EnteroSatys®, a novel probiotic that naturally modulates the appetite via the microbiome

Gregory LAMBERT - CEO
TargEDys Executive Summary

- Based on 15 years of research at Inserm (University of Rouen, France)
- Offices in Longjumeau, Paris area & Labs in Rouen, Normandy
- Financing
  - Raised 9 M€
  - Obtained 1.3 M€ in non-dilutive financing
- IP: 9 patent families and 6 trademarks
- Platform delivers both therapeutic and nutraceutical products
Role of the gut microbiota in host appetite control: bacterial growth to animal feeding behaviour

Sergei O. Fetisov

Nature Reviews Endocrinology (2016) | doi:10.1038/nrendo.2016.150
Published online 12 September 2016
The concept of molecular mimicry
ClpB / α-MSH Molecular mimicry

- Strong sequence homology between an exposed loop on the surface of ClpB and α-MSH
- Confirmation in HRM Mass Spectrometry after immunoprecipitation of enterobacteria proteins with α-MSH antibody
- ClpB is a MCR agonist

1. Tennoune et al., Transl Psy, 2014
2. Internal report from Biognosys, 2018

ClpB is the only protein with α-MSH aa pattern
ClpB is one of the most abundant proteins amongst candidates
Plasma ClpB levels correlate with ClpB DNA in gut microbiota in rats

ClpB is present in human plasma

ClpB DNA in human feces inversely correlates with BMI

ClpB is endogenously present and inversely correlates to BMI

From Breton et al., Int J Eat Dis 49: 805-808, 2016

Submitted Int.J.Obesity
Single intraperitoneal Injection (2 pmol): ClpB96 / ClpB25 / control buffer

Single injection of ClpB reduces significantly cumulative food intake

In vivo ClpB effect in mice
Oral gavage with Hafnia alvei in Genetic (ObOb) and Diet (HFD) mice obesity models
**Hafnia alvei vs Orlistat**

**Hybrid Model HF-HSD – ob/ob**

*Hafnia alvei* reduces food intake, body weight and insulin resistance and glycemia while Orlistat increases it.

Control of appetite is key to achieve sustainable weight and metabolic disease management.
**CMC development**

**Hafnia alvei 4597 - Ex-vivo SHIME model**

- *H. alvei* 4597 resists digestion (low sensitivity to pH and enzymes)
- *H. alvei* 4597 adheres to mucus
- *H. alvei* 4597 grows and is metabolically active in colon
Comparison of 2 GI-resistant formulations (DRCAPS™ et HPMC) in ex-vivo GI model:

- Study of the release of the bacteria
- Study of the ClpB integrity

DRCAPS™ provide a delayed bacteria release & protection of the ClpB from degradation.
Finished product Quality Control

- **Strain Identity**
  Petri dish cell count (CFU = cultivable bacteria)
  Flow cytometry (intact, intermediate stage and dead bacteria)
  All non-lysed bacteria alive or not contain and protect ClpB.

- **Water activity**

- **Zn and Cr assays**

- **Microbiology**

- **Weight & homogeneity of the capsules**

- **Protein and fragments characterization**
  Western Blot to characterize α-MSH pharmacophore & degradation
  Molecular mimicry is present even after partial degradation
Stability data on the first commercial batch – ongoing – results after 9 months
Ongoing Clinical Trial

- Double-blind, randomised, placebo-controlled study to evaluate benefit of ProbioSatys® on weight reduction in overweight subjects
- Probiotic strain & dosage: *Hafnia alvei* 4597 – $1.10^{11}$ cells/day
- 12 weeks of treatment, 2 capsules/day – 5 visits
- 3 centres in Germany
- 2 arms / 120 subjects par arm - BMI: 25 kg/m² – 29.9 kg/m²
- Main endpoints:
  - Body weight (kg and %)
  - Body fat and fat free mass
  - Waist and hip circumference
  - Lipid metabolism parameters
  - Glucose blood parameters
  - Feeling of satiety
  - General well-being parameters
  - Safety

A Human POC for ProbioSatys® Nutra and Therapeutic products
Key ProbioSatys benefits

