



Valbiotis announces the positive results of its clinical study on the bioavailability and mode of action of TOTUM•070, against hypercholesterolemia

- This innovative study is the first to characterize the metabolites of TOTUM•070 in humans and their mode of action in the liver in a population of 10 healthy volunteers. TOTUM•070 was tested at its clinical daily dose (5g), used also in the Phase II HEART clinical trial.
- Metabolomic analysis confirms the presence of 22 metabolites of interest in the serum of volunteers after oral ingestion of 5g of TOTUM•070.
- Mode of action results demonstrate that TOTUM•070 and its metabolites exert a dual effect on human liver cells:
 - Inhibition of the *de novo* synthesis pathway of cholesterol¹, a key mechanism in the fight against hypercholesterolemia;
 - Inhibition of cholesterol storage in the liver.
- These data confirm this active substance's potential for regulating cholesterol metabolism in humans.
- As per the announced schedule, the Phase II HEART clinical efficacy study results will be communicated in the second quarter of 2022, the primary endpoint being the reduction of blood LDL-cholesterol.

La Rochelle, March 29, 2022 (7:35 am CEST) - Valbiotis (FR0013254851 – ALVAL, PEA/SME eligible), a Research and Development company committed to scientific innovation for preventing and combating metabolic diseases, **announces the positive results of its clinical study on the bioavailability and mode of action of TOTUM•070 against hypercholesterolemia.**

This innovative protocol, involving 10 healthy volunteers, has first confirmed the presence of 22 metabolites² of interest in the serum³ of volunteers. The analyses were conducted following oral administration of the clinical dose of 5g of TOTUM•070, used also in the Phase II HEART study. Most of the 22 metabolites are already known for their activity on metabolism. Mode of action analyses then demonstrated, among other things, two effects of TOTUM•070 on human liver cells: inhibition of the cholesterol synthesis pathway and inhibition of cholesterol storage in hepatocytes. These two effects on cholesterol in the liver, which is one of the main metabolic organs, speak in favor of TOTUM•070's potential against hypercholesterolemia. Following on from these positive results, Valbiotis will announce the outcome of its Phase II HEART clinical efficacy study in the second quarter of 2022, as planned. Its primary endpoint is the reduction of blood LDL-cholesterol.

¹Cholesterol can be brought by food or produced by the body itself ("*de novo* synthesis").

²Molecules derived from TOTUM•070, following their intestinal absorption and passage into the blood.

³The fraction of blood remaining after all blood cells (red blood cells, leukocytes, platelets) and fibrinogen (a protein involved in clotting) have been removed.

Pascal SIRVENT, Director of Discovery and Preclinical and Translational Research and Member of the Board of Directors, states: *“For the first time, this clinical study has evaluated the bioavailability and hepatic mode of action of TOTUM•070 in humans. The results live up to our expectations: we can confirm that TOTUM•070 contains many metabolites of interest for regulating cholesterol. Most importantly, the results show that these metabolites are bioavailable in humans and have two significant effects on the regulation of cholesterol in the cells of the human liver, one of the main metabolic organs. These novel clinical data build on the positive preclinical results presented in 2021 and pave the way for further mode-of-action investigations in the liver. Above all, they confirm the potential of TOTUM•070 against hypercholesterolemia in humans, pending the imminent results of our Phase II clinical efficacy study.”*

Murielle CAZAUBIEL, Director of Medical, Regulatory and Industrial Affairs and Member of the Board of Directors, adds: *“During this clinical study on TOTUM•070, we used an innovative methodology adapted to our plant-based active substances that combines metabolomics and mode of action, which is now producing results. This is a positive clinical development and a very encouraging sign while we wait for the Phase II HEART clinical efficacy results, which will become available in the second quarter of 2022.”*

Results of the clinical study on bioavailability and mode of action

This study was conducted on 10 healthy volunteers in an open-label setting and followed a protocol combining metabolomics and mode of action, designed and implemented by Clinic'n'Cell. Professor Gisèle PICKERING, coordinator of the Clinical Investigation Center of the Clermont-Ferrand University Hospital, was Principal Investigator⁴.

Metabolomic analysis consists of characterizing the metabolites of an active substance in serum, i.e., the molecules derived from this active substance following their intestinal absorption and passage into the blood. After a single oral dose of 5g of TOTUM•070, which is the clinical daily dose, used also in the HEART clinical study (see below), analysis of the volunteers' serum confirmed the presence of 22 metabolites of interest, the majority of which are known to have a biological activity on metabolism. Kinetic measurements validated good bioavailability of these metabolites in serum within three hours of oral TOTUM•070 intake.

In a second step, the serum collected from volunteers after oral intake of 5g of TOTUM•070 – a serum rich in active metabolites from TOTUM•070 – was used to conduct *in vitro* tests on human liver cells exposed to massive lipid intake. In this context of “lipotoxic stress”, the volunteers' serum exerted two major effects on these human liver cell lines: inhibition of the *de novo* cholesterol synthesis pathway¹ and inhibition of cholesterol storage. It also showed no toxicity.

All analyses were conducted with a double control: cell cultures with and without lipotoxic stress, then with and without serum enriched in active metabolites.

Upcoming publication of the Phase II clinical results of TOTUM•070 on hypercholesterolemia

The Phase II HEART clinical trial results will be announced in the second quarter of 2022. This multi-center study will evaluate the efficacy of TOTUM•070 in reducing blood LDL-cholesterol levels *versus* placebo, in 120 volunteers with mild to moderate untreated hypercholesterolemia. These results will be decisive for the marketing of TOTUM•070, an innovative 100% plant-based active substance containing neither phytosterols nor red yeast rice, and for its positioning as a reference non-drug option against LDL-cholesterol.

⁴ID-RCB : 2021-A01211-40

About Valbiotis

Valbiotis is a 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.

Its products are intended to be licensed to players in the health sector.

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 / Marc DELAUNAY

+33 5 46 28 62 58

media@valbiotis.com

Financial communication

Actifin

Stéphane RUIZ

+33 1 56 88 11 14

sruiz@actifin.fr

Medias relations

PrPa

Damien MAILLARD

+33 6 80 28 47 70

damien.maillard@prpa.fr



Name: Valbiotis
ISIN code: FR0013254851
Mnemonic code: ALVAL
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