Orphan Drug
From Idea to Product

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ACTELION

From Idea to an Orphan Drug

- Develompent of an Orphan Drug
  - The endothelin story
  - The discovery of bosentan
  - The selection of clinical indications
  - TRACLEER in Pulmonary Arterial Hypertension
- Challenges with Orphan Drug development:

  What is the benefit/risk balance for the company?

Development of an Orphan Drug

- **The endothelin story**
- The discovery of bosentan
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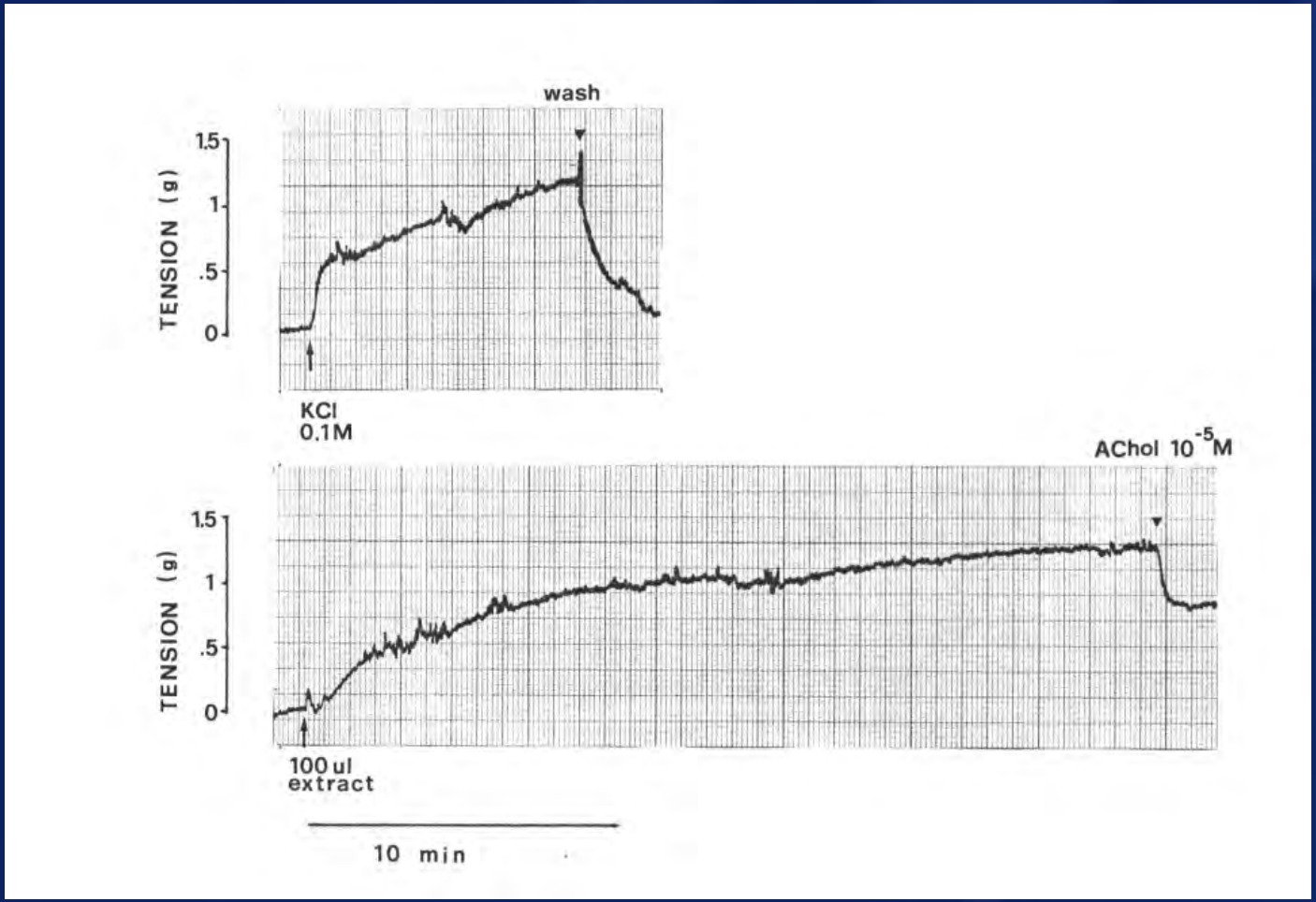
Conditioned Medium from Human Endothelial Cells Induces Constriction of Rat Aorta



