



Valbiotis will present significant preclinical results for its active substance TOTUM•448 against fatty liver diseases (NAFL and NASH), at the annual meeting of the American Association for the Study of Liver Diseases (AASLD)

- TOTUM•448 is an innovative plant-based patented active substance developed by Valbiotis, a young French SME, to counteract the development of metabolic liver diseases (NAFL and NASH¹).
- In two preclinical models that mimic the development of fatty liver disease in humans, two studies demonstrate the broad efficacy of TOTUM•448 on the key mechanisms of these diseases, from the earliest stages:
 - Reduction of fat accumulation in the liver, e.g. hepatic steatosis.
 - Reduction of hepatic inflammation, which causes damage to the liver.
 - Improvement of certain markers of fibrosis.
- These very promising results have been selected for presentation at the annual meeting of the AASLD, the leading American learned society for liver diseases, in Washington (USA), November 4-8, 2022.
- Metabolic liver diseases (NAFL, NASH), linked to overweight, are spreading throughout the world and can lead to severe liver damage requiring transplantation; its early management is all the more essential as no treatment is yet available.
- The studies were carried out by Valbiotis research teams at its Riom center (Puy-de-Dôme), in collaboration with the Hospices Civils de Lyon, and by the University of Leiden (Netherlands).

La Rochelle, October 27, 2022 (5:40 pm CEST) - Valbiotis (FR0013254851 – ALVAL, PEA/SME eligible), a Research and Development company committed to scientific innovation for preventing and combating metabolic and cardiovascular diseases, **will present the significant preclinical results of TOTUM•448, a non-drug, plant-based active substance, against metabolic liver diseases (NAFL and NASH), at the annual meeting of the American Association for the Study of Liver Diseases, from November 4 to 8, 2022.** These results demonstrate the efficacy of TOTUM•448 in the early stages of these diseases, on steatosis, inflammation and fibrosis of the liver. The two studies presented were conducted by Valbiotis teams at its R&D center in Riom (Puy-de-Dôme) in collaboration with the Hospices Civils de Lyon and by teams from the University of Leiden (Netherlands).

¹ NAFL: non-alcoholic fatty liver; NASH: non-alcoholic steatohepatitis.

Pascal SIRVENT, Chief Scientific Officer, member of the Valbiotis Board of Directors, states : *"The excellent results that will be presented acknowledge extensive work in designing, refining and testing TOTUM•448, an innovative plant-based active substance. TOTUM•448 is the result of our combined expertise in plant-based substances and in metabolic diseases, and was specifically designed for metabolic liver diseases, or fatty liver diseases such as NASH. The selection of these results by the AASLD annual meeting, the world reference in the field, is a recognition of the real potential of TOTUM•448 in metabolic liver diseases, which are growing rapidly worldwide and for which no specific treatment exists today. We would like to thank our academic partners on this project, the University of Leiden and the Hospices Civils de Lyon."*

TOTUM•448 results: broad efficacy on key parameters of fatty liver diseases, from the earliest stages

Two studies will be presented at the AASLD world congress in two preclinical models of fatty liver diseases, which mimic the development of the disease in humans. They showed the efficacy of TOTUM•448 on hepatic steatosis and inflammation and suggested an improvement in certain markers of fibrosis, the first three stages of the development of these diseases.

First study: preventive efficacy of TOTUM•448 against fatty liver disease

This first protocol evaluated the efficacy of this active substance in preventing the development of fatty liver diseases in a model of induced obesity in golden hamsters. The animals were separated into four groups: a control group and three groups fed a high-fat diet, two of which were simultaneously supplemented with TOTUM•448 at two different doses.

At the end of the study (12 weeks), TOTUM•448 significantly reduced hepatic steatosis with a dose-dependent effect. This accumulation of triglycerides and cholesterol in the liver, a consequence of an excessively rich diet, is the first step in the development of metabolic liver diseases. Concurrent limitation of blood triglyceride and cholesterol levels was recorded, suggesting a major preventive effect of TOTUM•448 on the regulation of lipid metabolism.

Second study: the "curative" efficacy of TOTUM•448 on already established fatty liver diseases

This second "reversal" protocol evaluated the efficacy of TOTUM•448 in a model of previously developed liver pathology. The animals were separated into five groups: a control group and four groups fed a high-fat diet only, for 12 weeks. Of these four groups that had developed liver disease, three were then supplemented with TOTUM•448 for four weeks at three different doses while continuing their high-fat diet.

By the end of the study, TOTUM•448 had reduced the level of fat in the liver (steatosis), but also reduced immune markers of liver inflammation and the ballooning score (swelling of the liver cells). At the same time, TOTUM•448 produced marked positive effects on metabolic parameters strongly involved in the early stages of the disease (insulin sensitivity, glucose tolerance).

In both studies, TOTUM•448 reduced the expression of genes involved in inflammation and liver fibrosis, two key steps in the progression of fatty liver diseases.

Vivien CHAVANELLE, PhD, Research officer and project manager of the TOTUM•448 program for Valbiotis, comments: *"We have developed TOTUM•448 for the management of fatty liver diseases in their early stages. The excellent results of these studies converge to demonstrate a strong efficacy of TOTUM•448 on these very early key mechanisms of fatty liver diseases: the initial accumulation of fat in the liver and inflammation. Our data even suggest an effect on fibrosis, which is observed at slightly later stages. This is a real success and opens the way to an effective and totally new, non-drug preventive approach. We are very proud to present these promising data to the scientific community and hepatology specialists gathered in Washington for the AASLD congress"*.

NAFL and NASH: an alarming global picture

Metabolic liver diseases or NAFLD (non-alcoholic fatty liver diseases) constitute a spectrum of diseases that extends from simple isolated non-alcoholic fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH).

These liver diseases are closely related to other metabolic disorders (obesity, insulin resistance, dyslipidemia, type 2 diabetes, hypertension). Their global prevalence, including all stages, is estimated at 25% worldwide².

NAFL, the first stage of these diseases, is characterized by the accumulation of fat in the liver and is estimated to affect 18.5 to 23.5% adults in the world³. It progresses to NASH when inflammatory processes and then fibrosis damage the liver tissue. At this advanced stage, the risk of liver failure, cirrhosis and hepatocellular carcinoma increases. In the United States, NASH is now the second most common reason for liver transplantation⁴.

No proven therapeutic or preventive solution is yet available for these liver diseases.

Posters presentation

Poster: #2559

Title: TOTUM•448 improves diet-induced non-alcoholic steatohepatitis in golden Syrian hamsters fed a western-diet

Authors: Chavanelle V. *et al.*

Poster: #2483

Title: The novel plant-based active principle TOTUM•448 decreases hepatic steatosis and inflammation in diet-induced NAFLD mice.

Authors: Lambooi JM. *et al.*

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 and cardiovascular 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

²Younossi ZM *et al.* Global epidemiology of nonalcoholic fatty liver disease, *Hepatology*, 2016.

³ Internal estimation, based on Younossi ZM *et al.* Global epidemiology of nonalcoholic fatty liver disease, *Hepatology*, 2016.

⁴Cholankeril G, *et al.* Liver Transplantation for Nonalcoholic Steatohepatitis in the US: Temporal Trends and Outcomes. *Dig Dis Sci.* 2017.

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