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**The determined efforts of our clinical development teams helped Tracleer® reach the market in only 26 months.**

In 2002, Actelion successfully strengthened its global reach by proving its skills in regulatory affairs as well as sales and marketing. The company expanded its development capabilities, capitalizing on the company's knowledge about the involvement of the endothelin system in various diseases, while simultaneously preparing for clinical programs with new compounds from Actelion's research efforts.

Actelion continues to manage its products through life-cycle teams with the goal of rapidly moving a drug from inception to initial commercialization and then to global sales. New indications for existing drugs and new drugs in new indications will allow Actelion to grow

above and beyond the significant peak-sales potential of Tracleer® in PAH, currently estimated at between USD 400 and 500 million.

A strong development function is key to ensure that a drug's potential is appropriately profiled in well-defined and executed clinical trials that satisfy the highest standards in the industry. With this in mind, Actelion has built up a development department staffed by professionals with years of experience in the pharmaceutical industry. Their efforts in the BREATHE studies have allowed Tracleer® to reach the market in a record time of less than 26 months after the first of two pivotal studies were initiated.

# Promising clinical data

Actelion's development efforts have concentrated on enlarging the potential indications for Tracleer® in other endothelin-related diseases (digital ulcerations, pulmonary fibrosis, metastatic melanoma) as well as evaluating the right dosing regimen for the company's intravenous dual endothelin-receptor antagonist Veletri™, which began evaluation in a Phase III program as a potential agent for the treatment of acute heart failure (AHF) in late 2002.

## PAH as a complication of scleroderma

Pulmonary arterial hypertension (PAH) is a frequent and often fatal complication of scleroderma, an autoimmune disease afflicting up to 200,000 patients worldwide. In these patients, endothelin acts as a pathogenic mediator, not only leading to PAH, but also at least two other major complications of scleroderma, pulmonary fibrosis and digital ulcerations.

In order to address the potential of Tracleer® in scleroderma, Actelion has chosen a development program to establish the effect of the drug in each complication. With PAH already approved, Actelion has moved its focus to digital ulceration, with a first study concluded in summer 2002. During the same year, Actelion began thorough discussions with key physicians on its clinical trial plans for Tracleer® in pulmonary fibrosis related to scleroderma. First studies will be initiated in early 2003.

## Preventing and treating digital ulcerations

Systemic sclerosis (scleroderma), an autoimmune rheumatic disease, is characterized by an increased accumulation of connective tissue in skin and internal organs as well as vascular injury and damage. Endothelin, as a pathogenic mediator, is implicated in the vascular damage. Complications in sclero-

derma, including pulmonary arterial hypertension (PAH) and digital ulcers, are the result of vasculopathy (vascular dysfunction).

Digital ulcerations are a common complication of scleroderma, occurring in 25% or more of patients, with approximately 5,000 severe cases worldwide. A result of the blockage of small blood vessels (obliterative vasculopathy), digital ulcers are very painful and difficult-to-heal open sores that occur on fingers and toes. They often lead to infections, leave depressed scars and adversely impact the ability to perform work and daily activities. In severe cases, gangrene develops, which requires surgery and even amputation.

In 2002, Actelion conducted an international, multi-center, double-blind, placebo-controlled clinical trial called RAPIDS-1 (**R**andomized **P**lacebo-controlled **I**nvestigation of **D**igital ulcers in **S**cleroderma). The study evaluated whether treatment with Tracleer® could prevent the occurrence of new ischemic digital ulcers in patients with scleroderma.

The results of RAPIDS-1, presented in the late-breaking session of the American College of Rheumatology in New Orleans, showed that patients with existing ulcers taking Tracleer® developed half as many new digital ulcers per patient as those treated with placebo. In this high-risk group, the proportion of patients that did not develop new ulcers during the trial was also greater in the treatment group. In addition, the patients treated with Tracleer® had a significant improvement in hand functionality such as their ability to dress and to wash their hands and hair.

Actelion is currently engaged in discussions with regulatory author-

ities worldwide to decide on the appropriate design of the next trial in digital ulcerations. The new study, called RAPIDS-2, is expected to commence in the second half of 2003. In the meantime, Actelion has initiated the process of applying for "orphan drug" status in this indication in both the United States and Europe.

## Tracleer® in other fibrotic diseases

In 2002, Actelion also focused on development opportunities for Tracleer® in other endothelin-related diseases such as pulmonary fibrosis, a progressive lung disease that is usually fatal. The idiopathic form (no known cause) of pulmonary fibrosis (IPF) afflicts some 100,000 patients worldwide.

In early 2003, as part of its clinical trial program to expand the use of Tracleer®, Actelion initiated two studies, BUILD-1 and 2 (**B**osentan **U**se in **I**nterstitial **L**ung **D**isease). One study addresses the idiopathic form of the disease and the other study addresses pulmonary fibrosis related to systemic sclerosis (scleroderma). Actelion has chosen an innovative trial design, using a walking test as the primary endpoint of the studies. First results are expected in 2005.

## Endothelin in interstitial lung diseases

Many acute and chronic lung disorders with variable degrees of pulmonary inflammation and fibrosis are collectively referred to as interstitial lung diseases (ILD). These diseases can be associated with underlying conditions such as systemic sclerosis. More than 75% of these patients develop pulmonary fibrosis, with one million cases worldwide.

