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# SUMMARY

**Research & Development company committed to scientific innovation  
for preventing and fighting against metabolic diseases.**

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## **VALBIOTIS**

R&D COMPANY COMMITTED TO SCIENTIFIC INNOVATION

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## **TOTUM-63**

A GLOBAL INNOVATION AGAINST THE EPIDEMIC OF TYPE 2 DIABETES

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## **METABOLIC DISEASES**

TYPE 2 DIABETES, DYSLIPIDEMIA, FATTY LIVER DISEASES, ARTERIAL HYPERTENSION

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TYPE 2 DIABETES

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DYSLIPIDEMIA

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NAFL/NASH

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ARTERIAL HYPERTENSION

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**2014** company foundation

**2015** discovery of TOTUM-63

**2017** Initial Public Offering on Euronext Growth (ALVAL)

**36** employees: 75% in R&D & >50% women

**3** locations in France (Périgny, La Rochelle & Riom)

**1,200** m<sup>2</sup> R&D platform in-house

**4** products in the pipeline

**4** patent families

**13** communications during scientific congresses

**23.7M** euros raised in equity since 2014



- A R&D company, committed to scientific innovation, for preventing and combating metabolic diseases, to address unmet medical needs.
- A new class of Nutrition Health products, dedicated to reduce the risk of developing major metabolic diseases, based on a multitarget approach enabled by the use of plants. Products that will benefit from strong clinical evidence and health claims.
- A solid intellectual property: four patent families applied for worldwide, including strategic patents granted in Europe and in the USA.
- A 1,200 m<sup>2</sup> R&D platform inhouse, in Riom.
- A Business Model validated by a first worldwide long-term strategic partnership.

# An expert management for healthcare innovation.



**Sébastien PELTIER, CEO.**

PhD - HDR

Chairman of the Board of Directors

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20 years' experience in Research & Development for drug and food supplement industries. Unique, proven experience with health claims referring to the reduction of a disease risk (EFSA - European Food Safety Authority - article 14.1a)

**Pascal SIRVENT, CSO.**

PhD - HDR

Member of the Board

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Over 15 years' research experience in the field of metabolic diseases, with leadership positions and a strong background in international scientific partnerships.

**Laurent LÉVY, PhD**

Chairman of the Supervisory Board

Remuneration Committee

CEO, co-founder of NANOBIOTIX

**Jean ZETLAOUI, MD, MBA**

Audit Committee

Member of Supervisory Board

Special Scientific Advisor of the CEO, NOVARTIS PHARMA

**Agnès TIXIER**

Audit Committee

Member of Supervisory Board

Investment Director, CM-CIC INVESTISSEMENT

**Jocelyn PINEAU, CFO.**

MBA

Member of the Board

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20 years' experience in project management positions as part of executive management boards, in the agro-food and food supplements industries.

**Murielle CAZAUBIEL, CMO.**

M.Sc

Member of the Board

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25 years' experience in health and nutrition. Founder and former Executive Director of Biofortis Mérieux Nutrisciences Europe.

**Sébastien BESSY**

Remuneration Committee

Member of Supervisory Board

Vice President Global Strategic Operations, IPSEN



# An advanced pipeline.

PRODUCT	INDICATION	PHASE II	PHASE II/III	HEALTH CLAIM	PARTNERSHIP
TOTUM-63	Prediabetes		Phase II/III to be launched		
TOTUM-070	Hyper-cholesterolemia	➡	Ready to move on to Phase II		
TOTUM-448	Fatty liver	➡	Ready to move on to Phase II		
TOTUM-854	Arterial hypertension	➡	Ready to move on to Phase II		



## A global **intellectual property strategy**.

**4 patent families application worldwide already**

Demonstrates that innovative combinations of plant extracts are patentable for a healthcare purpose in food, supplements or pharmaceuticals products.

→ **Plant extract / molecules**

All patents are registered worldwide, including USA, Europe, Canada, China, Australia, Russia, Japan, Brazil.

