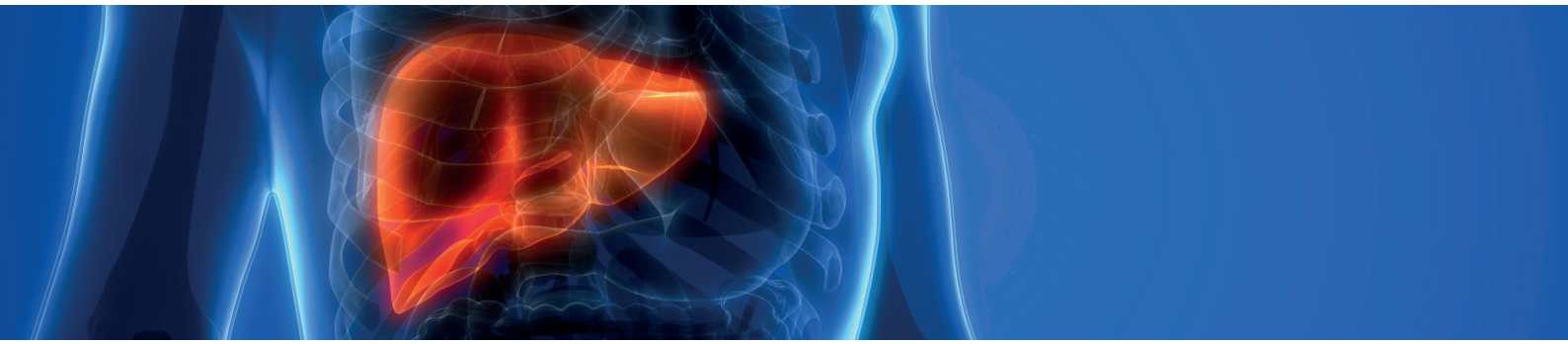
VALBIOTIS

PRESS RELEASE

VALBIOTIS announces expansion of application for VALEDIA to include NASH prevention

- **New results demonstrate the clinical potential of VALEDIA for NASH risk reduction.**
- **Studies on VALEDIA show complete reversion of hepatic steatosis in an *in vivo* preclinical model*.**
- **A mechanism of action on 3 key targets of hepatic steatosis, presented at the 2018 American Association for the Study of Liver Disease (AASLD) from 9 to 13 november 2018 in San Francisco (USA).**
- **New results on human, showing significant improvement in lipid profile, a strong asset for NASH prevention.**



La Rochelle, le 12 november 2018 (7:35 CET) - **VALBIOTIS** (FR0013254851 - ALVAL / PEA/SME eligible),), a French Research & Development company committed to scientific innovation for preventing and combating metabolic diseases, **today announced an expansion of application for VALEDIA to NASH prevention.**

This new field of application is based on new results that demonstrate the clinical potential for the reversion of non-alcoholic fatty liver (NAFL), for NASH** prevention. Studies conducted by the Leiden University (Netherlands), one of VALBIOTIS' scientific partners, have demonstrated a complete reversion of fatty liver by the active ingredient of VALEDIA, TOTUM-63, in NAFLD*** *in vivo* model, confirmed by histological data.

In parallel, *in vivo* studies have highlighted a mechanism of action of TOTUM-63 on three key cellular targets of the physiopathology of NAFLDs: the transcription factors Ppar ß/∂ and FXR as well as the Fsp27 protein. These data suggesting a mechanism of action focused on NAFLDs prevention will be presented at the American Association for the Study of Liver Diseases (AASLD) Conference, being held from November 9-13, 2018 in San Francisco, California.

Based on these results,the Company plans to launch Phase II clinical studies in addition to ongoing studies for the risk reduction of type 2 diabetes. This expanded field of application strengthens VALEDIA as a precursor product for new prevention strategies in the field of severe metabolic diseases, focused on managing the risk factors for this diseases. In addition to prediabetes, VALEDIA could be the first product for subjects with NAFL, the first stage of liver metabolic diseases prior to severe stages such as NASH. It is now estimated that these metabolic disorders affect 25% of the world's population and are expanding rapidly[1].

