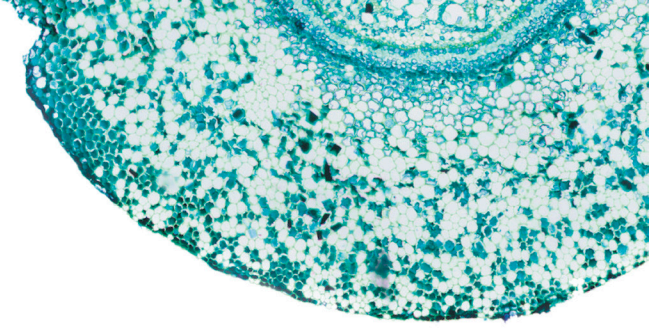

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Valbiotis announces positive results in the bioavailability and mode of action TOTUM•854 clinical study, against high blood pressure

- TOTUM•854 protects human cells of the vascular wall, particularly against inflammation and oxidative stress, which is key to preventing worsening of high blood pressure.
- TOTUM•854 also reduces angiotensin I-converting enzyme (ACE1) activity, one of the main modes of action known to reduce blood pressure.
- The bioavailability study also confirms the presence of 10 metabolites of interest in human serum after oral administration of 3.7 g of TOTUM•854, the daily clinical dose used in the Phase II/III INSIGHT clinical study.
- In line with the preclinical data, these very strong results confirm the potential of TOTUM•854 against mild to moderate high blood pressure in humans and provide strong prospects for late clinical development.
- With a view to marketing TOTUM•854, Valbiotis is targeting the signature of international partnerships and will market directly on the French market; the market for mild to moderate high blood pressure currently includes 123 million adults in the United States and Europe[1].

La Rochelle, January 30, 2023 (5:40 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 positive results in the bioavailability and mode of action clinical study conducted on TOTUM•854 against high blood pressure, the number one cardiovascular risk factor worldwide. The mode of action results demonstrate a protective effect of TOTUM•854 on vascular wall cells and a reduction in angiotensin I-converting enzyme (ACE1) activity in humans. These robust data confirm the potential of TOTUM•854 to reduce blood pressure at the earliest stages of arterial hypertension, which affect 123 million people in the US and Europe[1]. They hold great promise for the late-stage clinical development of TOTUM•854.**

Pascal SIRVENT, Director of Discovery and Preclinical and Translational Research and member of the Executive Committee, comments: *"These innovative bioavailability and mode of action studies once again demonstrate their scientific value for the development of our plant-based active substances. In line with our preclinical work, we can now confirm that TOTUM•854 preserves the integrity of the cells of the blood vessel wall, more specifically of its endothelium. Damage to the vascular wall is a major mechanism in the progression of high blood pressure. Moreover, we also discovered that this active substance acts on the angiotensin pathway, a well-known target of anti-hypertensive strategies. This first-in-human evidence confirms the relevance of TOTUM•854's positioning in the early stages of the disease and bodes well for the ongoing Phase II/III clinical efficacy studies in high blood pressure."*

[1]Elevated LDL, pre-HTA and NAFL preliminary market estimation, AEC Partners, 2020.

TOTUM•854, a patented active substance based on a combination of plant extracts, is developed to reduce blood pressure in people with mild to moderate hypertension, a risk factor for cardiovascular disease.

Mild to moderate arterial hypertension now affects 123 million adults in the United States and the 5 major European countries[1]. No non-drug product has strong clinical evidence or a specific health claim.

TOTUM•854 is currently in the final phase of clinical development before being marketed. Valbiotis aims to sign one or more international commercial partnerships while it will market this active substance in France itself, in accordance with the strategy announced on October 7, 2022 (press release of October 7, 2022). TOTUM•854 will be marketed in two stages. The first step will be based on the recommendation by healthcare professionals, thanks to the Phase II/III results. In a second step, obtaining a proprietary health claim will strengthen the medical positioning of TOTUM•854, especially with patients/consumers.

Enrollment in the first Phase II/III clinical trial (INSIGHT study) is expected to be completed by half-year 2023.

Results of the bioavailability and mode of action clinical study on TOTUM•854

The TOTUM•854 bioavailability and mode of action clinical study, conducted in 10 healthy volunteers, first confirmed the presence of 10 metabolites of interest[2], mainly polyphenolic compounds, in volunteers' serum[3]. These analyses were performed after taking 3.7 g of TOTUM•854 orally, the daily clinical dose also used in the Phase II/III INSIGHT clinical study.

Ex vivo mode of action analyses then demonstrated a triple protective effect of these metabolites on human blood vessel wall cells (endothelial cells):

- increased resistance and viability of these cells to stress induced by excess lipids;
- strong protection against inflammatory processes, with a significant decrease in the production of pro-inflammatory agents such as interleukin 1-ß (IL1-ß) and in the expression of MCP-1 and VCAM-2 markers;
- protection against oxidative stress with a decrease in the concentration of free radicals and a reduced expression of the Nox2 enzyme.

Mode of action tests also revealed a reduction in angiotensin I-converting enzyme (ACE1) activity, an enzyme well known in the pathophysiology of high blood pressure.

This protective effect on the vascular wall in humans confirms the data already obtained in preclinical studies and presented at the annual meetings of the American Heart Association (AHA), the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH) in 2022.
Above all, it confirms the preventive positioning of TOTUM•854 inthe early stages of high blood pressure. In the initial phasesof the disease, when blood pressure rises, the vascular wall undergoes damage involving inflammation and oxidative stress. Ultimately, these changes lead to the narrowing of blood vessels: hypertension worsens, becomes chronic and requires long-term pharmacological treatment. Protection of the vascular wall is therefore a major challenge in the management of early high blood pressure, in order to prevent the progression of the condition.

The innovative protocol of the TOTUM•854 bioavailability and mode of action clinical study

The study was conducted on 10 healthy volunteers in an open-label setting and followed a protocol combining metabolomics and mode of action. Prof. Gisèle PICKERING, coordinator of the Clinical Investigation Center at Clermont-Ferrand University Hospital, was the principal investigator[4].

Metabolomic analysis consists of characterizing the metabolites of an active substance in serum, i.e., the molecules derived from this active substance after their intestinal absorption and their passage into the blood. After a single oral intake of 3.7 g of TOTUM•854, the daily clinical dose also used in the INSIGHT Phase II/III clinical study, analysis of the volunteers' serum confirmed the presence of 10 metabolites of interest, polyphenolic compounds mostly known to exert biological activity on metabolism. Kinetic measurements confirmed good bioavailability of these metabolites in serum within three hours after oral administration of TOTUM•854.

[2]Molecules from TOTUM•854, after they have been absorbed from the intestine and passed into the bloodstream.
[3]The fraction of blood remaining after all blood cells (red blood cells, leukocytes, platelets) and fibrinogen (a protein involved in coagulation) have been removed.
[4]ID-RCB: 2021-A02695-36

In a second step, serum from volunteers was collected after oral intake of 3.7 g TOTUM•854. This serum rich in active metabolites was used to conduct *in vitro* mode of action tests on human umbilical vein endothelial cells (HUVECs), exposed to massive lipid intake, or lipotoxic stress, generating inflammation and oxidative stress.

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

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