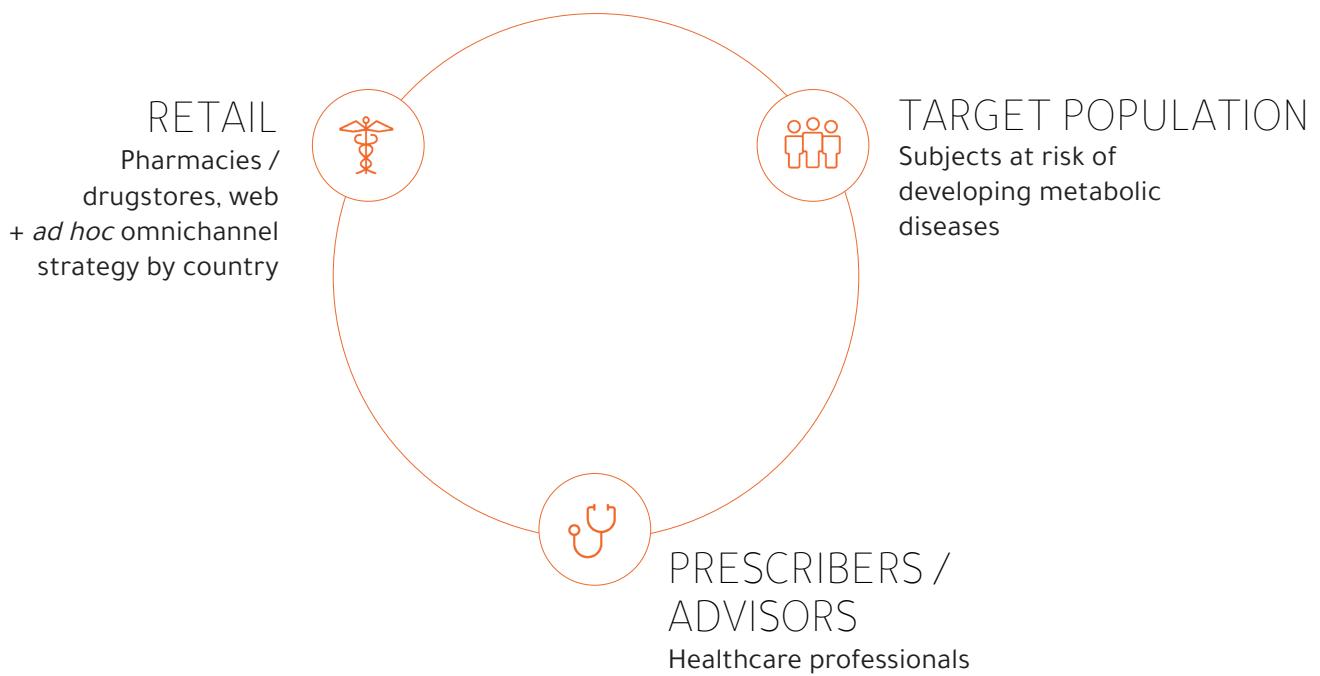
# Business model: **strategic partnerships with major healthcare players.**

## Strategic partnership

Global agreements along the products life cycle: last stages of clinical development, galenic development, supply, worldwide commercialization.

UPFRONT AND MILESTONES PAYMENTS - FUNDING OF CLINICAL STUDIES - ROYALTIES ON SALES

## Commercialization model



## A unique and historic partnership in the field of Nutrition Health



**A long-term strategic partnership for the development and commercialization of TOTUM-63 in prediabetes**

A worldwide contract signed before pivotal phase  
A license and supply agreement  
A 5 million CHF upfront, up to 66 million CHF milestones payments  
Progressive royalties on net sales  
Commercialization possible prior to health claim

**+ Joint Advisory Committee**

# A proprietary platform

## dedicated to metabolic diseases.



01.

### **Plant based chemistry**

Design of active substances (compliant with US and EU pharmacopeia).

Extraction processes, characterisation, purification, bio-engineering, pharmacological modulation.

02.

### **Discovery & preclinical**

*In vivo* screening on relevant models of metabolic diseases

*In vivo* and *in vitro* studies: efficacy, safety, mode of action.

1,200 m<sup>2</sup> platform: models of metabolic diseases, radiolabelling, micro-surgery & clamp, histology, cellular culture, molecular biology, biochemistry.

