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Emerging Company Profile

Metabolic Solutions: PPAR-less sensitization

By Michael Flanagan
Senior Writer

Metabolic Solutions Development Co. has identified an undisclosed mitochondrial target it believes is responsible for many of the beneficial effects of the thiazolidinedione class of diabetes drugs, without the unwanted cardiovascular side effects.

Results from a Phase IIa trial of the company's mitoglitazone, a thiazolidinedione analog selected for preferential binding to the mitochondrial target over PPAR gamma, support its hypothesis. The compound produced glycemic control similar to that of Actos pioglitazone, but produced a better lipid profile and no weight gain or fluid retention.

The company is now seeking to raise \$25 million to fund Phase IIb testing, which it hopes to begin next quarter.

The two marketed thiazolidinediones (TZDs), Actos and Avandia rosiglitazone, have long been thought to improve insulin sensitization by agonizing PPAR gamma. But CSO Jerry Colca, who led the research team in charge of developing Actos at Upjohn Co., was never convinced.

He said that in tissue-specific knockout models of PPAR gamma, the pharmacological effects of TZDs were maintained. He also noted it has never been elucidated how PPAR gamma-regulated transcription produces all of the pharmacological benefits of the TZDs. For example, he said, while Avandia is

Metabolic Solutions Development Co.

Kalamazoo, Mich.

Technology: Small molecule inhibitors of undisclosed mitochondrial target for Type II diabetes and other cardiometabolic disorders

Disease focus: Metabolic, cardiovascular, neurology

Clinical status: Phase IIa

Founded: 2006 by Jerry Colca and Rolf Kletzien

University collaborators: University of California at San Diego, University of Illinois at Chicago, Washington University and Western Michigan University

Corporate partners: USV Ltd.

Number of employees: 10

Funds raised: \$21.5 million

Investors: Hopen Therapeutics LLC, Southwest Michigan First Life Science Fund and high net worth individuals

CEO: Robert Beardsley

Patents: None issued

known to be the more effective PPAR gamma activator, Actos is known to produce more favorable effects on plasma lipids.

Colca focused on mitochondria because they were the only place he could find site-specific binding of Actos. Using a photoaffinity analog of the drug, he identified a protein in the mitochondrial membrane that correlated well with Actos in terms of binding location and affinity.

"This protein is part of a complex that mediates signaling that controls excessive oxidative metabolism, which ultimately results in decreased metabolism due to reduced insulin action, fatty acid oxidation and the eventual decrease in mitochondrial function and number," Colca said.

The next step was to select molecules based on known Actos metabolites that interacted with the mitochondrial target but had little ability to bind to PPAR gamma. Medicinal chemistry identified additional compounds with optimized insulin-sensitizing pharmacology.

The lead candidate from these efforts is mitoglitazone (MSDC-0160). Results from a pair of Phase I trials showed a 12-hour half-life, steady-state circulating pharmacokinetics and increased levels of adiponectin, a predictive marker for glycemic control. No safety issues were revealed.

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PO Box 1246
San Carlos CA 94070-1246
Voice: 650-595-5333
Fax: 650-595-5589
www.biocentury.com

DAVID FLORES
President & CEO

KAREN BERNSTEIN, Ph.D.
Chairman & Editor-in-Chief

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In May, the company reported preliminary results from a 28-day Phase IIa trial in 76 patients comparing mitoglitazone with Actos. Colca said the study was too short to demonstrate a full effect on HbA1c, but said the data suggest the improvement in glycemic control was comparable, while mitoglitazone showed the potential for having a greater effect on HDL compared to Actos, which itself has a greater effect than Avandia.

"This could be because of less negative effects of direct PPAR activation or because we are able to dose to a greater mitochondrial effect because of the lack of direct PPAR interactions," he said.

Unlike Actos, he added, mitoglitazone was not associated with weight gain or fluid retention.

Pending the close of its financing, the company plans to begin a 420-patient, 90-day Phase IIb trial of mitoglitazone for Type II diabetes next quarter. It expects data in H111, which it hopes to use to find a partner to conduct the Phase III program starting in 2012.

Rights to mitoglitazone in India and Central Asia are already licensed to **USV Ltd.**, which CEO Robert Beardsley said has a major marketing presence in the diabetes space in those territories.

The new money also would be used to run a Phase IIa trial of a second program, MSDC-0602, a more potent follow-up candidate, said Beardsley.

Colca hopes the expected safety profile of mitoglitazone eventually will allow the company to evaluate it as a preventative agent in pre-diabetic patients. "There are studies going on now that I am convinced will prove that Actos can delay the progression of pre-diabetes, so if we can remove the limitations brought on by its effects on PPAR gamma, then this could be extremely useful," he noted.

The company also plans to test mitoglitazone in combination with agents such as metformin, an angiotensin receptor blocker and a statin to treat diabetes, hypertension and dyslipidemia, respectively.

Upjohn Co. is now part of **Pfizer Inc.**, which held U.S. rights to Actos until 1995. **Takeda Pharmaceutical Co. Ltd.** now markets the product in the U.S. and co-markets the drug with **Eli Lilly and Co.** in various countries in Europe, Asia and other regions.

GlaxoSmithKline plc markets Avandia.

COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.

GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.

Metabolic Solutions Development Co., Kalamazoo, Mich.

Pfizer Inc. (NYSE:PFE), New York, N.Y.

Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan

USV Ltd., Mumbai, India