Clozel M., et al., October 1987

A novel potent vasoconstrictor peptide produced by vascular endothelial cells

Masashi Yanagisawa, Hiroki Kurihara†, Sadao Kimura, Yoko Tomobe, Mieko Kobayashi*, Youji Mitsui*, Yoshio Yazaki†, Katsutoshi Goto & Tomoh Masaki‡

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An endothelium-derived 21-residue vasoconstrictor peptide, endothelin, has been isolated, and shown to be one of the most potent vasoconstrictors known. Cloning and sequencing of preproendothelin complementary DNA shows that mature endothelin is generated through an unusual proteolytic processing, and regional homologies to a group of neurotoxins suggest that endothelin is an endogenous modulator of voltage-dependent ion channels. Expression of the endothelin gene is regulated by several vasoactive agents, indicating the existence of a novel cardiovascular control system.

Yanagisawa M., et al., Nature, 1988

The many roads to discover endothelin

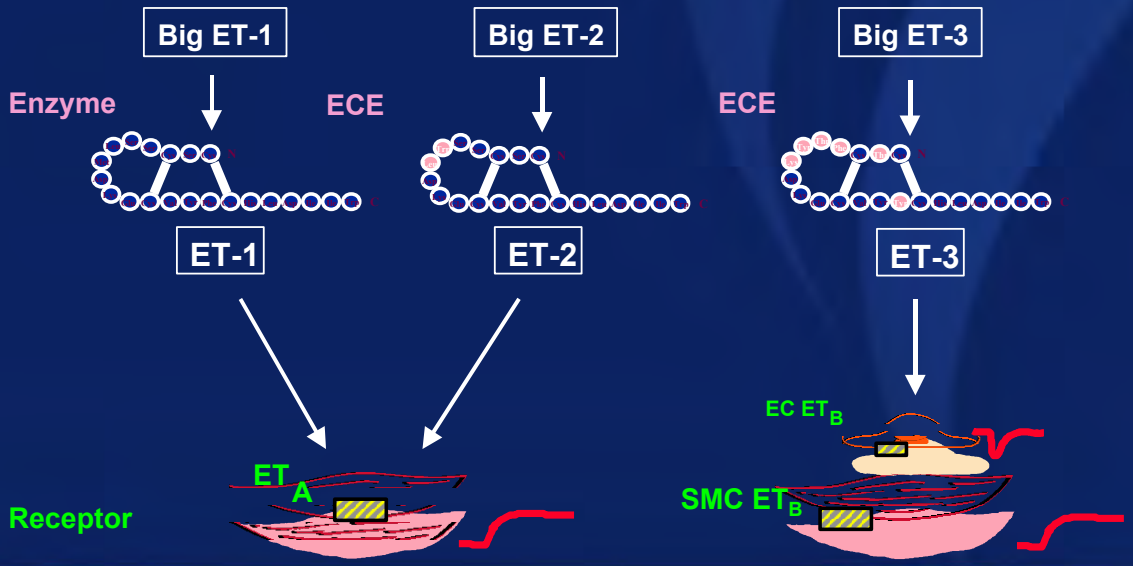
Israeli Mole Viper

(*Atractaspis engaddensis*)

Kloog Y., et al., Science, 1988

Involvement in all research phases to understand the endothelin system

- First evidence for production of endothelin by human cells (1988)
- First molecule ever antagonizing the endothelin receptors (1989)
- First evidence for a role of endogenous endothelin in pathological model in rats (1989). (Nature, October 21, 1993, Clozel M et al).
- First evidence for a vasoconstrictor role of ET_B receptors.



Detrimental Effects of Endothelin (ET)

ET plays a role in:

- Vasoconstriction
- Proliferation
- Fibrosis
- Inflammation

- ET is a key player in a number of pathological situations
- Effects of ET often involve both its ET_A & ET_B receptors

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Pharmacology Progresses with Chemistry

April 1988	First screening set up
September 1989	Synthesis of Ro 44-0248 First indication of the validity of the concept
September 1990	Synthesis of Ro 46-0254 First with systemic activity (i.v.)
December 1990	Synthesis of Ro 46-2005 First with oral activity
December 1991	Synthesis of Ro 47-0203 = **bosentan** **First clinical candidate**

Bosentan

Non-peptidic small-molecular-weight antagonist of ET_A and ET_B receptors

First synthesis: December 1991

- Oral activity
- Selectivity
- Vasodilator effect
- Improved endothelial function

