Actelion announces excellent financial results for 2016


FINANCIAL HIGHLIGHTS
• Sales growing to CHF 2,412 million (+15% at CER)
• Opsumit sales continue strong trajectory and grow to CHF 831 million (+57% at CER)
• Uptravi sales reach CHF 245 million in first year of launch – driven by the US
• US GAAP operating income grows to CHF 789 million (+14% at CER)
• Core operating income grows to CHF 992 million (+17% at CER)

USD 30 billion proposal by Johnson & Johnson to acquire Actelion

PROPOSED TRANSACTION HIGHLIGHTS
• 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
• Johnson & Johnson to acquire Actelion’s marketed products in particular its leading PAH franchise
• Johnson & Johnson to also acquire global rights to Actelion’s promising advanced late-stage therapies, ponesimod and cadazolid
• New R&D company launching with cash of CHF 1 billion to continue the culture of innovation with early stage R&D pipeline
• Johnson & Johnson will also receive an option on an endothelin receptor antagonist (ACT-132577) currently being developed for resistant hypertension

Financial Overview

<table>
<thead>
<tr>
<th>US GAAP results</th>
<th>FY 2016</th>
<th>FY 2015</th>
<th>% variance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Net revenue</td>
<td>2,412</td>
<td>2,045</td>
<td>18 15</td>
</tr>
<tr>
<td>Operating income</td>
<td>789</td>
<td>656</td>
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</tr>
<tr>
<td>Net income</td>
<td>696</td>
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<td>26 19</td>
</tr>
<tr>
<td>Diluted EPS</td>
<td>6.46</td>
<td>4.91</td>
<td>32 25</td>
</tr>
<tr>
<td>Core performance(2)</td>
<td></td>
<td></td>
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<tr>
<td>Product sales</td>
<td>2,412</td>
<td>2,042</td>
<td>18 15</td>
</tr>
<tr>
<td>Core operating income</td>
<td>992</td>
<td>814</td>
<td>22 17</td>
</tr>
<tr>
<td>Core net income</td>
<td>881</td>
<td>693</td>
<td>27 22</td>
</tr>
<tr>
<td>Core diluted EPS</td>
<td>8.18</td>
<td>6.16</td>
<td>33 27</td>
</tr>
</tbody>
</table>

Cash flow

<table>
<thead>
<tr>
<th>FY 2016</th>
<th>FY 2015</th>
</tr>
</thead>
<tbody>
<tr>
<td>Operating cash flow</td>
<td>920</td>
</tr>
<tr>
<td>Capital expenditure</td>
<td>(57)</td>
</tr>
<tr>
<td>Free cash flow</td>
<td>90</td>
</tr>
<tr>
<td>Net cash position as of 31 December</td>
<td>495</td>
</tr>
</tbody>
</table>

(1) CER percentage changes are calculated by reconsolidating both the 2015 and 2016 results at constant currencies (the average monthly exchange rates for 2015).
(2) Actelion continues to measure and report core operating performance, which management believes more accurately reflects the underlying business performance. The Group believes that these non-GAAP financial measurements provide useful supplementary information to investors. These non-GAAP measures are reported in addition to, not as a substitute for, US GAAP financial performance.

Jean-Paul Clozel, MD, Chief Executive Officer, commented: “With Johnson & Johnson’s proposed acquisition of Actelion and the spin-out of a new R&D company, we have created unprecedented value for all of our stakeholders. Our current PAH portfolio and our late-stage pipeline will have expanded potential as part of Johnson & Johnson. With the creation of a new R&D company we also have the opportunity to realize the value potential we have created with our discovery engine and early-stage pipeline. I am very proud of what we’ve achieved, and I am very excited about the challenges and opportunities ahead.”

Otto Schwarz, Chief Operating Officer, commented: “The significant clinical utility of Opsumit resulted in continued strong patient uptake with more than 21,000 patients currently receiving therapy. Moreover, after just one year on the US market, we can say that the Uptravi launch has been very successful by any standards, proving the high unmet medical need for oral prostacyclin therapy and validating our commercial strategy. I strongly believe that, as a part of the Johnson & Johnson family of companies, we will be...
able to serve even more patients by opening new markets and creating additional opportunities for our products.”

André C. Muller, Chief Financial Officer, commented: “Actelion’s 2016 performance has been impressive with the company delivering record sales and earnings. The proposed transaction with Johnson & Johnson announced on 26 January will enable Actelion shareholders to not only monetize their holdings at 280 US dollars per share but also retain future upside potential with the distribution of 1 share in the newly created R&D company for every Actelion share. Both companies are now working to finalize the operational and financial details of the split and prepare the listing of the new company.”

SALES UPDATE

Actelion’s excellent commercial performance during 2016 was driven by the outstanding Uptravi launch in the US and Opsumit’s sustained strong growth trajectory. During the fourth quarter of 2016, combined sales of the company’s outcome-based PAH portfolio – Opsumit, Uptravi and Veletri – reached 55% of total sales, demonstrating the significant progress made in the fundamental transformation of the PAH business.

In the US, sales increased by 25% at CER, driven by the strong Uptravi launch, the continued Opsumit momentum due to share gains in an expanding ERA market. European sales were 1% higher compared to 2015. A strong Opsumit performance and solid Tracleer use in the digital ulcer indication were impacted by continued pricing pressure and market erosion from bosentan generics, particularly in Spain. Sales in Japan increased by 19% at CER, driven by very strong sales of Opsumit (launched in June 2015), Tracleer momentum in the digital ulcer indication and Zavesca (Japanese trade name Brazaves).

Comparing average exchange rates for 2016 to 2015, the Swiss franc weakened, mostly against the US dollar, euro and Japanese yen, resulting in a positive currency variance of 63 million Swiss francs.

Sales by product – FY2016

<table>
<thead>
<tr>
<th>Product</th>
<th>FY 2016</th>
<th>FY 2015</th>
<th>% variance at CER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opsumit®</td>
<td>831</td>
<td>516</td>
<td>61%</td>
</tr>
<tr>
<td>Tracleer®</td>
<td>1,020</td>
<td>1,212</td>
<td>-16%</td>
</tr>
<tr>
<td>Uptravi®</td>
<td>245</td>
<td>-</td>
<td>nm</td>
</tr>
<tr>
<td>Veletri®</td>
<td>97</td>
<td>83</td>
<td>17%</td>
</tr>
<tr>
<td>Ventavis®</td>
<td>73</td>
<td>105</td>
<td>-30%</td>
</tr>
<tr>
<td>Valchlor®</td>
<td>35</td>
<td>27</td>
<td>30%</td>
</tr>
<tr>
<td>Zavesca®</td>
<td>104</td>
<td>92</td>
<td>13%</td>
</tr>
<tr>
<td>Others</td>
<td>8</td>
<td>7</td>
<td>7%</td>
</tr>
<tr>
<td>Total product sales</td>
<td>2,412</td>
<td>2,042</td>
<td>18%</td>
</tr>
</tbody>
</table>

*nm = not meaningful

Sales by region – FY 2016

<table>
<thead>
<tr>
<th>Region</th>
<th>FY 2016</th>
<th>FY 2015</th>
<th>% variance at CER</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1,306</td>
<td>1,026</td>
<td>27%</td>
</tr>
<tr>
<td>Europe*</td>
<td>646</td>
<td>634</td>
<td>2%</td>
</tr>
<tr>
<td>Japan</td>
<td>258</td>
<td>190</td>
<td>36%</td>
</tr>
<tr>
<td>Rest of the world</td>
<td>201</td>
<td>192</td>
<td>5%</td>
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<tr>
<td>Total product sales</td>
<td>2,412</td>
<td>2,042</td>
<td>18%</td>
</tr>
</tbody>
</table>

*Europe = EU28 and Switzerland

PAH FRANCHISE

Opsumit®

Sales of Opsumit (macitentan) amounted to 831 million Swiss francs for 2016, an increase of 57% at CER compared to 2015. The strong growth across all regions and all relevant markets (Opsumit is now available in almost 40 markets) was driven by solid quarterly increases in the number of patients treated in an expanding ERA market due to increased use in combination with PDE-5 inhibitors, and some upgrades from Tracleer, notably in Japan.

Uptravi®

Sales of Uptravi (selexipag) amounted to 245 million Swiss francs for 2016. Since the US launch at the beginning of January 2016, patient demand has continued to increase with sales of 232 million Swiss francs (which includes 30 million Swiss francs for the build-up of inventory in the US). For the fourth quarter, US
sales amounted to 77 million Swiss francs, compared to 66 million Swiss francs in the third quarter, 45 million Swiss francs in the second quarter and 15 million Swiss francs in the first quarter of 2016. In other geographies, Uptravi sales were driven by the particularly successful launch in Germany. Uptravi is also available in several other markets; it was most recently launched with full reimbursement in the Netherlands and Switzerland.

At the end of 2016, just over 2,400 patients were being treated with Uptravi globally, with more than 1,900 patients coming from the US.

Tracleer®
Sales of Tracleer (bosentan) amounted to 1,020 million Swiss francs for 2016, a decrease of 18% at CER compared to 2015. This was driven to a large extent by volume erosion resulting from the significant impact of Osmurti uptake on the Tracleer patient base and by increased generic competition, notably in Spain, where generic bosentan entered the market in January 2016. Tracleer sales were supported by the digital ulcer indication in Europe and Japan.

Following the Pediatric Investigation Plan (PIP) compliance statement from the European Committee for Medicinal Products for Human Use (CHMP), applications for extension of the Supplementary Protection Certificate (SPC) were granted in all possible 19 EU countries until the end of August 2017.

Veleti®
Sales of Veleti (epoprostenol for injection) amounted to 97 million Swiss francs for 2016, an increase of 12% at CER compared to 2015. This increase was mostly driven by France, Italy, Spain and the UK. Demand in Japan, where it is marketed as Epoprostenol ACT, remained strong, however sales growth was mitigated by a 12% price cut effective March 1, 2016. In February 2017, Actelion Pharmaceuticals Japan proudly announced that Epoprostenol ACT received a label extension for dosage and administration in pediatric patients with PAH.

Ventavis®
Sales of Ventavis (iloprost) amounted to 73 million Swiss francs for 2016, a decrease of 32% at CER compared to 2015 due to competitive pressures, including the availability of Uptravi. Underlying units decreased by 37%.

SPECIALTY PRODUCTS
Valchlor®
Sales of Valchlor (mechlorethamine) amounted to 35 million Swiss francs for 2016, an increase of 27% at CER compared to 2015. In the US, the company has made good progress in establishing Valchlor as a valuable option in the treatment algorithm for early-stage mycosis fungoides, a type of Cutaneous T-Cell Lymphoma (MF-CTCL).

In December 2016, the Committee for Medicinal Products for Human Use (CHMP), the scientific committee of the European Medicines Agency (EMA), issued a positive opinion for the use of chlormethine gel 160 micrograms/g (Ledaga®) for the treatment of mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in adult patients and recommended that the European Commission approves the product. The European Commission is expected to issue a final decision by the end of February 2017.

Zavesca®
Sales of Zavesca (miglustat) amounted to 104 million Swiss francs for 2016, an increase of 12% at CER compared to 2015.

Sales in the US were strong, due to a relatively low prior year base as a consequence of an inventory adjustment. In Europe, sales were flat due to the launch of generic miglustat (for the type 1 Gaucher disease indication only), which mitigated the continued strong, double-digit growth in the Niemann-Pick type C (NP-C) indication. Globally, the number of patients receiving Zavesca grew by 6%, compared to 2015, which was driven by a 13% increase in the treatment of patients with NP-C.

