ACTELION LTD
DELIVERING ON OUR STRATEGY

Company Presentation
February 2017
The following information contains certain “forward-looking statements”, relating to the company’s business, which can be identified by the use of forward-looking terminology such as “estimates”, “believes”, “expects”, “may”, “are expected to”, “will”, “will continue”, “should”, “would be”, “seeks”, “pending” or “anticipates” or similar expressions, or by discussions of strategy, plans or intentions. Such statements include descriptions of the company’s investment and research and development programs and anticipated expenditures in connection therewith, descriptions of new products expected to be introduced by the company and anticipated customer demand for such products and products in the company’s existing portfolio. Such statements reflect the current views of the company with respect to future events and are subject to certain risks, uncertainties and assumptions. Many factors could cause the actual results, performance or achievements of the company to be materially different from any future results, performances or achievements that may be expressed or implied by such forward-looking statements. Should one or more of these risks or uncertainties materialize, or should underlying assumptions prove incorrect, actual results may vary materially from those described herein as anticipated, believed, estimated or expected.
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ACTELION
AT A GLANCE
ACTELION PHARMACEUTICALS LTD

ACTELION IS A FULLY INTEGRATED BIOPHARMACEUTICAL COMPANY WITH INNOVATION AT ITS CORE

Leader in the science and medicine of pulmonary arterial hypertension (PAH)

ACTELION CENTER, ALLSCHWIL

Founded in 1997 in Allschwil, Switzerland

Total employees (December ‘16)
- Drug Discovery: 388
- Clinical Development: 452
- Marketing & Sales: 1,443
- Support Functions: 341

Global reach with more than 30 affiliates worldwide

7 Products on the Market:
- Opsumit®, Tracleer®, Uptravi®, Veletri®, Ventavis®, Valchlor®, Zavesca®

2016 Sales: CHF 2,412 Billion
Core earnings: CHF 992 million

Over 70'000 Patients currently treated with an Actelion medication

Extensive Research & Development portfolio
ACTELION TODAY
ACTELION TODAY

A UNIQUE COMPANY

1. Based on innovation
2. Fully integrated and global
3. Highly profitable
4. Comprehensive infrastructure
5. Unencumbered assets
ACTELION TODAY

A UNIQUE COMPANY

1. Based on innovation
   - Searching only for innovative products

2. Fully integrated and global
   - In-house research infrastructure from discovery to clinical development

3. Highly profitable
   - With a broad pipeline of interesting projects on novel targets

4. Comprehensive infrastructure

5. Unencumbered assets
ACTELION TODAY

A UNIQUE COMPANY

1. Based on innovation
2. Fully integrated and global
3. Highly profitable
4. Comprehensive infrastructure
5. Unencumbered assets

FULLY INTEGRATED AND GLOBAL

From Research to Commercialization
More than 30 operative affiliates worldwide
Product availability in >60 markets

Commercial Operations
R&D Centers
ACTELION TODAY
A UNIQUE COMPANY

1. Based on innovation
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CORE EARNINGS

Company presentation
ACTELION TODAY

A UNIQUE COMPANY

1. Based on innovation
2. Fully integrated and global
3. Highly profitable
4. Comprehensive infrastructure
5. Unencumbered assets

- Swiss company
- One discovery center in Switzerland
- Full global development capabilities
- Fully established infrastructure from process to buildings
- Focus on quality
ACTELION TODAY

A UNIQUE COMPANY

1. Based on innovation
2. Fully integrated and global
3. Highly profitable
4. Comprehensive infrastructure
5. Unencumbered assets

▶ Full rights to all products*
▶ Strong balance sheet and financing capacity
▶ No major alliances for own products

*Cooperation with Nippon Shinyaku in Japan for macitentan and selexipag
STRATEGY FOR VALUE CREATION

- SUSTAIN AND GROW THE PAH FRANCHISE
- BUILD ADDITIONAL SPECIALTY FRANCHISES
- OPTIMIZE PROFITABILITY
FOUR GOALS FOR ACTELION

Drive innovation forward
Pursue top quality science, internally and externally, balanced with medical need and commercial potential

Maximize the value of innovation
Develop projects ourselves and seek partners or out-license when necessary to maximize value

Leverage our global presence
Expand innovative commercial capabilities to new customers and regions. Manage alliances putting the product first

Insist on the highest quality in all we do
Quality is crucial and needs to be ingrained across all functions
Excellent performance across all areas of business

- **Products:** Strong sales of Opsumit & Uptravi
- **Innovation:** Significant pipeline progression
- **Value creation:** Actelion to be acquired by Johnson & Johnson for $30 billion with spin-out of new R&D company, listed on Swiss stock exchange
STRATEGY FOR VALUE CREATION

SUSTAIN AND GROW THE PAH FRANCHISE

BUILD ADDITIONAL SPECIALTY FRANCHISES

OPTIMIZE PROFITABILITY
Pulmonary arterial hypertension is a disease of the blood vessels carrying blood from the heart to the lungs - the pulmonary arteries.

When PAH develops, blood circulating through these vessels becomes restricted, and the right side of the heart is put under increasing strain to pump blood through the lungs.

Normal artery

Artery showing vasoconstriction

Diseased artery showing tissue thickening and fibrosis.
## CLINICAL SEVERITY OF PAH

### CLASSIFIED BY WORLD HEALTH ORGANIZATION (WHO)

This system grades PAH severity according to the functional status of the patient.

