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Press release

Valbiotis announces the success of the TOTUM•63 mode of action clinical study, against prediabetes and the early stages of type 2 diabetes

This latest step concludes the clinical development of this 100% plant-based active substance, with market launch in sight

- In addition to the efficacy studies, a clinical study on the mode of action was conducted at the Institute of Nutrition and Functional Foods (INAF) of Laval University in collaboration with the Quebec Heart and Lung Institute (IUCPQ) to establish the mechanisms of action of TOTUM•63 in subjects at risk of developing type 2 diabetes.

- The study confirms TOTUM•63's efficacy results, in particular the lasting reduction in glycated hemoglobin, one of the main markers of prediabetes and type 2 diabetes.

- In terms of mode of action, it shows three main effects of TOTUM•63 on the energy metabolism of subjects at risk:
  - Reduced inflammation (blood hsCRP and fibrinogen), involved in the development of insulin resistance;
  - Modulation of certain key gastrointestinal hormones (GIP and PYY), involved in the regulation of metabolism and satiety;
  - Enhanced metabolic response after meals, with a lesser increase in blood glucose and lipid levels leading to a decrease in insulin secretion.

- The metabolic response after a meal was improved from the first intake of TOTUM•63 and at the end of the study after 8 weeks of supplementation.

- After the remarkable results of the Phase II/III REVERSE-IT clinical trial unveiled in September, this latest success marks the final stage in the development of TOTUM•63, the first non-drug plant-based active substance to have such robust clinical and scientific evidence, for the benefit of subjects with prediabetes and the early stages of type 2 diabetes.

La Rochelle, November 7, 2023 (05:40 p.m CET) - **Valbiotis** (FR0013254851 – ALVAL, PEA/SME eligible), a commercially oriented Research and Development company committed to scientific innovation for preventing and combating metabolic and cardiovascular diseases, **announces the successful completion of the mode of action clinical study on TOTUM•63, against prediabetes and the early stages of type 2 diabetes.**

This study was conducted at the Institute of Nutrition and Functional Foods (INAF) of Laval University in collaboration with the Quebec Heart and Lung Institute (IUCPQ) as part of the global strategic partnership with Nestlé Health Science. It demonstrates TOTUM•63's multi-target mode of action in subjects at risk, improving the efficacy of energy metabolism, particularly after meals. The study also confirms TOTUM•63's efficacy on glycated hemoglobin (HbA1c), the main marker of type 2 diabetes, already evidenced by the Phase II/III REVERSE-IT study. This latest success rounds off 10 years of R&D on TOTUM•63, which now benefits from a complete set of clinical proofs of safety, efficacy and mode of action, unprecedented for a plant-based dietary supplement.

Clinical results: TOTUM•63 regulates energy metabolism

In addition to the positive clinical efficacy studies already conducted, the mode of action study was carried out on 19 overweight or obese volunteers at risk of developing type 2 diabetes. The goal was to explore the effects of TOTUM•63 on all the potential mechanisms underlying the disease in humans. All volunteers were supplemented with TOTUM•63 at a dose of 5 g/day for 8 weeks.

"The results show that TOTUM•63 exerts regulatory effects on energy metabolism, for example on inflammation and gastrointestinal hormones," says Prof. André MARETTE, Professor in the Faculty of Medicine at Laval University (Quebec) and researcher at IUCPQ and at INAF, the study's scientific coordinator. *"With TOTUM•63, the metabolic response at mealtimes is more effective: blood glucose and lipid levels are reduced, leading to a decrease in hyperinsulinemia. This is a very interesting mode of action that tends to correct the overall deterioration of metabolism in these at-risk subjects. These data are consistent with the efficacy results already obtained in subjects with untreated prediabetes or type 2 diabetes, explaining how TOTUM•63 limits the onset and progression of type 2 diabetes."*

After 8 weeks, supplementation initially reduced glycated hemoglobin, a clinical marker of prediabetes and type 2 diabetes, confirming the results obtained in the Phase II/III REVERSE-IT study. This effect was still observable 4 weeks after the end of supplementation.

TOTUM•63 reduces inflammation, a key mediator of insulin resistance

After 8 weeks of TOTUM•63 supplementation, blood levels of two key markers of inflammation were significantly reduced: hsCRP by 21.9% and fibrinogen by 7.1%. Metabolic inflammation in the body is a major cause of the loss of insulin efficacy, or insulin resistance, which contributes to type 2 diabetes. TOTUM•63's anti-inflammatory effect is consistent with the reduction in insulin resistance demonstrated in clinical efficacy studies.

TOTUM•63 modulates gastrointestinal hormone secretion (incretins)

Analyses showed a significant effect of TOTUM•63 on the levels of certain hormones secreted by the stomach or intestine. After 8 weeks, fasting PYY (peptide YY) level was significantly elevated by 27.3%. This hormone, known as an "anorectic" hormone, is recognized for promoting the sensation of satiety and for enhancing blood glucose management. The levels of GIP (Gastric Inhibitory Peptide), an intestinal hormone that potentiates insulin production, were also significantly reduced after a meal intake at the end of 8 weeks. All of these effects on gastrointestinal hormones participate in the mechanisms involved in the effects of TOTUM•63 on glucose homeostasis and metabolism.

TOTUM•63 improves metabolic response after meals

The experimental protocol included specific tests after a standardized meal, at the very start of supplementation and after 8 weeks. In both cases, at the start and end of the study, TOTUM•63 significantly improved metabolic response within three hours of the meal, with:

- a reduction in the levels of glucose and lipids in the bloodstream,
- a reduction in the post-prandial glycemic peak,
- lower insulin secretion.

