ACTOBIO THERAPEUTICS™

ACTOBIOTICS®, MICROBE-BASED BIOPHARMACEUTICALS
for expression and local delivery of therapeutics at disease sites
including the intestine, the mouth and the nasopharynx.

Corporate presentation - Pieter Rottiers, PhD, Chief Executive Officer, Director – JAN 2019
Some of the statements made in this presentation are forward-looking statements. These forward-looking statements are based upon our current expectations and projections about future events and generally relate to our plans, objectives and expectations for the development of our business.

Although management believes that the plans and objectives reflected in or suggested by these forward-looking statements are reasonable, all forward-looking statements involve risks and uncertainties and actual future results may be materially different from the plans, objectives and expectations expressed in this presentation. All information in this presentation is as of the date marked on the cover page, and ActoBio Therapeutics™ undertakes no duty to update this information unless required by law.
**ACTOBIO THERAPEUTICS™ - KEY INVESTMENT HIGHLIGHTS**

### PLATFORM

- Actobiotics® is a fully integrated, cost-effective & unique food microbe-based delivery platform for therapeutics, with potential for superior efficacy and safety through oral or local targeted delivery.
- Designed to perform specific biological interventions.
- Accelerates development and validated regulatory path for new IND candidates: <2yrs from inception to IND achieved with AG013 for oral mucositis.
- Strong R&D engine and large collection of strains, with potential for further development.

### PRODUCT PORTFOLIO

- Two Clinical stage programs in Phase IIb and Phase Ib, with other programs close to clinical stage.
- Broad therapeutic application across a wide set of diseases with strong growth dynamics.
- Target the (gut) mucosal immune system for:
  - Mucosal healing and decreasing local inflammation.
  - Targets the gut associated lymphoid tissue to steer the systemic immune system towards immune tolerance/desensitization.
- Can produce multiple biologicals, thereby acting as a combination therapy, to target multiple disease pathways.

### EXPERIENCE

- Straightforward and reliable cGMP manufacturing process.
- IP portfolio across the technology platform:
  - >250 granted patents.
  - >50 pending patent applications.
- Extensive regulatory acceptance of platform and applications.
- Experienced leadership team with unique expertise in bacterial engineering and strong scientific, regulatory and clinical backgrounds.
L. lactis has a long history of safe use in human nutrition
• Non-colonizing, non-human commensal species allowing for control of dosage and timing of exposure
• No known pathogenicity
• Oral delivery platform demonstrated safe for use in humans

Construction strategy allows for minimum genetic modifications
• Engineered through chromosomal integration of single or multiple genetic elements through precise, targeted double homologous recombination
• Host is engineered for environmental containment¹, preventing accumulation of bacteria outside the body
• Engineering process established in-house to allow for continual creation of new drug candidates

Industrial microorganism used for large scale food production
• cGMP manufacturing process established
• Following fermentation, the modified bacteria are freeze-dried and packaged

DELIVERY OF ACTOBIOTICS® THERAPEUTICS

1. Genetically engineered bacterium freeze dried and inserted into enteric coated capsule

2. Capsule opens and releases the bacterium directly at the disease target

3. Bacterium releases the therapeutic agent locally at target site (e.g. in GI tract)
**ACTOBIOTICS COMPARED TO EXISTING TREATMENTS**

**ActoBiotics**
- Can be delivered in an oral capsule or in a topical solution
- No known toxicity or immunogenicity observed
- Targeted delivery to mucosa
- Simultaneous delivery of multiple proteins

**Classic Protein Biologics**
- Intravenous administration
- Systemic toxicity, immunogenicity observed
- Limited tissue penetration (notably in the gut)
- Single protein administration

<table>
<thead>
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<th>Indication</th>
<th>Treatment with Biologics</th>
<th>ROA (Biological)</th>
<th>ActoBiotics ROA</th>
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<tr>
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<td>Palifermin (HSCT)</td>
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<td>Celiac Disease</td>
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<td>Oral capsule</td>
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ActoBiotics are as effective as injected biologicals even at 1/1000th the dose.
### ACTOBIOTICS

