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Press release

Valbiotis presents the full results of the Phase II/III REVERSE-IT study: impressive efficacy of TOTUM•63 against prediabetes and the early stages of type 2 diabetes, a first for a non-drug active substance

- The REVERSE-IT study has met its primary endpoint: TOTUM•63 reduced fasting blood glucose at 6 months *versus* placebo, on both a 3-intake/day and a 2-intake/day regimen, the optimal regimen for marketing and real-life patient compliance (press release, May 22).

- Detailed results today demonstrate TOTUM•63's impressive efficacy on glucose metabolism, including plasma glycated hemoglobin (HbA1c), a biomarker established for microvascular risk, used for monitoring type 2 diabetes, with results comparable to some anti-diabetic drugs in a similar population.

- Among the main results, TOTUM•63 supplementation at 5 g/day, in 2 intakes, after 6 months:
    - significantly reduces fasting blood glucose (-8.1 mg/dl), 2-hour blood glucose (-21.9 mg/dl), glycated hemoglobin (-0.18%) and the HOMA-IR insulin resistance score (-1.04 pts), the main markers assessed in clinical practice, compared with placebo;
    - significantly reduces progression towards type 2 diabetes, with a 40% relative reduction in new cases of type 2 diabetes at the end of the study *versus* placebo;
    - significantly reduces low-grade inflammation (-13% of patients above the threshold) involved in the pathogenesis of type 2 diabetes;
    - demonstrates its efficacy on fasting blood glucose and glycated hemoglobin in early-stage untreated type 2 diabetics.

- The study confirms TOTUM•63's excellent safety profile, with no risk of hypoglycemia, very good tolerability, notably digestive, and a compliance exceeding 97%.

- With such data, the REVERSE-IT study positions TOTUM•63 as an unparalleled non-drug innovation in the fight against the type 2 diabetes epidemic, benefiting the millions of people today facing the risks associated with this disabling chronic disease.

La Rochelle, September 11, 2023 (17:40 CEST) – **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 results of the international Phase II/III REVERSE-IT study, demonstrating TOTUM•63's impressive efficacy on key markers of glucose metabolism, with efficacy results comparable to those of some leading anti-diabetic drugs, in a similar population. With REVERSE-IT, TOTUM•63 now has unrivaled proof of efficacy for a non-drug health product against prediabetes and the untreated early stages of type 2 diabetes. This new, natural, clinically proven product will benefit people affected by the risks associated with diabetes and support them in the fight against the progression of this disease, alongside their physician.**

Sébastien PELTIER
co-founder and Chairman
of the Valbiotis Executive Committee

"With the data announced today, the REVERSE-IT study is a breakthrough for the prevention of type 2 diabetes: TOTUM•63, a non-drug, plant-based active substance reduces glycated hemoglobin and fasting blood glucose with results at least comparable to some drugs, such as metformin, in a similar population. We also demonstrated a 40% reduction in the number of new diagnoses of type 2 diabetes among prediabetics. The objective we set ourselves with our partner Nestlé Health Science has been achieved: to demonstrate with unequivocal clinical evidence that we can act successfully at a very early stage, for the benefit of patients. I would like to underline the great joint success of our partnership with Nestlé Health Science, with whom we have an exclusive and global licence agreement on TOTUM•63. For Valbiotis, it is a tremendous achievement, and one that will lead to further successes in the future. But above all, it is a real breakthrough for the patients and people at risk who will benefit from this global innovation."

Diabetes: a global public health challenge

Around 537 million adults (aged 20-79) live with diabetes worldwide, 90% of whom have type 2 diabetes, according to the International Diabetes Federation[1]. In addition to this growing number, there are almost 900 million people affected by prediabetes, including 128 million in the United States and the five main European countries[2].

TOTUM•63 responds to an essential need that has been neglected until now: early intervention in the metabolic impairments associated with type 2 diabetes, particularly in prediabetes. No other non-drug health product currently boasts a level of efficacy as clearly demonstrated as TOTUM•63. With the completion of its clinical development, TOTUM•63 opens up new prospects both for people facing the risks associated with diabetes and for doctors, who currently lack reliable solutions dedicated to prevention.

[1]The IDF Diabetes Atlas (2021) https://idf.org/
[2]AEC Partners data on Valbiotis' key markets, 2019

TOTUM•63: a worldwide innovation in health nutrition for prediabetic and type 2 diabetic patients

In the field of prediabetes and untreated type 2 diabetes, the REVERSE-IT study surpasses studies carried out to date using nutritional approaches, both in terms of its scale (636 volunteers) and the number of centers involved internationally (52 centers in 7 countries). In terms of methodology, the REVERSE-IT study complies with the recommendations of international learned societies, in particular those of the American Diabetes Association, the world's leading learned society for diabetes.