➢ First clinical candidate

First publication: Clozel M. et al., *J. Pharmacol. Exp. Ther.,* 1994

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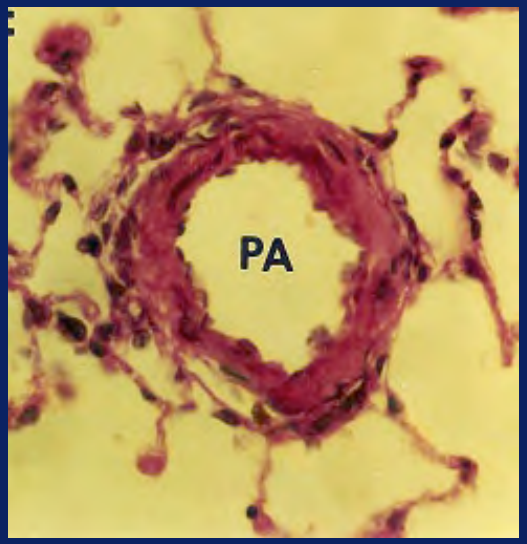
World wide research on bosentan

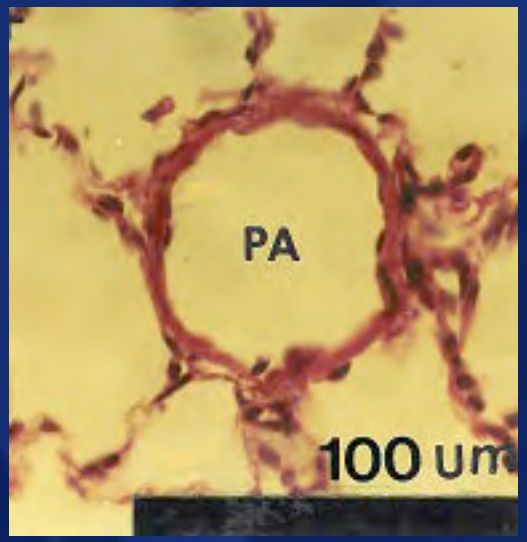
- Distribution of bosentan to hundreds of university labs
- Publication of > 500 papers to date on bosentan
- Wider scientific knowledge on the endothelin system and the potential of endothelin receptor antagonists (ERA)

Bosentan reverses vascular hypertrophy in a rat model of pulmonary hypertension

Hypertrophy is an intrinsic feature of PAH



6 wks hypoxia
+ 4 wks placebo



6 wks hypoxia
+ 4 wks bosentan
100 mg/kg/d

Chen S-J, et al., *J Appl Physiol,* 1995

Selection of clinical indication

- Compatibility of the disease with the action of ET-1
  - Upregulation of the ET system in lungs of PAH patients
  - Bosentan efficacy in animal models
- Medical need: progressive disease with high mortality

➢ **Pulmonary Arterial Hypertension (PAH)**
a life-threatening, orphan disease

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Founding of Actelion Pharmaceuticals

- **Founded end-1997** by former Roche R&D specialists:
  - Martine Clozel
  - Jean-Paul Clozel
  - Walter Fishli
  - Thomas Widman
- **Vision:** Build up a fully integrated biopharmaceutical company, that
  - discovers,
  - develops,
  - registers &
  - markets novel medicines

History of bosentan at Actelion (I)

- **1998:** Lisencing-in of bosentan from Roche
- **1999:** Phase III study in Pulmonary Arterial Hypertension (PAH) initiated with bosentan
- **2000:** Significant positive results in first pivotal trial with 32 PAH patients
- **2001:** Confirmatory resuts from second pivotal trial with 214 patients

Basis for Approval: Risk/Benefit ratio (I)