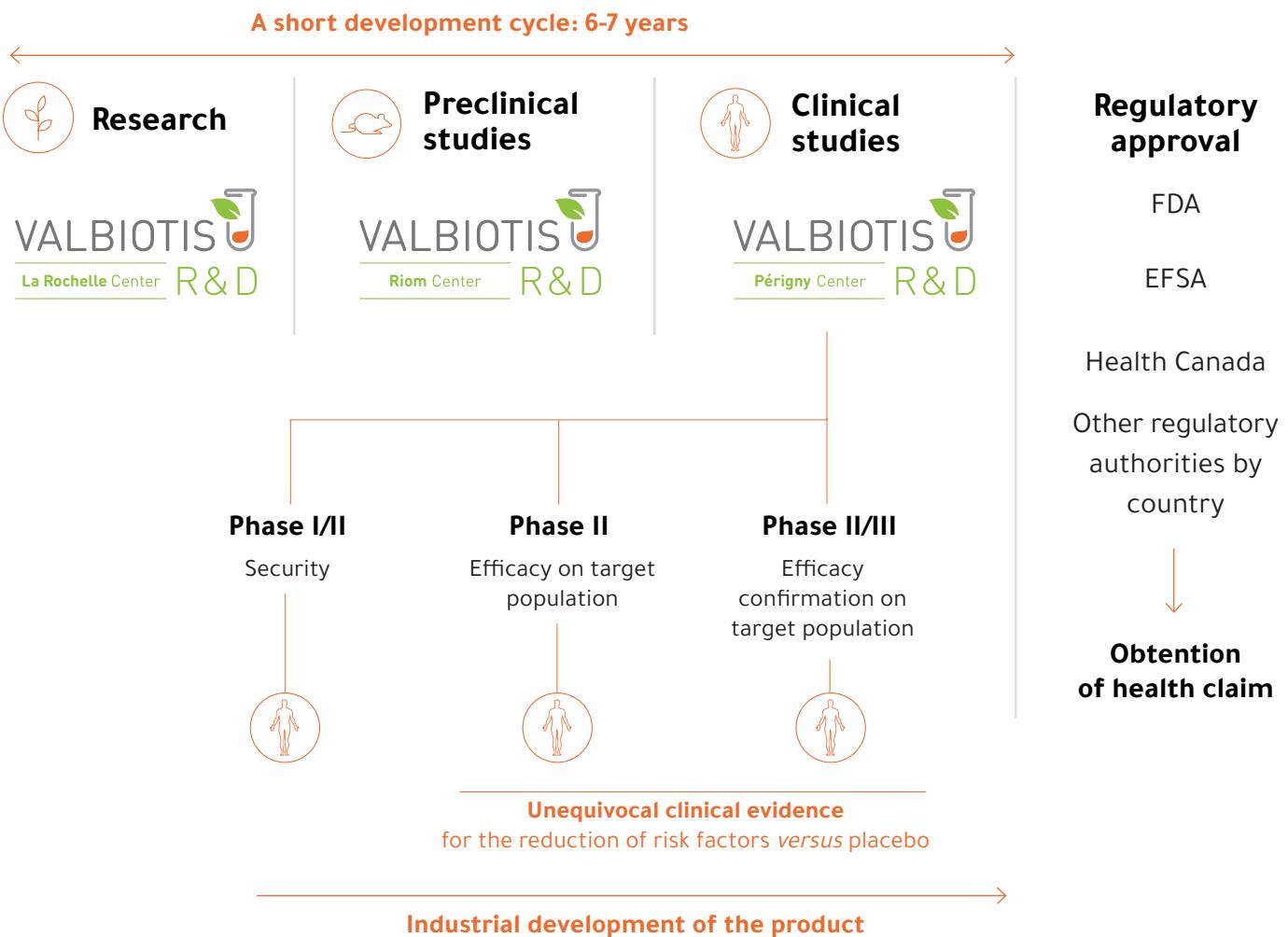
03.

### **Clinical development**

Design, monitor and carry out of all clinical studies (Phases I/II - II- II/III).

