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Safety Issues Hamper Dual PPAR Agonists Is Partial Antagonism the Solution? *

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Glitazars have elicited high hopes and deep disappointment as potential new drugs. Also known as peroxisome proliferator-activated receptor (PPAR) alpha/gamma (PPARα/PPARγ) dual agonists, glitazars offer potential for the treatment of diabetes as well as components of its precursor--the metabolic syndrome. Disappointingly, full PPAR agonists have been plagued by certain adverse side effects. On the up side, partial PPAR agonists have the potential to retain the desired efficacy and beneficial effects of full PPAR agonists while diminishing their unwanted effects.

Glitazars are designed to treat both insulin resistance (the inability of tissues such as muscle and fat to utilize insulin efficiently for the uptake of glucose) and key aspects of the dyslipidemia that contributes to the high risk of cardiovascular disease (CVD) in diabetics. The two lead compounds in this class were muraglitazar (Bristol-Myers Squibb's Pargluva) and tesaglitazar (AstraZeneca's Galida), both of which were considered promising. However, as discussed below, both drugs were discontinued in May 2006.

The economic boon to these drugs' developers could have been substantial. At one time, analysts at Friedman Billings Ramsey estimated that Pargluva would have 2008 sales of $950 million. In addition, Morgan Stanley's peak sales forecast for Pargluva was $1.4 billion.

Diabetes is on the rise, making the development of safe and efficacious drugs to treat it all the more critical. The prevalence of diabetes among Americans is predicted to more than double by 2050, according to the Centers for Disease Control and Prevention (CDC). Last year, 5.62% of Americans had been diagnosed with some form of diabetes. CDC officials warn that the prevalence of diabetes in 2050—estimated at 12%—could in fact be even higher if the rate of obesity among Americans continues to rise.

PPAR Primer

PPARs belong to the class of molecules known as nuclear receptors. Nuclear receptors are transcription factors that are activated by specific ligands, which are usually lipophilic small molecules. Binding of these ligands results in conformational changes in the receptors that facilitate their interaction with coactivator proteins in the cell's nucleus. The resulting protein complexes activate transcription of specific target genes, resulting in the induction of intracellular signaling cascades that mediate the

physiological effects of the ligands. The best-understood class of nuclear receptors is the steroid receptors; other well-known nuclear receptors are receptors for thyroid hormone, vitamin D, and retinoic acid.

Mammalian PPARs are of three types: PPARα, PPARγ, and PPARδ. All of these molecules are targets for treatment of metabolic syndrome, a cluster of risk factors for cardiovascular disease and diabetes that includes abdominal obesity, atherogenic dyslipidemia (elevated triglycerides, small LDL [low-density lipoprotein] particles, low HDL [high-density lipoprotein] cholesterol, or "good cholesterol"), elevated blood pressure, hypertension, insulin resistance, and elevated fasting blood glucose. Functions of the PPARs and conditions that are the targets of PPAR agonists are summarized in Table 1.

Table 1: Human PPARs as Targets in the Metabolic Syndrome

Receptor	Functions	Conditions targeted by agonists
PPARα	Controls lipid metabolism.	Atherogenic dyslipidemia (elevated serum triglycerides and low HDL). Target of fibrate drugs.
PPARγ	Controls glucose metabolism and adipocyte differentiation.	Insulin resistance in type 2 diabetes. Target of thiazolidinediones.
PPARδ	Appears to control multiple aspects of the metabolic syndrome.	Metabolic syndrome, obesity, atherosclerosis.

Source: Haberman Associates

PPARγ is the target for the thiazolidinedione (TZD) insulin-sensitizing antidiabetic drugs pioglitazone (Takeda/Lilly's Actos) and rosiglitazone (GlaxoSmithKline's Avandia), which are agonists of PPARγ. Pioglitazone and rosiglitazone achieved combined 2004 global sales of US $3.96 billion shared between Takeda and Eli Lilly (52%) and GlaxoSmithKline (48%), according to La Merie Business Intelligence. In 2005, Avandia achieved worldwide sales of $2.45 billion.

PPARα is the target of the fibrate drugs, which can decrease serum triglycerides and moderately increase serum HDL in patients with metabolic syndrome. However, fibrates are weak agonists of PPARα, and high doses are required for effective treatment. Researchers and companies have therefore been working on developing potent, specific agonists of PPARα for treatment of atherogenic dyslipidemia (e.g., Ligand/Lilly's LY674, in Phase II clinical trials) as well as the glitazar class of PPARα/PPARγ agonists.