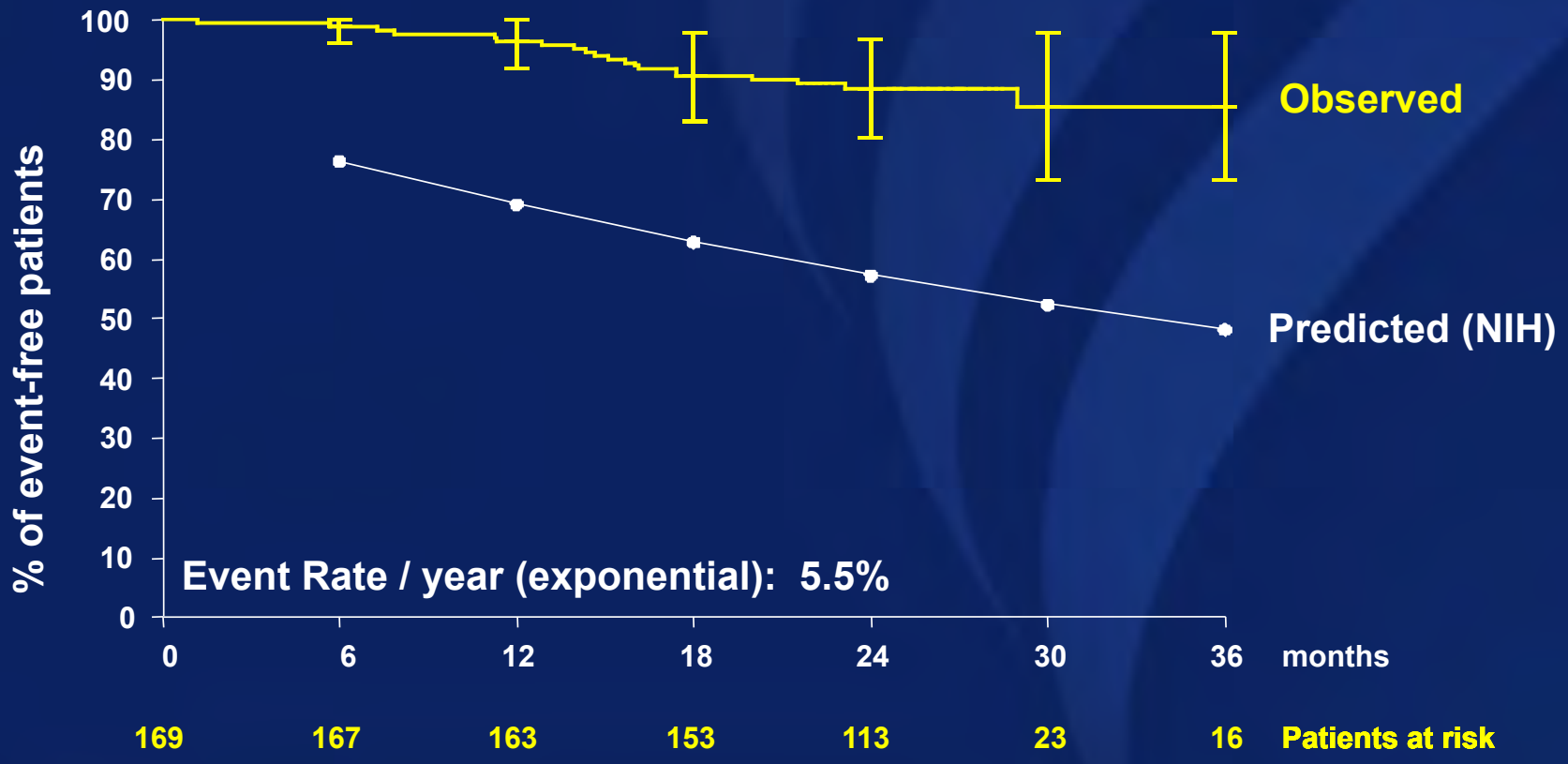
- **Efficacy** in patients with PAH:

  2 pivotal studies: 32 & 214 patients

  - Significantly increased exercise capacity
  - Improved pulmonary hemodynamics
  - Improved WHO Class
  - Significant reduction in rate of clinical worsening

Long term follow up over 3 years

Kaplan-Meier survival estimates of observed and predicted survival



McLaughlin et al., *Eur Respir J,* 2005; 25: 244-249

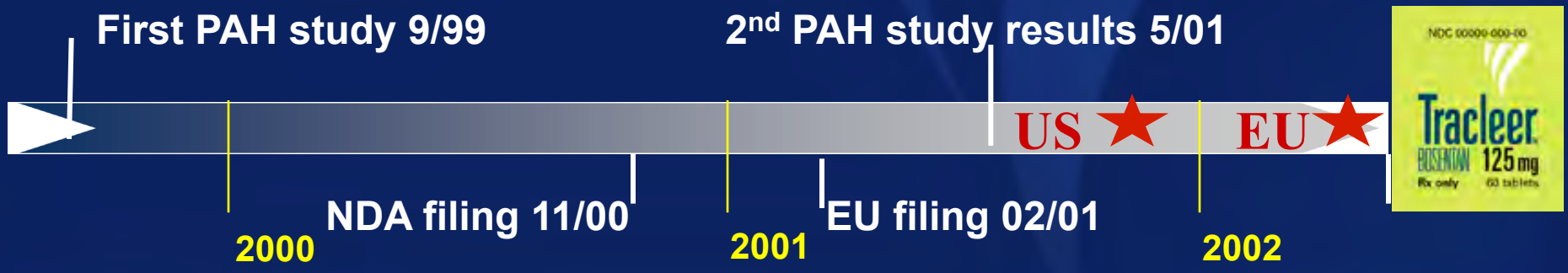
Basis for Approval: Risk/Benefit ratio (II)

