to Race, edema and hematocrit are affected via different mechanisms. "They are not TIF-2-mediated activities, but the studies we've done have shown that we do not decrease hematocrit significantly, and we do not see any edema," he said. CareX hopes to start Phase I trials in the second quarter of 2005.

### Making both bets

Jose Caro, vice president of endocrine research at LLY, also

believes that the clinical profile of a PPAR compound is determined by the different co-factors with which it causes PPAR to associate. Under a discovery collaboration with Ligand Pharmaceuticals Inc. (San Diego, Calif.), LLY is developing two kinds of next-generation PPARs. LY818 is a partial agonist of PPAR gamma and alpha that has completed Phase II testing, and LLY929 is a dual agonist in Phase I trials.

In a double-blind Phase II trial, 151 patients were randomized to receive 0.04, 0.2, 0.8 or 1.2 mg of LY818, 8 mg rosiglitazone or placebo. All doses of LY818 significantly reduced mean fasting serum glucose compared to placebo, the primary endpoint. The two highest doses of LY818 also significantly reduced HbA1c, increased mean HDL and reduced fasting triglycerides compared to placebo.

Rosiglitazone did not significantly reduce fasting serum glucose levels, increase HDL or decrease fasting triglycerides compared to placebo. Increases in LDL were similar between patient groups, and weight gain did not differ significantly between groups. Data were presented at the American Diabetes Association meeting in Orlando.

Caro said LY818 has gamma activity more potent than the marketed PPAR gamma modulators, and alpha activity 40 times more potent than the fibrates. The compound's ratio of gamma to alpha activity is 1:17.

LLY929's gamma to alpha ratio is 1:1, and LLY believes the compound will have utility in both Type II diabetes and metabolic syndrome. The Phase I trial is being conducted in an undisclosed number of obese subjects who are otherwise healthy. Caro said LLY chose obese subjects because "they have insulin resistance and probably high triglycerides."

Finally, Tularik Inc. has yet another take on how to improve the class. While its T131 acts on PPAR gamma to selectively activate or inactivate subsets of the genes regulated by PPAR, the company hopes that its compound will avoid the known side effects because it has an altered backbone. T131 is in Phase II testing to treat Type II diabetes.

TLRK (South San Francisco, Calif.), which is merging with Amgen Inc. (AMGN, Thousand Oaks, Calif.), would not comment on T131. But previously reported preclinical data comparing T131 to Avandia showed that T131 caused less weight gain and gave improved hematocrit levels. In rats, T131 also showed cardiac hypertrophy similar to placebo, while Avandia caused a significant increase in cardiac hypertrophy versus placebo.