*Studies conducted by the Leiden University (Netherlands) in NAFLD murine models
** Non-Alcoholic Steatohepatitis
*** Non-Alcoholic Fatty Liver Diseases

New additional results from the Phase I/II clinical study conducted in 2017 on VALEDIA have also confirmed significant improvement in lipid profile, including a significant reduction in blood triglycerides and total cholesterol levels. Lipid profile and insulin sensitivity, which improvement by VALEDIA had already been demonstrated in this first clinical study, are two metabolic components known to have a strong link with the development of fatty liver disease.

VALEDIA, A GLOBAL PLAN FOR THE PREVENTION OF TYPE 2 DIABETES AND NASH FROM 2021

Once clinical development is complete in prediabetic subjects, VALEDIA will be marketed with a health claim related to the risk reduction of type 2 diabetes by 2021. Beyond this initial label, VALEDIA may also be recommended by healthcare professionals for subjects with NAFL without prediabetes. This recommendation could be made based on the first clinical data issued by VALEDIA studies in steatotic patients.

Obtaining a specific health claim for the reduction of NAFL and the risk reduction of NASH will be targeted in 2023. This claim will allow to meet the needs of this entire NAFL population, without prediabetes, estimated by the Company to be 13.3% of the general population in the USA and 4.5% in Europe.

Phase II clinical development of VALEDIA for NASH risk reduction will start with a Phase IIA randomized, placebo-controlled study, with planned launch in 2019 in a target population with NAFL. The primary endpoint will be the reduction of hepatic steatosis. The initial steatosis and its evolution will be evaluated by a non-invasive method.

Pr Samy Hadjadj
Diabetologist and endocrinologist ,
Nantes University Hospital

« At the current time, NAFL and NASH are highly prevalent in patients with an existing metabolic disease or disorder, related to insulin-resistance. Consequently, there is a genuine need for preventive strategies at the NAFL stage, to efficiently reduce liver fat, as the prognosis is poor for patients who develop NASH and no treatment is yet established except liver transplant for advanced stages. Regarding fat liver reduction, the results on VALEDIA are very promiseful, by correcting hepatic steatosis despite the continuation of a high fat diet. If these experimental results are confirmed in clinical studies, VALEDIA could constitute a valuable option for patients at risk of developing NASH.»

« We are excited to see that the new data on VALEDIA suggests its relevance for the reversion of fatty liver. VALEDIA holds a unique and strong objective : to become the backbone of metabolic diseases prevention and meet the needs of a broad population, at risk of developing type 2 diabetes or NASH. »