<table>
<thead>
<tr>
<th>FUNCTIONAL CLASS</th>
<th>SYMPTOMATIC PROFILE</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause dyspnoea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>II</td>
<td>Patients with pulmonary hypertension resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>III</td>
<td>Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain, or near syncope.</td>
</tr>
<tr>
<td>IV</td>
<td>Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.</td>
</tr>
</tbody>
</table>
P.A.H

TREATMENT PATHWAYS

ENDOTHELIN RECEPTOR ANTAGONISTS (ERA)

PHOSPHODIESTERASE-5-INHIBITORS (PDE-5i)

PROSTACYCLIN RECEPTOR AGONISTS

IP RECEPTOR AGONIST

PGI2 ANALOGUES
SIGNIFICANT PROGRESS IN THE FIELD OF PAH

PAH targeted therapies

1990

1st PGI2

IMPROVEMENT IN SYMPTOMS, MEASURED BY 6MWD

2000

1st Oral ERA 1st Oral PDE-5i

DISEASE WORSENING, MEASURED BY TIME TO CLINICAL WORSENING

2010

Multiple approved therapies in 2010

DISEASE PROGRESSION OVER YEARS, MEASURED BY MORBIDITY/MORTALITY

INCREASING DISEASE AWARENESS

REFERENCE CENTERS

PATIENT ASSOCIATIONS

CONTROLLED CLINICAL TRIALS

PRECLINICAL/Clinical Research

NATIONAL NETWORKS

DISEASE REGISTRIES

EVIDENCE-BASED GUIDELINES

SCREENING HIGH-RISK GROUPS

1990 2000 2010

DISEASE WORSENING, MEASURED BY TIME TO CLINICAL WORSENING

IMPROVEMENT IN SYMPTOMS, MEASURED BY 6MWD

DISEASE PROGRESSION OVER YEARS, MEASURED BY MORBIDITY/MORTALITY

INCREASING DISEASE AWARENESS

REFERENCE CENTERS

PATIENT ASSOCIATIONS

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PRECLINICAL/Clinical Research

NATIONAL NETWORKS

DISEASE REGISTRIES

EVIDENCE-BASED GUIDELINES

SCREENING HIGH-RISK GROUPS

ERA: endothelin receptor antagonist
PDE-5i: phosphodiesterase-5 inhibitor
PGI2: prostacyclin

PROCEEDINGS FROM 3RD WORLD CONGRESS 2003

ESC 2004 GUIDELINES

PROCEEDINGS FROM 4TH WORLD CONGRESS 2008

ESC/ERS 2009 GUIDELINES
## ORAL THERAPIES IN PAH

### RANDOMIZED CONTROLLED TRIALS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Study</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>No. of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosentan</td>
<td>Study-351,2</td>
<td>12 weeks</td>
<td>6-MWD</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>BREATHE-1</td>
<td>16 weeks</td>
<td>6-MWD</td>
<td>213</td>
</tr>
<tr>
<td></td>
<td>EARLY</td>
<td>24 weeks</td>
<td>PVR, 6-MWD</td>
<td>185</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>SUPER-1</td>
<td>12 weeks</td>
<td>6-MWD</td>
<td>277</td>
</tr>
<tr>
<td>Tadalafil</td>
<td>PHIRST</td>
<td>16 weeks</td>
<td>6-MWD</td>
<td>405</td>
</tr>
<tr>
<td>Ambrisentan</td>
<td>ARIES-1,8</td>
<td>12 weeks</td>
<td>6-MWD</td>
<td>202</td>
</tr>
<tr>
<td></td>
<td>ARIES-2</td>
<td>12 weeks</td>
<td>6-MWD</td>
<td>192</td>
</tr>
<tr>
<td></td>
<td>AMBITION</td>
<td>78.6 weeks</td>
<td>Clinical failure</td>
<td>610</td>
</tr>
<tr>
<td>Macitentan</td>
<td>SERAPHIN</td>
<td>103.9 weeks</td>
<td>Morbidity/Mortality</td>
<td>742</td>
</tr>
<tr>
<td>Selexipag</td>
<td>GRIPHON</td>
<td>76.4 weeks</td>
<td>Morbidity/Mortality</td>
<td>1,156</td>
</tr>
</tbody>
</table>

A wealth of data concerning PAH management has emerged in recent years
- Not only from RCTs, but also clinical practice, including disease registries
- This has led to published management guidelines\(^1\), updated recommendations\(^2\), and approval of multiple therapies

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ACTELION’S PAH PORTFOLIO
ACTELION’S PRODUCT PORTFOLIO

- Endothelin pathway
- Nitric Oxide pathway
- Prostacyclin pathway
TRANSFORMING OUR PAH PORTFOLIO

MOVING TO OUTCOME-BASED THERAPY
UNIQUELY POSITIONED TO BUILD & SERVE PAH

COVERING CONTINUUM OF CARE WITH OUTCOME-BASED MEDICINES

FC II  FC III  FC IV

+/- PDE-5 inhibitor

Opsumit® macitentan

Uptravi® selexipag tablets

VELETRI® epoprostenol for injection
TRACLEER: OUR FIRST SUCCESS
Tracleer (bosentan) is an orally available endothelin receptor antagonist (ERA) approved for the treatment of PAH in over 60 countries, including the United States in November 2001, the European Union in May 2002 and Japan in April 2005.
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TRANSITIONING TO OPSUMIT

- Dynamics driven by Opsumit impact, generic erosion in selected markets and DU growth (esp. Japan)