These results establish several mechanisms of action of TOTUM•63 on human energy metabolism. They provide a coherent explanation for all the clinical efficacy data recorded in the Phase I/II, Phase II and Phase II/III studies.

TOTUM•63: the culmination of an unprecedented R&D effort to prevent type 2 diabetes

This study concludes the scientific and clinical development of TOTUM•63, which now totals 4 human studies, including 2 randomized, placebo-controlled trials, involving 720 people in all. *"After validating TOTUM•63's safety and demonstrating its efficacy, we are now establishing its mode of action in humans, with a proven effect on disease mechanisms from the earliest stages"*, says Murielle CAZAUBIEL, Director of Medical, Regulatory and Industrial Affairs and member of Valbiotis' Executive Committee. This plan has generated an unrivaled body of scientific and clinical evidence for a dietary supplement in the field of prediabetes and type 2 diabetes. Murielle CAZAUBIEL concludes: *"TOTUM•63 is no longer a project: it is a proven health product, based on the potential of plants and validated by clinical evidence. It is a game changer in the prevention of type 2 diabetes. We are very proud to open up this new perspective for all those concerned by the risks associated with this disabling disease, and for the healthcare professionals who support them."*

This latest mode of action study on TOTUM•63 had been co-designed with the teams from the Institute of Nutrition and Functional Foods (INAF) at Laval University in collaboration with the Quebec Heart and Lung Institute (IUCPQ) and Nestlé Health Science, as part of the global strategic partnership. Its success triggers a milestone payment from Nestlé Health Science.

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TOTUM•63

Mode of action clinical study

This latest step concludes the clinical development of this 100% plant-based non-drug innovation with such robust clinical evidence against prediabetes and early stages of type 2 diabetes

Focus on TOTUM•63

- **10 years of R&D**
- **A unique and patented combination** of 5 plant extracts which targets the pathophysiological mechanisms of type 2 diabetes.
- An innovation that has been the subject of **4 clinical studies** involving 720 people, a first for a healthy nutrition product.
- **An efficacy proven by REVERSE-IT study:** TOTUM•63 significantly reduced the main markers used for the diagnosis and monitoring of type 2 diabetes, and prevented the progression of prediabetes to type 2 diabetes, with a relative reduction of 40% in the number of new cases.

The study: facts and key figures

Conducted in Québec, at the **INAF* in collaboration with the IUCPQ****

On **19 overweight or obese volunteers** at risk of developing type 2 diabetes

A dose of **5g/day** for 8 weeks

Objective: explore the effects of TOTUM•63 on all the potential mechanisms underlying the disease in humans

Experimental protocol: tests after a standardized meal, at the very start of supplementation and after 8 weeks

Results: effects of TOTUM•63 on metabolism

1

Reduces one of the main clinical markers of prediabetes and type 2 diabetes: glycated hemoglobin

Significant decrease observable following 8-week supplementation

2

Reduces inflammation, a key mediator of insulin resistance

hsCRP by -21.9%

fibrinogen by -7.1%

two key markers of inflammation

3

Modulates gastrointestinal hormone secretion

+27.3% of fasting PYY level, hormone stimulating the sensation of satiety

Significant decrease in GIP levels, intestinal hormone potentiating insulin production

4

Improves metabolic response after meals

Within 3 hours of the meal:

Reduction in the levels of glucose and lipids in the bloodstream

Reduction in the post-prandial glycemic peak

Lower insulin secretion

*Institute of Nutrition and Functional Foods, at Laval University in Quebec City (Canada)
**Quebec Heart and Lung University Institute

About TOTUM•63

TOTUM•63 is a unique and patented combination of 5 plant extracts which targets the pathophysiological mechanisms of type 2 diabetes, and benefits from an unrivaled clinical demonstration of efficacy for a non-drug active substance. This innovation, both natural and clinically proven, offers new perspectives to the millions of people confronted with the risks of type 2 diabetes, as well as to all doctors and healthcare professionals currently lacking reliable, targeted preventive solutions.
TOTUM•63 benefits from intellectual property validated by patents in the world's major markets including Europe (covering 39 countries), the United States, Canada, China, Japan, Australia, Mexico, etc.
TOTUM•63 already has marketing authorizations linked to its status in Europe.
In February 2020, Valbiotis signed a long-term global strategic partnership with Nestlé Health Science for the development and worldwide commercialization of TOTUM•63.

About Valbiotis

Valbiotis is a commercially oriented Research & Development company, committed to scientific innovation for preventing and combating metabolic and cardiovascular diseases in response to unmet medical needs.
Valbiotis has adopted an innovative approach, aiming to revolutionize healthcare by developing a new class of health nutrition products designed to reduce the risk of major metabolic and cardiovascular diseases, relying on a multi-target strategy enabled by the use of plant-based terrestrial and marine resources.
Internationally, its products are intended to be the subject of licensing and/or distribution agreements with global or regional health and nutrition players. In France, Valbiotis will be responsible for marketing its own products.
Created at the beginning of 2014 in La Rochelle, the Company has forged numerous partnerships with leading academic centers. The Company has established three sites in France – Périgny, La Rochelle (17) and Riom (63) – and a subsidiary in Quebec City (Canada).
Valbiotis is a member of the "BPI Excellence" network and has been recognized as an "Innovative Company" by the BPI label. Valbiotis has received major financial support from the European Union for its research programs via the European Regional Development Fund (ERDF). Valbiotis is a PEA-SME eligible company.
For more information about Valbiotis, please visit: www.valbiotis.com.

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