Clinical studies conducted in specialized clinical investigation centers following GCP standards (Good Clinical Practices), the results of which are promoted by scientific publications and communications.

# A high level of evidence for prevention.



# TOTUM

# 63

## TOTUM-63, a worldwide innovation against Type 2 Diabetes epidemic

TOTUM-63 is the first Nutrition Health product designed to reduce the metabolic risk factors of Type 2 Diabetes. It is developed for people with prediabetes, which prevalence is rising in the world, and will allow efficient preventive management.



### A Nutrition Health product, based on plants, to act at the prediabetes stage

Resulting of a several years' intensive research and development program, TOTUM-63 is a unique and patented combination of 5 plant extracts, with a multi-targeted action on metabolism: liver, adipose tissue, muscle, pancreas, gut.

TOTUM-63 is developed for prediabetic people, at high risk of developing Type 2 Diabetes, who do not have any other efficient solution than a significant change in lifestyle, difficult to sustain in time.

### A clinically-proven product against Type 2 Diabetes risk factors

TOTUM-63 has been proven effective in clinical studies, including a Phase II study in people with prediabetes, *versus* placebo.

In this study, TOTUM-63 significantly reduced the main risk factors of type 2 diabetes, compared to placebo: fasting hyperglycemia and post-meal hyperglycemia (OGTT). TOTUM-63 also significantly reduced body weight and waist circumference, compared to placebo.

**Positive Phase II clinical results,  
versus placebo**

**-9.3%**

reduction in fasting glycemia

**-22.5%**

reduction in 2h post-meal glycemia (OGTT)

**Patents already obtained in key territories**

This plant-based active substance has been protected by a global intellectual property strategy. Patents already granted in more than 40 countries, including USA, Europe and Russia, acknowledge this innovation and its value for human health. Applications have been made in other key territories such as China, Japan, Brazil, and Australia.

**A recognition from regulatory authorities and the scientific community**

To prove its efficacy, at the end of its development, TOTUM-63 could benefit from the first health claim related to the reduction of a Type 2 Diabetes risk factor in Europe and in North America. After non-equivocal proof of efficacy is provided, these claims are delivered by regulatory authorities: EFSA (European Food Safety Agency) in Europe, FDA (Food and Drug Administration) in the USA and other authorities depending on the country.

From a scientific standpoint, TOTUM-63 was the subject of 9 communications in international congresses, including the scientific sessions of the American Diabetes Association (2016, 2017 and 2019), annual congress of the European Association for the Study of Diabetes (2018 and 2019) and annual congress of the International Diabetes Federation (2017).

**TOTUM-63**

**-1.9 kg**

reduction in body weight

**-4.48 cm**

reduction in waist circumference

**Nutrition Health: a novel approach for the prevention of metabolic diseases**

TOTUM-63 is the first of a new class of Nutrition Health products, dedicated to meet the challenge of preventing metabolic diseases. These innovative products, plant-based and clinically proven, have been designed for multi-targeted action. They are clinically developed with a common objective: reduce the risk of developing metabolic diseases.

# Type 2 diabetes & prediabetes: a global health burden

Type 2 diabetes is characterized by a chronic hyperglycemia primarily associated with overweight and sedentary lifestyle.

The disease is spreading throughout the population in all countries, leading to serious and possible fatal complications, affecting the heart, blood vessels, eyes, kidneys and nerves. Its treatment is based on lifestyle changes, combined with pharmacological treatments that get heavier when as the disease progresses.

Preventing type 2 diabetes is possible, by acting at the stage of prediabetes, when hyperglycemia is still moderate and reversible.

## Type 2 diabetes: hyperglycemia linked to lifestyle

Type 2 diabetes, a chronic disease, results from the body's inability to properly use and sufficiently produce insulin.

Insulin is a hormone secreted by the pancreas which theoretically helps regulate sugar level in the blood.

This regulation is impaired in diabetic patients, leading to hyperglycemia: blood glucose level gets too high.

Unlike type 1 diabetes, which is a genetic disorder, type 2 diabetes is strongly linked to lifestyle. Overweight and inactivity pave the way for the disease to develop, typically from the age of 40 to 45. However, it has also begun to affect teenagers and young adults.