- Generic Update: Spain: strong generic competition, 2016 sales: - 83%
ENGINE OF TRANSFORMATION
Opsumit (macitentan) is an orally available endothelin receptor antagonist (ERA) approved for the treatment of PAH in over 45 countries, including the United States in October 2013, the European Union in December 2013 and Japan in March 2015.
The effect of macitentan to reduce combined morbidity/mortality events
- a multi-center, event driven long-term, placebo controlled study
- average duration of exposure approximately 2 years,
- in 742 patients
- with symptomatic PAH
- WHO functional class (FC) II-III
- who were randomized to placebo (n=250), 3mg macitentan (n=250),
  or 10mg macitentan (n=242) once daily
- Patients were treated with Opsumit® monotherapy or in combination with
  phosphodiesterase-5 inhibitors or inhaled prostanoids
SUSTAINED SALES GROWTH DYNAMICS

CHF million


5 15 38 59 68 95 113 147 162 178 200 218 235
OPENING THE PROSTACYCLIN PATHWAY TO MANY MORE PATIENTS
Uptravi® (selexipag) is an orally available, selective IP prostacyclin receptor agonist, targeting and activating the prostacyclin pathway.
OPENING THE PROSTACYCLIN PATHWAY TO MANY MORE PATIENTS

CHF million

Q1 2016 | Q2 2016 | Q3 2016 | Q4 2016
---|---|---|---
35 | 56 | 70 | 85
Selexipag for the Treatment of Pulmonary Arterial Hypertension

Olivier Sitbon, M.D., Richard Channick, M.D., Kelly M. Chin, M.D., Aline Frey, Pharm.D., Sean Gaine, M.D., Nazzareno Galiè, M.D., Hossein-Ardeschir Ghofrani, M.D., Marius M. Hoeper, M.D., Irene M. Lang, M.D., Ralph Preiss, M.D., Lewis J. Rubin, M.D., Lilla Di Scala, Ph.D., Victor Tapson, M.D., Igor Adzerikho, M.D., Jinming Liu, M.D., Olga Moiseeva, M.D., Xiaofeng Zeng, M.D., Gérald Simonneau, M.D., and Vallerie V. McLaughlin, M.D., for the GRIPHON Investigators*
UPTRAVI is indicated for the treatment of pulmonary arterial hypertension (PAH, WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH.

Adverse reactions occurring more frequently (>5%) on UPTRAVI compared to placebo are headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, and flushing.

Source: US Prescribing Information, December 2015
**LAUNCH PRIORITIES**

1. Establish as prostacyclin therapy of 1st choice
2. Expand prostacyclin therapy patients base
3. Expand prostacyclin therapy prescriber base

- **1** Establish as prostacyclin therapy of 1st choice
- **2** Expand prostacyclin therapy patients base
- **3** Expand prostacyclin therapy prescriber base

- **1** Establish as prostacyclin therapy of 1st choice
- **2** Expand prostacyclin therapy patients base
- **3** Expand prostacyclin therapy prescriber base
EXPANDING THE CLINICAL UTILITY OF UPTRAVID

MANAGING THE LIFE CYCLE

- TRANSIT study assesses tolerability and safety of the transition from inhaled treprostinil to oral selexipag in adult patients with PAH

- TRITON study compares efficacy and safety of initial triple oral treatment regimen of macitentan together with tadalafil and selexipag versus initial dual oral treatment regimen in newly diagnosed, treatment-naïve patients with PAH

- Intravenous (i.v.) formulation of selexipag is being developed for the treatment of patients with PAH who are prescribed oral selexipag and who are temporarily unable to take oral medication.

- Working closely with health authorities, Actelion is in the process of developing a strategy for investigating the use of Uptravi in children with PAH
I.V. THERAPY MADE A LITTLE EASIER
Veletri (Epoprostenol for Injection) is intravenous prostacyclin. Unlike other epoprostenol formulations approved for PAH, Veletri is stable at room temperature (77 F, 25 C) for up to 48 hours when administered immediately upon reconstitution and dilution, making the use of frozen gel packs unnecessary. Approved in 17 countries including the United States since 2010 and some European markets since 2013.
CONTINUED SIGNIFICANT GROWTH

Growth continues due to:

- Strong performances led by France and well enhanced by Spain, Italy and UK
- Japan* +2% despite a 12% price cut on 1 March 2016

*Trade name Epoprostenol "ACT"
SUSTAINING OUR BUSINESS
Ventavis (inhaled iloprost) is an inhaled formulation of iloprost, a synthetic compound that is structurally similar to prostacyclin (PGI2), a naturally occurring molecule that causes blood vessels to dilate, limits cellular hypertrophy, and inhibits platelet aggregation.
EXPANDING THE CLINICAL UTILITY OF MACITENTAN
OBJECTIVES OF MACITENTAN CLINICAL PROGRAM

- Better characterize macitentan in specific PAH patient population
- Extend use beyond PAH in other forms of Pulmonary Hypertension
- Develop for diseases beyond PH
CLINICAL CLASSIFICATION OF PULMONARY HYPERTENSION (PH) – 2015

1. PAH
   1.1 Idiopathic PAH (iPAH)
   1.2 Heritable PAH
   1.3 Drugs and toxin induced
   1.4 Associated with (APAH):
      1.4.1 Connective tissue disease
      1.4.2 HIV infection
      1.4.3 Portal hypertension
      1.4.4 CHD
      1.4.5 Schistosomiasis
      1.4.6 Chronic hemolytic anemia
   1.5 Persistent pulmonary hypertension of the newborn

