

Metabolic Disease Type 2 Diabetes Program

DECEMBER 2009

→ PLX-204

PLX-204 is a novel, oral PPAR (peroxisome proliferator-activated receptor) pan-agonist for the treatment of Type 2 diabetes that has advanced to Phase 2 clinical trials. PLX-204 targets all three PPAR receptors—alpha, gamma and delta. This combination is designed to reduce triglycerides and LDL, increase HDL and reverse cholesterol transport, while at the same time lowering glucose.

PLX-204 is currently available for license.

→ Phase 2 Trial Shows Promising PLX-204 Data

- Dose-dependent decrease in glucose demonstrated in Phase 2 clinical trials
- Efficacy of PLX-204 75 mg comparable to Actos® 30 mg
- Dose-dependent increase in HDL well-tolerated
- Complete toxicology package available:
 - 2-year carcinogenicity studies (2 species)
 - 12-month monkey tox study

→ Benefits of Plexxikon's PPAR Pan-Agonist for Diabetes

Although treatments for Type 2 diabetes are currently available, their usefulness is limited because of their failure to ameliorate concurrent hyperglycemia and hyperlipidemia, or to raise HDL cholesterol. In addition, these current treatments have certain undesirable side effects.

In contrast, Plexxikon's multi-targeted compound is designed to be less potent on each individual receptor, potentially enabling broader therapeutic activity and a wider safety profile than currently available therapies. PLX-204 represents an entirely new class of orally active, anti-hyperglycemic, lipid-modulating, insulin-sensitizing compounds.

→ Rationale for PLX-204—A PPAR Pan-Agonist

	ALPHA	GAMMA	DELTA
BENEFITS	▼ TG	▼ TG	▼ GLUCOSE
		▼ GLUCOSE	▲ INSULIN SENSITIVITY
	▲ HDL	▲ INSULIN SENSITIVITY	▲ HDL
	▼ LDL-C		▼ LDL-C
ADVERSE EVENTS	MYOPATHY	EDEMA	MYOPATHY
	▲ TRANSAMINASES	WEIGHT GAIN	
	▼ RENAL FUNCTION	HEART FAILURE	
		ANEMIA	

- Targets all three PPAR receptors, broadening efficacy and requiring lower potency
- Partial agonism, particularly on gamma, and few overlapping toxicities improves safety
- Pan-agonist offers best therapeutic benefit and improved safety

Program Highlights

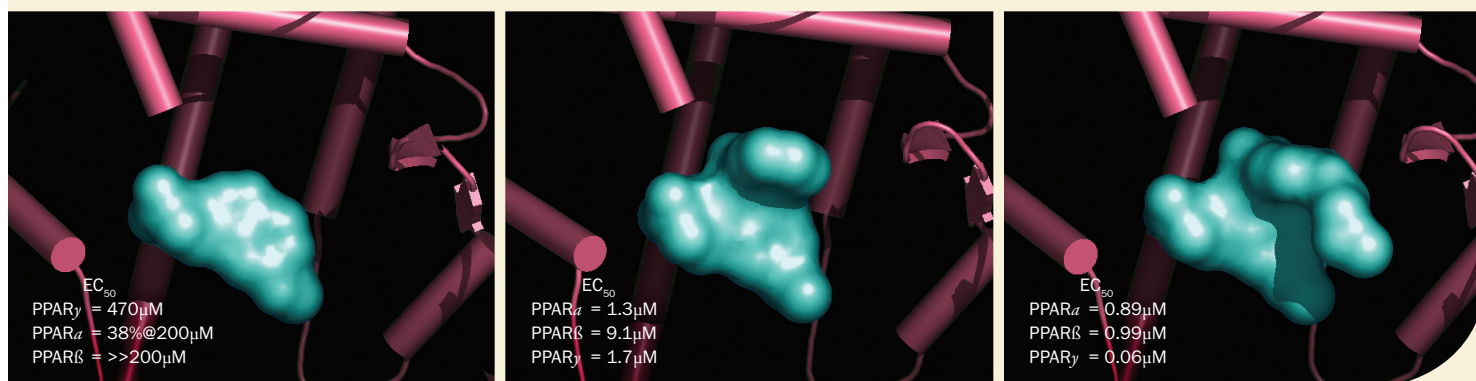
- Phase 2 clinical trials
- PPAR candidates in pre-development for obesity

→ Plexikon's Platform Well-Suited to Development of Selective, Dual or Pan PPAR Agonists

Plexikon's Scaffold-Based Drug Discovery™ platform has yielded significant PPAR assets:

- Over 2,000 PPAR compounds, with varying profiles against the three PPAR receptors as well as partial to full agonism
- Multiple scaffolds characterized
- Demonstrated pharmaceutical properties, including excellent oral bioavailability
- Selection of compounds with good blood-brain permeability
- In vitro and in vivo characterization for selected compounds, with demonstrated efficacy

In less than two years, Plexikon advanced PLX-204 from discovery to a first-in-man study in September 2004.



EVOLUTION OF PLEXIKON'S DIABETES PPAR PAN-AGONIST COMPOUND FROM SCAFFOLD TO LEAD

→ Beyond Diabetes

Plexikon is able to design PPAR compounds with activity against any of the three PPAR receptors or any combination of receptors, as well as vary the degree of agonism. The company owns a significant portfolio of novel PPAR compounds with attractive pharmaceutical properties. In addition to diabetes and obesity, Plexikon has also demonstrated preclinical efficacy in models of multiple sclerosis and inflammatory bowel disease.

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