- Reduction of food intake
- Reduction in body weight
- Improvement of body composition
- Activation of lipolysis
- Decrease of fasting glycemia
  (Improvement of glucose tolerance)
- Activation of central satiety pathways
ProbioSatys®

Nutraceutic based approaches
- Cheese strain = food
- Self affirmed GRAS in the USA
- Dietary supplement
- Functional foods

Therapeutic based approaches
- The ClpB or ClpB fragments as API
- Life Biotherapeutic with *Hafnia alvei*

Pet Food/supplement
Food supplement
Ingredient
LBP
ClpB

Looking for partners
On the market

PETF DRE
NUTRA
PHARMA

Winner Nutra Ingredients Awards 2019

Weight Management

www.targedyss.com
Regulate your appetite via your microbiome!

- *Hafnia alvei 4597*, THE connected strain
- Zinc & Chromium to rebalance your metabolism
- The only probiotic with a validated molecular level mechanism of action
- Proven efficacy
- Gastro-resistant capsules
- 2 capsules per day (breakfast and lunch)
- Feel satiety after only one week
- Reduce body weight after one month

**Ingredients**

<table>
<thead>
<tr>
<th>Ingredients</th>
<th>Defined Daily Dose</th>
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<tbody>
<tr>
<td><em>Hafnia alvei 4597</em></td>
<td>50 million CFU’s</td>
</tr>
<tr>
<td></td>
<td>100 billion cells</td>
</tr>
<tr>
<td>Zinc (bisglycinate)</td>
<td>5 mg or 50% of ARs</td>
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<tr>
<td>Chromium (picolinate)</td>
<td>20 μg or 50% of the ARs</td>
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Enterosatys® consumer study

METHODOLOGY
- Consumer experience study after 1 and 3 months of EnteroSatys® use
- Inclusion criteria: volunteer people who bought at least 2 boxes
- Reward: 1 free box

POSSIBLE LIMITATIONS
- Self-assessment / no placebo
- Incentive box

Number of subjects
- Subjects = 65
- Average age = 48.6 years / Average BMI = 29.36 kg/m²
- Responders at 1 month = 60
- Responders at 3 months = 36
Study results
Eating behaviour

- 77% have reported at least 1 effect on their eating habits
- 83% have reported at least 1 effect on their eating habits and/or weight loss
- Majority of people have reported their first effects within first 10 days

<table>
<thead>
<tr>
<th>Impact</th>
<th>Percentage</th>
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<tbody>
<tr>
<td>At least one effect</td>
<td>77%</td>
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<tr>
<td>Decreased appetite</td>
<td>56%</td>
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<tr>
<td>Less sweet cravings</td>
<td>38%</td>
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<tr>
<td>Less snacking</td>
<td>48%</td>
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<tr>
<td>Smaller portions</td>
<td>52%</td>
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</tbody>
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Lead time to first reported effects:
- 77% have reported at least 1 effect on their eating habits
- 83% have reported at least 1 effect on their eating habits and/or weight loss
- Majority of people have reported their first effects within first 10 days

Graphs showing:
- Decreased appetite
- Less snacking
- Less sweet cravings
- Smaller portions

% of people reporting different impacts on their eating habits

### Lead time to first reported effects
- **< 10 days**
- **10 days - 3 weeks**
- **After 3 weeks**
Weight loss

Average BMI at T0: 29.36 kg/m²

After 1 month:
- Average weight loss: -2.7% (-2.2 kg)
  - 33% lost more than 3%
  - 17% lost more than 5%

After 3 months:
- Average weight loss: -6% (-4.9 kg)
  - 71% lost more than 3%
  - 41% lost more than 5%

Average BMI (1 month):
- Average weight loss: 28.83 kg/m² (-0.53 kg/m²)

Average BMI (3 months):
- Average weight loss: 27.62 kg/m² (-1.72 kg/m²)
Other improvements reported after 3 months of programme

- Waist circumference* (67%)
- Digestive comfort (58%)
- Feeling better in their body (76%)
- Improved relation with food (71%)

*Tightened their belt at least by one notch (2 cm)

83% would recommend the product after the first month

94% would recommend the product after 3 months

Compliance

- 88% report to be compliant during the 1st month
- 61% report to be compliant during the 3rd month