CORE R&D EXPENDITURE

The excellent commercial performance enabled Actelion to advance both the late and earlier stage pipeline, resulting in increased R&D expenditure which translates into a ratio of R&D core operating expenses to sales of 21%, slightly higher than in 2015. Core R&D expenses amounted to 509 million Swiss francs, an increase of 25% at CER. This increase was driven by higher clinical trial expenses, mainly driven by the strong recruitment in the Phase III OPTIMUM study (ponesimod in multiple sclerosis; announced in April 2015) and the Phase III IMPACT study (Cadazold in Clostridium difficile associated diarrhea), as well as costs related to the preparation and initiation of Phase II studies for Actelion’s new ERA in specialty cardiovascular disorders and DORA in insomnia.

CORE OPERATING INCOME
Core operating income amounted to 992 million Swiss francs, an increase of 17% at CER.

CORE EPS
Diluted core earnings per share were CHF 8.18 for the full year 2016, an increase of 27% at CER compared to the same period of 2015.

DELIVERING VALUE TO SHAREHOLDERS

In keeping with its commitment to maximizing shareholder value, Actelion returned 428 million Swiss francs to shareholders through the second-line share buyback as well as the increased dividend of CHF 1.50 per share, paid in May 2016. Actelion’s shares performed strongly throughout 2016 regardless of the extraordinary volatility created by the strategic discussions initiated in late November. The unaffected share price performance up until the strategic discussions became public was an increase of approximately 15%. At the end of the year, Actelion’s stock traded at 220.5 Swiss francs per share, an increase of 58% for the calendar year. The resulting total shareholder return (TSR) for 2016 amounted to 59%.

On 26 January 2017, Actelion and Johnson & Johnson jointly announced that they have entered into a definitive transaction agreement under which Johnson & Johnson will launch an all-cash tender offer in Switzerland to acquire all of the outstanding shares of Actelion for 280 US dollars per share. Additionally, Actelion shareholders will receive one share of a newly created R&D company that will be spun out concurrently with the closing of the proposed transaction.
CLINICAL DEVELOPMENT PIPELINE
The pipeline continued to strengthen with substantial progress made with several compounds:

- The ongoing Phase III program IMPACT investigating cadazolid treatment in patients suffering from *Clostridium difficile*-associated diarrhea is progressing well; results are expected in the first half of 2017.

- In the third quarter of 2016, Actelion announced the initiation of the Phase III POINT study, which investigates the use of combination therapy with ponesimod, an orally active, selective sphingosine-1-phosphate receptor 1 (S1P) immunomodulator, and dimethyl fumarate (Tecfidera®) for patients with relapsing multiple sclerosis (RMS). The POINT study - which will be conducted under a Special Protocol Assessment (SPA) agreement with the FDA - is the first to assess the concurrent administration of two oral therapies in MS with the objective to improve disease control in this progressive, debilitating neurological disorder. Ponesimod is also being studied in the Phase III OPTIMUM study to compare the efficacy and safety of ponesimod with teflufloxin (Aubagi®) in patients with RMS. The study is making good progress, with enrollment expected to be complete in Q1 2017.

- Also in the third quarter of 2016, the company advanced its new dual orexin receptor antagonist (DORA) into Phase II development in patients with insomnia. The Phase II program consists of two studies, one in adult and one in elderly patients, and is designed to evaluate the effect of Actelion’s DORA versus placebo on sleep maintenance and sleep initiation, as well as next-day residual effect and next-day performance. The study in adults also includes a zolpidem reference arm. The decision to move into a Phase II program was based on excellent data collected from the preclinical and Phase I clinical program, as well as a thorough understanding of the potential of dual orexin receptor antagonism on sleep efficacy and architecture.

- With macitentan (Opsumit), the company is conducting a pediatric study, TOMORROW, to evaluate the effect of macitentan on delaying disease progression in children with PAH using a pediatric formulation of macitentan. Recruitment is expected to start in Q1 2017.

- Actelion will assess the efficacy and safety of macitentan in stable Fontan-palliated adolescents and adults in the Phase III study RUBATO. The primary objective of this study is to assess the effect of macitentan as compared to placebo on exercise capacity through cardiopulmonary exercise testing (peak VO2). The duration of the study is expected to be approximately 28 months; the start is planned for mid-2017.

- A Phase II study with macitentan, MERIT, assessed the efficacy, safety and tolerability of macitentan in patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH). The study was completed in September 2016 and delivered very positive results, meeting its primary endpoint of a significant reduction in pulmonary vascular resistance (PVR) with macitentan compared with placebo, and also showing a significant positive effect on exercise capacity for macitentan over placebo.

- A Phase III study with macitentan, MAESTRO, assessed the effects of macitentan on exercise capacity in patients with Eisenmenger Syndrome. The study was completed in January 2017, but did not meet the primary endpoint of significantly improving exercise capacity with macitentan compared with placebo.

- Lucerastat is being evaluated for the treatment of Fabry disease. In an initial Phase Ib study, patients receiving enzyme replacement therapy who were treated with lucerastat demonstrated a marked decrease in the accumulation of metabolic substrates thought to be responsible for the lesions characteristic of this disease. Actelion is currently in discussions with health authorities to move directly to Phase III.

<table>
<thead>
<tr>
<th>Compound</th>
<th>Indication</th>
<th>Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cadazolid1</td>
<td><em>Clostridium difficile</em>-associated diarrhea</td>
<td>IMPACT</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Macitentan1</td>
<td>Pediatric PAH</td>
<td>TOMORROW</td>
<td>Initiating</td>
</tr>
<tr>
<td>Macitentan1</td>
<td>Portopulmonary hypertension (PoPH)</td>
<td>PORTICO</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Macitentan1</td>
<td>Fontan-palliated patients</td>
<td>RUBATO</td>
<td>Initiating</td>
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<td>Ponesimod1</td>
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<tr>
<td>Channel Blocker2</td>
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</tbody>
</table>

1 Upon completion of the proposed transaction these assets would be developed by Johnson & Johnson
2 Upon completion of the proposed transaction these assets would be developed by the new R&D company
HUMAN RESOURCES
At the end of 2016, Actelion employed 2,624 permanent employees worldwide, an increase of 3% (or 77 permanent positions) compared to the end of 2015.

ANNUAL REPORT

NOTES TO SHAREHOLDERS:
The next General Meeting of Shareholders will take place on or around 05 April, 2017, the date will be confirmed with the publication of the offer prospectus by Johnson & Johnson on or around 16 February 2017.

In light of the expected completion of the proposed transaction with Johnson & Johnson, the Board of Directors will propose to carry forward the 2016 accumulated profit and therefore not distribute any cash dividend.

RESULTS DAY CENTER
Investor community: To make your job easier, we provide links to all relevant documentation, such as a full financial review, reconciliation US-GAAP to Core results and geographical breakdown by product, from the Results Day Center on our corporate website: www.actelion.com/results-day-center.

NOTES TO THE EDITOR

ABOUT ACTELION LTD.
Actelion Ltd. is a leading biopharmaceutical company focused on the discovery, development and commercialization of innovative drugs for diseases with significant unmet medical needs.

Actelion is a leader in the field of pulmonary arterial hypertension (PAH). Our portfolio of PAH treatments covers the spectrum of disease, from WHO Functional Class (FC) II through to FC IV, with oral, inhaled and intravenous medications. Although not available in all countries, Actelion has treatments approved by health authorities for a number of specialist diseases including Type 1 Gaucher disease, Niemann-Pick type C disease, Digital Ulcers in patients suffering from systemic sclerosis, and mycosis fungoides type cutaneous T-cell lymphoma.

Founded in late 1997, with now over 2,600 dedicated professionals covering all key markets around the world including Europe, the US, Japan, China, Russia and Mexico, Actelion has its corporate headquarters in Allschwil / Basel, Switzerland.

Actelion shares are traded on the SIX Swiss Exchange (ticker symbol: ATLN) as part of the Swiss blue-chip index SMI (Swiss Market Index SMI®). All trademarks are legally protected by their respective owners.

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+41 61 565 62 62
www.actelion.com

The above 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.
Actelion Ltd. is a leading biopharmaceutical company focused on the discovery, development and commercialization of innovative drugs for diseases with significant unmet medical needs. The company has its corporate headquarters in Allschwil/Basel, Switzerland where it was founded in 1997. Its shares have been listed on the SIX Swiss Exchange (ticker symbol ALTN) since 2000. In September 2008, Actelion shares began trading as part of the blue-chip SMI® (Swiss Market Index).

The company has proven its ability to discover new compounds and to rapidly move them from research through development to commercialization. In particular, Actelion scientists were among the first to work in the field of endothelin receptor antagonists (ERA), leading to Tracleer® and now the tailored ERA Opsumit®.

Actelion has over 30 operative affiliates around the world including the United States, Canada, Brazil, Australia, Japan, Switzerland and a number of EU countries. These subsidiaries provide distribution, sales and marketing services.

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- Drug Discovery
- Development Pipeline
- Actelion’s Partnerships
- Company Milestones
FINANCIAL OVERVIEW

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<thead>
<tr>
<th>in CHF millions (except for per share data)</th>
<th>FY Results 2016</th>
<th>FY Results 2015</th>
<th>% Variance in CHF</th>
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</tr>
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<td>6.46</td>
<td>4.91</td>
<td>32</td>
<td>25</td>
</tr>
<tr>
<td>No of shares in calculation (million)</td>
<td>107.8</td>
<td>112.5</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

The full financial statements can be found on www.actelion.com.

COMPANY STRATEGY

Since its founding more than fifteen years ago, Actelion has become a new kind of biopharmaceutical company: one that blends biotech’s innovation, speed and flexibility with big pharma’s operating discipline and excellence in execution. With the intrinsic belief that innovation in all domains is the key to growth, Actelion has built a promising pipeline, seven approved products, and commercial operations in over 30 countries. Actelion’s more than 2,600 employees have a common purpose: to improve patients’ lives by creating innovative medicines that make a real difference.

Driving growth

Our strategy is built on four principles:

- **Drive innovation forward.** Pursue top quality science, internally and externally, balanced with medical need and commercial potential.
- **Leverage our global presence.** Expand innovative commercial capabilities to new customers and regions. Manage alliances, putting the product first.
- **Maximize the value of innovation.** Develop projects ourselves and seek partners or out-license when necessary to maximize value.
- **Insist on the highest quality in all we do.** Quality is crucial and needs to be ingrained across all functions.

EMPLOYEES

Employees Actelion Group Total: 2,624

(December 2016)

- Clinical Development
- Corporate Functions
- Drug Discovery
- Marketing & Sales

Total: 2,624

- 1,443
- 341
- 388
- 452

Actelion’s employees are dedicated to innovation and excellence, committed to improving patients’ lives through the development of innovative medicines.
**MARKETED PRODUCTS**

**Our PAH Franchise**

Pulmonary arterial hypertension (PAH) is a chronic, life-threatening disorder characterized by abnormally high blood pressure in the arteries between the heart and lungs of an affected individual.

Actelion’s PAH franchise encompasses oral, inhaled and intravenous formulations of compounds, for patients at various stages in the course of this disease (PAH Functional Classes II–IV), enabling us to deliver treatments across the entire continuum of care.