# TYPE 2 DIABETES



## Asymptomatic disease with serious complications

Initially asymptomatic, the disease is often incidentally and lately discovered, following a physical exam or the appearance of complications. Over time, elevated blood glucose level leads to possibly severe impairments: heart attack, cerebral vascular accidents, blindness, foot ulcers and risk of amputation, erectile dysfunction or renal failure.

## Progressive and complex treatments

After onset and diagnosis, type 2 diabetes is treated, first and foremost, through lifestyle and dietary measures similar to those applied to prediabetes: balanced diet and physical exercise.

In case glycemia does not decrease, oral antidiabetics (OADs) are prescribed. If the disease continues to progress despite this first line treatments, insulin injections become necessary: at this stage, the patient is said to be "insulin-dependent". Insulin therapy is difficult to handle, and may lead to strong adverse events.

In parallel, diabetic patients are often treated to avoid or manage the complications of diabetes.

Type 2 diabetes is hard to manage once it is installed. But preventing the disease is possible, with an early and appropriate intervention at the prediabetes stage.

## Key figures

### Diabetes pandemic

More than 8.5% of the adult population suffers from diabetes (10% type 1, and 90% type 2), the direct cause of 4.2 million deaths each year. And the epidemic is spreading: more than 700 million people will be affected in 2045, *versus* 463 million today (2019).

In France, more than 3.7 million people are treated for diabetes, with an annual growth rate reaching 3%.

**+ 237 million**

diabetes cases in the world, by 2045.

## Prediabetes: the second epidemic

Type 2 diabetes is always preceded by a long phase (5 to 10 years according to studies) known as “prediabetes”. Blood glucose levels are higher than normal but have not yet reached the disease threshold. The diagnosis is easy, with a single blood test. Like type 2 diabetes, prediabetes is a worldwide epidemic: In the world, 900 million people would have prediabetes today. It is estimated that over 130 million people are prediabetic in the United States, Canada and the 5 main European countries. In the USA, almost 86 million adults have prediabetes today, which represents one adult out of three!

### Fasting glycemia

#### Prediabetes

From 1.00 g/L to 1.25 g/L

#### Type 2 diabetes

$\geq 1.26$  g/L



### Prediabetes: a key moment to prevent diabetes

Prediabetes is reversible, as long as it is efficiently managed with a long-term corrective intervention on lifestyle. The main measures target overweight management. A balanced diet, healthy eating habits (3 meals a day without snacking), physical activity on a regular basis and quitting smoking are the cornerstones of a good health and limit the risk for hyperglycemia. A necessary preventive approach, since more than 70% of prediabetics will develop type 2 diabetes.

This strategy faces one difficulty: a strict and long term compliance to these lifestyle changes.

# Dyslipidemias: alert on arteries!

Dyslipidemia, or abnormal levels of fat in the blood, and more specifically hypercholesterolemia is omnipresent in the global population. These conditions contribute to the development of several cardiovascular diseases.

Their treatment, prevention or cure involves lifestyle changes combined, if necessary, with pharmacological treatments.