1’. Pulmonary veno-occlusive disease and/or pulmonary capillary hemangiomatosis

1”. Persistent PH of the newborn (PPHN)

2. PH due to left heart disease

3. PH due to lung disease and/or hypoxemia

4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions

5. PH with unclear and/or multifactorial mechanisms
   5.1 Hematological disorders
   5.2 Systemic disorders
   5.3 Metabolic disorders
   5.4 Other

Galiè et al. Eur Heart J 2015
MANAGING THE LIFE CYCLE

- TOMORROW (Pediatric PAH)
- PORTICO (Portopulmonary Hypertension)
- OPUS (US observational, drug registry of Opsumit new users in clinical practice)
- SYMPHONY & ORCHESTRA (psychometric validation of QoL questionnaire – USA and FR, IT, ES respectively)
- REPAIR (Right Ventricular Stroke Volume)
- SOPRANO (PH after left ventricular assist device implantation)
- MERIT (CTEPH - Chronic Thromboembolic Pulmonary Hypertension)
- RUBATO (Fontan-palliated patients)
SIGNIFICANT MEDICAL NEED IN PEDIATRIC PAH

- No globally approved treatment for PAH in children
- Pediatric PAH physicians have to mostly rely on research data collected in adults when weighing up treatment options
- Pediatric studies must be conducted with minimal burden on the patient
  - Clinical studies in children are associated with specific requirements
    - Study endpoints must be meaningful for children
    - Study assessments must be suitable and safe for children
    - A child's growth and development can be affected by a drug
    - A child, if considered developmentally capable, must be involved in the decision to participate
    - Appropriate formulation to ensure accurate dosing and drug compliance
LABEL-ENABLING CHARACTERIZATION: TOMORROW

STUDY OVERVIEW

- TOMORROW: long-term benefits of macitentan in children with PAH
- Wide age range as well as the use of safe, non-invasive measurements
- Dose determination phase with staggered patient recruitment by age category
- Dispersible tablet pediatric formulation in multiple strengths
- Global program received endorsement from the US FDA and in Europe’s EMA
PORTOPULMONARY HYPERTENSION

- Portopulmonary hypertension is PAH that is associated to liver disease, often cirrhosis, and portal hypertension

- Moderate to severe PAH is a contraindication for transplant – and often only diagnosed via pre-liver transplant assessment

- No approved treatment to reduce pulmonary arterial pressure and allow transplant

- Compelling data supports the use of PAH-specific therapies in portopulmonary hypertension with the aim of improving pulmonary hemodynamics
The observed safety profile of macitentan, particularly in respect of its effect on the liver makes it ideal to be used in this patient population.

Placebo controlled study to evaluate the efficacy and safety of macitentan for the treatment of patients with portopulmonary hypertension.

Primary outcome measure is the relative change from baseline to Week 12 in pulmonary vascular resistance (PVR).
POST-LAUNCH CHARACTERIZATION

OVERVIEW

- SYMPHONY & ORCHESTRA: Psychometric validation of PAH-SYMPACT (new patient-reported outcome instrument for PAH), with the objective to demonstrate the psychometric characteristics of reliability and construct validity of the method.

- OPUS (Opsumit Users Registry®): Characterizes the safety profile of macitentan and describes clinical characteristics and outcomes of patients newly treated with macitentan in the real-world post-marketing setting.

- REPAIR: Evaluates effect of macitentan on Right Ventricular Stroke Volume assessed by magnetic resonance imaging (MRI) and on PVR assessed with right heart catheterization (RHC) in patients with symptomatic PAH.

- SOPRANO: Assesses efficacy and safety of macitentan in patients with pulmonary hypertension after Left Ventricular Assist Device Implantation.
Patients with chronic obstructions of the lung arteries

Pulmonary thromboendarterectomy (PTE) is the gold standard in operable patients – potentially curative. Many patients are considered inoperable though due to distal vasculopathy and/or comorbidities.

MERIT was Phase II prospective, randomized, placebo-controlled, double-blind, multi-center, parallel-group study to assess the efficacy, safety and tolerability of 10 mg macitentan in inoperable CTEPH.

80 patients were randomized in a 1:1 ratio into 2 treatment groups (macitentan 10 mg or placebo) over a 24 week treatment period.

Patients with symptomatic PH in WHO Functional Class III or IV at baseline were allowed to receive PH background therapy throughout the study, including PDE-5 inhibitors or oral/inhaled prostanoids.

Operability was adjudicated by an experienced surgeon or central adjudication committee.
NEW INDICATIONS: MERIT

STUDY RESULTS

- Significant 16% reduction in PVR at 16 weeks with macitentan compared with placebo (95% CL: −30%, −1%; p=0.04, ITT)

- Significant positive effect of macitentan compared to placebo on exercise capacity – 6-MWD least-squares mean difference at Week 24 was 34.0 meters between macitentan and placebo (95% CL: 2.9, 65.2 m; p=0.03, ITT)

- Observed efficacy was consistent across all sub-groups, inc. patients receiving background PH specific therapy at baseline (61%), inc. PDE-5 inhibitors (59%)

- Macitentan was well tolerated in this patient population, most frequently reported AE’s that occurred with higher frequency on macitentan vs. placebo were peripheral edema (22.5% vs. 10.0%) and events related to anemia (17.5% vs. 2.5%)

- Actelion will now fully analyze the data and discuss the findings with health authorities
NEW INDICATIONS: RUBATO

