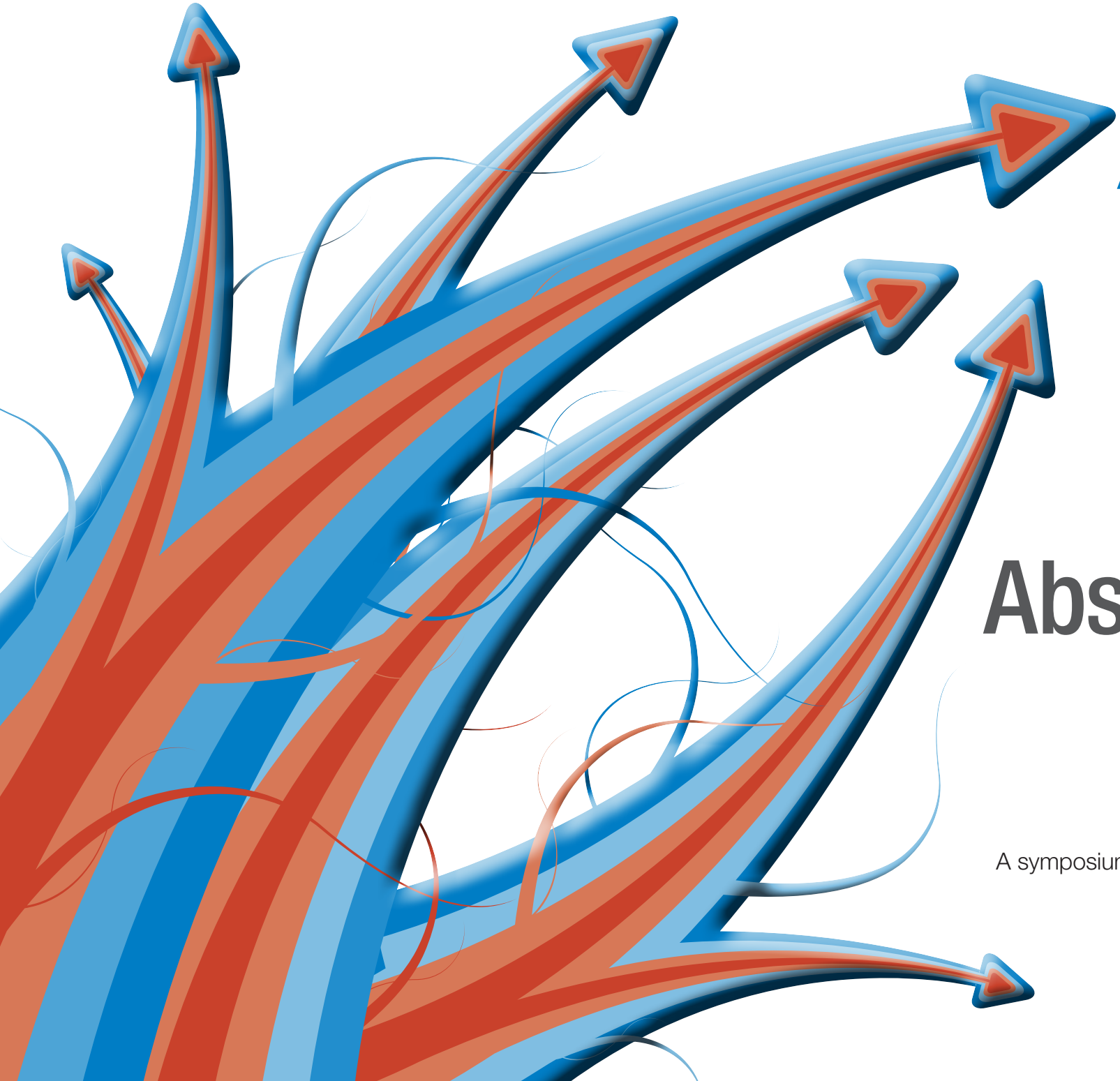


Inspiring Approaches to Clinical Challenges

in Pulmonary Hypertension

Abstract Book

A symposium sponsored by Bayer Schering Pharma
at ERS 2008 Annual Congress

Bayer HealthCare
Bayer Schering Pharma

www.ventavis.com

Welcome

Vallerie McLaughlin,
University of Michigan,
Ann Arbor, MI, USA

Vallerie McLaughlin MD is Associate Professor of Medicine and Director of the Pulmonary Hypertension Program at the University of Michigan. She is a Fellow of the American College of Cardiology (ACC), the American College of Chest Physicians and the American Heart Association (AHA), and a member of the American Thoracic Society. She is Chair of the ACC/AHA Clinical Expert Consensus Committee on Pulmonary Hypertension and Chair of the Pulmonary Hypertension Association Scientific Leadership Council. She is a former Editor-in-Chief of *Advances in Pulmonary Hypertension* and Chairman of the AHA Women in Cardiology Committee. Her research interests focus on pulmonary hypertension.

Dear Colleague,

It is my pleasure to welcome you to the satellite symposium, Inspiring Approaches to Clinical Challenges in Pulmonary Hypertension. This symposium will highlight some of the challenges facing the pulmonary hypertension (PH) community and the steps that are being taken to overcome them, culminating in the presentation of an emerging PH therapy with an entirely new mode of action.

Despite many advances in the treatment of PH during the past decade, significant unmet needs remain. Patients with PH have a poor prognosis, and currently available therapies have a number of limitations including intravenous or subcutaneous administration, inconvenient dosing, liver toxicity and inadequate response. Furthermore, these therapies are approved only for the treatment of patients with pulmonary arterial hypertension (PAH); their role in the treatment of patients with other forms of PH remains under debate.