**Opsumit®**

Opsumit (macitentan), an orally available endothelin receptor antagonist, resulted from a tailored drug discovery process in Actelion’s laboratories.

Opsumit is commercially available in over 45 markets, including the US (since November 2013), Germany (since January 2014) and Japan (since June 2015). The registration process for other countries is ongoing.

**Tracleer®**

Tracleer (bosentan), an orally available endothelin receptor antagonist, was the first oral treatment approved for PAH.

Tracleer is commercially available in over 60 markets, including the US (since November 2001), the European Union (since May 2002), and Japan (since April 2005).

In addition to the indication in PAH, Tracleer is approved in the EU for the reduction in the number of new digital ulcers in patients suffering from systemic sclerosis and ongoing digital ulcer disease.

**Uptravi®**

Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, is the only approved oral, selective IP receptor agonist targeting the prostacyclin pathway in PAH.

Uptravi is commercially available in 9 countries including the US (since January 2016) and Germany (since June 2016). Market authorization has been received in Australia, Canada, the European Union, Japan, New Zealand, South Korea, Switzerland and the US. The registration process for other countries is ongoing.

**Veletri®**

Veletri (epoprostenol for injection), an intravenous prostacyclin, is stable at room temperature (77°F/25°C) for up to 24 hours, removing the need for patients to carry ice packs.

Veletri is commercially available in 17 markets, including the US (since 2010), Switzerland and Canada, marketed as Caripul® (since 2012), Japan, marketed as Epoprostenol "ACT", and some European markets (since 2013). The registration process for other countries is ongoing.

**Ventavis®**

Ventavis (iloprost), an inhaled formulation of iloprost, is a synthetic compound structurally similar to prostacyclin (PGI2).


More information on our products can be found in Actelion's Marketed Products fact sheet.
Our Specialty Products
Actelion is creating specialty franchises alongside PAH – discovering, developing and/or in-licensing/acquiring products in new therapeutic areas.

Valchlor®

Valchlor (mechlorethamine) 0.016% gel is applied topically once daily to affected areas of the skin. Valchlor is currently only available in the US and is approved for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy.

Valchlor is commercially available in the US (since November 2013) and Israel (since April 2016).

Zavesca®

Zavesca (miglustat) available as oral capsules, is a glucosylceramide synthase inhibitor indicated as monotherapy for the treatment of adult patients with mild to moderate type I Gaucher disease (GD-1) for whom enzyme replacement therapy is not a therapeutic option.

Zavesca is commercially available for the treatment of GD-1 in 47 countries, including the US and the European Union (since 2003).

In the European Union, Zavesca is also indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C (NP-C) disease, a very rare, invariably progressive and eventually fatal neurodegenerative genetic disorder affecting both children and adults.

Zavesca is commercially available for the treatment of NP-C in 46 countries, including the European Union (since 2009) and Japan, marketed as Brazaves® (since 2012).

More information on our products can be found in Actelion’s Marketed Products fact sheet.
CLINICAL DEVELOPMENT

Actelion’s promising development pipeline comprises novel compounds addressing a broad range of diseases, including cardiovascular and immunological disorders as well as central nervous system disorders and infectious disease.

Actelion’s late-stage product candidates include: a novel antibiotic, cadazolid, under investigation for *Clostridium difficile*-associated diarrhea (CDAD) and a S1P1 receptor modulator, ponesimod, investigated in multiple sclerosis.

More information on these and our other development activities can be found in Actelion’s Clinical Development fact sheet.

DRUG DISCOVERY

Actelion’s efforts in drug discovery focus on the design, synthesis and optimization of small molecular weight molecules, which are active on molecular target families. This focus allows high productivity in the generation of innovative compounds potentially addressing a wide range of high unmet medical needs.

Initially, the company looked solely at G-protein coupled receptors (GPCRs) and a specific enzyme family known as aspartic proteinases. As the company’s capabilities have expanded, so too have the target platforms, adding anti-infective’s, ion channels and a broad range of soluble enzymes.

More information on our platforms of expertise can be found in Actelion’s Drug Discovery fact sheet.
## Development Pipeline – Actelion's Focus on High Unmet Medical Needs

<table>
<thead>
<tr>
<th>Phase</th>
<th>Compound</th>
<th>Indication</th>
<th>Study</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase III</td>
<td>Cadazolid</td>
<td><em>Clostridium difficile</em>-associated diarrhea</td>
<td>IMPACT</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>Pediatric PAH</td>
<td>TOMORROW</td>
<td>Initiating</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>Portopulmonary hypertension (PoPH)</td>
<td>PORTICO</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>Fontan-palliated</td>
<td>RUBATO</td>
<td>Initiating</td>
</tr>
<tr>
<td></td>
<td>Ponesimod</td>
<td>Multiple sclerosis</td>
<td>OPTIMUM</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Ponesimod</td>
<td>Multiple sclerosis</td>
<td>POINT</td>
<td>Ongoing</td>
</tr>
<tr>
<td>Phase II</td>
<td>Cenerimod</td>
<td>Systemic lupus erythematosus</td>
<td></td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Clazosentan</td>
<td>Reversal of vasospasm associated with aneurysmal subarachnoid hemorrhage</td>
<td>REVERSE</td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Dual Orexin Receptor Antagonist</td>
<td>Insomnia</td>
<td></td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Endothelin Receptor Antagonist</td>
<td>Specialty cardiovascular disorders</td>
<td></td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Macitentan</td>
<td>Chronic thromboembolic pulmonary hypertension</td>
<td>MERIT</td>
<td>Complete</td>
</tr>
<tr>
<td>Phase Ib</td>
<td>Lucerastat</td>
<td>Fabry disease</td>
<td></td>
<td>Complete</td>
</tr>
<tr>
<td>Phase I</td>
<td>New Chemical Entity</td>
<td>Cardiovascular disorders</td>
<td></td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>New Chemical Entity</td>
<td>Inflammatory disorders</td>
<td></td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>Selective Orexin 1 Receptor Antagonist</td>
<td>Neurological disorders</td>
<td></td>
<td>Ongoing</td>
</tr>
<tr>
<td></td>
<td>T-type Calcium Channel Blocker</td>
<td>Neurological disorders</td>
<td></td>
<td>Ongoing</td>
</tr>
</tbody>
</table>
**ACTELION’S PARTNERSHIPS**

Actelion has a dedicated team focused on identifying innovation from external sources that complements our business approach. Once identified, Actelion is rapid, proactive and open in creating benefits for both parties. We commit ourselves to the project we share with our partner, to make the product a global success.

**Actelion/ReveraGen**

Actelion has obtained an exclusive option to in-license ReveraGen’s lead compound vamorolone for the treatment of Duchenne Muscular Dystrophy at two different stages in its development.

**Actelion/Nippon Shinyaku Alliance**

Actelion and Nippon Shinyaku entered into an exclusive worldwide alliance in April 2008 to collaborate on selexipag, the first selective oral prostacyclin IP receptor agonist, for patients suffering from pulmonary arterial hypertension (PAH). This compound was originally discovered and synthesized by Nippon Shinyaku.

**Actelion/Bayer Schering Pharma AG Alliance**

Actelion holds the exclusive US rights for inhaled iloprost, sold under the brand name Ventavis®, the first approved inhaled treatment for pulmonary arterial hypertension (PAH), licensed from Bayer Schering Pharma (through the acquisition of CoTherix Inc.).

**COMPANY MILESTONES**

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2017</td>
<td>Actelion enters into a definitive transaction agreement with Johnson &amp; Johnson</td>
</tr>
<tr>
<td>2016</td>
<td>Agreement on in-licensing option for vamorolone from ReveraGen</td>
</tr>
<tr>
<td>2015</td>
<td>Initiation of a Phase III program with macitentan in children with PAH</td>
</tr>
<tr>
<td>2014</td>
<td>Selexipag meets primary endpoint in pivotal Phase III GRIPHON outcome study in patients with PAH</td>
</tr>
<tr>
<td>2013</td>
<td>Initiation of Phase III program with cadazolid in patients with <em>Clostridium difficile</em>-associated diarrhea</td>
</tr>
</tbody>
</table>

**2012**

Macitentan meets primary endpoint in pivotal Phase III SERAPHIN outcome study in patients with pulmonary arterial hypertension

**2010**

Veletri is launched in the US further strengthening Actelion’s PAH franchise

**2009**

Tracleer receives EU approval of pediatric formulation for the treatment of PAH

Zavesca receives EU approval for Niemann–Pick type C disease

**2008**

Tracleer receives EU approval for treatment of patients with mildly symptomatic PAH

Actelion and Nippon Shinyaku enter into a license agreement on novel orally available IP receptor agonist for the treatment of PAH

**2007**

Tracleer receives EU approval for reduction of number of new digital ulcerations in systemic sclerosis patients

**2006**

Definitive agreement to acquire US-based CoTherix, Inc. adding Ventavis® to Actelion’s product offerings in the US

**2003**

First approval of Zavesca® for the treatment of Type 1 Gaucher disease

**2001**

First approval of Tracleer for the treatment of pulmonary arterial hypertension (PAH)

**2000**

Initial Public Offering (IPO); Actelion shares are listed on the Swiss New Market Stock Exchange with a record valuation of CHF 1.2 billion

**1997**

Foundation of Actelion December 17, 1997
Financial performance for the full year 2016.

2016 was an outstanding year for Actelion with the company delivering record sales and earnings alongside a continued focus on maximizing shareholder value. During 2016, product sales rose 15% at CER\(^1\) to reach 2,412 million Swiss francs. This excellent performance was mostly driven by the strong Uptava\(^\text{®}\) launch in the United States and continued strong Opsumit\(^\text{®}\) uptake in markets around the globe.

Actelion continues to measure and report on its core operating results which more accurately reflect the underlying business performance. Core results exclude contract revenues, as well as costs related to employees stock compensation programs, depreciation, amortization, impairments and other items that management deems exceptional.

The strong commercial performance coupled with tight financial oversight resulted in core operating income growth of 17% at CER to 992 million Swiss francs and core earnings per share growth of 27% at CER to 8.18 Swiss francs.

US GAAP operating income increased by 14% whilst US GAAP diluted EPS increased by 25%, both at CER.

\(^1\) CER percentage changes are calculated by reconsolidating both the 2016 and 2015 results at constant currencies (the average monthly exchange rates for 2015)
In the US, sales increased by 25% at CER, driven by the strong Uptravi launch, the continued Opsumit momentum resulting in share gains in an expanding ERA market. European sales were 1% higher compared to 2015. A strong Opsumit performance and solid Tracleer use in the digital ulcer indication was impacted by continued pricing pressure and market erosion from bosentan generics, particularly in Spain. Sales in Japan increased by 19% at CER, mostly driven by very strong sales of Opsumit (launched in June 2015), the Tracleer momentum in digital ulcer indication and Zavesca® (Japanese trade name Brazaves®).

Comparing average exchange rates for 2016 to 2015, the Swiss franc weakened, mostly against the US dollar, euro and Japanese yen, resulting in a positive currency variance of 63 million Swiss francs.

Actelion’s excellent commercial performance during 2016 was driven by the outstanding Uptravi launch in the US and Opsumit’s sustained strong growth trajectory. During the fourth quarter of 2016, combined sales of the company’s outcome-based PAH portfolio, Opsumit, Uptravi and Veletri®, reached 55% of total sales, demonstrating the significant progress made in the fundamental transformation of the PAH business.