FONTAN-PALLIATED PATIENTS

- "Fontan" is a surgical procedure in children born with complex congenital heart defects, enabling a single ventricle to support blood circulation to the body and the lung
- This is a life-saving procedure; patients who survive are relatively stable through childhood
- Decline in exercise capacity accelerates at adolescence with risk of poor long-term outcome
- An estimated 1’200 Fontan procedures performed annually in the US – with between 17’000 and 24’000 Fontan-palliated patients currently living worldwide
NEW INDICATIONS: RUBATO

STUDY OVERVIEW

- Assess the efficacy and safety of macitentan in stable Fontan-palliated adolescents and adults
- Primary objective to assess the effect of macitentan on exercise capacity through peak VO$_2$
- Secondary objectives to evaluate:
  - effect of macitentan on N-terminal prohormone of brain natriuretic peptide (NT-proBNP)
  - safety and tolerability of macitentan in this patient population
STRATEGY FOR VALUE CREATION

- Sustain and grow the PAH franchise
- Build additional specialty franchises
- Optimize profitability
BUILD ADDITIONAL SPECIALTY FRANCHISE

MARKETING BY ACTELION IN THE US ONLY
Valchlor (mechlorethamine) gel 0.016% is applied topically once-a-day and dries on the skin. Valchlor is the only US FDA approved topical formulation of mechlorethamine, a chemotherapeutic agent for the treatment of early stage mycosis fungoides, a type of Cutaneous T-Cell Lymphoma. Launched in the US in November 2013.
Mycosis fungoides is the most common type of Cutaneous T-Cell Lymphoma (CTCL), a rare form of non-Hodgkin's lymphoma.

The cause of mycosis fungoides remains unknown and there is no known cure.

Unlike most non-Hodgkin's lymphomas, mycosis fungoides is caused by a mutation of T-cells. The malignant T-cells in the body initially migrate to the skin, causing various lesions to appear.

These lesions typically begin as what appears to be a rash and may progress to form plaques and disfiguring tumors.
BUILD ADDITIONAL SPECIALTY FRANCHISE
Miglustat, the active ingredient of Zavesca, is an orally available molecule with a large volume of distribution.

Zavesca is approved for the treatment of Niemann-Pick type C disease in 46 countries, including the European Union since 2009 and Japan since 2012.

Zavesca is approved for the treatment of mild to moderate type 1 Gaucher disease in 47 countries, including the US and the European Union since 2003.
NIEMANN-PICK TYPE C DISEASE (NP-C)

A RARE AND DIFFICULT TO DIAGNOSE GENETIC LYSOSOMAL STORAGE DISORDER

- Devastating neurological genetic disorder which is ultimately fatal
- Onset from early childhood until adult age
- Pathophysiology
  - Abnormal intracellular lipid transport
  - Cytotoxic accumulation of glycosphingolipids in neurons
- Symptoms become progressively more severe and include:
  - Severe disabilities in swallowing, ambulation, eye movements, language, cognition, muscle control
  - Lipid accumulation can also lead to an enlarged liver and/or spleen.
TYPE 1 GAUCHER DISEASE (GD1)

A RARE GLYCOSPHINGOLIPID DISORDER

- An inherited metabolic lysosomal storage disorder
- Characterized by an accumulation of lysosphingolipids
- The accumulation leads to multiple clinical manifestations:
  - an enlarged spleen and liver
  - anemia and a low platelet count
  - bone pain and bone deterioration
- Symptoms can appear at any age
BUILD ADDITIONAL SPECIALTY FRANCHISE

CADAZOLID

CLOSTRIDIUM DIFFICILE-ASSOCIATED DIARRHEA
International, Multi-center Program Assessing Cadazolid Treatment in patients suffering from *Clostridium difficile* associated diarrhea (CDAD)

Cadazolid is an investigational drug in development and not approved or marketed in any country.
Investigated for the treatment of Clostridium difficile-associated diarrhea (CDAD)

Clostridium difficile is a spore-forming bacteria that is best known for causing antibiotic-associated diarrhea

Cadazolid:
- Strong inhibitor of Clostridium difficile protein synthesis leading to strong suppression of both toxin and spore formation
- Narrow spectrum – very limited effect on normal gut microflora – potential for selective treatment for Clostridium difficile in the gut = less recurrence
- In vitro tests demonstrate low propensity for resistance development
- Early results indicate it may be safe and well tolerated with negligible absorption
- US FDA designated cadazolid as both a Qualified Infectious Disease Product (QIDP) and a Fast Track development program
CADAZOLID SHOWS MINIMAL EFFECTS ON THE GUT MICROFLORA

QRT-PCR QUANTIFICATION OF BACTERIAL NUMBERS IN STOOL SAMPLES FROM PHASE II (T. LOUIE)

C. difficile

C. leptum

Bifidobacterium

Prevotella

Bacteroidetes

Lactobacillus

CFU/g stool

Cadazolid is an investigational drug in development and not approved or marketed in any country.
PHASE II EFFICACY ENDPOINTS

MODIFIED CURE RATE, RECURRENCE RATE, SUSTAINED CURE (MITT)


Cadazolid is an investigational drug in development and not approved or marketed in any country.
Two identical multi-center, randomized, double-blind studies designed to demonstrate:

- Non-inferior clinical response with cadazolid compared to vancomycin
- Superior sustained clinical response with cadazolid compared to vancomycin
- Efficacy on hypervirulent strains

Cadazolid is investigational, in development and not approved or marketed in any country.
BUILD ADDITIONAL SPECIALTY FRANCHISE