A review of data on the long-term use of inhaled iloprost (Ventavis®) for the treatment of PAH will be presented, and delegates will see the first presentation of results from phase 2 clinical trials of the soluble guanylate cyclase stimulator, riociguat (BAY 63-2521), in patients with PH. Experts in the field will also review the monitoring and treatment of children with PH, and will provide a timely update on the treatment of patients with chronic thromboembolic PH (CTEPH).

Thank you for reserving time for what promises to be an exciting and informative symposium.

Vallerie McLaughlin MD

University of Michigan, Ann Arbor, MI, USA

Programme

Time	Topic	Speaker
17:15	Welcome and introduction	Vallerie McLaughlin *Ann Arbor, MI, USA*
17:30	Pulmonary hypertension in children: measuring treatment success and identifying unmet needs	Maurice Beghetti *Geneva, Switzerland*
17:50	Management of the patient with CTEPH: evolving pharmacological treatment options	Irene Lang *Vienna, Austria*
18:10	Review of clinical data: long-term treatment with inhaled iloprost in pulmonary hypertension	Horst Olschewski *Graz, Austria*
18:30	Soluble guanylate cyclase stimulation: an emerging option in pulmonary hypertension therapy	Ardeschir Ghofrani *Giessen, Germany*
18:50	Questions and closing comments	Vallerie McLaughlin *Ann Arbor, MI, USA*
19:15	Meeting close	

Maurice Beghetti

Pulmonary hypertension in children: measuring treatment success and identifying unmet needs

Recent advances in the field of pulmonary hypertension (PH) have provided clinicians with a range of treatment options, but effective disease management in children presents a unique challenge. Understanding the epidemiology and natural history of paediatric PH (PePH) is essential for guiding management decisions, but epidemiological data have been lacking. Several national registries have reported or will soon report their results, but large numbers of patients are required, which is a challenge with this rare disease. The first international registry for PePH, the Tracking Outcomes in Paediatric Pulmonary Hypertension (TOPP) registry, began recruitment this year and promises to become a vital resource.