The full financial statements can be found on www.actelion.com.
Core cost of sales for 2016 increased by 17% at CER to 209 million Swiss francs. Royalty expenses on sales for 2016 were 7% lower compared to 2015 at CER. This decrease was mainly due to ceased royalty obligations, following the patent expiry of Tracleer® in the US (late November 2015) and Ventavis (mid-March 2015) and a favorable product mix with a low single-digit royalty rate paid on Opsumit sales compared to a high single-digit rate paid on Tracleer sales in markets where Tracleer is still under patent protection. This decrease was partially offset by mid-teen royalty payments to Nippon Shinyaku related to Uptravi sales outside of Japan. Royalty expenses on profit sharing relate to the collaboration with Nippon Shinyaku for the commercialization of Opsumit in Japan and amounted to 20 million Swiss francs for 2016 as Opsumit sales in Japan increased strongly. Cost of goods sold increased by 31% in 2016. The increase was driven by higher sales along with a different product mix and some one-off Uptravi launch inventory write-offs.

The excellent commercial performance enabled Actelion to advance both the late and earlier stage pipeline resulting in increased R&D expenditure which translates into a ratio of R&D core operating expenses to sales of 21%, slightly higher than in 2015. Core R&D expenses amounted to 509 million Swiss francs, an increase of 25% at CER. This increase was driven by higher clinical trial expenses, mainly driven by the strong recruitment in the Phase III OPTIMUM study (ponesimod in multiple sclerosis announced in April 2015) and the Phase III IMPACT study (Cadazoloid in Clostridium difficile associated diarrhea), as well as costs related to the preparation and initiation for Phase II studies for DORA in insomnia and Actelion’s new endothelin receptor antagonist in specialty cardiovascular disorders.

Core marketing, selling and distribution expenses amounted to 501 million Swiss francs, an increase of 7% at CER. This increase was driven mostly by costs relating to launch activities of Uptravi in the United States, Germany and other geographies. Additionally, the company continued the roll-out of Opsumit and Veletri in various markets around the globe. G&A expenses increased by 6% to 202 million Swiss francs as the company expanded its global footprint.

Core operating income amounted to 992 million Swiss francs, an increase of 17% or 135 million Swiss francs at CER. The weakening of the Swiss franc against the major currencies affecting Actelion’s performance had a positive impact of 43 million Swiss francs on core operating income.

The increase in core and US GAAP EPS was driven by higher net income and the decrease in number of common shares. The average share count for diluted EPS decreased by 4.7 million shares as the average number of dilutive instruments decreased by 1.0 million shares despite an increase in the average share price (158.02 Swiss francs per share during 2016 compared to 126.96 Swiss francs during 2015).
SHARES AT A GLANCE
The registered shares of Actelion Ltd were listed on the SWX New Market on April 6, 2000 (symbol: ATLN). A total of 1,000,000 primary shares were placed at the company’s Initial Public Offering (IPO), at a price of CHF 260 per share, raising CHF 246.6 million.

On 8 July 2008, the Management Committee of the SIX Swiss Exchange added Actelion shares (ATLN, CH0010532478) to the Swiss Market Index SMI®. Actelion shares have traded as part of the SMI since 22nd September 2008.

On 22 August 2016, Actelion announced that it completed its first-line share purchase program (initiated on 9 December 2013) on 19 August 2016. During this time, Actelion purchased 10,000,000 of its own shares, which represents 8.31% of the issued shares at the time of the start of the share purchases. The shares were used for the reactive servicing of existing employee option and share ownership programs.

On 8 April 2015, Actelion commenced the repurchase of up to 10 million shares of the company’s common stock over the next three years via a second trading line on the SIX Swiss exchange. At subsequent Annual General Meetings, the Board of Directors will propose that the shares bought through this process be cancelled and the issued share capital reduced accordingly.

Actelion Ltd is part of the following indices: SMI, SPI, SLI, SPIMLC, SPI20, SPISMC, SXSP, SXDP, SBC100, SNSPIX, SMHCAX, SDLI, SXI LIFE SCIENCES and SXI

Key Share Data
As of 31 December 2016:

<table>
<thead>
<tr>
<th>Shares outstanding</th>
<th>107.8 million</th>
</tr>
</thead>
<tbody>
<tr>
<td>Closing share price</td>
<td>220.5</td>
</tr>
<tr>
<td>Market capitalization</td>
<td>23.8 billion</td>
</tr>
<tr>
<td>52-week high</td>
<td>223.90</td>
</tr>
<tr>
<td>52-week low</td>
<td>122.50</td>
</tr>
<tr>
<td>YTD price change</td>
<td>58%</td>
</tr>
<tr>
<td>Average daily volume</td>
<td>536k</td>
</tr>
<tr>
<td>Free float</td>
<td>95.7%</td>
</tr>
</tbody>
</table>

Shareholdings
As of 31 December 2016:

| Number of registered shareholders | 10,727 |

Major shareholders

<table>
<thead>
<tr>
<th>Management &amp; Directors</th>
<th>&gt;5 %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Actelion Ltd</td>
<td>&gt;3 %</td>
</tr>
<tr>
<td>Rudolf Maag</td>
<td>&gt;3 %</td>
</tr>
<tr>
<td>Dan Och</td>
<td>&gt;3 %</td>
</tr>
<tr>
<td>Blackrock</td>
<td>&gt;5 %</td>
</tr>
</tbody>
</table>

ACTELION’S MARKETED PRODUCTS

Actelion has over 1,000 highly experienced sales, marketing and medical professionals with a proven track record in both specialty and GP markets. The company has over 30 operative affiliates and reaches more than 30 additional markets through partner arrangements. This global reach, means that Actelion is fully equipped to optimize returns from current opportunities, as well as launch and commercialize future assets.

Our commercial operations are aligned to:

- Focus on all of Actelion’s opportunities and create accountability close to the customer.
- Allow scalability, from both organizational and managerial perspectives to be able to manage growth flexibly.
- Ensure an efficient and effective interaction across functions and with partners.

Business Strategy & Operations has highly experienced people with a proven track record in both specialty and GP markets to compete in an increasingly complex business environment. Together the group is now well placed to not only drive commercial excellence and leverage our unrivalled PAH leadership and orphan drug expertise, but also lead transformational growth initiatives and shape markets and medical utility for the potential which lies ahead.
OUR PAH FRANCHISE

Pulmonary arterial hypertension (PAH) is a chronic, life-threatening disease characterized by abnormally high blood pressure in the arteries between the heart and lungs of an affected individual.

Actelion’s PAH franchise encompasses oral, inhaled and intravenous formulations of compounds, for patients at various stages in the course of this disease (PAH Functional Classes II–IV), enabling Actelion to deliver treatments across the entire continuum of care.

**Opsumit** (macitentan)
Opsumit (macitentan), an orally available endothelin receptor antagonist, resulted from a tailored drug discovery process in Actelion’s laboratories.

**Tracleer** (bosentan)
Tracleer (bosentan), an orally available endothelin receptor antagonist, was the first oral treatment approved for PAH.

**Uptravi** (selexipag)
Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, is the only approved oral, selective IP receptor agonist targeting the prostacyclin pathway in PAH.

**Veletri** (epoprostenol for injection), an intravenous prostacyclin, is stable at room temperature (77°F/25°C) for up to 24 hours, removing the need for patients to carry ice packs.

**Ventavis** (iloprost), an inhaled formulation of iloprost, is a synthetic compound structurally similar to prostacyclin (PGI2). It is marketed by Actelion in the US and by Bayer Healthcare elsewhere.
CURRENT INDICATIONS
In the US, Opsumit is indicated for the treatment of PAH, WHO Group I to delay disease progression. Disease progression included: death, initiation of intravenous (IV) or subcutaneous prostanoids, or clinical worsening of PAH (decreased 6-minute walk distance, worsened PAH symptoms and need for additional PAH treatment). Opsumit also reduced hospitalization for PAH.

Effectiveness was established in a long-term study in PAH patients with predominantly WHO FC II-III symptoms treated for an average of 2 years. Patients were treated with Opsumit monotherapy or in combination with phosphodiesterase-5 inhibitors or inhaled prostanoids. Patients had idiopathic and heritable PAH (57%), PAH caused by connective tissue disorders (31%), and PAH caused by congenital heart disease with repaired shunts (8%).

In Europe, Opsumit is indicated, as monotherapy or in combination, for the long-term treatment of PAH in adult patients of WHO Functional Class (FC) II to III. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.

Opsumit is very likely to cause major birth defects. It is contraindicated for use in pregnancy. In the US, Opsumit is distributed under a risk evaluation and mitigation strategy.

PRODUCT AVAILABILITY & REGULATORY STATUS
Opsumit is commercially available in over 45 markets, including the US (since November 2013), Germany (since January 2014) and Japan (since June 2015). The registration process for other countries is ongoing.

For the current availability status, visit www.actelion.com.

AVAILABLE CLINICAL DATA
SERAPHIN, a global, pivotal Phase III study, was designed to evaluate the efficacy and safety of macitentan in patients with symptomatic PAH, through the primary endpoint of time to first morbidity and all-cause mortality event.

A total of 742 patients were randomized to placebo (n=250), macitentan 3 mg (n=250), or macitentan 10 mg (n=242). The primary endpoint occurred in 46.4%, 38.0%, and 31.4% of the patients in these groups, respectively. The hazard ratio for macitentan 3 mg versus placebo was 0.70 (97.5% CI, 0.52 to 0.96; p=0.0108) and the hazard ratio for macitentan 10 mg versus placebo was 0.55 (97.5% CI, 0.39 to 0.76; p<0.0001). Worsening of pulmonary arterial hypertension was the most frequent primary endpoint event. Patients were allowed to receive PAH background therapy throughout the study, either PDE-5 inhibitors or oral/inhaled prostanoids. The effect of macitentan on the endpoint was observed irrespective of background therapy for pulmonary arterial hypertension. The most commonly reported adverse drug reactions with Opsumit were nasopharyngitis (14.0%), headache (13.6%) and anemia (13.2%).

MILESTONES
2014 Opsumit launched in the EU
2013 Opsumit launched in the US
2013 FDA approval & EMA market authorization of Opsumit in PAH
2012 SERAPHIN outcome study meets the primary endpoint
2007 Initiation of Phase III SERAPHIN study in PAH patients

KEY SCIENTIFIC LITERATURE
• Iglarz M et al. J Pharmacol Exp Ther. 2008;327(3):736-45

MARKETED PRODUCTS
OPSUMIT®
TRACLEER®
UPTRAVI®
VELETRI®
VENTAVIS®
OUR SPECIALTY PRODUCTS
VALCHLOR®
ZAVESCA®
TRACLEER®

Tracleer (bosentan), an orally available endothelin receptor antagonist, was the first oral treatment approved for PAH.

CURRENT INDICATIONS
In the US, Tracleer is indicated for the treatment of PAH (WHO Group 1) to improve exercise ability and to decrease clinical worsening.

Studies establishing effectiveness included predominantly patients with NYHA Functional Class II–IV symptoms and etiologies of idiopathic or heritable PAH (60%), PAH associated with connective tissue diseases (21%), and PAH associated with congenital systemic-to-pulmonary shunts (18%).

Considerations for use: Patients with WHO class II symptoms showed reduction in the rate of clinical deterioration and a trend for improvement in walk distance. Physicians should consider whether these benefits are sufficient to offset the risk of liver injury in WHO class II patients, which may preclude future use as their disease progresses.