PONESIMOD

Ponesimod is investigational, in development and not approved or marketed in any country.
Short half-life and rapid reversibility (easy 'on-off')
allow:
- restoration of immune system
- management of opportunistic infections
- vaccinations
- pregnancy management
- combination with other immunomodulators

Provides physicians with greater flexibility and better control of patient treatment
STUDY OVERVIEW

- OPTIMUM: A Multicenter, randomized, double-blind, parallel-group, active-controlled, superiority study to compare the efficacy and safety of ponesimod to teriflunomide in subjects with relapsing multiple sclerosis

- Pivotal Phase III study
  - ~200 centers in North America, Latin America, Eastern and Western Europe, Pacific (planned)
  - ~1100 patients randomized in 2 groups in a 1:1 ratio to receive either ponesimod 20 mg or teriflunomide 14 mg
  - New titration scheme implemented

Ponesimod is investigational, in development and not approved or marketed in any country.
STUDY OBJECTIVES

► Primary objective
  – To determine whether ponesimod is more efficacious than teriflunomide in terms of reducing relapses in subjects with relapsing multiple sclerosis

► Secondary objectives
  – To assess the effect of ponesimod on disability progression and on other aspects of multiple sclerosis disease control;
  – To assess the safety and tolerability of ponesimod in subjects with relapsing multiple sclerosis

Ponesimod is investigational, in development and not approved or marketed in any country.
CHOICE OF ACTIVE CONTROL

- Ponesimod compared to Teriflunomide 14 mg
  - Oral comparator facilitates recruitment and blinding
  - Recently approved first-line therapy for relapsing multiple sclerosis
  - Superiority study possible given incomplete effect of teriflunomide on ARR
  - 14 mg but not 7 mg approved in EU and Australia
OPTIMUM study is enriched with additional endpoints aiming at further differentiation:

- PRO, MRI endpoints, disease activity, prospectively included in protocol
- Compliance enhancement and monitoring tool using electronic device

Additional study in multiple sclerosis to further characterize:

- Clinical utility
- Differentiation
- Discussed with Health Authorities
PONESIMOD DIFFERENTIATION

A NEW DIRECTION IN MS TREATMENT?

- Relative reduction of Annual Relapse Rates drives current perception of efficacy of MS therapies
- However, on current therapies – on average – 1 in 5 patients will experience a relapse
- Combination therapy could improve long-term outcome for patients
- Ponesimod – with its rapid reversibility – is ideally suited for use in combination therapy

Ponesimod is investigational, in development and not approved or marketed in any country.
First oral combination therapy (on top of Tecfidera)

Primary objective:

- Determine whether add-on therapy reduces relapse frequency as compared to placebo in patients with active relapsing multiple sclerosis who are treated with Tecfidera.

- The primary endpoint is the Annualized Relapse Rate (ARR), which is defined as the number of confirmed relapses per patient and year, from randomization up to the end of the study.
Prospective, multicenter, randomized, double-blind, parallel group, add-on, placebo-controlled, superiority study with ponesimod in patients with RMS.

- ~600 patients receiving dimethyl fumarate twice daily for at least 6 months
- randomized in a 1:1 ratio to ponesimod 20 mg or placebo.
- Treatment given until last patient enrolled treated for 60 weeks, expected average treatment duration of 2 years, maximum duration 3 years

Ponesimod is investigational, in development and not approved or marketed in any country.
PHASE II STUDY
IN SYSTEMIC LUPUS
ERYTHEMATOSUS

CENERIMOD

An investigational compound, in development and not approved or marketed in any country.
KEY PROPERTIES

- Very potent S1P₁ receptor modulator with highly selective profile
- Prevents lymphocytes from leaving lymph nodes
- Lymphocyte reduction is rapid, dose-dependent and reversible
- Pharmacokinetic profile suitable for once-daily oral dosing with no need for up-titration regimen
- Potential in multiple autoimmune diseases
**WHY S1P\textsubscript{1} MODULATOR FOR SYSTEMIC LUPUS ERYTHEMATOSUS?**

**UNMET MEDICAL NEED & SCIENTIFIC RATIONALE**

- **Unmet need:**
  - Severe organ damage and significant mortality in subset of patients
  - Impaired physical and mental QoL
  - Therapy is largely empirical with use of corticosteroids and other immunosuppressants
  - Only one biologic with limited efficacy gained approval

- **Scientific rationale for S1P\textsubscript{1} receptor modulation in SLE:**
  - T and B cells play a key role in pathogenesis
  - S1P\textsubscript{1} receptor modulators have shown efficacy in different preclinical models of SLE: MRL/lpr and BXSB mice

Cenerimod is investigational, in development and not approved or marketed in any country.
**CENERIMOD IN SYSTEMIC LUPUS ERYTHEMATOSUS**

**PHASE II DOSE-ESCALATION STUDY DESIGN**

- Prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, dose-response study to investigate the biologic activity, pharmacokinetics, safety, & tolerability of cenerimod in adult subjects with systemic lupus erythematosus

- ~ 64 subjects enrolled to receive either 0.5, 1, 2 or 4 mg over the course of 12 weeks

- ~ 20 sites and expected to last approximately 20 months

Cenerimod is investigational, in development and not approved or marketed in any country.
BUILD ADDITIONAL SPECIALTY FRANCHISE

CLAZOSENTAN

CEREBRAL VASOSPASM POST-ANEURISMAL SUBARACHNOID HEMORRHAGE (aSAH)

Clazosentan is investigational, in development and not approved or marketed in any country.
Highly soluble ETA selective ERA ideal for intravenous administration

>1’500 patients treated with clazosentan providing significant experience in vasospasm post aSAH and a well documented safety profile

CONSCIOUS-2  aneurysm secured by clipping  
Lancet Neurology 2011;10(7):618-625

CONSCIOUS-3  aneurysm secured by coiling  

Clazosentan is an investigational drug in development and not approved or marketed in any country.
CONSCIOUS-3 STUDY - EVENT RATE FOR THE COMPONENTS OF THE 1° COMPOSITE ENDPOINT

Clazosentan is an investigational drug in development and not approved or marketed in any country.