In addition to the paucity of epidemiological data, studies of therapies for PePH are also sparse and treatment is generally guided by the adult treatment algorithm, with some adaptations. Current treatment options for PePH include calcium channel blockers, prostacyclin analogues, endothelin receptor antagonists and phosphodiesterase-5 inhibitors. However, invasive management options, such as the continuous infusion of prostacyclin, even if effective, remain a challenge in the paediatric population. Inhaled prostacyclin may be an alternative treatment option, but further research is required to develop appropriate treatment strategies, formulations and doses for PePH. Measures of treatment success must also be defined, and the applicability of endpoints used in adult clinical studies remains open to question.

In summary, further data are needed on the epidemiology and treatment of PH in children. The international TOPP registry will provide valuable insight, but this will need to be complemented by data from research and development of adapted paediatric therapies. Dedicated childhood PH services have the potential to optimize diagnosis and management of this life-threatening disease.

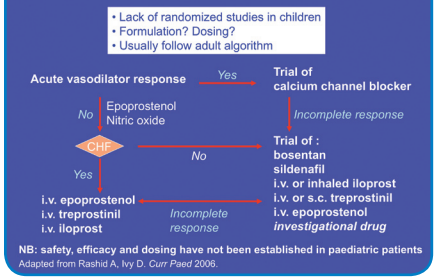
Maurice Beghetti,
University Hospital of Geneva,
Geneva, Switzerland

Professor Maurice Beghetti MD is Head of the Paediatric Cardiology Unit at the University Hospital of Geneva. He is a former president of the Swiss Paediatric Cardiology Society, and is currently President of the Swiss Society for Pulmonary Hypertension, Vice Chair of the Association for Paediatric Pulmonary Hypertension and Treasurer of the Paediatric Cardiovascular Intensive Care Group. He is an editorial board member of *Cardiology in the Young* and *Pediatric Research*, and has authored numerous articles, book chapters and books. His primary research interests are pulmonary hypertension and congenital heart defects in paediatric patients.

TOPP registry

- Lack of epidemiological data in children with pulmonary hypertension
- First international registry in paediatric pulmonary hypertension
- 22 countries participating:
  - Australia, Austria, Belgium, Brazil, Canada, China, Denmark, France, Germany, Greece, Hungary, Italy, Japan, Mexico, The Netherlands, Norway, Poland, Portugal, Switzerland, Turkey, UK, USA
- 38 sites registered for participation

Paediatric treatment: expert suggestions



NB: safety, efficacy and dosing have not been established in paediatric patients

Adapted from Rashid A, Ivy D. *Curr Paed* 2006.

Measuring treatment success in paediatric pulmonary hypertension

- Survival
- Functional class
- Quality of life
- 6-minute walk distance or cardiopulmonary exercise testing
- Echocardiography
- Haemodynamics (right heart catheterization)
- Biological markers (BNP/NT-proBNP)
- Combined endpoints (studies): clinical worsening versus improvement??

Notes

Irene Lang

Irene Lang,
Medical University of Vienna,
Vienna, Austria

Irene Lang MD is Professor of Vascular Biology at the Medical University of Vienna. She qualified from and trained at the University of Vienna, before taking up a postdoctoral research fellowship at the University of California (UCSD) and Scripps Research Institute, La Jolla, CA, USA. In 1994, she returned to complete her cardiology training in Vienna, where she now leads clinical and experimental groups in vascular medicine. She was nominated as a 'Caring Physician of the World' by the World Medical Association in 2006.

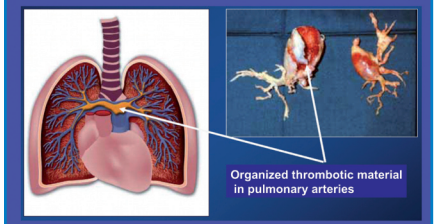
Management of the patient with CTEPH: evolving pharmacological treatment options

Chronic thromboembolic pulmonary hypertension (CTEPH) is a life-threatening condition in which organized thrombi obstruct the pulmonary vessels, causing increased pulmonary vascular resistance, progressive pulmonary hypertension (PH) and right heart failure. Misguided thrombus clearance, triggered by infection, inflammation, autoimmunity and malignancy, plays a key role in the disease. CTEPH is diagnosed by a lung perfusion scan, and operability is assessed by pulmonary angiography. Untreated, patients with CTEPH have a poor prognosis. Pulmonary haemodynamics are critical: over half of the patients with a mean pulmonary arterial pressure above 50 mmHg die in the year following diagnosis, whereas significant reduction of pressure following surgery is associated with increased survival.