In Europe, Tracleer is approved for treatment of PAH Functional Class III to improve exercise capacity and symptoms, as well as PAH Functional Class II, where some improvements have also been shown.

In the EU, Tracleer is also indicated to reduce the number of new digital ulcers in patients with systemic sclerosis and ongoing digital ulcer disease.

A quadrisect, dispersible 32 mg tablet formulation of Tracleer has been approved in the EU for children. In addition, Tracleer is approved for the treatment of PAH in children aged from 1 year old.

Tracleer can cause serious liver damage, including in rare cases liver failure, and is very likely to cause major birth defects. It is contraindicated for use with cyclosporine A, glyburide, and in pregnancy and breast feeding. In the US, Tracleer is distributed under a risk evaluation and mitigation strategy.

PRODUCT AVAILABILITY & REGULATORY STATUS
Tracleer is commercially available in over 60 markets, including the US (since November 2001), the European Union (since May 2002), and Japan (since April 2005).

For the current availability status, visit www.actelion.com.

AVAILABLE CLINICAL DATA
A comprehensive clinical trial program has been conducted to evaluate the efficacy and safety of Tracleer across a broad range of PAH patient populations.

For a detailed analysis of the study results, refer to the scientific publications - reference information is given in the key scientific literature section.

MILESTONES
2015 Additional pediatric data included in the Tracleer European Product Information
2009 Tracleer receives EU approval of pediatric formulation for the treatment of PAH
2005 Tracleer launched in Japan
2002 Tracleer launched in the EU
2001 Tracleer launched in US

KEY SCIENTIFIC LITERATURE
• Study 351: Channick RN et al. Lancet. 2001;358:1119-23
• Breathe-4: Sitbon O et al. Am J Respir Crit Care Med. 2004;170:1212-17
• Breathe-5: Galiè N et al. Circulation. 2006;114:48-54
• Early: Galiè N et al. Lancet. 2008;371:2093-100

MARKETED PRODUCTS
OPSUMIT® TRACLEER® UPTRAVI® VELETRI® VENTAVIS® OUR SPECIALTY PRODUCTS VALCHLOR® ZAVESCA®
UPTRAVI®

Uptravi (selexipag), originally discovered and synthesized by Nippon Shinyaku, is the only approved oral selective IP receptor agonist targeting the prostacyclin pathway in PAH.

CURRENT INDICATIONS
In the US, Uptravi is indicated for the treatment of PAH (WHO Group I) to delay disease progression and reduce the risk of hospitalization for PAH. Effectiveness was established in a long-term study in PAH patients with WHO Functional Class II-III symptoms. Patients had idiopathic and heritable PAH (58%), PAH associated with connective tissue disease (29%), and PAH associated with congenital heart disease with repaired shunts (10%).

In Europe, Uptravi is indicated for the long-term treatment of PAH in adult patients with WHO functional class II-III, either as combination therapy in patients insufficiently controlled with an endothelin receptor antagonist (ERA) and/or a phosphodiesterase type 5 (PDE-5) inhibitor, or as monotherapy in patients who are not candidates for these therapies. Efficacy has been shown in a PAH population including idiopathic and heritable PAH, PAH associated with connective tissue disorders, and PAH associated with corrected simple congenital heart disease.

As with other therapies targeting the prostacyclin pathway, hyperthyroidism has been observed with Uptravi. If there are any signs of pulmonary edema, the possibility of pulmonary veno-occlusive disease should be considered and, if confirmed, Uptravi should be discontinued. Other adverse events observed with Uptravi usage were similar in nature to those expected with prostacyclin receptor agonists.

PRODUCT AVAILABILITY & REGULATORY STATUS
Uptravi is commercially available in 9 countries, including the US (since January 2016), and Germany (since June 2016).

Market authorization has been received in Australia, Canada, the European Union, Japan, New Zealand, South Korea, Switzerland and the US.

Submission of the registration dossier to other health authorities is ongoing.

For current information, visit www.actelion.com.

AVAILABLE CLINICAL DATA
GRIPHON, a global, pivotal Phase III study, was designed to demonstrate a prolongation of time to the first morbidity/mortality event for selexipag compared to placebo and to evaluate the safety of selexipag in PAH patients.

A total of 1'156 patients were randomized to receive placebo or selexipag. Utilizing a dosing scheme that titrated patients up to their individualized doses, dosing in GRIPHON was initiated at 200 micrograms (mcg) twice daily (b.i.d) and increased weekly in steps of 200 mcg up to a maximum of 1600 mcg b.i.d. If patients were unable to tolerate a dose, the dose was reduced to previously tolerated dose. A primary endpoint event occurred in 397 patients – 41.6% of those in the placebo group and 27.0% of those in the selexipag group (hazard ratio in the selexipag group as compared with the placebo group, 0.60; 99% confidence interval, 0.46 to 0.78; P<0.0001). Disease progression and hospitalization accounted for 81.9% of the events. At baseline, 80% of patients were receiving oral medication specific for PAH: either an ERA, a PDE-5 inhibitor, or a combination of the two.
The effect of selexipag with respect to the primary endpoint was similar in the subgroup of patients who were not receiving treatment for the disease at baseline and in the subgroup of patients who were already receiving PAH-specific treatment at baseline (including those who were receiving a combination of both ERA and PDE-5 inhibitor). Adverse reactions occurring more frequently on Uptravi compared to placebo by ≥3%, over the course of the study, were headache, diarrhea, jaw pain, nausea, myalgia, vomiting, pain in extremity, flushing, arthralgia, anemia, decreased appetite and rash. These adverse reactions were more frequent during the dose titration phase. Hyperthyroidism was observed in 1% (n=8) of patients on selexipag and in none of the patients on placebo.

**MILESTONES**
- 2016 Market authorization for Uptravi in the EU
- 2016 Uptravi launched in the US
- 2015 Uptravi approved by US FDA
- 2014 GRIPHON outcome study meets the primary endpoint
- 2008 Actelion in-licensed selexipag from Nippon Shinyaku

**KEY SCIENTIFIC LITERATURE**
**CURRENT INDICATIONS**

In the US, Veletri is indicated for the treatment of PAH (WHO Group 1) to improve exercise capacity. Studies establishing effectiveness included predominantly patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH or PAH associated with connective tissue diseases.

In some EU countries, Veletri is indicated for the treatment of PAH (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III–IV symptoms to improve exercise capacity. Veletri is also indicated for use in haemodialysis in emergency situations, when the use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated.

Veletri must be reconstituted and diluted only as directed using Sterile Water for Injection, or Sodium Chloride 0.9% Injection. Veletri must not be reconstituted or mixed with any other intravenous medications or solutions prior to or during administration. Most common side effects include headache, jaw pain, flushing, diarrhea, nausea and vomiting, hypotension, abdominal pain, arthralgia, flu-like symptoms, decreased platelet count, bleeding, tachycardia, bradycardia, chest pain, rash, pain, and anxiety/nervousness. Sepsis and septicemia, mostly related to delivery system for Veletri were commonly reported. In order to reduce the risk of catheter related blood stream infections, the care of the central venous catheter and the catheter exit site should follow established medical principles. Excessive doses of Veletri may acutely result in systemic low blood pressure, rapid heartbeat, jaw pain, headache, flushing, nausea and vomiting, diarrhea, flu-like symptoms, or anxiety; excessive doses administered continuously can lead to extreme restlessness and high-output cardiac failure.

Abrupt withdrawal or sudden large reductions in dosage of Veletri may result in symptoms associated with rebound pulmonary hypertension, including dyspnea, dizziness, and asthenia and may result in death. Therefore abrupt withdrawal should be avoided.

**PRODUCT AVAILABILITY & REGULATORY STATUS**

Veletri is commercially available in 17 markets, including the US (since 2010), Switzerland and Canada - marketed as Caripul® - (since 2012), Japan - marketed as Epoprostenol “ACT” - and some European markets (since 2013). The registration process for other countries is ongoing.

For current availability status, visit www.actelion.com

**MILESTONES**

- **2013** Veletri launched in some European markets and Japan (marketed as Epoprostenol “ACT”)
- **2012** Veletri launched in Switzerland and Canada (marketed as Caripul)
- **2010** Veletri launched in the US
- **2009** Actelion acquired Veletri from GeneraMedix Inc.
- **2008** FDA approved epoprostenol for injection for treatment of primary pulmonary hypertension in the US

**KEY SCIENTIFIC LITERATURE**


**MARKETED PRODUCTS**

- UPTRAVI®
- TRACLEER®
- VALCHLOR®
- VENTAVIS®
- ZAVESCA®
- OUR SPECIALTY PRODUCTS
- OUR PAH FRANCHISE
- VELETRI®
VENTAVIS®

Ventavis (iloprost), an inhaled formulation of iloprost, is a synthetic compound structurally similar to prostacyclin (PGI2).

CURRENT INDICATIONS
In the US, Ventavis is indicated for the treatment of PAH (WHO Group 1) to improve a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and lack of deterioration.

Studies establishing effectiveness included predominately patients with NYHA Functional Class III-IV symptoms and etiologies of idiopathic or heritable PAH (65%) or PAH associated with connective tissue diseases (23%).

PRODUCT AVAILABILITY & REGULATORY STATUS

AVAILABLE CLINICAL DATA
In a controlled clinical trial, Ventavis improved a composite endpoint consisting of exercise tolerance, symptoms (NYHA Class), and the absence of clinical deterioration.

For patients with PAH (WHO Group 1) with NYHA Class III or IV symptoms, Ventavis has been shown to:

- Significantly increase (p = 0.0033) patient improvement after 12 weeks of treatment compared to baseline on a composite endpoint of improved exercise capacity 30 minutes after dosing, improvement of at least one NYHA class and no clinical deterioration.
- Significantly improve 6-minute walk distance at week 12 with a 10% or greater increase in individual walk distance (p < 0.01).
- Significantly improve patients’ functional class at week 12 (p = 0.03).

Most common (>3% placebo adjusted) adverse reactions are vasodilation (flushing), cough increased, headache, trismus, insomnia, nausea, hypotension, vomiting, alkaline phosphatase increased, flu syndrome, back pain, tongue pain, palpitations, syncope, GGT increased, muscle cramps, hemoptysis, and pneumonia.

In December 2006, data from the Phase II/III clinical trial STEP, evaluating the use of Ventavis (iloprost) inhalation solution therapy in patients with PAH already undergoing treatment with bosentan, were published. The analysis of this study showed that the combination of Ventavis added to bosentan therapy was well tolerated, and was consistent with the safety profile observed in patients receiving only iloprost.

MILESTONES

2009  Ventavis receives US approval for increased 20 mcg/ml strength formulation

2007  Actelion acquires CoTherix Inc, adding Ventavis to its product offerings

2004  FDA approved inhaled iloprost for treatment of PAH in the US

KEY SCIENTIFIC LITERATURE

- Ivy et al. J Am Coll Cardiol. 51(2):161-9; 2008
- Hoeper et al. Eur Respir J. 26(5):858-63; 2005
OUR SPECIALTY PRODUCTS

Actelion is creating specialty franchises alongside PAH – discovering, developing and/or in-licensing/acquiring products in new therapeutic areas.

Valchlor®

Valchlor (mechlorethamine) 0.016% gel is applied topically once daily to affected areas of the skin. Valchlor is currently only available in the US and is approved for the topical treatment of Stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma in patients who have received prior skin-directed therapy.

