MEDIA ADVISORY

Metabolic Solutions Development Company presents *Case Study: A new approach to insulin sensitizers* during Phacilitate-Metabolic Leaders Forum 2012

Overview

Metabolic Solutions Development Company, LLC (MSDC) is developing novel insulin sensitizers that exert their pharmacological effects through an as yet undisclosed mitochondrial molecular target. This breakthrough understanding has significant implications for the discovery of new drugs to treat type 2 diabetes and will be previewed during the Phacilitate meeting *Metabolic Leaders Forum 2012* in San Francisco, March 12 – 14, 2012.

MSDC compounds MSDC-0160 and MSDC-0602 are insulin sensitizers that are selective for a mitochondrial molecular target (mTOT™) identified by MSDC researchers. mTOT occupies a key position at the "crossroads of metabolism," connecting mitochondrial metabolism to important cell functions perturbed in type 2 diabetes and other conditions associated with age-related mitochondrial dysfunction.

MSDC-0160 is one of two oral mTOT Modulators™ the company is developing to treat type 2 diabetes. MSDC recently completed a 90-day Phase 2b study of this compound and will present these data at the American Diabetes Association 72nd Scientific Sessions in June. Results from a recently completed Phase 2a study of the company's second oral insulin sensitizer, MSDC-0602, showed its potential to achieve significant glucose control, reduce HbA1c, and increase insulin sensitivity in type 2 diabetes patients. The company plans to initiate a 90-day Phase 2b study of MSDC-0602 in 2012.

Oral Presentation

Monday, March 12, 12:30 p.m.
Section: Small molecules: Early state updates on new classes of drug that are showing greatest promise in changing the progression of the disease
The Westin San Francisco, Market Street

President, chief scientific officer and co-founder Jerry Colca will present the thinking and science behind Metabolic Solutions' new approach to developing two new effective oral insulin sensitizers to treat type 2 diabetes without the side effects associated with the currently marketed agents.

Key points:

- Safe and effective anti-diabetic medicines are needed more than ever – especially insulin sensitizers, which treat the root cause of type 2 diabetes – insulin resistance. According to the American Diabetes Association and the U.S. Centers for Disease Control, 25.8 million children and adults in the United States—8.3% of the population—have diabetes and of these, seven million are undiagnosed. There are an additional 79 million people in the U.S.

with prediabetes. In adults, type 2 diabetes accounts for about 90% to 95% of all diagnosed cases of diabetes.

- Over the last decade hundreds of millions of dollars have been spent trying to selectively activate a particular transcription factor called PPARγ, through which insulin sensitizers have been proposed to exert their pharmacology.
- MSDC scientists questioned the conventional wisdom that these compounds exert their insulin sensitizing activity through PPARγ, and have subsequently shown that such activity is achieved through a novel a mitochondrial molecular target called mTOT.
- MSDC's mTOT Modulators have been shown to be safe and effective at lowering glucose and reducing HbA1c without the side effects associated with currently marketed agents.
- Interaction with mTOT favors lipid oxidation, increased insulin sensitivity, generation of brown fat, and preservation of beta cells.

For more information about the meeting, please visit the Phacilitate Metabolic Leaders Forum 2012 website at http://www.phacilitate.co.uk/event.php?eid=9&pid=484&opstatus=confrence.

A copy of the abstract of Dr. Colca's case study presentation can be obtained from Molly Watson (contact below).

About Metabolic Solutions Development Company
Metabolic Solutions Development Company (www.msdrx.com) is a drug discovery and development company investigating novel molecular targets and developing new therapeutics to treat metabolic diseases associated with age-related mitochondrial dysfunction, especially type 2 diabetes. The company was founded in 2006 by former researchers of The Upjohn Company, Jerry Colca, PhD and Rolf Kletzien, PhD, and it has raised more than $55 million to support development of its lead compounds, MSDC-0160 and MSDC-0602, which are novel insulin sensitizers in Phase 2 clinical trials for the treatment of type 2 diabetes.

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A New Approach to Insulin Sensitizers

It is generally accepted that reduced responsiveness of tissues to insulin, or "insulin resistance", is a key factor in metabolic diseases such as type 2 diabetes. For this reason, there is also consensus of opinion that compounds that could safely improve insulin sensitivity, i.e., insulin sensitizers, would be an ideal way to treat such diseases. However, two of the first generation insulin sensitizers from the thiazolidinedione (TZD) class, troglitazone and rosiglitazone have been removed from the market (troglitazone in 2000) or essentially removed from the market for different reasons (hepatoxicity for troglitazone; potential to increase CV disease for rosiglitazone). In contrast, pioglitazone, the last of the first generation compounds to be approved in the summer of 1999, remains the only one of these compounds to be used clinically and it has been reported to have positive effects on cardiovascular and cancer outcomes. However, this compound also causes fluid retention and its use is curtailed for safety concerns. Over the last decade hundreds of millions of dollars have been spent by the pharmaceutical industry by trying to selectively activate a particular transcription factor called PPARγ, through which all of these compounds have been proposed to exert their pharmacology. We have questioned the conventional wisdom that these compounds, which were discovered empirically without regard to mechanism a decade *before* the discovery or PPARγ, actually exert their insulin sensitizing activity through this transcription factor. Our skepticism is punctuated by the failure to improve on these molecules using this singular focus despite considerable effort by many investigators. We have employed a photaffinity crosslinker approach together with biochemical purifications and mass spectrometry to identify a previously unappreciated complex in the mitochondria through which we now believe all of these compounds exert insulin sensitizing effects. We have termed the key protein in the complex "mTOT" (mitochondrial target of TZDs) and the description of this target and mechanism will be disclosed later this year. In contrast to direct activation of PPARγ , which drives a program of lipid storage and volume expansion, effects which limit the use of pioglitazone, the interaction with mTOT favors lipid oxidation and increased insulin sensitivity. Signaling though mTOT also significantly increases production of functional brown adipose cells, which are specially designed to burn fat. Given this insight, we now believe that the approach to insulin sensitizers should be to design *away* from *all* interactions with PPARγ while maintaining the interactions with mTOT. MSDC is developing two modified TZDs, designed to reduce binding to PPARγ while maintaining mTOT modulating pharmacology. These two compounds are in phase 2 clinical trials for the treatment of type 2 diabetes and have shown the ability to lower glucose to the same extent as pioglitazone with reduced PPARγ side effects. Detailed clinical results will be presented later this year. This new approach to insulin sensitizers may provide effective agents to treat and prevent metabolic diseases such as type 2 diabetes.