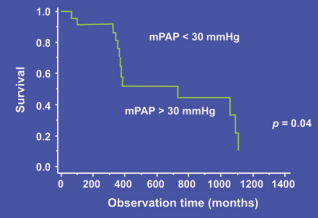
Treatment of choice is surgical endarterectomy of the pulmonary obstructions, which restores normal pulmonary haemodynamics at rest in approximately 80% of patients. In expert centres, surgical mortality is less than 10%. However, surgery is not possible for 10–50% of patients (inoperable CTEPH), because of surgically inaccessible thrombi or comorbidities conferring an unacceptably high risk. Furthermore, 10–15% of patients with operable CTEPH have residual PH following surgery. In these situations, pharmacotherapies may be useful, but none has yet been approved.

Vasodilator drugs for pulmonary arterial hypertension (PAH) are attracting growing interest as potential pharmacotherapies for CTEPH, because CTEPH has recently become regarded as a 'dual' pulmonary vascular disorder in which major vessel obstruction and remodelling is combined with a small vessel arteriopathy that is histologically indistinguishable from the classic pulmonary arteriopathy observed in PAH. Inhaled iloprost, subcutaneous treprostinil, oral sildenafil and endothelin receptor blockers have demonstrated efficacy in the treatment of CTEPH in small studies. BENEFIT, the randomized, placebo-controlled study of the endothelin receptor antagonist bosentan in patients with inoperable CTEPH or residual PH following surgery, recently demonstrated beneficial haemodynamic effects. Research is now required to establish the efficacy of other pharmacological vasodilators in CTEPH.

Chronic thromboembolic pulmonary hypertension



Prognosis of chronic thromboembolic pulmonary hypertension



mPAP, mean pulmonary arterial pressure

Lewczuk J *et al. Chest* 2001;119:818–23

BENEFIT: summary of key results

- Clinically relevant improvement in cardiac haemodynamics
  - Pulmonary vascular resistance decreased ($p < 0.0001$)
  - Cardiac index increased
  - NT-proBNP decreased
- No effect on exercise capacity ($p = 0.5449$)
- Improvement in Borg dyspnoea index
- Safety and tolerability
  - Consistent with previous controlled trials with bosentan in pulmonary arterial hypertension

Notes

Horst Olschewski

Horst Olschewski,
Medical University of Graz, Austria

Professor Horst Olschewski MD PhD is Director of the Pulmonology Department at the Medical University of Graz, and leads a research group investigating functional genomics and treatment of lung vascular remodelling in pulmonary hypertension. He was a member of the steering committees for the AIR, TRIUMPH and ARIES studies, and the Scientific Advisory Board of the Pulmonary Hypertension Association. He is a member of the European Society of Cardiology and the European Respiratory Society working groups on pulmonary circulation and right ventricular function. He is also a reviewer for *Circulation*, the *European Respiratory Journal* and the *American Journal of Respiratory and Critical Care Medicine.*

Review of clinical data: long-term treatment with inhaled iloprost in pulmonary hypertension

Prostacyclin and its analogues (prostanoids) are potent vasodilators that exhibit antithrombotic, antiproliferative and anti-inflammatory properties by acting on vascular smooth muscle cells, thrombocytes, endothelial cells and fibroblasts. Pulmonary arterial hypertension (PAH) is characterized by vasoconstriction, thrombosis and proliferation, and is associated with reduced synthesis of endogenous prostacyclin. This provides a strong rationale for the use of prostanoids to treat PAH, a concept that is now supported by more than two decades of clinical research and experience. Prostanoids have clearly demonstrated efficacy in severe PAH, and have shown beneficial effects in combination with phosphodiesterase-5 inhibitors and endothelin receptor antagonists. For patients with New York Heart Association/World Health Organization functional class IV PAH, intravenous prostanoids are regarded as first-choice therapy. Recent research suggests that iloprost may also antagonize the pathological changes that take place in the small pulmonary arteries of patients with PAH.