Zavesca®

Zavesca (miglustat) available as oral capsules, is a glucosylceramide synthase inhibitor indicated as monotherapy for the treatment of adult patients with mild to moderate type I Gaucher disease for whom enzyme replacement therapy is not a therapeutic option.

In the European Union, Zavesca is also indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C (NP-C) disease, a very rare, invariably progressive and eventually fatal neurodegenerative genetic disorder affecting both children and adults.
Valchlor (mechlorethamine) gel 0.016% is applied topically once a day to affected areas of the skin. Valchlor is the first and only FDA-approved topical formulation of mechlorethamine.

**CURRENT INDICATIONS**
In the US, Valchlor gel 0.016% is indicated for the topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (MF-CTCL) in patients who have received prior skin-directed therapy.

**PRODUCT AVAILABILITY & REGULATORY STATUS**
Valchlor is commercially available in the US (since November 2013) and Israel (since April 2016).

Regulatory review with the European health authorities is ongoing.

**AVAILABLE CLINICAL DATA**
The efficacy of Valchlor was assessed in a randomized, multicenter, observer-blind, non-inferiority trial of 260 patients. Patients were stratified based on Stage (IA vs IB and IIA) and then randomized to receive Valchlor gel 0.016% w/w of mechlorethamine (equivalent to 0.02% mechlorethamine HCl) or Aquaphor®-based mechlorethamine HCl 0.02% ointment (compounded mechlorethamine). Patients had received at least one prior skin-directed therapy. Qualifying prior therapies included topical corticosteroids, phototherapy, Targretin® gel, and topical nitrogen mustard. Patients were not required to be refractory to or intolerant of prior therapies. Treatments were applied topically on a daily basis for 12 months.

60% of the patients on the Valchlor arm and 48% of patients on the comparator arm achieved a response based on the Composite Assessment of Index Lesion Severity (CAILS) score. Valchlor was non-inferior to the comparator based on a CAILS overall response rate ratio of 1.24 (95% CI 0.98, 1.58). Complete responses constituted a minority of the CAILS or Severity Weighted Assessment Tool (SWAT) overall responses. The onset of CAILS overall response for both treatment arms showed a wide range from 1 to 11 months.

The most common adverse reactions (≥5%) were dermatitis (56%), pruritus (20%), bacterial skin infection (11%), skin ulceration or blistering (6%), and skin hyperpigmentation (5%). These reactions may be moderately severe or severe. Elderly patients aged 65 and older may be more susceptible. Depending on severity, treatment reduction, suspension, or discontinuation may be required.

**MILESTONES**
- 2013 Valchlor launched in the US
- 2013 Actelion acquires Ceptaris Therapeutics, Inc., adding Valchlor to its specialty product offerings in the US
- 2013 Valchlor approved in the US

**KEY SCIENTIFIC LITERATURE**
CURRENT INDICATIONS
In the US, Zavesca is indicated as monotherapy for the treatment of adult patients with mild to moderate type 1 Gaucher disease (GD-1) for whom enzyme replacement therapy is not a therapeutic option (e.g. due to allergy, hypersensitivity, or poor venous access).

In the European Union, Zavesca is also indicated for the treatment of progressive neurological manifestations in adult patients and paediatric patients with Niemann-Pick type C (NP-C) disease, a very rare, invariably progressive and eventually fatal neurodegenerative genetic disorder affecting both children and adults.

PRODUCT AVAILABILITY & REGULATORY STATUS
Zavesca is commercially available for the treatment of mild to moderate type 1 Gaucher disease in 47 countries, including the US and the European Union since 2003.

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

For full availability listing, visit www.actelion.com

AVAILABLE CLINICAL DATA
The approval for Zavesca in type 1 Gaucher disease was based on three international open-label clinical trials. The rationale for the use of miglustat in type 1 Gaucher disease is to help balance the overall level of glucosylceramide by reducing its production to a level compatible with breakdown by residual glucocerebrosidase activity, a mode of action known as “substrate reduction therapy”. Results from a pooled analysis of the three open-label clinical trials have shown that Zavesca monotherapy may reduce the incidence of bone crisis and improve bone mineral density in type 1 Gaucher disease patients, including those with a history of splenectomy and/or osteoporosis.

The most common adverse reactions (incidence ≥5%) diarrhea, weight loss, stomach pain, gas, nausea and vomiting headache including migraine, tremor, leg cramps, dizziness, weakness, vision problems, thrombocytopenia, muscle cramps, back pain, constipation, dry mouth, heaviness in arms and legs, memory loss, unsteady walking, anorexia, indigestion, paresthesia, stomach bloating, stomach pain not related to food, and menstrual changes.

Outside of the US, the approval for Zavesca in Niemann-Pick type C disease was based on a set of clinical data obtained from one clinical trial OGT918-007 and two multicenter retrospective cohort studies in patients with NP-C. In both the clinical trial and the case series, miglustat was associated with clinically relevant stabilization or improvement in neurological manifestations of the disease.

MILESTONES
2012 Miglustat approved and launched for NP-C in Japan (marketed as Brazaves®)
2009 Zavesca approved and launched for NP-C in the EU
2004 Zavesca launched for GD-1 in the US
2003 Zavesca approved and launched for GD-1 in the EU; approved for GD-1 in the US
2002 Zavesca in-licensed

KEY SCIENTIFIC LITERATURE
IN TYPE 1 GAUCHER DISEASE
• Giraldo P. et al. Haematologica. 2006; 91:125-8

IN NIEMANN-PICK TYPE C DISEASE

ZAVESCA®
Zavesca (miglustat) is an orally active competitive, reversible inhibitor of glucosylceramide synthase.
ACTELION’S CLINICAL DEVELOPMENT

DEVELOPMENT PROCESS
Actelion’s focus of bringing innovative medicines to patients in areas with high unmet medical needs can only be realized with rigorous testing of the compounds in its pipeline and thorough analysis and interpretation of the data.

Our clinical development department aims to fully explore and comprehensively describe the benefits of our compounds for patients. At the same time, we continuously assess and monitor the potential risks of new drug candidates. The group works to efficiently develop and bring innovative pharmaceutical products with an excellent benefit–risk profile to patients worldwide.

Actelion’s clinical and pharmacological research comprises multiple functions: clinical science, pharmacology, biostatistics and data management, drug safety, drug regulatory affairs, life cycle management, and clinical operations functions.

Life cycle teams, formed from representatives of preclinical and clinical development functions, technical operations and business strategy and operations, ensure an efficient development of a new medicine. They steer the compounds from the definition of a target profile and entry-into-human studies through to submission of the dossier to health authorities and commercialization until loss of exclusivity of the medicine in the major markets and beyond. They also ensure that all appropriate measures are undertaken to optimize the value creation potential of each product. The collection of innovative compounds in Actelion’s pipeline, in combination with each compound’s different phase of clinical development and the medicine’s stage of commercialization, makes this work highly diverse and demanding, yet it also satisfies our expectations for speed and cost-effectiveness in bringing new therapies to the patient.

Actelion’s clinical development functions collectively manage clinical programs to the appropriate scientific, medical and operational standards to generate the information required by health authorities worldwide.
<table>
<thead>
<tr>
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<th>Compound</th>
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<th>Status</th>
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<td>III</td>
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<td>Ponesimod</td>
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<td>Ponesimod</td>
<td>Multiple sclerosis</td>
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<tr>
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<td>Systemic lupus erythematosus</td>
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<td>Fabry disease</td>
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<td>-</td>
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<td>-</td>
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<tr>
<td></td>
<td>T-type Calcium Channel Blocker</td>
<td>Neurological disorders</td>
<td>-</td>
<td>Ongoing</td>
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</tbody>
</table>
In preclinical studies cadazolid showed potent in vitro activity against *Clostridium difficile* isolates and a low propensity for resistance development. In a human gut model of *Clostridium difficile*-associated diarrhea (CDAD), cadazolid had a very limited impact on the normal gut microflora.

Cadazolid absorption is negligible resulting in high gut lumen concentrations and low systemic exposure, even in severe cases of CDAD where the gut wall can be more damaged and drug absorption potentially increased.

The US FDA has designated cadazolid as both a Qualified Infectious Disease Product (QIDP) and a Fast Track development program for the treatment of CDAD.

**CURRENT STATUS**

Cadazolid is evaluated in the IMPACT program (International Multi-center Program Assessing Cadazolid Treatment in patients suffering from *Clostridium difficile*-associated diarrhea). The program comprises two Phase III studies comparing the efficacy and safety of cadazolid (250 mg administered orally twice daily for 10 days) versus vancomycin (125 mg administered orally four times daily for 10 days).

The IMPACT program is designed to determine whether the clinical response after administration of cadazolid is non-inferior to vancomycin in subjects with CDAD, and whether administration of cadazolid is superior to vancomycin in the sustained clinical response. The program commenced enrollment in the fourth quarter 2013 with a target of approximately 1,260 subjects worldwide, and results are expected in mid-2017.
AVAILABLE CLINICAL DATA
Cadazolid was studied in a Phase II multi-center, double-blind, randomized, active reference, parallel group, therapeutic exploratory study. The study evaluated the efficacy, safety and tolerability of a 10-day, twice daily oral administration of 3 doses (250 mg, 500 mg or 1,000 mg b.i.d.) of cadazolid in subjects with CDAD. As the current standard of care for CDAD, oral vancomycin (125 mg qid for 10 days) was used as the active reference. The study was completed in December of 2012, after having enrolled 84 subjects with CDAD. The results of the Phase II study indicate that the effect of all doses of cadazolid were numerically similar to, or better than vancomycin on key endpoints including CDAD clinical cure rates as well as sustained cure rates. Clinical cure rate was defined as the resolution of diarrhea and no further need for CDAD therapy at test-of-cure 24 to 72 hours after the last dose of treatment, while sustained cure rate was defined as clinical cure with no recurrence of CDAD up to 4 weeks post-treatment. Recurrence rates were numerically lower for all doses of cadazolid as compared to vancomycin. Cadazolid was safe and well tolerated.

MILESTONES
2014 Cadazolid receives US FDA QIDP & Fast Track designation for development in CDAD
2013 Initiation of Phase III development
2012 Completion of Phase II development

KEY SCIENTIFIC LITERATURE

CLINICAL DEVELOPMENT PIPELINE
- MACITENTAN
- PONESIMOD
- CENERIMOD
- CLAZOSENTAN
- DUAL OREXIN RECEPTOR ANTAGONIST
- ENDOTHELIN RECEPTOR ANTAGONIST
- OTHERS
**MACITENTAN**

Macitentan is an orally available endothelin receptor antagonist (ERA) that resulted from a tailored drug discovery process in Actelion’s laboratories.

Macitentan (Opsumit®) is currently approved for the treatment of pulmonary arterial hypertension (PAH), a chronic, life-threatening disorder which severely compromises the function of the lungs and heart. The product is commercially available in over 35 markets, including the US (since November 2013), Germany (since January 2014) and Japan (since June 2015). The registration process for other countries is ongoing.

**CURRENT STATUS**

Macitentan is currently being further evaluated in multiple studies to expanding the clinical utility of this important product in PAH and beyond.

**MERIT (Macitentan in the Treatment of Inoperable chronic Thromboembolic pulmonary hypertension)** was a 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 patients with inoperable chronic thromboembolic pulmonary hypertension (CTEPH).

In MERIT, 80 inoperable patients were randomized in a 1:1 ratio into 2 treatment groups (macitentan 10 mg or placebo) over a 24 week treatment period. The study started in August 2014 and was completed in September 2016.