#### CLINICAL AND DEVELOPMENT PIPELINE

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<td>AG019</td>
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<td>&gt; 70 K new cases per year</td>
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ACTOBIO THERAPEUTICS KEY MILESTONES

**Target selection**

- IBD

**Clinical strain selection & GMP production**

- AG017 Celiac Disease
- AG018 CRSwNP

**IND/CTA**

- AG019 T1D (IND)
- AG019 T1D (CTA)

**First patient in study**

- AG019 T1D

**DSMB review/data primary endpoint**

- AG013 OM (DSMB)
- AG019 T1D (DSMB)

**Last patient out of study**

- AG017 CeD
- AG019/ AG013 T1D

- Interim EOP2b
- Interim EOP2a
- Interim EOP1b

- PKU
- IBD
- Allergy

**Metabolic Disease**

- PKU

**Skin Disease**

- Interim EOP2a
- Interim EOP1b

**1Q18**

- 1Q18
- 2Q18
- 3Q18
- 4Q18

**2Q18**

- 2Q19
- 3Q19
- 4Q19

**3Q18**

- 1Q20
- 2Q20
- 3Q20
- 4Q20

- *1 month Follow-up; **1 year Follow-up
- # 1 year Follow-up
- * 6 months Follow-up, ** 1 year Follow-up
ActoBio Therapeutics™ in Autoimmune & Allergic Diseases
Induction of Antigen-Specific Tolerance by Oral Administration of Lactococcus lactis Delivered Immunodominant DQ8-Restricted Gladin Peptide in Sensitized Nonobese Diabetic Ab° Dq8 Transgenic Mice

Inge L. Huibregtse, Eric V. Marietta, Shadi Rashak, Frits Koning, Pieter Rottiers, Chella S. David, Sander J. H. van Beventer, and Joseph A. Murray

Active delivery of recombinant autoantigens or allergens at the intestinal mucosa by genetically modified Lactococcus lactis (L.L.) provides a novel therapeutic approach for the induction of tolerance. Celiac disease is associated with either HLA-DQ-2 or HLA-DQ-8-restricted responses to specific antigenic epitopes of gluten, and may be treated by induction of Ag-specific tolerance. We investigated whether oral administration of L.L-delivered DQ8-specific gladin epitope induces Ag-specific tolerance. L.L. was engineered to secrete a denatured DQ8 gladin epitope (L.L-DQ8D) and the induction of Ag-specific tolerance was studied in NOD AB° Dq8 transgenic mice. Tolerance was assessed by delayed-type hypersensitivity reaction, cytokine measurements, DQ8-specific proliferation, and regulatory T cell analysis. Oral administration of L.L-DQ8D induced suppression of local and systemic DQ8-restricted T cell responses in NOD AB° Dq8 transgenic mice. Treatment resulted in an Ag-specific decrease of the proliferative capacity of intestinal lymph node (ILN) cells and lamina propria cells. Production of IL-10 and TGF-β and a significant induction of Foxp3 regulatory T cells were associated with the DQ8-specific suppression induced by L.L-DQ8D. These data provide support for the development of effective therapeutic approaches for gluten-sensitive disorders using orally administered Ag-secreting L.L. Such treatments may be effective even in the setting of established hypersensitivity. The Journal of Immunology, 2009, 183: 2396–2396.

Research article

Reversal of autoimmune diabetes by restoration of antigen-specific tolerance using genetically modified Lactococcus lactis in mice

Tatiana Takishii, Hamnelot Korf, Tor L. Van Belle, Sofie Robert, Paolo A. Greco, Silvio Cakic, Matthias Luhr, Heiko Sympolak, Lothar Steiner, Karoline Van Huygen, Peter Damerter, Olle Wiesebergh, Mark A. Atkinson, Francesco Dotti, Peter Rottiers, Danny Wyfflemans, and Chantal Mathieu