DIND = Delayed ischemic neurological deficits; Macdonald R et al. Stroke 2012.
ADAPTED STRATEGY: REVERSAL VS. PREVENTION

- Phase III study under discussion with HA’s
- Primary objective to determine whether clazosentan is an efficacious treatment of cerebral vasospasm
- **Open question:** How early is the effect of clazosentan on reversing vasospasm?
- **REVERSE:** Phase II study to evaluate whether clazosentan has an early effect in reversing angiographically-confirmed cerebral vasospasm in approximately 25 subjects

Clazosentan is an investigational drug in development and not approved or marketed in any country.
BUILD ADDITIONAL SPECIALTY FRANCHISE

DUAL OREXIN RECEPTOR ANTAGONIST

Insomnia

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country.
RAT EEG DATA: SLEEP EFFICACY / ARCHITECTURE

Time spent in sleep and wake stages (% of total time) over the first 6h of the active phase following administration

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country.
PHASE I PROGRAM

- Single-ascending dose study in healthy young male adults
  - Doses evaluated from 5 mg to 200 mg
- 3-part study in male and female young adults and elderly
  - Multiple-ascending dose in adults
  - Single-ascending dose in elderly
  - Multiple night-time dosing in adult and elderly

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country.
IDEAL PHARMACOKINETIC PROFILE FOR AN INSOMNIA MEDICATION

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country.
PHARMACODYNAMIC PROFILE: FAST ONSET OF ACTION IN ADULT & ELDERLY

Adult Healthy Volunteer – Daytime dosing
Elderly Healthy Volunteer – Daytime dosing

Reduced speed of eye movements

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country
PHARMACODYNAMIC PROFILE: APPROPRIATE DURATION OF ACTION IN ADULT & ELDERLY

Reduced tracking performance

Person performing adaptive tracking test

Adult Healthy Volunteer – Daytime dosing
Elderly Healthy Volunteer – Daytime dosing

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country.
NEXT-DAY PHARMACODYNAMIC PROFILE
NO SLEEPINESS REPORTED ON NEXT MORNING

Karolinska Sleepiness Scale Score

Healthy adult with night-time administration

1= very alert,  3=alert, normal level,  5=neither alert nor sleepy,  7=sleepy, but no effort keeping awake,  9=very sleepy

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country
INITIAL SAFETY PROFILE FROM PHASE I PROGRAM

- No SAEs, no unexpected AEs after 110 healthy adults and elderly exposed
- Starting at 25 mg, transient AEs of mild to moderate intensity were observed such as: Disturbance of attention, somnolence, fatigue, headache and dizziness
- No significant effect on vital signs, ECG, and laboratory parameters

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country
PHASE II PROGRAM OVERVIEW

- Two studies in adult and elderly patients to evaluate the effect of Actelion’s DORA versus placebo
- Assessing sleep maintenance, sleep initiation, next day residual effect and next day performance
- Study 1: ~300 adult insomnia patients – treatment duration 4 weeks
- Study 2: ~50 elderly insomnia patients
- Adult study will also include an active-reference arm with zolpidem
ACTELION’S NEW DORA SUMMARY

- Actelion has significant expertise in the discovery and development of DORAs.
- DORAs have the potential to promote sleep and maintain a natural sleep architecture.
- PK/PD profile of Actelion’s New DORA suggests an optimal combination of effect on the CNS and low residual concentration next-day for a sleep medication.
- Phase II program will show whether the Phase I data will translate into both adult and elderly insomnia patients.
- Phase II program will provide all data required to design a differentiated Phase III program.

Actelion’s New DORA is an investigational drug in development and not approved or marketed in any country.
ACTELION’S NEW DUAL ERA IN RESISTANT HYPERTENSION

ACT-132577
Resistant hypertension is defined by uncontrolled hypertension despite three antihypertensive drug therapies from different classes at optimal doses including a diuretic.

- Represents a small sub-set of hypertensive population
- High cardiovascular risk factor in comparison to non-resistant hypertension
- Endothelin has not been targeted in systemic hypertension despite evidence supporting ERAs as a therapeutic strategy
- Renal denervation studies continue despite initial failure, exemplifying medical need in resistant hypertension
- Results of the NIH-sponsored SPRINT study show that even more hypertensive patients than thought are not well controlled
ACT-132577 IN RESISTANT HYPERTENSION

ACT-132577 PROFILE

- Dual $\text{ET}_A$ and $\text{ET}_B$ receptor antagonist
- Potential for an oral, potent, once-a-day drug with long-lasting effect on blood pressure
- Active metabolite of macitentan
- Evaluated in a Phase II dose-finding study to explore the effects ACT-132577 – at different dose strengths – on the efficacy, safety and tolerability in patients with essential hypertension
- Patients are randomized to 6 groups in a 1:1:1:1:1:1 ratio: placebo; dose 1, dose 2, dose 3, dose 4 of Actelion's ERA; and lisinopril 20 mg
- Clinical development pathway in resistant hypertension aligned with FDA
EXTENSIVE RESEARCH & DEVELOPMENT
A CHAIN OF EXPERTISE