Safety in patients with PAH **:**

- **Clinical Safety Database:**
  - 2400 patients
  - 1481 patients from 8 PC trials
  - 2 PC trials in PAH – 174 pts
- Increased liver enzymes (11% of patients)
- Potential teratogenicity

Timeline for development of Tracleer® in PAH: 26 months

Drug Approval	FDA	EMEA
Orphan Designation	Oct 2000	Feb 2001
NDA/ MAA submission	Dec 2000	Feb 2001
Approval	**Nov 2001**	**May 2002**



Health Authority evaluation

- **Positive benefit:risk profile**

First oral treatment	-	**New class** of medicines
Life-threatening disease	-	**Limited safety data** available in PAH

- **Same conclusions from FDA and EMEA :**
  - **Warnings and Monitoring requirements:**
    - Monthly liver enzymes test
    - Pregnancy test
  - **Risk management programs**
  - **Controlled distribution**

Risk Management of Tracleer in the EU

- **Post Marketing Surveillance Programme**
- Web-based system (TRAX)
- **Prescribers' Kit:** Provided to every prescriber
  - Information about safety issues and proper use
  - Given to every prescriber
- **Patient Reminder Card**
  - Addressing liver toxicity and pregnancy
  - Included in every pack of Tracleer

Conclusions
Post Approval Commitments

- **Risk management programme successful**
  - No new safety concerns
  - Confirmation of clinical trial data
  - Enhanced spontaneous reporting
  - More complete safety profile
- **Capturing of ~80% of patients treated in EU**
- **SO lifted**

Conclusions
Post Approval Commitments cont'

- **Doesn't come for free**
  - Resource and cost intensive
  - Requires elaborate infrastructure & representaiton in all EU countries
  - High maintenance

- **Transfer of risk management system to other products**

Licensing-in of another orphan drug

- **Zavesca (miglustat)**
  - 1st oral treatement for mild to moderate Gauchers' Disease type 1
  - Same Post-Marketing Surveillance Programme as for Tracleer requested by CPMP
- **Continued clinical development in liposomal storage diseases**
  - Gauchers' Disease type 3
  - Lat-Onset Tay-Sachs
  - Niemann-Pick C

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- **Challenges with Orphan Drug development:**

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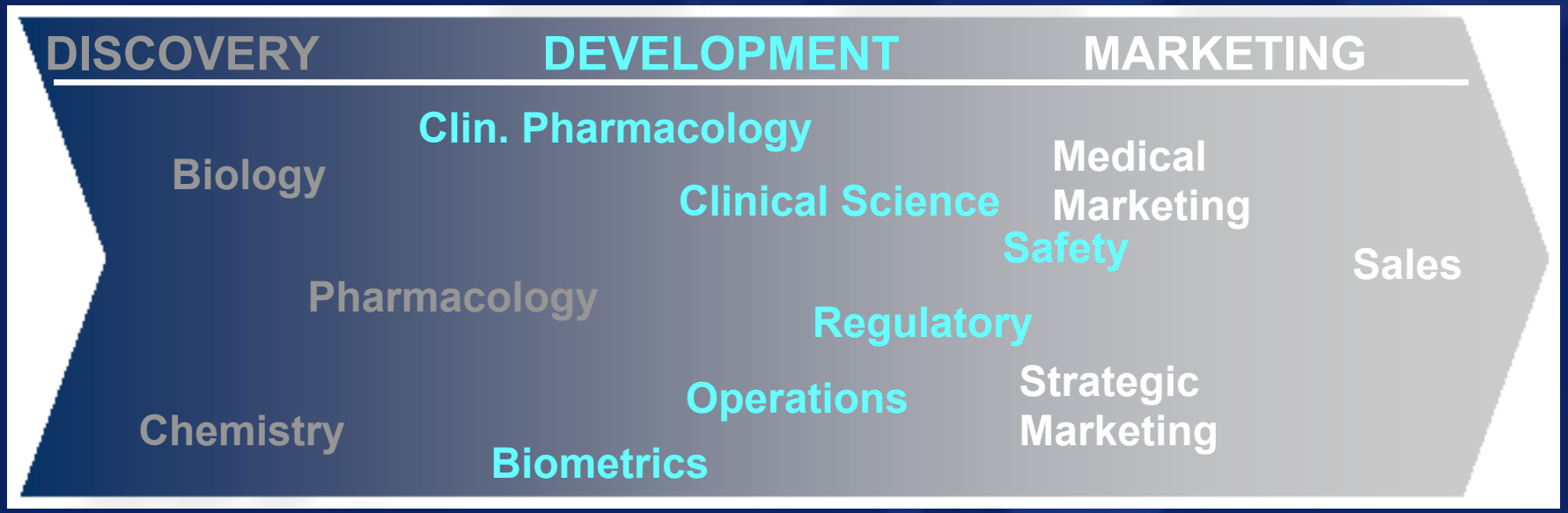
From idea to orphan drug – required company infrastructure