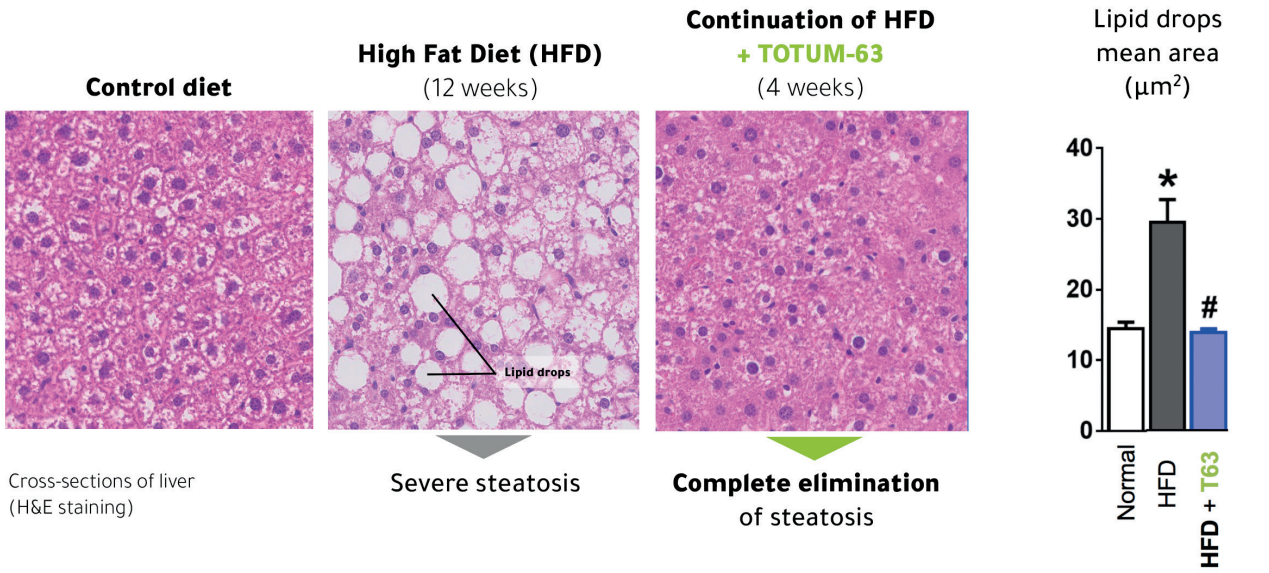
Sébastien PELTIER
CEO of VALBIOTIS

DETAILED DATA FOR TOTUM-63, THE ACTIVE INGREDIENT OF VALEDIA, ON NON-ALCOHOLIC FATTY LIVER

1. A complete reversion of fatty liver demonstrated in a steatosis model

Within a scientific partnership with Leiden University, a study evaluated the efficacy of TOTUM-63 in an *in vivo* preclinical model with severe steatotic liver. During this "reversion" study, the addition of the active ingredient of VALEDIA restored the liver to a non-steatotic state, within 4 weeks. The elimination of steatosis was demonstrated by histological analyses and associated with a drastic improvement in insulin sensitivity (HOMA-IR index), back to control level.

Reversion of fatty liver obtained by TOTUM-63, active ingredient of VALEDIA
in a NAFLD preclinical model



Bruno GUIGAS
Researcher and Assistant professor
University of Leiden (Netherlands)

« We conducted analyzes on histological, biochemical and physiological parameters of fatty liver: all converge towards a very significant demonstration of TOTUM-63 efficacy for the reversion of steatosis.»

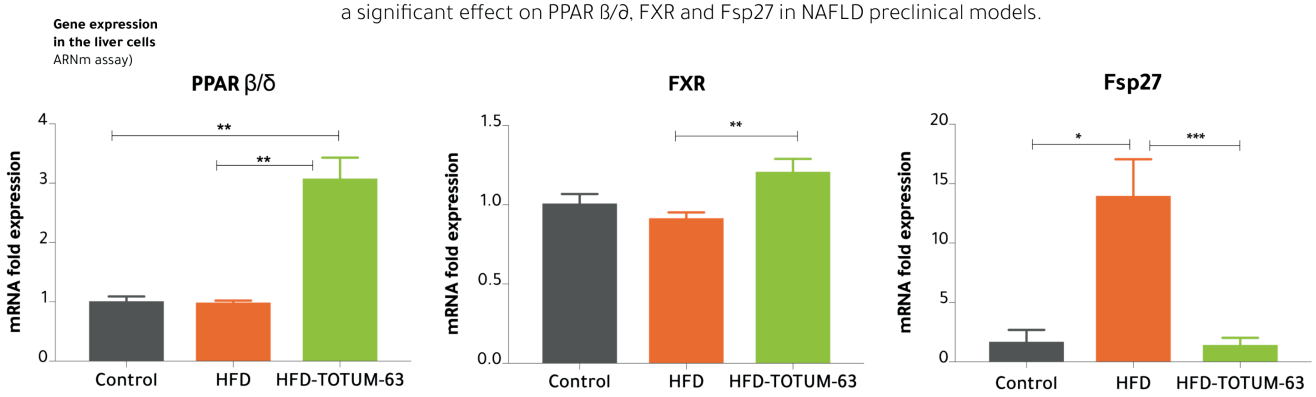
2. A mechanism of action on 3 essential cellular targets for the prevention of hepatic steatosis

In an *in vivo* model of NAFLD, supplementation with TOTUM-63, the active ingredient of VALEDIA, simultaneously with a high-fat diet for 16 weeks prevented the development of severe hepatic steatosis, observed in non-supplemented models.

Mechanism of action studies revealed a significant increase in gene expression of Ppar ß/∂ (increased by a factor 3) and FXR (+30%), both key transcription factors of the hepatic energy metabolism. Simultaneously, the active ingredient of VALEDIA almost completely inhibited the expression of the protein Fsp27, which regulates lipid storage and is specifically expressed in steatotic livers. This mechanism of action, which targets control of the hepatic metabolism, represents a major asset in reducing the risk of NASH in the early stages of the disease.