In IPF and in ILD caused by scleroderma, inflammation and accumulation of connective tissue (fibrosis) in the lungs destroys structure and function of the respiratory system. Endothelin has major profibrotic and pro-inflammatory effects. Since endothelin concentrations are strongly elevated in ILD, there is solid evidence that endothelin might be involved in these diseases as well. Endothelin receptor antagonism, therefore, may be an effective therapeutic strategy.

## Tracleer® in cancer

In the first quarter of 2003, Actelion will initiate a first series of studies with Tracleer® in malignant (metastatic) melanoma. Several pre-clinical experiments have shown that in malignant

### Growing Actelion – Beyond Tracleer® in PAH

Study Name	2002	2003	2004	2005
RAPIDS-2		◀		
BUILD-1	▶			
BUILD-2	▶			
MM	▶			
RAPIDS-2	Randomized Placebo-controlled Investigation of Digital Ulcers			
BUILD	Bosentan Use in Interstitial Lung Disease			
BUILD-1	Phase II/III study in IPF = Idiopathic Pulmonary Fibrosis			
BUILD-2	Phase II/III study in FASSc = Fibrosing alveolitis in systemic sclerosis			
MM	Metastatic Melanoma			

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# Addressing unmet medical needs

melanoma, endothelin plays a role in the proliferation of abnormal, cancerous cells. In 2002, development plans for Tracleer® in these proliferative diseases were discussed with key experts in the field and experienced personnel were hired to maximize the chances of success of Tracleer®.

The incidence of metastatic melanoma, which may spread locally or metastasize to major organs, is 15 per 100,000 and the disease has a death rate of 2.5 per 100,000. Since current treatments have a response rate of only 15-20% and a cure rate of less than 5%, there is a high unmet medical need for an effective therapy.

## New studies with Veletri™

In 2002, a dose-optimization study evaluated Veletri™ (tezosentan), an intravenous dual endothelin receptor antagonist, for the treatment of acute heart failure (AHF). The study was the result of the full evaluation of an earlier clinical trial program (RITZ), which was concluded unsuccessfully in 2001. The dose-optimization study showed that lower doses are efficacious in terms of improvements in important hemodynamic parameters such as cardiac index (CI) and pulmonary capillary wedge pressure (PCWP). These improvements were not associated with clinically relevant side effects.

Based on these results showing the potential of Veletri™, and taking into consideration the need for an AHF drug providing more than symptomatic relief, Actelion has decided to proceed with two registration studies (Phase III) with Veletri™ evaluat-

**To realize a drug's true potential, clinical trials must be well designed and executed according to the highest industry standards.**

ing mortality/morbidity benefits (Value of Endothelin Receptor Inhibition with Tezosentan in Acute heart failure Study). With preparations already well advanced and the results of the dose-optimization trial obtained slightly ahead of schedule, the registration study should be initiated in Q1 2003 and last between 18 and 24 months.

## Exploring Zavesca®

Given its unique mode of action, Zavesca® could potentially benefit patients with lipid-storage disorders other than type 1 Gaucher's disease. Under investigation are diseases unsuitable for available enzyme replacement therapy, such as type 3 Gaucher's, Niemann-Pick disease and Late Onset Tay-Sachs syndrome.

## First urotensin II receptor antagonist

Actelion has begun Phase I clinical testing of the first orally active urotensin II receptor antagonist. Urotensin II is a peptide hormone and has been described as one of the most potent vasoconstrictor substances known today. The urotensin system appears to be activated in various cardiovascular diseases, and may also be involved in metabolic disorders. Actelion is pioneering the clinical development of urotensin II receptor antagonists, a new and innovative therapeutic principle for cardiovascular and metabolic diseases.

## Hesperion's clinical research expanded

Actelion continues to carry out part of its clinical development studies through the clinical research organization Hesperion, in which the company holds a controlling majority. Hesperion, which also works increasingly for third parties, concluded a collaboration agreement in March 2002 with Berna Biotech for the development of vaccines. This partnership combines the strengths of both companies.

## Substantial need for new AHF therapies

AHF, the leading cause of hospitalization worldwide, is a life-threatening condition in which the ability of the heart to pump enough blood to meet the body's metabolic needs is rapidly and seriously impaired. Each year, nearly two million people in the industrialized world are hospitalized with AHF. Patients suffering from AHF typically experience symptoms such as dyspnea, edema and fatigue, and often show signs of poor blood flow. In some cases, the onset of AHF is abrupt, with rapid fluid build-up in the lungs (pulmonary edema), which can impair breathing so drastically that the patient requires intubation and a ventilator for assisted breathing. In other cases, AHF can lead to cardiogenic shock, an abrupt disruption of blood flow that can follow a massive heart attack or surgery.

At the end of 2002, an agreement was reached with Hesperion that part of its operations would be better managed directly by Actelion. Consequently, resources were transferred to Actelion, allowing Hesperion to focus even more on those services most often requested by third parties (i.e. biometrics and data management).

Actelion itself has a well-established quality management and control function. In 2002, the Quality Control (QC) Laboratory in Allschwil, Switzerland received the GMP (Good Manufacturing Practices) certification. This certification allows Actelion to perform in-house GMP release and stability analyses for commercial pharmaceutical products and clinical trial material. Now that Actelion is no longer dependant on contractors for these activities, the company is in the position to react with more flexibility to requests from Research, Supply Chain Management, Production and Drug Regulatory Affairs.