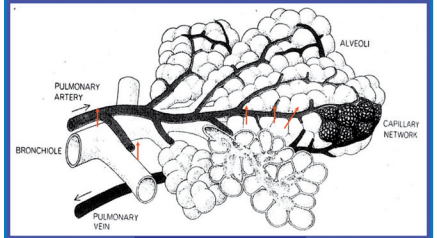
Iloprost is administered by inhalation, and thus avoids most of the systemic side effects associated with intravenous or subcutaneous prostanoid infusion. Efficacy and a favourable safety profile were shown in a pivotal randomized controlled trial (AIR).

A recent randomized, controlled, double-blind study (STEP) investigated the effects of adding inhaled iloprost to bosentan therapy in patients with PAH. Results showed that this combination had a favourable safety profile and improved event-free survival. In the open-label extension period, 1-year survival was high (97%), with no deaths occurring in patients treated with combination therapy from the beginning of the study. Patients treated with combination therapy during the double-blind phase also had fewer and later clinical deteriorations than those who were treated with bosentan and placebo in the double-blind phase, suggesting that early initiation of iloprost therapy can be beneficial.

A German prospective multicentre study investigating the long-term safety and clinical effects of inhaled iloprost showed that it provided clinical benefit, with long-term maintenance of exercise and functional capacity. Long-term iloprost therapy appeared to be well-tolerated and no significant dose increase was required to maintain clinical efficacy.

In summary, although these long-term studies were open-label and uncontrolled, their results suggest that inhaled iloprost may improve survival in PAH.

Inhalation with iloprost



Pulmonary selectivity
Intrapulmonary selectivity

AIR 2 study: effect of iloprost on 2-year survival rate

- Analysis including patients with premature end of study (ITT population)
  - Overall 2-year survival 78% [67;89]
  - 2-year survival in IPAH 87% [76;98]
  - 2-year survival in non-IPAH 62% [41;82]
- For comparison, IPAH survival
  - NIH data: 63%
  - Primary bosentan therapy (ITT population): 89%[1] and 87%[2]

IPAH, idiopathic pulmonary arterial hypertension; ITT intent-to-treat

[1]McLaughlin VV *et al. Eur Resp J* 2005
[2]Provencher S *et al. Eur Heart J* 2006

AIR 2 study
2-year event-free survival

- Event-free survival*
  - Overall 66% [54;78]
  - IPAH 74% [60;88]
  - Non-IPAH 52% [31;72]
- For comparison, IPAH event-free survival:
  - Primary bosentan therapy 55%[1†] and 45%[2‡]

*Event-free survival: the avoidance of death, lung transplantation, or need for alternative therapy, calculated using Kaplan–Meier methods
†Percentage of initial cohort who were alive and on bosentan monotherapy at 2 years
‡Survival without transplantation, prostanoid initiation or hospitalization for right heart failure

[1] McLaughlin VV *et al. Eur Resp J* 2005
[2] Provencher S *et al. Eur Heart J* 2006

Notes

Ardeschir Ghofrani

Soluble guanylate cyclase stimulation: an emerging option in pulmonary hypertension therapy

Although significant advances have been made in recent years, the prognosis for patients with pulmonary hypertension (PH) remains poor. Nitric oxide (NO) is an endogenous vasodilator, levels of which are regulated across the lung in order to ensure preferential perfusion of well-ventilated regions. Drugs that act in synergy with endogenous NO would therefore promote pulmonary vasodilation preferentially in well-ventilated regions of the lung, maintaining optimal gas exchange.