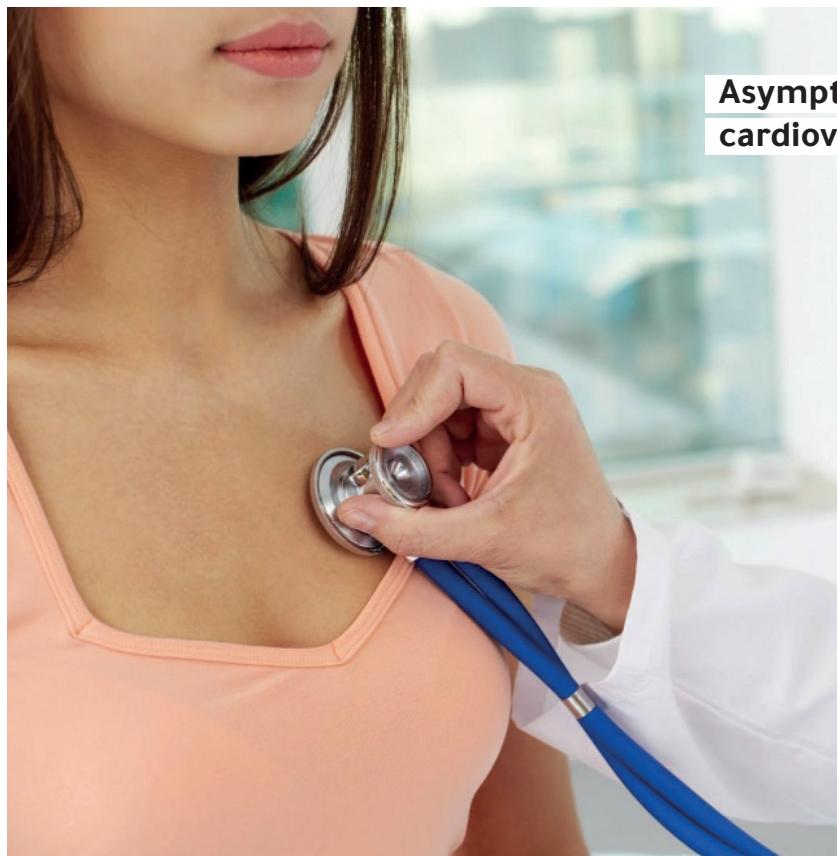
## Excessive fat in the blood

Dyslipidemia refers to abnormal serum lipid concentrations, characterized by high levels of "bad" cholesterol (LDL hypercholesterolemia), triglycerides (hypertriglyceridemia) or both (mixed hyperlipidemia).

Low levels of "good" cholesterol (HDL) may also be found.



# DYSLIPIDEMIA



## Asymptomatic cardiovascular risk

Dyslipidemias cause fat deposits to form along the artery walls (atheroma plaques), ultimately narrowing and even clogging the arteries. Atherosclerosis can lead to various cardiovascular conditions: acute coronary syndromes, cerebrovascular accidents (CVAs), transient ischaemic attacks (TIAs) or peripheral artery disease (PAD).

There are no visible symptoms of dyslipidemia. Physical manifestations often appear only once the arteries are affected, at a point when swift intervention is required.

### Screening: blood analyses under surveillance

Since cholesterol problems are frequent, regular biological check-ups are recommended, especially in people with cardiovascular risk factors.

In people already presenting another cardiovascular risk factor (overweight, hypertension, etc.), the recommended maximum blood LDL-cholesterol level is:

**1.30 g/L**

### Recommended values in people without other cardiovascular risk factor:

#### Total cholesterol

**< 2 g/L**

#### HDL cholesterol

**> 0.40 g/L**

#### LDL cholesterol

**< 1.60 g/L**

#### Triglycerides

**< 1.50 g/L**

## **Lifestyle: a dominant factor despite various causes**

Some dyslipidemias, known as primary dyslipidemias, may be linked to genetic mutations.

However, the majority of dyslipidemias are linked to external factors: a sedentary lifestyle combined with an excessive intake of saturated fats, cholesterol and trans fatty acids. People with overweight or obesity are thus among the most likely to be affected by these conditions.

Other extrinsic factors may also contribute, including pathologies (diabetes, a kidney, liver or thyroid condition, etc.) or treatments (oral contraceptive, beta blocker, glucocorticoid, etc.).



### **Dyslipidemia: prevention and treatment**

The primary objective when treating dyslipidemia is to lower LDL-c or triglyceride levels. For this reason, the primary risk factors should be addressed, by making dietary changes, engaging in physical exercise and losing weight.

For the most severe dyslipidemias, treatments prescribed by a healthcare professional may also be used to help control the levels of circulating lipids.

# NAFL & NASH: emerging liver diseases

NASH refers to the most advanced stage of non-alcoholic fatty liver disease, involving a combination of fat accumulation, inflammation and lesions in the hepatocyte cells. In particular, these impairments can lead to cirrhosis or liver cancer.

Associated with sedentary lifestyles and poor eating habits, this epidemic has been silently spreading across developed countries. Prevention and treatment of the risk factors are the only therapeutic solutions currently available.

