Late Breaking Poster Shows a Novel Oral Insulin Sensitizer Azemiglitazone (MSDC-0602K) Could Substantially Preserve Lean Muscle in Combination with Weight-Loss GLP1s

Azemiglitazone (MSDC-0602K) working through a newly identified mitochondrial target adds cardiometabolic benefit to GLP-1 receptor agonists

Benefit includes preservation of lean muscle, which could expand the usefulness of the new class of GLP-1 weight loss drugs

Recent paper in press in Hepatology emphasizes the important effect of reducing fasting insulin and posters at ADA in Orlando later in June

Kalamazoo, MI., June 5, 2024 – Cirius Therapeutics, a privately-held clinical stage biopharmaceutical company is presenting new data demonstrating the unique potential of combining their second-generation insulin sensitizer azemiglitazone (MSDC-0602K) with GLP-1 receptor agonists (GLP-1s).

Cirius Therapeutics together with the Dr. Kyle McCommis lab of St. Louis University are presenting a late breaking poster at the European Association for the Study of Liver Disease (EASL) annual meeting, June 5-8 in Milan, Italy, that describes how the second generation insulin sensitizer azemiglitazone may address body composition issues caused by GLP-1s.

The poster presents both a post-hoc analysis of the 23 patients with biopsy-proven MASH in the 52-week Phase 2B EMMINENCE trial who also had concomitant type 2 diabetes and were already on a stable dose of a GLP-1, and data from a pre-clinical study in diabetic db/db mice with GLP-1 liraglutide.

These data show:

- The addition of any dose of azemiglitazone to patients on a GLP-1 improved all circulating parameters, especially HbA1c and liver histology.
- In the accompanying preclinical study in diabetic db/db mice:
    - The combination of azemiglitazone and the GLP-1 liraglutide, new body composition measurements demonstrated a *significant preservation of lean body mass (or muscle) in the combined presence of azemiglitazone*, whereas liraglutide alone decreased lean body mass.

- Together, the combination also produced a synergistic improvement in glucose tolerance that occurred with less elevation of circulating insulin and an increase in pancreatic insulin content.
- Azemiglitazone also increased the amount of brown adipose tissue (BAT) alone and in combination with liraglutide. BAT is known for its ability to burn calories and store energy.

GLP-1s are highly effective weight loss drugs, but they do not directly affect the underlying insulin resistance, are usually used for finite periods of time, and cause loss of both adipose and lean mass, which may limit their use in certain patient populations. Together these new data suggest this combination could optimize metabolic control and produce healthier weight loss and weight maintenance.

Dr. Jerry Colca, Chief Scientific Officer of Cirius Therapeutics said, "This second-generation insulin sensitizer was designed to take advantage of the newly discovered mitochondrial target of the thiazolidinediones (TZDs), which is the mitochondrial pyruvate carrier (MPC). Azemiglitazone avoids the direct activation of PPAR-γ, which has resulted in a significantly improved safety profile versus the first-generation insulin sensitizers. The *aha* realization here is that this novel identified mechanism of action of TZDs could provide a differentiated solution to the limitations with GLP-1 receptor agonists. Based on these new preclinical results, azemiglitazone could allow patients to lose fat without having to lose muscle. This finding together with the additive benefit on all other parameters could make azemiglitazone the optimal partner for the GLP-1s."

Dr. Kyle McCommis, Assistant Professor in Biochemistry and Molecular Biology at St. Louis University said, "Our lab has been interested in the implications of this newly identified MPC target, which sits at the crossroads of regulating metabolism in many cell types. We have only recently recognized the positive effects on skeletal muscle and body composition, and we look forward to more detailed studies into the potential of this newly identified mechanism of action."

EASL Annual Meeting

Title:	**Azemiglitazone in Combination with GLP1 Agonists Increases Benefit and Could Preserve Lean Mass**
Late Breaking Poster	LB-10, June 5-9 2024
Discussions	Late Breaking poster allows for discussions throughout the meeting
Presenting author:	Jerry R. Colca, PhD

Additional New Publication and Posters at American Diabetes Association Meeting in Orlanda, Florida:

- Harrison SA, Dubourg J, Knott M, Colca J. Hyperinsulinemia, an overlooked clue and potential way forward in metabolic dysfunction-associated steatotic liver disease. *Hepatology, online and in press.*
- 2024-1582-P Fasting Insulin as an Independent Predictor of Metabolic Dysfunction–Associated Steatohepatitis (MASH) Severity. Authors: Stephen A. Harrison, Julie Dubourg, Sophie Jeannin, Jerry R. Colca, and Vlad Ratzu.
- 2024-892-P: Potential for New Oral Insulin Sensitizers in Combination with GLP-1 Agonists. Author: Jerry R. Colca

About Azemiglitazone

Azemiglitazone is a novel once-daily, oral second-generation insulin sensitizer that was designed to exert pharmacology similar to pioglitazone without directly activating the transcription factor PPAR-γ. This allows dosing to full effect on the recently identified mitochondrial target, the mitochondrial pyruvate carrier (MPC), and directly impacts the underlying dysmetabolism of chronic metabolic disease. Azemiglitazone has completed all preclinical studies including 2-year carcinogenicity studies and 7 US clinical trials, including a 52-week dose-ranging study in subjects with MASH with and without type 2 diabetes (and mostly overweight and obese). Phase 3 clinical development will examine the potential of azemiglitazone to fulfill the original promise of insulin sensitizing pharmacology, which is the underlying pathophysiology of chronic metabolic disease. Of particular interest will be the ability to work in combination with weight loss approaches such as the GLP-1s.

About Cirius Therapeutics

Cirius is a clinical-stage biopharma company focused on the development and commercialization of innovative therapies for the treatment of metabolic diseases. Its lead product candidate, azemiglitazone (MSDC-0602K), is a potential best-in-class small molecule being developed as a once-daily oral therapy. selectively designed to modulate the mitochondrial target MPC, which mediates at the cellular level the effects of overnutrition, a major cause of Type 2 Diabetes, Obesity, MASH, and other metabolic disorders.

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