Mechanism of action of TOTUM-63, the active ingredient of VALEDIA:

a significant effect on PPAR ß/∂, FXR and Fsp27 in NAFLD preclinical models.

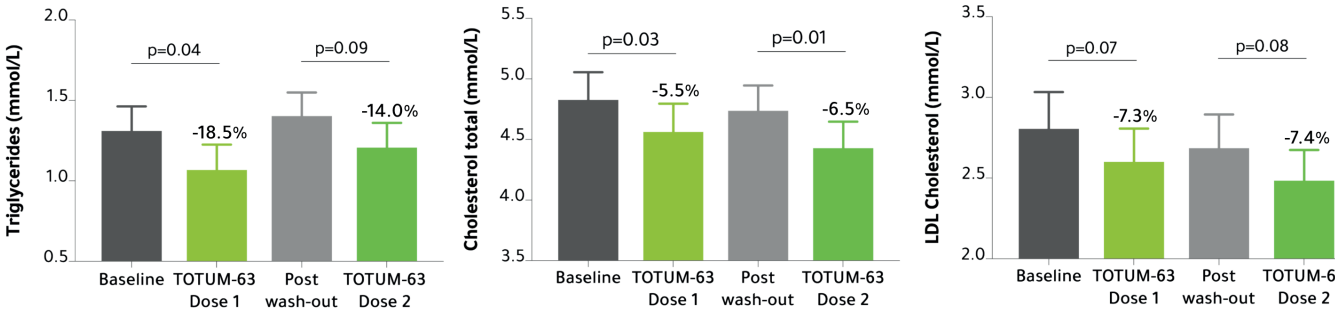


3. In human trials, a significant improvement in two metabolic components strongly linked to the development of NAFLDs

The Phase I/II clinical study conducted in 2017 on TOTUM-63, the active ingredient of VALEDIA, had already demonstrated improvement in insulin sensitivity. New results from this initial study show an improvement in the lipid profile, including the significant reduction in blood levels of total cholesterol (-5.5%) and triglycerides (-18.5%) with the first tested dosage (2.5 g/day). No elevation of blood LDL-cholesterol was observed (-7,3% with 2,5 g/day, p=0,07; -7,4% with 5 g/day, p=0,08), whereas it is an adverse event already encountered for an active ingredient acting on the FXR pathway. Insulin resistance and dyslipidemia are recognized to be strongly associated with the development of NAFL and then NASH.

Improvement in lipid profile by TOTUM-63 (healthy volunteers)

Two 4-week periods of supplementation, with 2 different dosages
(2.5 g/day then 5 g/day), with a 15-day wash-out period in between.



ABOUT NAFLDs

A broad need for prevention against the NAFLD epidemic

Worldwide, the prevalence of NAFLD is estimated to be more than 25%[1]. It affects 50 to 70% of diabetic patients[2], 60 to 75% of obese subjects and 50% of dyslipidemic patients[3]. Correlated to the diabetes and obesity pandemic, the number of subjects with NAFL or NASH is constantly increasing in high-income countries: the projections anticipate a growth of + 21% for NAFL and of + 63% for NASH by 2030[4].

The Fatty Liver Index: a follow-up method achievable routinely in primary care

One of the difficulties in the clinical assessment of these liver disorders is the need for liver biopsy. Nevertheless, scores based on routine examinations exist and are easily achievable in general practice.