## Fatty liver diseases

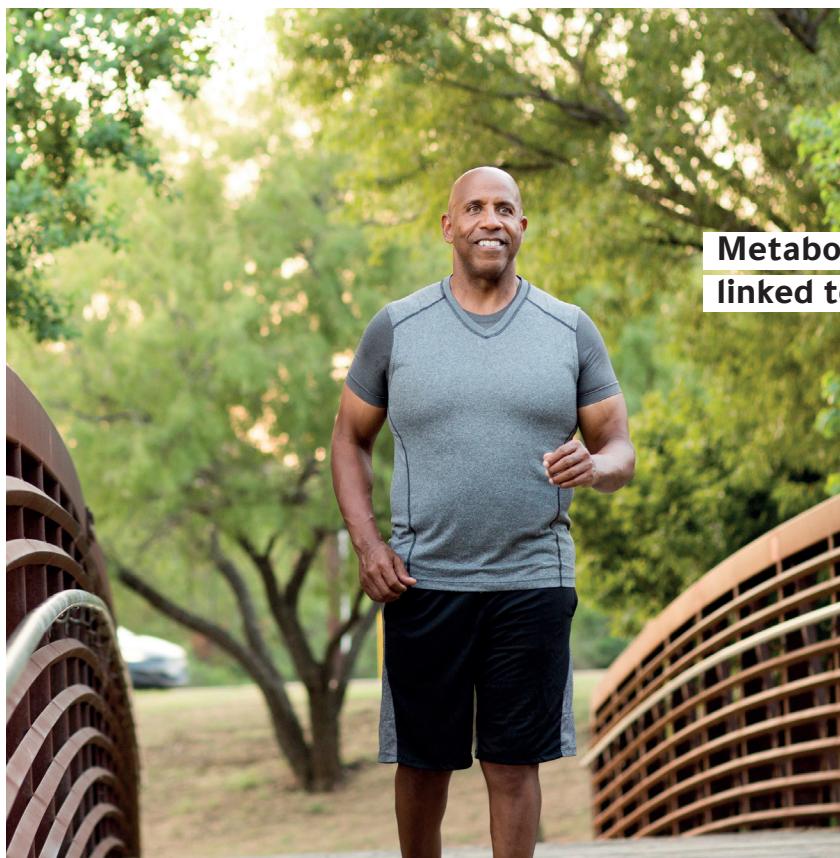
Non-alcoholic fatty liver disease (NAFLD) and its most advanced stage, non-alcoholic steatohepatitis (NASH), are associated with the presence of fat in over 5% of the liver cells. This is the reason why they are called "fatty liver diseases".

In the case of NASH, excess lipids cause inflammation and tissue lesions which can lead to fibrosis (scarring), similar to the symptoms found in alcoholic cirrhosis.

Available studies estimate that 40% of people with NAFL will progress to NASH.



# NAFL NASH



## Metabolic diseases linked to lifestyle

NASH is mainly diagnosed in patients suffering from overweight, type 2 diabetes, insulin resistance or dyslipidemia. NASH is also likely to contribute to the development of cardiovascular diseases, type 2 diabetes, and some non-hepatic cancers.

### A silent progression until advanced stages

Patients with NAFLD or NASH do not have clear symptoms, however some may feel fatigued or may experience abdominal discomfort. Only a few late signs can suggest NASH at its more advanced stage: hepatic deficiency, hepatocellular decompensation or carcinoma.

### Key figures

#### NASH: a threat of epidemic proportions

In correlation with the diabetes and obesity pandemic, the number of cases of NAFLD and NASH has been constantly increasing in industrialized countries. The prevalence of NAFLD is therefore predicted to be higher than 25% on a global scale (Europe and USA 24%, Asia 27-37%). The prevalence of NASH will exceed 9% on average.

Current forecasts mainly predict growth of over 21% for NAFLD and over 63% for NASH by 2030, contributing to a 178% increase in the number of deaths linked to liver disorders.

**25 %**

of the world population could have non alcoholic fatty liver today.

## Toward systematic screening?

Often detected late due to the lack of characteristic symptoms, the diagnosis of NASH relies on physical and biological examinations in the first instance, which can reveal an increase in liver volume and a rise in certain enzymatic levels (GGTs and transaminases).