388 PROFESSIONALS (DECEMBER 2016)

- Molecular Biologists
- Cell Biologists
- Pharmacologists
- Toxicologists
- Pharmacokineticists
- Formulation Specialists
- Clinical Scientists
- Structural Biologists
- Medicinal Chemists
- Biochemists
- Process Research Chemists

DRUG DISCOVERY ORGANIZATION
ACTELION’S DRUG DISCOVERY STRATEGY

All important research functionalities in-house
(e.g. MedChem, AssayTech, DMPK, Pharmacology)

Highly regulated service activities outsourced
(e.g. Toxicology, Production, Formulation)
CULTURE OF INNOVATION

- Single-center approach
- Fully integrated research informatics
- Focus on small molecules
- Few platforms of expertise
- Multiple therapeutic areas
- High medical input
452 PROFESSIONALS (DECEMBER 2016)

- Life Cycle Management
- Clinical Pharmacology
- Global Drug Safety
- Global Drug Regulatory Affairs
- Clinical Science
- Biometry
- Global Clinical Operations
- Strategic Clinical Development
## EXTENDING THE CORE PAH FRANCHISE

<table>
<thead>
<tr>
<th>Drug</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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### Notes
- I.V. formulation
- Macitentan
- Macitentan & Selexipag
- TRITON
- TOMORROW
- RUBATO
- SERENADE
- MERIT
- Selexipag
- I.V. formulation
# Diversification into New Areas

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<tr>
<th>Product</th>
<th>Indication</th>
<th>Regulatory Filing</th>
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<tbody>
<tr>
<td>Cadazolid</td>
<td>Clostridium difficile assoc. diarrhea</td>
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<tr>
<td>Ponesimod</td>
<td>Multiple Sclerosis</td>
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<tr>
<td>Cenerimod</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Clazosentan</td>
<td>Reversal of vasospasm post-aSAH</td>
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<td>Dual orexin receptor antagonist</td>
<td>Insomnia</td>
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<tr>
<td>Endothelin Receptor Antagonist</td>
<td>Specialty cardiovascular disorders</td>
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<td>Lucerastat</td>
<td>Fabry’s disease</td>
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<td>New Chemical Entity</td>
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<td>Selective orexin 1 receptor antagonist</td>
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<tr>
<td>T-type Calcium Channel Blocker</td>
<td>Neurological disorders</td>
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OUR RICH DISCOVERY PIPELINE

▶ >15 promising projects advancing in Drug Discovery

▶ Focus towards specialty markets and rare diseases with high unmet medical need

▶ Current clinical pipeline to build solid portfolio for future revenue growth
STRATEGY FOR VALUE CREATION

- SUSTAIN AND GROW THE PAH FRANCHISE
- BUILD ADDITIONAL SPECIALTY FRANCHISES

OPTIMIZE PROFITABILITY
FINANCIAL OVERVIEW
BY REPORTING PERIOD
## STRONG PERFORMANCE

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<th>FY 2015</th>
<th>FY 2016</th>
<th>CHF</th>
<th>CER</th>
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<td>Product sales</td>
<td>2,042</td>
<td>2,412</td>
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<td>CHF million</td>
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<td>Core operating income</td>
<td>814</td>
<td>992</td>
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<td>17%</td>
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<tr>
<td>CHF million</td>
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<tr>
<td>Core diluted EPS</td>
<td>6.16</td>
<td>8.18</td>
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<tr>
<td>CHF</td>
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<tr>
<td>Operating income</td>
<td>656</td>
<td>789</td>
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<td>CHF million</td>
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<td>US GAAP diluted EPS</td>
<td>4.91</td>
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Actelion to be acquired by Johnson & Johnson for $30 billion with spin-out of new R&D company, listed on Swiss stock exchange
Actelion shareholders to receive 280 US dollars per Actelion share in all-cash tender offer and one share of new R&D company for each Actelion share as stock dividend
MANAGEMENT & BOARD
THE RIGHT PEOPLE FOR THE NEXT GROWTH PHASE

ACTELION MANAGEMENT TEAM

Jean-Paul Clozel
Founder, CEO
Joined in 1997

Otto Schwarz
COO
Joined in 2008

André Muller
CFO
Joined in 2013

Nicholas Franco
Chief BD Officer
Joined in 2011

Guy Braunstein
Head of Global CD
Joined in 2009

Martine Clozel
Founder, CSO
Joined in 1997

Christian Albrich
Head of Global HR
Joined in 2005

Andrew Weiss
Head of IR & CC
Joined in 2014

Marian Borovsky
General Counsel
Joined in 2003

Rudi Frank
Head of Global Quality Management
Joined in 2000
THE RIGHT PEOPLE FOR THE NEXT GROWTH PHASE

ACTELION BOARD OF DIRECTORS

Jean-Pierre Garnier
Chairman
Joined in 2011

Juhani Anttila
Joined in 2005

Robert J. Bertolini
Joined in 2011

Jean-Paul Clozel
Joined in 2000

John J. Greisch
Joined in 2013

Peter Gruss
Joined in 2012

Michael Jacobi
Joined in 2009

Jean Malo
Joined in 2004

David Stout
Joined in 2015

Herna Verhagen
Joined in 2015
THANK YOU FOR YOUR INTEREST IN ACTELION