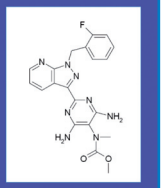
Riociguat is an oral stimulator of the NO receptor, soluble guanylate cyclase. It sensitizes soluble guanylate cyclase to low levels of bioavailable NO, and has shown a favourable safety and efficacy profile in healthy volunteers and in a proof-of-concept study in patients with PH. In a recently completed phase 2 study, 75 patients with pulmonary arterial hypertension (PAH) or chronic thromboembolic pulmonary hypertension (CTEPH) were treated with oral riociguat three times daily for 12 weeks. Doses were titrated according to peripheral systolic blood pressure and tolerability. Riociguat at total daily doses of 3–7.5 mg was well-tolerated and had a favourable safety profile. The most common drug-related side effects included gastrointestinal, nervous system and vascular disorders.

In the phase 2 study, riociguat significantly decreased pulmonary arterial pressure and pulmonary vascular resistance (PVR), and significantly increased cardiac output and cardiac index from baseline. Systemic blood pressure and systemic vascular resistance (SVR) were also reduced, but PVR:SVR ratio showed a trend towards pulmonary selectivity. These findings were corroborated by echocardiography, which showed significant decreases in Tei index, pulmonary arterial systolic pressure and tricuspid annular plane systolic excursion (TAPSE). Six-minute walking distance increased significantly from baseline in patients with PAH and those with CTEPH, and a significant increase was also observed in a subgroup of six patients receiving previous and concomitant treatment with bosentan. NT-proBNP levels, Borg dyspnoea scores and World Health Organization functional class also improved.

In summary, riociguat exerts strong effects on pulmonary haemodynamics and exercise capacity in patients with PAH and those with CTEPH, and warrants further investigation in phase 3 trials.

Riociguat: sGC stimulator

- Oral stimulator of soluble guanylate cyclase (sGC)
- Acts independently of nitric oxide (NO)
- Targets reduced form of sGC
- Enhances the sensitivity of sGC to low levels of bioavailable NO
- Efficacy and anti-remodeling properties in experimental models of pulmonary hypertension (PH)
- Efficacy and favorable safety profile in healthy volunteers (phase I) and patients with PH (proof-of-concept)

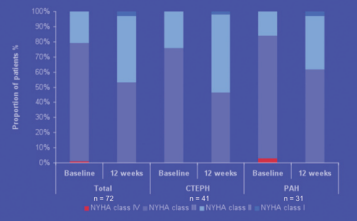


Stasch JP *et al. Nature* 2001;410:212–15
Evgenov OV *et al. Circulation* 2004;110:2253–9
Dumitrascu R *et al. Circulation* 2006;113:286–95
Evgenov OV *et al. Nat Rev Drug Discov* 2006;5:755–68
Schermuly *et al. Eur Respir J* 2008; Jun 11 [Epub ahead of print]
Frey *et al. J Clin Pharmacol* 2008;48:926–34

Riociguat phase 2 study

- Multicenter, open-label, individual dose titration study
- Primary objective: to investigate the safety, tolerability and feasibility of individual titration of riociguat according to peripheral systolic blood pressure
- Secondary objective: to assess the pharmacodynamics and pharmacokinetics of riociguat