Current interventions for arresting autoimmune diabetes have yet to strike the balance between sufficient efficacy, minimal side effects, and lack of generalised immunosuppression. Introduction of antigens via the gut represents an appealing method for induction of antigen-specific tolerance. Here, we developed a strategy for tolerance induction using mucosal delivery in mice of biologically contained Lactococcus lactis genetically modified to secrete the whole pancreatic autoantigens along with the immunosuppressive cytokine IL-10. We show that combination therapy with low-dose systemic anti-CD3 readily reversed diabetes in NOD mice and increased frequency of local Tregs, which not only accumulated in the pancreatic islets, but also suppressed immune response in an autoantigen-specific way. Caused mice maintained responsive disease-relevant autoantigens, which argues against excessive immunosuppression. Application of this therapeutic tool achieved gut mucosal delivery of a diabetes-relevant autoantigens and a biologically active immunosuppressive cytokine, IL-10, and, when combined with a low dose of systemic anti-CD3, was well tolerated and induced antigen-specific long-term tolerance, allowing reversal of established autoimmune diabetes. Therefore, we believe this method could be an effective treatment strategy for type 1 diabetes in humans.

Introduction

Type 1 diabetes (T1D) is an autoimmune disease characterized by breach in tolerance toward pancreatic islet-producing β cells. β-cell destruction occurs at the stage of immune deviation toward β-cell-specific autoimmunity, which in auto-body-positive or newly diagnosed patients, has not been unmasked, with the goal to bridge the gap between immunological deviation such as endomysial or basal bodies of pancreatic immune with higher doses, however, clearly confirmed the potential of anti-CD3 to modulate T1D (9).

More importantly, the existence of the immune system should be accompanied by compartmentalization toward tolerance for full-spike-tolerant autoantigens (α) and, conversely, when presented at higher doses, could reverse disease when administered before onset of auto-
THE BURDEN OF AUTOIMMUNE DISEASES

A QUICK AUTOIMMUNE DISEASE BREAKDOWN

The National Institutes of Allergy and Infectious Diseases (NIAID) has estimated that:

$100BN Estimated cost of treating autoimmune diseases in the US

50M Estimated number of Americans with an autoimmune disease

AND THAT’S WITHOUT TAKING INTO ACCOUNT TYPE 1 DIABETES!

CHALLENGES & OPPORTUNITIES

Top Challenges to Antigen-Specific Immune Tolerance Therapies

- Identification, validation and targeting of key antigens
- Complex clinical heterogeneity: < 100 autoimmune diseases
- Achieving durable tolerance while ensuring safety and efficacy

Top Opportunities in Antigen-Specific Immune Tolerance Therapies

- Rapid identification and validation of key antigens
- Developing combined therapies to target multiple antigens in complex disease
- Achieving specific tolerization of self-reactive immune cells without altering host immunity
- Reducing development and production costs compared to traditional antibody or immune transplant approaches

Mucosal immune system
(Intestinal, Buccal, Gingival, Sublingual)

- Targeted delivery at mucosal immune system
- Efficacy at lower amounts vs. oral purified protein
- Co-delivery of multiple antigens/allergens
- Co-delivery of antigen/allergen with cytokines
- Reduction of local & systemic response
- Proof of concept demonstrated in autoimmune and allergic models

Oral Immune Tolerance Desensitization

ANTIGEN-SPECIFIC TREGS MIGRATE TO INFLAMED TISSUE

- Pancreas – T1D AG019
- GI-tract - CeD AG017

GI-tract food allergy
Joints - RA
Respiratory tract Asthma/Rhinitis

CNS - MS
Oral L. lactis Secreting Ovalbumin Induces Ovalbumin-Specific Immune Tolerance – Superior efficacy versus purified protein

- Oral Ovalbumin (OVA) secreting L. lactis proved to be very efficient in suppressing OVA-induced DTH
  - Indicate suppression of systemic T cell responses
- Superior efficacy versus oral purified OVA

- Treatment is accompanied by a local and systemic OVA-specific increase in IL-10 production
- Treatment suppresses OVA-specific CD4+ T cell proliferation mediated by T-reg cells
- Induced Treg cells following LL-OVA Treatment can transfer OVA tolerance in vivo