PPARδ is also a target for drug discovery and development. Preclinical studies in rhesus monkeys suggest that agonists of PPARδ may increase serum HDL while lowering fasting blood glucose. (Oliver, Shenk, Snaith et al. 2001). GlaxoSmithKline's PPARδ agonist GW501516 is in Phase II clinical trials aimed at raising serum HDL in patients with atherogenic dyslipidemia.

Table 2 lists major PPAR agonists in development that are discussed in this article.

Table 2: Selected PPAR Agonists in Development

Agent	Company	Target	Stage
Muraglitazar (Pargluva)	Bristol-Myers Squibb	PPARα/PPARγ (dual agonist)	Preregistration, type 2 diabetes; discontinued, May 2006
Tesaglitazar (Galida)	AstraZeneca	PPARα/PPARγ (dual agonist)	Phase III, type 2 diabetes; discontinued, May 2006
LY674	Ligand/Lilly	PPARα	Phase II, dyslipidemia
GW501516	GlaxoSmithKline	PPARδ	Phase II, dyslipidemia
Metaglidisen	Metabolex	PPARγ (partial agonist)	Phase II/III, type 2 diabetes
FK614	Astellas	PPARγ (partial agonist)	Phase II, type 2 diabetes
PA-082	Roche	PPARγ (partial agonist)	Preclinical, type 2 diabetes

Source: Haberman Associates

Muraglitazar & Tesaglitazar—High Hopes Thwarted by Adverse Cardiovascular Events

Clinical trials with muraglitazar demonstrated efficacy, coupled with troubling safety problems.

A Phase III randomized, controlled clinical trial with 1,159 type 2 diabetics whose blood glucose was inadequately controlled with metformin compared treatment with muraglitazar to treatment with pioglitazone, both in combination with metformin (Kendall, Rubin, Mohideen et al. 2006). This study showed that muraglitazar plus metformin gave a significantly greater average improvement in long-term glycemic control, as measured by reductions in serum levels of hemoglobin A1c (HbA1c; a glycosylated form of hemoglobin), than pioglitazone plus metformin. After 12 weeks of treatment, muraglitazar also reduced mean plasma triglycerides by 28% as compared to 14% for pioglitazone, and muraglitazar increased mean plasma HDL by 19% as compared to 14% for pioglitazone. All these differences were statistically significant.

As the result of positive clinical trial data for muraglitazar presented to the US Food and Drug Administration (FDA) by Bristol-Myers Squibb (BMS) and Merck (which was BMS' development partner for the drug) in support of its New Drug Application, an FDA Advisory Committee voted 8 to 1 to approve the use of muraglitazar for controlling blood glucose levels in type 2 diabetics in September 2005. However, in October of the same year, the FDA issued an approvable letter for muraglitazar requesting additional data on the drug's cardiovascular safety. Two days later, researchers at the Cleveland

Clinic published an independent analysis of Phase II and Phase III data (available as publicly disclosed documents on the FDA Web site), focusing on safety issues, as an advance online publication in the *Journal of the American Medical Association*; it appeared in print in November 2005. The researchers found that death, nonfatal myocardial infarction (MI), or stroke occurred in 1.47% of patients treated with muraglitazar as compared to 0.67% of patients in combined control groups (i.e., treated with pioglitazone or placebo). With respect to a more comprehensive composite outcome that included the incidence of death, nonfatal MI, stroke, congestive heart failure (CHF), and transient ischemic attack (TIA), the incidence was 2.11% of muraglitazar-treated patients as compared to 0.81% for the control groups. These differences were statistically significant. On the basis of their analysis, the researchers recommended that muraglitazar not be approved until a dedicated clinical trial designed to assess cardiovascular outcomes is performed (Nissen, Wolski and Topol 2005.)

As the result of the FDA's issuance of the approvable letter, Merck pulled out of its collaboration with BMS in October 2005. In May 2006, BMS discontinued muraglitazar, citing that in the amount of time it would take to complete the trials, better therapies would likely be available.

Because of these safety concerns and increased regulatory scrutiny, AstraZeneca (AZ) in late 2005 delayed its filing target for its Phase III glitazar, tesaglitazar, until 2007, so that it could conduct additional safety trials. In May 2006, AZ discontinued development of tesaglitazar. The company cited higher than expected blood creatinine levels in patients treated with the drug, which indicates potential kidney toxicity. Thus, the two glitazars that were the most advanced in development, muraglitazar and tesaglitazar, were both discontinued in the same month. This puts development of other glitazars by such companies as Lilly, Ligand, Roche, Mitsubishi, and Novartis, as well as PPAR pan-agonists (i.e., alpha, beta, and gamma agonists), which are being developed by GlaxoSmithKline and Plexxicon, under a dark cloud.