Effect of riociguat on functional class

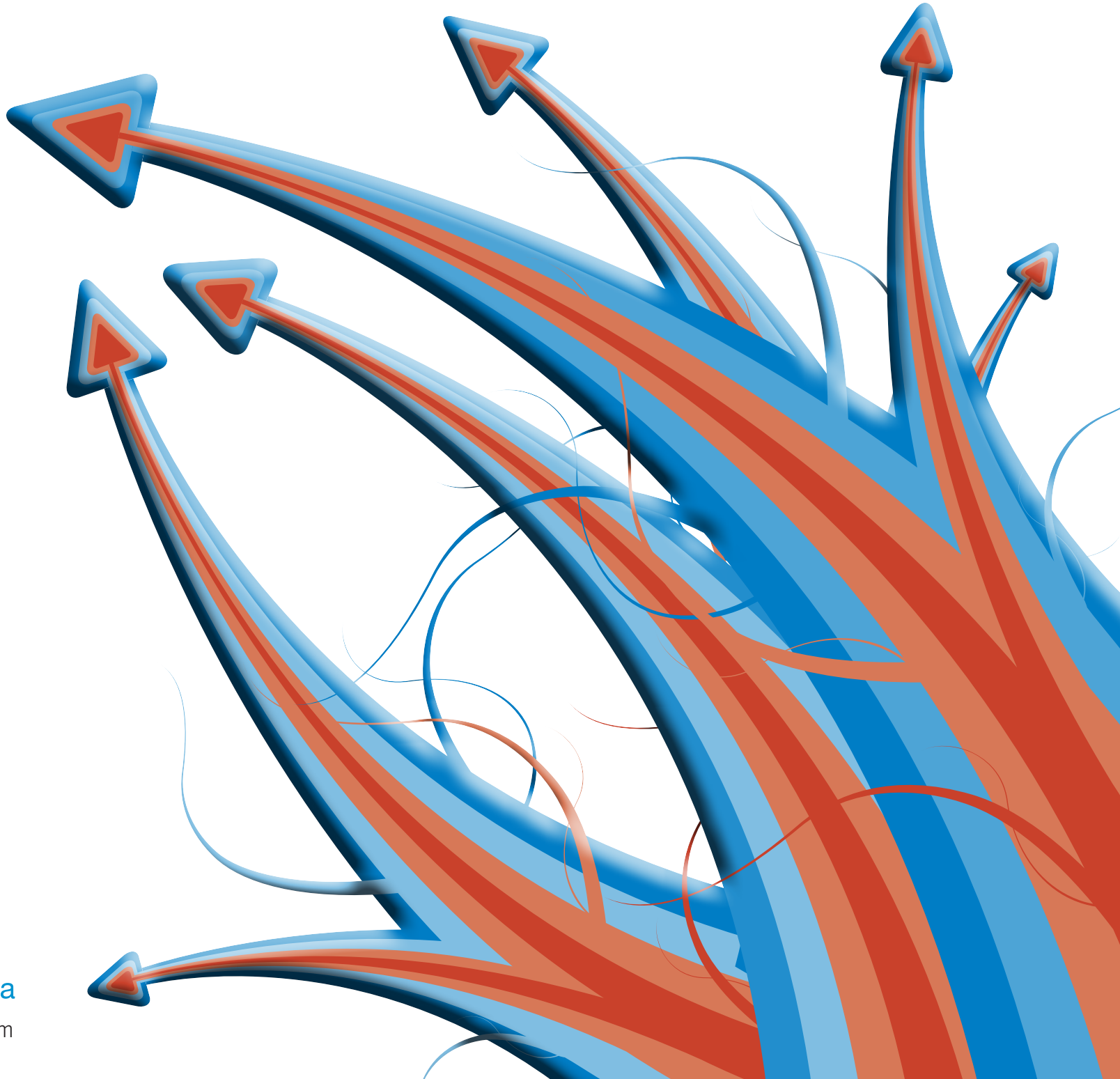


CTEPH, chronic thromboembolic pulmonary hypertension; NYHA, New York Heart Association; PAH, pulmonary arterial hypertension

Ardeschir Ghofrani,
University Hospital Giessen,
Giessen, Germany

Professor Ardeschir Ghofrani is Head of the Pulmonary Hypertension Division in the Department of Internal Medicine at University Hospital Giessen, and leads a collaborative cardiopulmonary vascular system research group. He has participated in the therapeutic development of prostanoids, phosphodiesterase inhibitors, endothelin receptor antagonists, combination therapies and soluble guanylate cyclase stimulators for pulmonary hypertension, and tyrosine kinase inhibitors for pulmonary vascular disease. He is a reviewer for several journals including the *American Journal of Respiratory and Critical Care Medicine*, *Circulation* and the *Lancet*. His research interests centre on pulmonary vascular science for which he has received four awards.

Notes



Bayer HealthCare
Bayer Schering Pharma

www.ventavis.com