2 Huibregtse et al., Gastroenterology 2007.
ActoBiotics® in Type 1 Diabetes

Case Study
CURRENT TREATMENT

- Exogenous insulin
- Diet and lifestyle modification

Disadvantages

- Lifelong treatment with exogenous insulin required for survival
- Impact on quality of life due to fear of hypoglycemia and day-to-day management

Unmet Need

- No disease-modifying treatment available

ACTOBIOTICS OPPORTUNITY

- Value Proposition
  - First disease-modifying treatment that can prevent, delay or reverse T1D

- Mode of Action
  - Induction of antigen-specific Treg cells will re-establish long-lasting immunological tolerance to islet-antigens aiming to maintain functional β-cell mass
  - Enhance efficacy by combination with broad immunoregulatory agents (e.g. anti-CD3)

GLOBAL MARKET SIZE/EPIDEMIOLOGY

2018 Addressable Population:
> 70,000 newly diagnosed children per year

United States: 36,133
European Union: 40,046
AG019 IN TYPE 1 DIABETES - OPPORTUNITY

89% of new-onset T1D in animals cured by AG019 plus low-dose anti-CD3

- AG019 (LL-[PINS] + IL-10) + anti-CD3 mAb most effective
- 60% of diabetic mice
  - Reverted to normal blood sugar levels
  - Preserved residual β-cell function
  - Halted insulitis progression
  - Treatment induced specific FoxP3+ Treg cells for long-term disease suppression
  - Normoglycemia remained stable for the least 15 weeks post-treatment that was followed

- Treatment effective in 89% of mice treated at the early stage of diabetes
  - Starting glycemia and insulin autoantibody (IAA+) positivity at study entry predicted therapeutic success

Takiishi et al., 2012

Takiishi et al., 2012. Diabetes.

Enrollment criteria predict therapeutic success (89% of mice cured)
PINS-specific FoxP3+ Treg cells accumulate and proliferate in the pancreatic & peripheral lymph nodes.
• **L. lactis** delivering hPINS and hIL-10 – Capsule formulation

• Intended for the treatment of clinical recent-onset TID in patients with residual functional β-cell mass

• High efficacy when combined with low dose systemic anti-CD3
  • Treatment effective in 89% of mice treated at the early stage of diabetes
  • Superior efficacy compared to monotherapy (AG019 or anti-CD3 alone)

• PK, safety pharmacology and Repeat Dose Toxicity (RDT) studies completed

• cGMP production of AG019 DS/DP completed

• IND open; CTA submitted (Belgium)

• **First Patient Dosed in October 2018**

• **Interim End Of Phase Ib/Ila data – Q1 2020**
• **STUDY TITLE:** A prospective, multi-center, Phase Ib/IIa study to assess the safety and tolerability of different doses of AG019 administered alone or in association with teplizumab [anti-CD3] in patients with clinical recent-onset Type 1 Diabetes Mellitus (T1D).

• **INDICATION:** Clinical recent-onset T1D in patients with residual functional β-cell mass.

• **STUDY OBJECTIVES:**
  - The primary objective of this study is to assess the safety and tolerability of different doses of AG019 alone (monotherapy) as well as AG019 in association with teplizumab (co-administration therapy).
  - The secondary objectives of this study are to obtain pharmacodynamic data of AG019 alone as well as AG019 in association with teplizumab; and to determine the potential presence of AG019 in systemic circulation and the presence of *L. lactis* bacteria in fecal excretion (pharmacokinetic profile).

• **STUDY DESIGN:**
  - **The Phase Ib (AG019 monotherapy)** part of the study will enroll 4 sequential AG019 cohorts of 4-6 patients, in ascending dose cohorts and descending age cohorts. All patients in these cohorts will be treated with AG019 in an open label fashion.
  - **The Phase IIa (AG019 combination therapy)** part of the study will evaluate 2 cohorts of patients administered AG019 and teplizumab. The first 2 patients will be treated with double active treatment in an open label fashion. Patients 3-12 will be randomized (4:1) to receive double active treatment or double placebo in a double-blind fashion.