After 16 weeks the treatment effect was a significant 16% reduction in pulmonary vascular resistance (PVR) with macitentan compared with placebo (95% CL: −30%, −1%; p=0.04 intention-to-treat (ITT)). The efficacy observed was consistent across all sub-groups, included patients receiving background PH specific therapy at baseline (61%), including PDE-5 inhibitors (59%). Mean PVR decreased from baseline in both macitentan and placebo groups (geometric mean percent ratios of Week 16/baseline 73.0% and 87.2%, respectively).

The study also showed a significant positive effect of macitentan compared to placebo on exercise capacity. After 24 weeks of treatment, the mean change in 6-minute walk distance (6-MWD) from baseline was an increase of 35 meters (m) in macitentan and 1 m in placebo. The 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).

Macitentan was well tolerated in this patient population and safety was in general consistent with the known safety profile for macitentan from previous clinical studies. The most frequently reported adverse events 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%). Hemoglobin decreases were observed in both macitentan and placebo groups and in only one subject in each group hemoglobin values decreased below 100 g/L during the study.
TOMORROW (pediatric use of macitentan to delay disease progression in PAH Worldwide) is a multicenter, controlled, randomized, open-label event-driven study to assess the efficacy, safety and pharmacokinetics of a pediatric formulation of macitentan versus standard of care in children with PAH. The study will enroll children between the age of 1 month and 18 years in more than 20 countries and is expected to last up to 6 years.

PORTICO (PORtopulmonary Hypertension Treatment with macitentan — a randomized Clinical Trial) is a randomized, double-blind, placebo-controlled, prospective, multicenter, parallel group Phase IV study to assess the safety and efficacy of macitentan in patients with portopulmonary hypertension (PoPH). The primary objective of the study is to evaluate the effect of 10 mg macitentan on pulmonary vascular resistance (PVR) as compared to placebo. Secondary objectives include the evaluation of the safety and tolerability of macitentan as compared to placebo in stable Fontan-palliated patients. The duration of the study is expected to be approximately 28 months; the start is planned for mid-2017.

RUBATO is a Phase III prospective, multi-center, double-blind, placebo-controlled parallel group study to assess the efficacy and safety of macitentan in stable Fontan-palliated adolescents and adults. The primary objective is to assess the effect of macitentan 10 mg as compared to placebo on exercise capacity through cardiopulmonary exercise testing (peak VO2). Secondary objectives include the evaluation of the safety and tolerability of macitentan as compared to placebo in stable Fontan-palliated patients. The duration of the study is expected to be approximately 28 months; the start is planned for mid-2017.
AVAILABLE CLINICAL DATA
Macitentan has been studied in SERAPHIN, a multicenter, double-blind, placebo-controlled, parallel-group, event-driven, Phase III outcome study in 742 patients with symptomatic PAH, who were randomized to three treatment groups (placebo [N = 250], 3 mg [N = 250] or 10 mg [N = 242] of macitentan once daily), to assess the long-term effect on morbidity or mortality.

Treatment with macitentan 10 mg resulted in a 45% risk reduction (hazard ratio [HR] 0.55; 97.5% CI: 0.39 to 0.76; logrank p < 0.0001) of the composite morbidity-mortality endpoint up to end of treatment (EOT) when compared to placebo. The treatment effect was established early and was sustained. In patients already on background therapy for PAH treatment with macitentan 10 mg resulted in a 38% risk reduction (HR 0.62; 97.5% CI: 0.43 to 0.8; logrank p=0.0094) of the composite morbidity-mortality endpoint compared to placebo. The risk of PAH related death or hospitalization for PAH up to EOT was reduced by 50% (HR 0.50; 97.5% CI: 0.34 to 0.75; logrank p < 0.0001) in patients receiving macitentan 10 mg (50 events) compared to placebo.

Efficacy of macitentan 10 mg on the primary endpoint was consistent across subgroups of age, sex, ethnic origin, geographical region, aetiology, by monotherapy or in combination with another PAH therapy and by WHO FC (I/II and III/IV).

The most commonly reported adverse drug reactions are nasopharyngitis (14.0%), headache (13.6%) and anaemia (13.2%, see section 4.4). The majority of adverse reactions are mild to moderate in intensity.

MILESTONES
2013  Opsumit approved by the US FDA and the EU Commission
2012  SERAPHIN outcome study meets its primary endpoint
2007  Initiation of Phase III SERAPHIN study in PAH patients
2005  Initiation of Phase II dose ranging study
2004  Entry-into-man
2003  Selection of macitentan for initiation of preclinical studies

KEY SCIENTIFIC LITERATURE
• Sidharta PN et al. 2011; 67(10):977-84.
PONESIMOD

Ponesimod is a potent orally active, selective sphingosine-1-phosphate receptor 1 (S1P₁) immunomodulator.

Ponesimod prevents lymphocytes from leaving lymph nodes, thereby reducing circulating blood lymphocyte counts and preventing infiltration of lymphocytes into target tissues. The lymphocyte count reduction is rapid, dose-dependent, sustained upon continued dosing, and quickly reversible upon discontinuation. Initial data suggest that ponesimod does not cause lymphotoxicity by destroying/depleting lymphocytes or interfering with their cellular function. Other blood cells e.g. cells of the innate immune system are largely unaffected. Ponesimod is therefore considered a promising new oral agent for the treatment of a variety of autoimmune disorders.

CURRENT STATUS

OPTIMUM (Oral Ponesimod versus Teriflunomide In relapsing MUltiple sclerosis) is a Phase III multi-center, randomized, double-blind, parallel-group, active-controlled superiority study to compare the efficacy and safety of ponesimod to teriflunomide (Aubagio®) in patients with relapsing multiple sclerosis (RMS). The study aims to determine whether ponesimod is more efficacious than teriflunomide in reducing relapses. The study is expected to enroll approximately 1'100 patients, randomized in 2 groups in a 1:1 ratio to receive ponesimod 20 mg/day or teriflunomide 14 mg/day, and is expected to last a little over 3 years.

POINT (POnesImod aNd Tecfidera) is a prospective, multicenter, randomized, double-blind, parallel group, add-on, placebo-controlled, superiority study with ponesimod in patients with RMS. The study is designed to compare the efficacy, safety, and tolerability of add-on therapy with ponesimod 20 mg vs. placebo in adult patients with active RMS who are treated with dimethyl fumarate (Tecfidera®). Approximately 600 patients receiving dimethyl fumarate twice daily for at least 6 months will be randomized in a 1:1 ratio to ponesimod 20 mg or placebo. Treatment will be given until the last patient enrolled into the study has been treated for 60 weeks, with expected average treatment duration of 2 years, and for a maximum duration of 3 years. Enrollment has commenced and the study is being conducted under a Special Protocol Assessment (SPA) agreement with the FDA.

AVAILABLE CLINICAL DATA

CLINICAL DEVELOPMENT PIPELINE: MACITENTAN, CADAZOLID, OTHERS

PONESIMOD, CENERIMOD, CLAZOSENTAN, DUAL OREXIN RECEPTOR ANTAGONIST, ENDOThELIN RECEPTOR ANTAGONIST
The decision to move into Phase III development was based on the Phase IIb dose-finding study with ponesimod in patients with relapsing-remitting multiple sclerosis. A total of 464 patients were randomized into this study and the efficacy, safety and tolerability of three ponesimod doses (10, 20, and 40 mg/day) versus placebo, administered once daily for 24 weeks.

The primary endpoint of this study was defined as the cumulative number of new gadolinium-enhancing lesions on T1-weighted magnetic resonance imaging (MRI) scans at weeks 12, 16, 20, and 24 after study drug initiation. A key secondary endpoint of this study was the annualized relapse rate over 24 weeks of treatment. Patients who completed 24 weeks of treatment were offered the opportunity to enter into an extension study. This ongoing trial is investigating the long-term safety, tolerability, and efficacy of 10 and 20 mg/day of ponesimod in patients with relapsing-remitting multiple sclerosis, in a double-blind fashion. The study continues to provide extensive safety and efficacy information for ponesimod in this indication, with some patients treated for more than 6 years. The safety database from all studies with ponesimod now comprises more than 1,300 patients and healthy volunteers.

**MILESTONES**

- 2015 Phase III program in multiple sclerosis initiated
- 2011 Phase IIb dose-finding study in multiple sclerosis successfully completed
- 2006 Entry-into-humans
- 2004 Preclinical development initiated

**KEY SCIENTIFIC LITERATURE**

CENERIMOD

Cenerimod is Actelion’s second selective sphingosine-1-phosphate receptor 1 (S1P₁) immunomodulator, it is both potent and orally active.

Cenerimod blocks the egress of lymphocytes from lymphoid organs thereby reducing the availability of circulating effector T and B cells that can invade target organs. This pharmacodynamic effect is sustained with continued daily oral dosing and is reversible upon drug discontinuation.

CURRENT STATUS

Cenerimod is being evaluated in a Phase II prospective, multicenter, multinational, randomized, double-blind, placebo-controlled, dose-response study to investigate the biological activity, safety, and tolerability of cenerimod in adult subjects with systemic lupus erythematosus (SLE). Approximately 64 subjects will be enrolled to receive either 0.5, 1, 2 or 4 mg/day of cenerimod over a treatment period of 12 weeks. The study is being conducted at approximately 20 sites and is expected to last around 20 months.

AVAILABLE CLINICAL DATA

In the Phase I program, cenerimod showed marked and sustained lymphocyte lowering effects, supporting further exploration in patients.

MILESTONES

2015  Initiation of Phase II clinical development in systemic lupus erythematosus

KEY SCIENTIFIC LITERATURE

Clazosentan is being developed as an intravenous infusion to treat cerebral vasospasm in patients post aneurysmal subarachnoid hemorrhage (aSAH). The product was granted orphan medicinal product status in Europe in 2003, and in the US in 2006.

**CURRENT STATUS**

**REVERSE** (REversal of Vasospasm with clazosEntan post-aneuRysmal Subarachnoid hEmorrhage), is a Phase II prospective, multi-center, open-label, single arm study to evaluate whether clazosentan has an early effect in reversing angiographically-confirmed cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage treated by endovascular coiling or surgical clipping. The study is expected to enroll approximately 25 subjects, and clazosentan will be administered at the dose of 15 mg/h for a maximum of 10 days.

**AVAILABLE CLINICAL DATA**

Clazosentan has been investigated for prevention of angiographic vasospasm in patients with aSAH in the Phase IIb CONSCIOUS-1 (Clazosentan to Overcome Neurological ISChemia and Infarct OccUrring After Subarachnoid Hemorrhage) study. Clazosentan (1, 5, and 15 mg/h doses) dose-dependently prevented the occurrence of significant angiographic vasospasm, with a 65% relative risk reduction with the highest dose (P<0.0001); this suggests that endothelin-1 plays an important role in the pathogenesis of vasospasm. Compared with placebo, pulmonary complications, anemia, and hypotension were more common in patients receiving clazosentan.