Discovering, researching, developing and bringing to the market of a drug requires seamless interphases

Barriers to Orphan Drug Development

- **Clinical trials issues:**
  - **Few experts available to treat disease**
  - **Low number of patients**
  - **Geographic dispersion of patients**
  - **Surrogate markers as endpoints**
- **It's a long & costly process:**
  - Average about 10 yrs, ~500-800 mio Eur
- **Small market vs development costs**

➢ **potential low ROI**

➢ **Incentives needed to stimulate R&D of orphan drugs**

Why Develop OMPs? Financial Incentives in the EU

- **National incentives: tax cuts and grants**
- **Fee reductions** for centralised applications
- 10 years **Market Exclusivity**
  - But: can be reduced to 6 yrs if designation criteria are no longer met
- **Guidelines on**
  - Definition of ‚sufficiently profitable' in Art 8
  - Definition of a ‚similar' product – how broad is protection?

- **Significant impact on protection for pioneering work**

Circle of Growth & Development

Research

- New Tracleer indications
- New Zavesca indications

Re-investment

Sales

Development

- Paediatric Formulation for Tracleer

Filing

From 4 to 848 people in 7 years

One of the fastest growing biopharmaceutical companies

Marketing & Sales (21 countries)

Europe

CH

Middle East

Latin America

USA

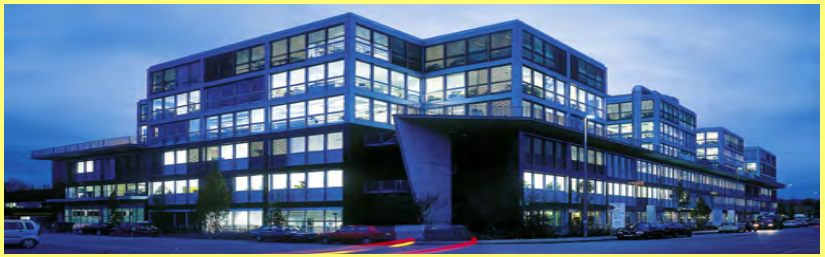
Canada

Australia

Japan

Clinical Development (194)

Drug Discovery (174)



Regulatory / QA (25)

Support functions (105)

Headcount Dec 04: 848

Lessons learned
Orphan Drug development

- **What is special about ‘orphan’?**
  - High risk to develop new class
  - No precedents to follow
  - Potential low Return on Investement
  - How good is really the protection for an orphan?
  - One product can lead to another

Lessons learned
SME perspective

- Logistic & resource requirements: a challenge
- Handling of global submission: a challenge
- Affiliates not established in every MS
- SMEs considered ‘less important’ by HAs
- Fulfilling PACs – an additional hurdle after approval
- Potential for futher orphan indictaions
- New Clinical Trial Application: demanding

➢ **Complex & challenging but feasible**

From lab...

… to Man

… to Patients


Tracleer 125 mg
BOSENTAN
56 Filmtabletten
ACTELION
Tracleer 62,5 mg
Filmtabletten
BOSENTAN
56 Filmtabletten

Thank you!

Martine Clozel, MD

Senior VP, Head of Preclinical Research

Co-founder of Actelion Pharmaceuticals Ltd.