• **STUDY POPULATION:** 8 single dose patients (treatment for 1 day) and up to 48 repeat dose patients (treatment for 8 weeks) aged 12-40 years will be enrolled in up to 25 sites in USA and Belgium.
ActoBiotics® in Gastrointestinal Diseases
STRATEGY BUILT ON RESEARCH FOUNDATION

Active Delivery of Trefoil Factors by Genetically Modified Lactococcus lactis Prevents and Heals Acute Colitis in Mice

KLAAS VANDENBROUCKE,* WOLFGANG HANS,* JACQUES VAN HUYSE,* SABINE NEIRYNCK,*,§
PIETER DEMETTER,* ERIK REMAUT,* PIETER ROTTIERS,* and LOTHAR STEIDLERT,*§

*Department for Molecular Biomedical Research, Flanders Interuniversity Institute for Biotechnology, and Ghent University, Ghent, Belgium;
†Department of Pathology, Ghent University Hospital, Ghent University, Ghent, Belgium; and §Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland

Vandenbroucke et al. Gastroenterology 2004

Orally administered L. lactis secreting an anti-TNF Nanobody demonstrate efficacy in chronic colitis

K Vandenbroucke1,2,3, H de Haard4, E Beirnaert4, T Dreier4, M Lauwereys4, L Huyck1,2, J Van Huyse5, P Demetter5, L Steidler3, E Remaut1,2, C Cuvelier5 and P Rottiers1,2,3

Vandenbroucke et al. Mucosal Immunol. 2010

TREATMENT OF MURINE COLITIS BY LACTOCOCCUS LACTIS SECRETING INTERLEUKIN-10

The cytokine interleukin-10 (IL-10) has shown promise in clinical trials for treatment of inflammatory bowel disease (IBD). Using two mouse models, we show that the therapeutic dose of IL-10 can be reduced by localized delivery of a bacterium genetically engineered to secrete the cytokine. Intragastric administration of IL-10-secreting Lactococcus lactis caused a 50% reduction in colitis in mice treated with dextran sulfate sodium and prevented the onset of colitis in IL-10−/− mice. This approach may lead to better methods for cost-effective and long-term management of IBD in humans.

Steidler et al. Science 2000

Vandenbroucke et al. Gastroenterology 2004

MUCOSAL IMMUNOLOGICAL RESPONSES TO LACTOCOCCUS LACTIS STRAINS

Vandenbroucke et al. Mucosal Immunol. 2010
COMBINATION THERAPY TO TARGET MULTIPLE MUCOSAL DISEASE PATHWAYS

Oro-Gastrointestinal mucosal receptors
• Oral capsules offer better patient compliance
• Targeted delivery to mucosal tissues without systemic exposure
• Efficacy through localized release at the (inflamed) intestinal mucosa
• No evidence of problems demonstrated with systemic therapy
• No known immunogenicity
• POC demonstrated superior efficacy in experimental IBD models
• Can deliver combinations of bioactive proteins

Mucosal Immunotherapy

Oral cavity - OM AG013

GI-tract - IBD AG020

Liver - Metabolic/inflammatory diseases

OPPORTUNITIES IN GASTROINTESTINAL DISEASES WITH ORAL ACTOBIOTICS
Outcome of PK studies with oral *L. lactis* in mice with chronic colitis\(^3\) - **Targeted delivery to mucosa**

*L. lactis* locates to the inflamed gut tissue as seen in confocal and electron microscopic analysis.

Immunohistochemistry analysis demonstrated active delivery of anti-TNF antibodies at the intestinal mucosa.