Safety Issues with PPAR Agonists

Throughout the history of development of PPAR agonists, many of these agents have been plagued with safety issues. The first TZD PPARγ agonist for type 2 diabetes to be approved, troglitazone (Warner-Lambert's Rezulin), was launched in the US in 1997. It was voluntarily withdrawn in 2000 in response to reports of serious hepatotoxicity seen in a small number of patients during the postmarketing period. The currently approved TZD PPARγ agonists, pioglitazone and rosiglitazone, do not display this toxicity. Using studies in cell culture, researchers are attempting to understand the idiosyncratic hepatotoxicity of troglitazone. For example, troglitazone was found to cause a greater degree of perturbation of gene expression in hepatocytes in several pathways that may be involved in toxicity, as compared to pioglitazone and rosiglitazone (Vansant, Pezzoli, Saiz et al. 2006).

However, treatment with both pioglitazone and rosiglitazone is associated with peripheral edema in approximately 3–5% of patients treated with a TZD as a monotherapy, and at a higher incidence when the TZD is combined with other antidiabetics (Nesto, Bell, Bonow et al. 2003). CHF is also seen in approximately 1–2% of patients treated with both one of the approved TZDs and insulin, but is less than 1% in patients treated with a TZD as a monotherapy. Edema and CHF were seen as adverse effects of muraglitazar treatment as well. High-dose muraglitazar treatment resulted in large percentages of patients exhibiting peripheral edema (24.9% and 40.1% for 10- and 20- milligram doses, respectively); as a result, FDA approval was

sought only for lower doses of the drug (Nissen, Wolski, and Topol 2005). The pathogenesis of edema in TZD- or glitazar-treated patients is unknown.

Another more common adverse effect of pioglitazone and rosiglitazone is weight gain, which was also seen with the dual agonist muraglitazar. This weight gain is dose-dependent, and is more severe with combination therapy of insulin and a TZD (Nesto, Bell, Bonow et al. 2003). The major cause of this weight gain is that PPARγ is a transcription factor that is involved in adipocyte differentiation and enlargement, including triglyceride loading in adipocytes. The beneficial insulin-sensitizing effects of PPARγ agonists are independent of fat storage, however, because the two activities are controlled by different sets of coactivators.

Another important safety issue with PPAR agonists is their potential carcinogenicity. In 2004, the FDA ruled that two-year carcinogenicity studies in rodents be completed and draft reports submitted for agency review before beginning clinical trials longer than six months in duration with PPAR agonists (FDA Web site, 2004).

These safety issues with PPAR agonists make development of these agents, with their proven usefulness at least in treatment of type 2 diabetes, challenging.

Partial Agonists to the Rescue?

Especially in the case of PPARγ agonists, companies are developing partial agonists, with the goal of retaining the beneficial effects of this class of agents, while diminishing their adverse effects. Companies that are developing such agents include Metabolex, Roche, Evolva, and Astellas.

Metabolex's lead candidate metaglidasen has a different chemical structure and mechanism of action than the insulin sensitizers currently on the market. Unlike pioglitazone and rosiglitazone, metaglidasen is not a TZD. Whereas drugs from the TZD class are full agonists of the PPAR-γ receptor, metaglidasen, in contrast, is a partial agonist of the PPAR-γ receptor and selectively modifies gene expression needed for insulin sensitization without activating the genes responsible for weight gain and edema.

According to Metabolex, metaglidasen has the potential to capture a large share of the global market for insulin sensitizers, which in 2004 totaled more than $4 billion.

On June 10, 2006, Metabolex announced that it had initiated a Phase II/III clinical trial of metaglidasen in patients with type 2 diabetes. In a previous Phase II clinical trial, metaglidasen was well tolerated and lowered blood glucose and triglycerides. Unlike PPARγ full agonists, metaglidasen did not cause weight gain or edema.