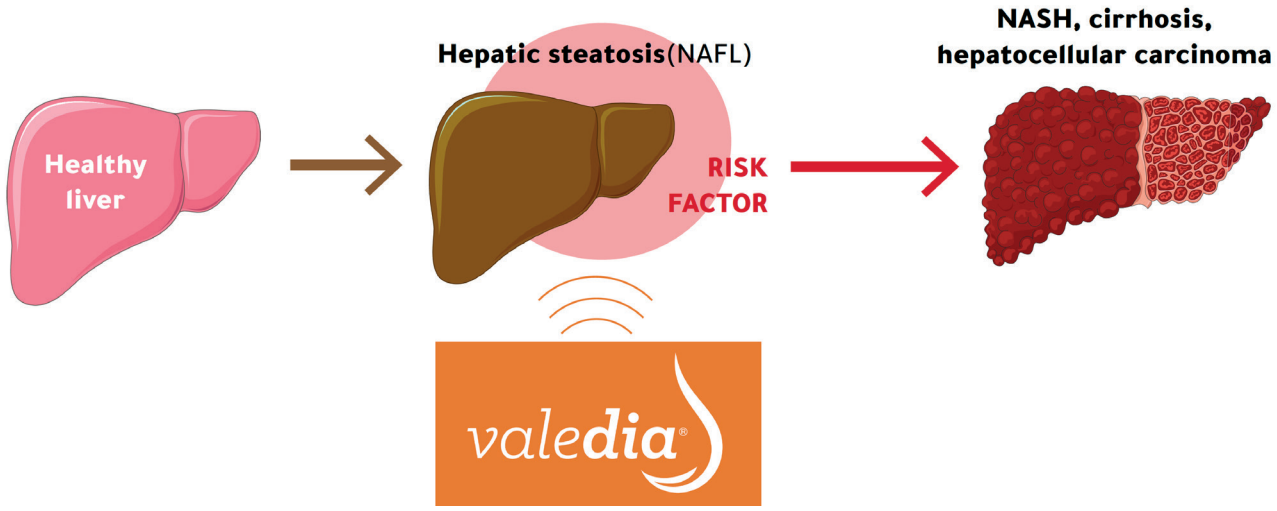
Nevertheless, scores based on routine examinations exist and are easily achievable in general practice. One of these scores, the Fatty Liver Index (FLI) is calculated from 4 routine measurements: blood triglycerides level, Body Mass Index, blood Gamma Glutamyl Transferases (GGT) level and waist measurement. FLI can be considered as an indirect marker of hepatic steatosis and can be used for screening and monitoring patients with suspected steatosis[5]. Non-invasive imaging techniques are also available and have the advantage of being inexpensive and repeatable[6].

NAFL, a risk condition for developing NASH

Fatty liver corresponds to hepatic steatosis, an accumulation of fat in hepatic cells. In NASH, steatosis is complicated by inflammation and tissue damage. With a poor prognosis, - 38% survival at 10 years, NASH can progress to fibrosis and cirrhosis, causing liver failure and, in some cases, liver cancer[7].

Available studies estimate that 40% of people with fatty liver will progress to NASH[8]. Non-alcoholic fatty liver, or NAFL, is considered a risk condition for developing NASH[9].

The course of NAFLDs, from NAFL to NASH and its complications



[1]Younossi Z.M. et al. Hepatology, 2016
[2]Anstee, Targher et al. 2013
[3]Assy, Kaita et al. 2000
[4]Estes C. et al., Hepatology, 2018
[5]Bedogni G., BMC Gastroenterology, 2006
[6]Papagianni M et al. World J Hepatol 2015;7(4):638-648
[7]World Gastroenterology Organisation Global Guidelines. Non-alcoholic Fatty Liver Disease and Non-alcoholic Steatohepatitis. http://www.worldgastroenterology.org/assets/export/userfiles/2012_NASH%20and%20NAFLD_Final_long.pdf
[8]McPherson S et al. J Hepatol 2015;62(5):1148-55
[9]Vizuete J et al. J Clin Transl Hepatol 2017;5(1):67-75

ABOUT VALBIOTIS

VALBIOTIS is a French Research & Development company committed to scientific innovation for preventing and combating metabolic diseases. Its products are made for manufacturers in the agri-food and pharmaceutical industries. VALBIOTIS particularly focuses on solutions to prevent type 2 diabetes, NASH (nonalcoholic steatohepatitis), obesity and cardiovascular diseases. VALBIOTIS was founded in La Rochelle in early 2014 and has formed numerous partnerships with top academic centers in France and abroad, including the La Rochelle University, the CNRS and the Clermont Auvergne University located in Clermont-Ferrand. These partnerships have enabled VALBIOTIS to benefit from strong financial leverage, particularly thanks to experts and technical partners who support its projects. The company is located at 3 sites in France - Périgny, La Rochelle (17) and Riom (63) - in addition to an american office in Boston (MA).

VALBIOTIS is a member of the "BPI Excellence" network and received the "Innovative Company" status accorded by BPI France. VALBIOTIS has also been awarded "Young Innovative Company" status and has received major financial support from the European Union for its research programs by obtaining support from the European Regional Development Fund (ERDF).

Find out more about VALBIOTIS:
www.valbiotis.com

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