Design of the Phase II/III REVERSE-IT study

REVERSE-IT studied the overall efficacy of TOTUM•63, a plant-based active substance, on key markers of glucose metabolism in a randomized, placebo-controlled trial. It included 636 people: 501 prediabetics and 135 early-stage, untreated type 2 diabetics. Patients were divided into three arms, each with over 200 participants:

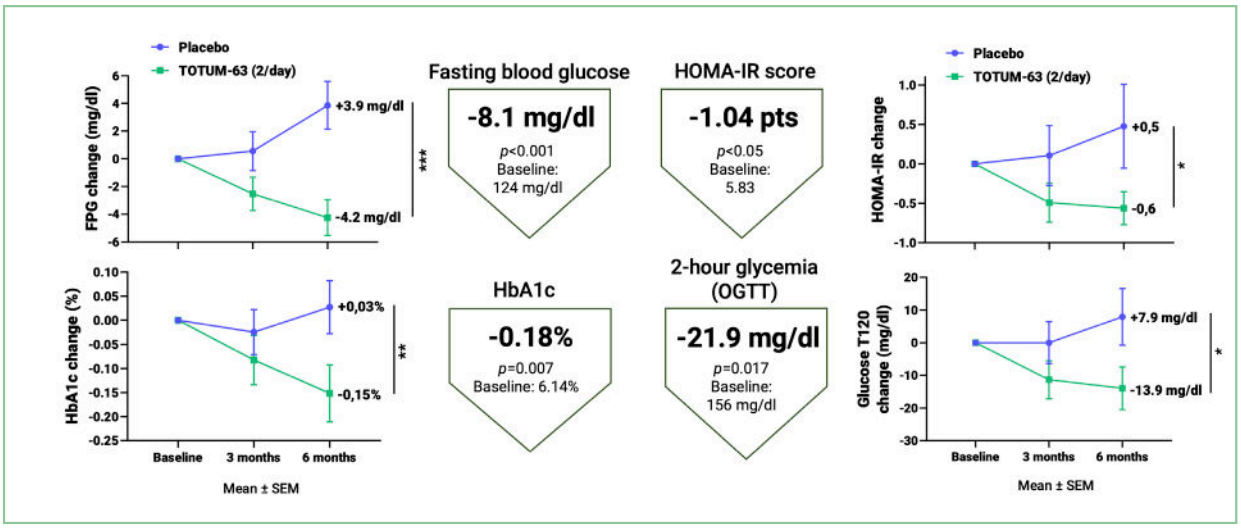
- A blind arm supplemented with TOTUM•63 (5 g/day) in 3 intakes per day,
- An open arm supplemented with TOTUM•63 (5 g/day) in 2 intakes per day,
- A placebo arm.

The duration of supplementation was 6 months. All participants received identical dietary and physical activity advice, with no significant difference between groups at the end of the study.

Widely demonstrated efficacy in prediabetic and early-stage untreated type 2 diabetic patients

The primary endpoint of the study, a reduction in fasting blood glucose levels after 6 months of TOTUM•63 supplementation at 3 intakes per day *versus* placebo, was achieved (-5.8 mg/dl, p=0.015), as it was with TOTUM•63 at 2 intakes per day (-8.1 mg/dl, p<0.001). No statistically significant differences were observed between the 3 and 2 intakes per day groups. The main markers of glucose metabolism – 2-hour blood glucose (-21.9 mg/dl), glycated hemoglobin (HbA1c, -0.18%) and insulin resistance (HOMA-IR, -1.04 points) – were also significantly reduced by TOTUM•63 taken twice daily *versus* placebo.

Figure: TOTUM•63 efficacy results on key glycemic parameters after 6 months compared with placebo.



These results demonstrate the overall efficacy of TOTUM•63 on key markers of glucose metabolism in both prediabetic and early-stage untreated type 2 diabetic patients. Moreover, in prediabetic patients, TOTUM•63 reduced disease progression and the number of new cases of type 2 diabetes by 40% after 6 months, compared with placebo, with two intakes per day.

The results also showed a benefit on low-grade inflammation, with a 13% reduction in the number of volunteers above the inflammation threshold (hsCRP). These chronic low-grade inflammatory processes are directly involved in the pathogenesis of type 2 diabetes.

With efficacy values comparable to those of certain anti-diabetic drugs such as metformin, in a similar population, particularly in terms of fasting blood glucose and glycated hemoglobin[3], TOTUM•63 can easily find its place in strategies for both the prevention in prediabetics and early stages of type 2 diabetes.

Samy HADJADJ
Professor of Endocrinology, Diabetology and Metabolic Diseases, Hospital Practitioner at Nantes University Hospital and Scientific Advisor to the REVERSE-IT study

"The complete data from the REVERSE-IT study are remarkable: they show TOTUM•63's efficacy on glucose homeostasis, even reducing plasma glycated hemoglobin levels, a biomarker established for microvascular risk, used for monitoring type 2 diabetes. Achieving such results in a population at a very early stage is a clinical challenge. It is very beneficial to have an active substance that is both clinically proven and widely usable in a preventive or early-stage setting, to limit the incidence of type 2 diabetes, a chronic disease with often severe long-term complications and a major impact on patients' quality of life."