On the basis of CONSCIOUS-1, two Phase III studies (CONSCIOUS-2 and CONSCIOUS-3) were designed to assess the effect of clazosentan on the incidence of cerebral vasospasm-related morbidity and all-cause mortality within 6 weeks post-aSAH. In CONSCIOUS-2, patients who had their aneurysm secured by clipping received placebo or clazosentan 5 mg/h; however, the treatment effect of clazosentan did not reach statistical significance. In CONSCIOUS-3, patients who had their aneurysm secured by coiling received placebo or clazosentan 5 or 15 mg/h. Recruitment into this study was halted prematurely after the results of CONSCIOUS-2 were known, because the 5 mg/h dose did not achieve its primary end point in clipped patients. However, analysis of the data collected in CONSCIOUS-3 showed that clazosentan 15 mg/h significantly reduced cerebral vasospasm-related morbidity and all-cause mortality, with a 44% relative risk reduction (p=0.0074). This dose also significantly reduced the incidence of delayed ischemic neurological deficit (DIND) with a 54% relative risk reduction (p=0.0038). In addition, clazosentan reduced the need for rescue therapy for vasospasm. Clazosentan did not improve outcome, possibly due to the imbalance in the use of rescue therapy. The safety profile in CONSCIOUS 2 and 3 was similar to that observed in the CONSCIOUS 1 study.

**MILESTONES**

- **2015** Initiation of Phase II proof of concept to treat vasospasm in subjects with aSAH
- **2011** Phase III CONSCIOUS-3 study discontinued
- **2010** Phase III CONSCIOUS-2 study concluded - primary endpoint not met
- **2006** Orphan status granted in US
- **2003** Orphan status granted in Europe
- **2003** Axovan acquisition

**KEY SCIENTIFIC LITERATURE**

As part of its drug discovery efforts on G-Protein Coupled Receptors, Actelion has built a library of potent dual oral orexin receptor antagonists. These compounds are active on both OX1 and OX2, the receptors which mediate the actions of orexins. Actelion’s work with dual orexin receptor antagonism has demonstrated that blocking the activity of the orexin receptors offers the potential to restore normal physiological sleep.

CURRENT STATUS

In July 2016, Actelion announced that the company is initiating a Phase II program with its new dual orexin receptor antagonist in patients with insomnia.

The Phase II program consists of two studies, one in adult and one in elderly patients. It is designed to evaluate the effect of Actelion’s DORA versus placebo on sleep maintenance and sleep initiation, as well as next-day residual effect and next-day performance. The adult study will also include an active reference arm with zolpidem, as the most widely used insomnia treatment targeting GABA-A receptors. Both studies will also generate information on sleep architecture and sleep quality.

The first study is a multi-center, double-blind, randomized, placebo-controlled, active reference, parallel-group, dose-response study to evaluate the efficacy and safety of Actelion’s DORA. The study is expected to commence enrollment in Q4 2016 and will recruit approximately 300 adult patients diagnosed with insomnia. The study will comprise 6 treatment arms: placebo; zolpidem; 5, 10, 25, and 50 mg of Actelion’s DORA. Treatment duration is 4 weeks. The primary endpoint is wake-time after sleep onset (WASO) at day 1 & 2.

The second study is a multi-center, double-blind, randomized, placebo-controlled, crossover, dose-response study to evaluate the efficacy and safety of Actelion’s DORA. The study is also expected to commence enrollment in Q4 2016 and will recruit approximately 50 elderly patients diagnosed with insomnia. The study has a 5-period crossover design with 5 treatment arms: placebo; 5, 10, 25 and 50 mg of Actelion’s DORA. Treatment duration in each period is 2 days. The primary endpoint is WASO at day 1 & 2.

Secondary objectives of both studies include evaluation of Actelion’s DORA versus placebo on latency to persistent sleep (LPS) as well as subjective latency to sleep onset (sLSO) and subjective WASO (sWASO). Safety and tolerability will also be evaluated.

AVAILABLE CLINICAL DATA

Data from an extensive Phase I program have confirmed the optimal pharmacokinetic and pharmacodynamic profile for a sleep medication, together with excellent safety and tolerability.

MILESTONES

2014 Initiation of Phase I clinical program

KEY SCIENTIFIC LITERATURE

- Roth T. 2007;3 Suppl 5:S7-10.
Actelion is a leader in the field of endothelin receptor antagonism, with macitentan (Opsumit®), an orally available endothelin receptor antagonist (ERA) that resulted from a tailored drug discovery process in Actelion’s laboratories.

**CURRENT STATUS**

Actelion’s latest ERA (ACT-132577) is evaluated in a Phase II prospective, multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, dose-finding study in patients with essential hypertension (grade 1 and 2) to establish a dose-effect relationship. The results from this study will form the basis for development decisions in specialty cardiovascular disorders. Patients will be randomized in the 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.

**AVAILABLE CLINICAL DATA**

Pharmacokinetic, pharmacodynamic, safety and tolerability data from a Phase I program support further exploration of ERA in patients with cardiovascular disorders.

**MILESTONES**

- 2015: Initiation of Phase II dose-response study
- 2014: Initiation of Phase I clinical program

**KEY SCIENTIFIC LITERATURE**

PHASE I COMPOUNDS

Actelion has developed platforms of expertise in families of molecular targets which allow high productivity in the generation of innovative compounds potentially addressing a wide range of high unmet medical needs.

Actelion currently has five compounds in Phase I clinical development. These include a selective orexin 1 receptor antagonist (SORA) and a T-type calcium channel blocker, both being developed in the field of neurology, one cardiovascular compound, one anti-inflammatory compound and lucerastat in Phase Ib development for Fabry disease.
Scientists at Actelion use an inquisitive drug hunting approach to discover and develop novel medicines to improve patients’ lives.

From the outset, Actelion’s founders wanted to create a company with a bold, pioneering spirit, one that understands the true nature of innovation. The founders understood that innovation could not be taught, but the right environment to allow innovation can be fostered. Actelion’s productivity is evidence that from creative freedom, innovative ideas flourish.

By removing the barriers to innovation, such as bureaucracy and hierarchy, the founders set out to empower “their” people. In turn, Actelion’s people take ownership of their projects and grasp opportunities.

There are many barriers to overcome when guiding a compound that addresses an unmet medical need from the bench to the market. To maximize success, the Research and Development teams must know which projects are most promising, which compounds should be promoted, and where to focus their efforts.

The only way to make the correct choices is to base these decisions on all facts available. This means open, effective communication within teams and across functions in an integrated approach.

This sharing of knowledge stimulates and builds scientific intuition. By using this approach, innovation can be translated into evidence-based medicine.

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DRUG DISCOVERY PROCESS
To maximize output from its focus on target families, Actelion implements appropriate state-of-the-art technologies. The Drug Discovery group, comprising more than 380 professionals at the end of 2016, combines technology with human expertise and teamwork in a single research center based in Allschwil to make the best use of Actelion’s toolbox.

Actelion has over 100 medicinal and process chemists creating low molecular weight compounds which go through a cyclic drug discovery process for optimization.

These innovative compounds are then characterized by molecular biologists and biochemists in relation to the chosen molecular drug targets. The characterization includes the development of a variety of assays and execution of activity screens. The vast quantities of assay result data generated, are managed and analyzed by data-management programs developed in-house.

A lead compound is then passed to our pharmacologists, neurobiologists, immunologists and electrophysiologists to further characterize the compounds. These lead compounds are then passed back through this cycle until an optimized compound is available for preclinical development by our pharmacokineticists, formulation specialists, and toxicologists.

Actelion’s platform approach, combined with our technological capabilities and in-house expertise, has resulted in a promising clinical development pipeline of compounds discovered and optimized in Actelion’s laboratories.

DRUG DISCOVERY PLATFORMS
Actelion’s efforts in drug discovery focus on the design, synthesis and optimization of small molecular weight molecules, which are active on molecular target families. This focus allows high productivity in the generation of innovative compounds potentially addressing a wide range of high unmet medical needs.

Initially, the company looked solely at G-protein coupled receptors (GPCRs) and a specific enzyme family known as aspartic proteinases. As the company’s capabilities have expanded, so too have the target platforms, adding anti-infectives, ion channels and a broad range of soluble enzymes.

The productivity of Actelion’s drug discovery endeavors is demonstrated by more than 3,800 pending patent applications and/or granted patents currently in Actelion’s portfolio, including 8 priority patent applications filed in 2016.

New chemical entities (NCE)
Actelion’s research focuses on the design and synthesis of novel low molecular weight drug-like molecules. Experience has shown that small molecules generally lend themselves to easier formulation, have a broader array of dosage forms, have greater potential for bioavailability, in particular after oral administration, and are more efficiently manufactured. While Actelion’s medicinal chemistry and high-throughput chemistry groups synthesize smaller quantities of structurally diverse molecules, process research chemists prepare the quantities of selected compounds needed for further studies.

G-Protein coupled receptors
G-Protein coupled receptors (GPCRs), also known as seven transmembrane domain receptors (7TMs), are integral membrane proteins. They can be activated by external signals, such as hormones, neurotransmitters, or odors. This activation induces a conformational change of the receptor which in turn causes activation of G-proteins and the subsequent transmission of biochemical signals within the cell. There are more than a hundred known GPCRs in humans, and many of them are involved in a broad range of diseases. Some of these receptors are the subject of our development programs, such as the endothelin receptors ETA and ETB, or the sphingosine-1-phosphate receptor S1P1.

Enzymes
Enzymes are proteins that catalyze chemical reactions and are involved in almost all metabolic pathways in a living cell. They speed up the
conversion of a substrate into a new product. Enzymes are specific for a given molecular substrate and are classified by the mechanism by which they act on the substrate. Actelion currently works on several different enzyme targets in its research programs, most of them being soluble intracellular proteins.

**Anti-infectives**
Due to the development of resistance to currently available antibiotics and the emergence of new pathogens, the medical need for new antibiotic compounds is high. In order to address this high unmet medical need, Actelion initiated, in 2004, a research program in the field of antibiotics.

Actelion’s focus is on the discovery of novel classes of antibiotics that may offer improved properties, such as increased potency, coverage of multi-resistant pathogens, and a decreased inherent liability for resistance development. A portfolio of projects has been established focusing on both antibiotics for intravenous treatment of severe hospital infections, and oral antibiotics for community acquired infections around the globe.

**Ion channels**
Ion channels are transmembrane pores that allow the passage of ions (charged molecules) into or out of a cell. There are hundreds of different ion channels, distinguished by ion selectivity, opening mechanism, and protein sequence. Ion channels can be opened by chemical ligands, voltage fluctuations, acidity changes, temperature variations, or mechanical stimuli (e.g. touch or sound).

Initially, Actelion established an in-house in-vitro electrophysiology group to provide internal support for early preclinical evaluation of drug safety in the area of cardiac electrophysiology. Since the scientific knowledge and technical capabilities required in this area are very similar to those in the area of cardiovascular ion channel therapies, research programs were soon initiated looking for modulators of selected ion channels to treat cardiovascular diseases.

Expansion of the electrophysiology group and integration of new expertise and technologies led to the initiation of research projects targeting ion channels to treat neurological and immunological diseases.

**PROJECT SELECTION**
Actelion selects its molecular drug targets on the basis of the established platforms of expertise, capabilities, technologies and the professionals at its research center. Actelion’s inquisitive researchers all have the opportunity to suggest a new target and follow the evaluation process. Additional selection criteria which the proposed projects are required to demonstrate include:

- medical need
- therapeutic novelty
- pharmacology models
- clinical feasibility

**THERAPEUTIC AREAS**
We use our expertise to address a variety of therapeutic areas including cardiovascular disorders, central nervous system disorders, infectious diseases, fibrosis, neurodegeneration, cancer, immunological disorders.

We aim to tackle diseases through multiple mechanisms, delivering novel therapies to patients, with maximum impact on the selected diseases.