Predictive scores (NAS score, Fatty Liver Index) are also a simple way to assess disease progression.

If suspected, NASH can be confirmed by liver biopsy, or by new diagnostic methods based on ultrasound or elastography, less cumbersome, some of which being in development.



### **Treatment: managing the causes of NASH**

Preventing or slowing down the development of NASH is the best approach in order to avoid the onset of other problems. There is no direct treatment: the aim is to eliminate the potential causes and risk factors, such as overweight, diabetes and hyperlipidemia.

This objective is achieved by adopting a healthier lifestyle and improving eating habits, as well as practising physical exercise.

# Arterial hypertension (AHT) :

## the leading chronic disease

Arterial hypertension is a major public health issue and affects more than 30% of the world's adult population. This silent disease with multiple causes (smoking, diet, sedentary lifestyle, etc.) is a precursor to various cardiovascular, renal, cerebral and ophthalmic diseases.

A healthy lifestyle and regular medical check-ups can effectively prevent this condition. Successful management of the disease relies on lifestyle improvements and antihypertensive treatments.

### Criteria for diagnosis

Often called a "silent killer", arterial hypertension (AHT) involves an abnormal increase in both blood pressure variables:

Systolic blood pressure (SBP), the higher figure, measured when the heart contracts,

Diastolic blood pressure (DBP), the lower figure, measured when the heart relaxes.

Hypertension is globally defined as blood pressure with values greater than or equal to 140/90 millimeters of mercury (doctors are more likely to refer to this as 14/9 cm Hg), except in the USA, where the threshold was recently revised to 130/80 mmHg. In people with metabolic syndrome (see below), hypertension is established when blood pressure exceeds 130/80 mmHg.

In any case, the higher the numbers, the more severe the hypertension and the greater the health risk.





## Significant repercussions on health

The higher the blood pressure, the greater the risk of damage to the heart and blood vessels. Hypertension is now responsible for more than a third of cardiovascular events (myocardial infarction, stroke, etc.) and the associated mortalities, i.e. 7 million deaths per year worldwide. Because of the effect of hypertension on blood circulation in the kidneys, eyes and brain, it can also lead to kidney failure, blindness or cognitive impairment.

### No specific symptoms, but clearly-identified, modifiable risk factors

There are no characteristic symptoms in the early stages of hypertension. It is usually diagnosed by chance during general medical check-ups. Nonetheless, there are many risk factors which contribute to the development or severity of this disease. Some of these factors can be mitigated, such as dyslipidemia, overweight, stress, sedentary lifestyle, smoking and overconsumption of salt and alcohol. Other factors are immutable, such as age (>50 years for men, >60 years for women), genetics or the presence of chronic diseases.

### Key figures

#### The whole world affected by hypertension

In less than 45 years, the number of people with high blood pressure has risen from 594 million to over 1.1 billion, with an average of 59.3 million new cases each year. In France, arterial hypertension affects over 11 million people, nearly one in three adults and one in two people over the age of 65. What's more, health authorities estimate that 3 to 4 million French citizens are unaware that they have high blood pressure.

**10 million**

deaths from high blood pressure, the leading cause of premature death worldwide.

## **Prevention and control: above all, patients must adopt a healthy lifestyle**

Changes to lifestyle are essential for patients to actively manage arterial hypertension. The main objectives being to lose weight if overweight, moderate alcohol consumption (less than 2 glasses per day, not every day) and salt intake (< 5 g/day), stop smoking and exercise regularly (ideally for >30 min/day).

Another essential factor in reducing the risk of hypertension is the control of glucose (diabetes) and lipid (hypercholesterolemia) parameters by means of a specially adapted diet and, if necessary, medicinal treatment.



### **A key component of metabolic syndrome**

Metabolic syndrome is a group of disorders that increase the likelihood of developing heart disease and diabetes, or of experiencing a stroke or other health problems. There are five risk factors: low "good" cholesterol (HDL cholesterol), hyperglycemia, high triglycerides, abdominal overweight and of course, arterial hypertension starting at 130/80 mmHg. Hypertension must therefore be treated while simultaneously managing any other health problems that may affect the patient.