Jean-Marie BARD
Emeritus Professor of Biochemistry and Hospital Pharmacy Practitioner, Scientific Advisor to the REVERSE-IT study

"In addition to its efficacy on blood glucose parameters, the results of the REVERSE-IT study show a positive impact of TOTUM•63 on the pathogenesis of the disease, with a clear reduction in insulin resistance and a significant benefit in terms of inflammation. This is an important factor demonstrating the ability of this active substance to slow disease progression. In clinical terms, TOTUM•63's safety and very good tolerability, particularly at the gastrointestinal level, are also a major advantage for patients over existing drug approaches, in a preventive context."

Following these excellent results, the next scientific steps will include the submission of clinical data from the REVERSE-IT study to international congresses and publication in international peer-reviewed journals.

In addition, the results of the mode-of-action clinical study on TOTUM•63 conducted by INAF in Quebec City are expected in the second half of 2023.

[3]Knowler et al., Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin, NEJM, 2002.

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TOTUM•63

REVERSE-IT STUDY

A clinical success against prediabetes and early stage type 2 diabetes

An international Phase II/III multicentric, randomized, double blind placebo-controlled study, compliant with the standards required by international learned societies, particularly by the American Diabetes Association (ADA). **Positive efficacy results on the main glycemic parameters after 6 months: primary endpoint and numerous secondary endpoints met.**

TOTUM•63: a non-drug innovation against early stage glycemic disorders

WHAT?
TOTUM•63: a non-drug and exclusive plant-based active substance.

WHAT FOR?
To reduce the main markers of glucose metabolism.

FOR WHOM?
People with prediabetes and early stage untreated type 2 diabetes.

HOW?
In addition to lifestyle interventions.

STUDY KEY FIGURES

POPULATION
636 volunteers

CHARACTERISTICS
79% Prediabetics

21% Early stage type 2 diabetics (untreated)

DOSE
5g in 2 or 3 intakes/day

COMPLIANCE
97% in the 3 groups (placebo, 2 intakes/d, 3 intakes/d)

DURATION
6 months

THE RESULTS*

Efficacy on the glycemic parameters and on diabetes progression

- After 6 months *vs* placebo, TOTUM•63 significantly reduces:
  - Fasting glycemia: **-8.1mg/dl.**
  - 2h-glycemia (after an oral glucose intake): **-21.9mg/dl.**
  - Glycated hemoglobin (HbA1c): **-0.18%.**
  - Insulin resistance (HOMA-IR score): **-1.04pts.**
- In prediabetics: **40% relative reduction in new cases of type 2 diabetes** after 6 months *vs* placebo.
- In early stage untreated type 2 diabetes:
  - Significant reduction in fasting glycemia: **-7.13mg/dl.**
  - Significant reduction in glycated hemoglobin (HbA1c): **-0.45%.**

Additional BENEFITS

- A reduction in low grade inflammation **(-13% of patients with hsCRP ≥ 2mg/L).**
- A statistically **significant weight loss** at 6 months *vs* placebo.

Tolerance PROFILE

- At six months, TOTUM•63 safety and tolerance profile was very favourable:
  - **No reported hypoglycemia.**
  - **Good gastro-intestinal tolerance.**

*TOTUM•63: 5g (2 intakes/day)

TOTUM•63 has shown efficacy results at least comparable to some leading anti-diabetic drugs in a similar population

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: Europe (covering 39 countries), the United States, Russia, China, Japan, Mexico, Indonesia, Israel, South Africa, New Zealand, Singapore, Saudi Arabia, Australia, Algeria, Ukraine, Malaysia, Chile, India, South Korea, and national phases are still underway in Brazil, Argentina, Canada, Thailand, Qatar and the United Arab Emirates.
TOTUM•63's industrial production capacity, in line with North American and European standards, has been validated. 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. This unique partnership in the field of Health Nutrition provides for the marketing of TOTUM•63 by Nestlé Health Science worldwide, possibly before obtaining a health claim depending on the area. It will also finance the final stages of TOTUM•63's development.

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 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 or distribution agreements with global and 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 also been awarded "Young Innovative Company" status and 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

Contacts

Corporate communication
Valbiotis
Carole ROCHER
Communication
and Public Affairs Director
+33 6 77 82 56 88

Marc DELAUNAY
Communication Manager
media@valbiotis.com

Financial communication
Seitosei Actifin
Marianne PY
Senior consultant
+33 1 80 48 25 31
mpy@actifin.fr

Jennifer JULLIA
DE BELLABRE
Press relations
+33 1 56 88 11 19
jjullia@actifin.fr

Medias relations
Agence Monet
Victoire BEAU
Mélanie DA RUI-PONS
+33 1 45 63 12 43
valbiotis@monet-rp.com

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ISIN code: FR0013254851
Ticker symbol: ALVAL
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