At the Keystone Symposia Scientific Conference in Hayward , CA in January 2006, Metabolex announced the results of a preclinical study of metaglidasen, which indicated that it is a partial agonist of PPARγ. As with other partial agonists of nuclear receptors, it recruits coactivators in a agonist rosiglitazone. This may explain different manner than the full PPARγ the observed different pattern of gene expression seen with metaglidasen as opposed to rosiglitazone. Specifically, metaglidasen appears to be less active in activating pathways that result in adipocyte differentiation and enlargement. In animal models, metaglidasen improved glycemic control in an equivalent manner to rosiglitazone, but with less weight gain and less cardiac

hypertrophy. Preclinical studies also indicate that metaglidasen treatment preserves the function of insulin-producing pancreatic beta cells. Because beta-cell function is often lost over time in type 2 diabetics, resulting in the need for insulin treatment, this is a potential advantage of metaglidasen if this finding is confirmed in human clinical trials.

In vitro studies by researchers from Astellas and Roche also indicate that their PPARγ partial agonists (FK614 and PA-082, respectively) activate pathways that ameliorate insulin resistance without stimulating fat accumulation in adipocytes (Fujimura, Kimura, Oe et al. 2006; Burgermeister, Schnoebelen, Flament et al. 2006).

Intriguingly, in vitro and animal studies indicate that two angiotensin II receptor blockers (ARBs) approved for the treatment of hypertension, telmisartan (Abbott/Boehringer Ingelheim's Micardis) and irbesartan (Sanofi-Aventis/BMS' Avapro) are also partial agonists of PPARγ (Schupp, Clemenz, Gineste et al. 2005). This is not a class effect of all ARBs (and is independent of angiotensin II blocking activity), and telmisartan in particular appears to function as a PPARγ partial agonist at pharmacologically relevant concentrations. Both of these agents have established safety profiles. Because the metabolic syndrome includes hypertension as well as insulin resistance, these findings with telmisartan and irbesartan suggest the potential of developing safe and effective drugs that treat both aspects of the syndrome.

Studies with partial agonists of PPARγ suggest that a focus on partial PPAR agonists may be a way of developing agents that have the desired efficacy of PPAR agonists without at least some of their potential adverse effects. However, development of PPAR agonists remains a challenging endeavor.

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References

E Burgermeister, A Schnoebelen, A Flament et al. "A novel partial agonist of peroxisome proliferator-activated receptor-gamma (PPARgamma) recruits PPARgamma-coactivator-1alpha, prevents triglyceride accumulation, and potentiates insulin signaling in vitro." *Molecular Endocrinology* 20: 809–830, 2006.

FDA Web site: "Preclinical and clinical safety assessments for PPAR agonists." 2004; http://www.fda.gov/cder/present/DIA2004/Elhage.ppt.

T Fujimura, C Kimura, T Oe et al. "A selective peroxisome proliferator-activated receptor gamma modulator with distinct fat cell regulation properties." *Journal of Pharmacology and Experimental Therapeutics* 318: 863–871, 2006.

DM Kendall, CJ Rubin, P Mohideen et al. "Improvement of glycemic control, triglycerides, and HDL cholesterol levels with muraglitazar, a dual (alpha/gamma) peroxisome proliferator-activated receptor activator, in patients with type 2 diabetes

inadequately controlled with metformin monotherapy: a double-blind, randomized, pioglitazone-comparative study." *Diabetes Care* 29: 1016–1023, 2006.

RW Nesto, D Bell, RO Bonow et al. "Thiazolidinedione use, fluid retention, and congestive heart failure: a consensus statement from the American Heart Association and the American Diabetes Association." *Circulation* 108: 2941–2948, 2003.

SE Nissen, K Wolski, and EJ Topol. "Effect of muraglitazar on death and major adverse cardiovascular events in patients with type 2 diabetes mellitus." *Journal of the American Medical Association* 294: 2581–2586, 2005.

WR Oliver Jr., JL Shenk, MR Snaith et al. "A selective peroxisome proliferator-activated receptor delta agonist promotes reverse cholesterol transport." *Proceedings of the National Academy of Sciences USA* 98: 5306–5311, 2001.

M Schupp, M Clemenz, R Gineste et al. "Molecular characterization of new selective peroxisome proliferator-activated receptor gamma modulators with angiotensin receptor blocking activity." *Diabetes* 54: 3442–3452, 2005.

G Vansant, P Pezzoli, R Saiz et al. "Gene expression analysis of troglitazone reveals its impact on multiple pathways in cell culture; a case for in vitro platforms combined with gene expression analysis for early (idiosyncratic) toxicity screening." *International Journal of Toxicology* 25: 85–94, 2006.