\(^3\) Waeytens et al., 2007. *Infl Bowel Dis.*; Vandebroucke et al., 2010. *Mucosal Immunol.*
EFFECT OF ACTOBIOTICS TREATMENT ON COLITIS IN MOUSE MODEL

Oral *L. lactis* secreting IL-10 (LLmIL10) significantly reduces colitis - **Targeted delivery to mucosa**

Treatment daily for 2 or 4 weeks efficiently:

- (A) Cured colitis in chronic DSS model
- (B) Prevented onset of colitis in IL-10−/− mice
- With ActoBiotics LLmIL10, a 10,000-fold lower dose was as effective as injected mL10
- Demonstrates local delivery of therapeutic agents at disease site

LLmIL10 = *L. lactis* secreting mL10
Bars represent the mean ± SEM. *P < 0.025; **P = 0.0151

Oral L. lactis Secreting anti-TNF Demonstrate Efficacy in Chronic Colitis\textsuperscript{5}

- Assessment of oral L. lactis anti-TNF and purified anti-TNF (oral and systemic) for efficacy in established chronic enterocolitis
- Proof of concept demonstrated in mouse colitis models with oral ActoBiotics:
  - Superior efficacy versus purified anti-TNF (oral and systemic): ActoBiotics represents a nearly ~50% decrease in intestinal inflammation versus ~25% and ~5% with oral and systemic purified anti-TNF, respectively
  - No immunogenicity issues in contrast with systemic purified anti-TNF
  - Activity restricted to intestine - No interference with systemic bacterial infections

\textsuperscript{5} Vandebroucke et al., Mucosal Immunol. 2010
ActoBiotics® in Inflammatory Bowel Disease

Case Study
DISEASE SNAPSHOT

- **Risk Factors:**
  - Complex interactions between genetics, environment and gut microbiota

- **Symptoms:**
  - Vary depending on the location and severity of inflammation, but may include diarrhea, bleeding ulcers, abdominal pain, weight loss, anemia and extra-intestinal manifestations

CURRENT TREATMENT PARADIGM

- **Current Treatment Pathway:**
  - Aminosalicylates
  - Corticosteroids
  - Immunomodulators (AZA, 6-MP, anti-TNF, etc.)

- **Disadvantages of Current Treatments:**
  - Systemic administration with risks for infections, cancer, immunogenicity
  - Lack of full remission and loss of response

- **Unmet Need:**
  - Efficacious drugs or drug combinations without side-effects and more convenient administration

GLOBAL MARKET SIZE/EPIDEMIOLOGY

2019 Addressable Population:

- **US:** 52,000 (UC) / 44,000 (CD)
- **EU:** 94,000 (UC) / 62,000 (CD)
- **Japan:** 8,600 (UC) / 2,800 (CD)

Target Patient Demographic

1L Mild / Moderate CD
2L Mild / Moderate UC
• ActoBiotics® demonstrated therapeutic efficacy in animal models of IBD.
  • When orally delivered by ActoBiotics, the anti-inflammatory cytokine IL-10, mucosal healing trefoil factors (TFF) 1, 2 and 3, and antibodies against TNFα, each individually showed an initial level of reduction of inflammation in mice models of disease.

• ActoBiotics® have also been demonstrated to be safe and tolerated in human Phase 1 clinical trials.

• Seek to improve upon these positive results by combining multiple treatments in a single dosage, targeting established as new disease pathways identified by recent research. Development strategy based on:
  • Oral therapy
  • High efficacy through topical delivery
  • Novel mechanisms/combination approaches to improve efficacy
  • Superior efficacy/safety to systemic biologicals
  • Favorable safety/cost profile allows for sustained treatment over years vs. days/weeks

• Test this multiple effector approach in validated animal disease models and then enter human clinical trials.
ACTOBIONICS®, MICROBE-BASED BIOPHARMACEUTICALS for expression and local delivery of therapeutics at disease sites including the intestine, the mouth and the nasopharynx

A unique delivery platform precisely tailored for specific disease modification

Specifically designed to target disease areas with high unmet need

Rapid development of new candidates

Targeted delivery via oral capsule, oral rinse or topical solution

Demonstrated safety and tolerability

Robust and scalable manufacturing process

Feel free to contact us for more information:
communications@actobio.com

Our factsheet can be downloaded in the investors section on actobio.com
KEY PUBLICATIONS

Clinical

Preclinical

Platform