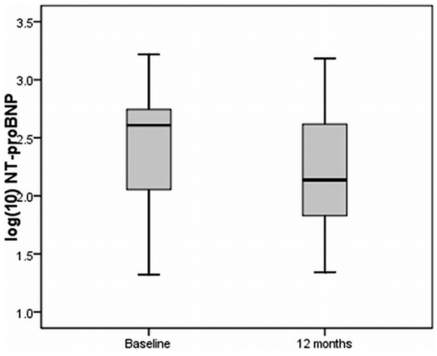


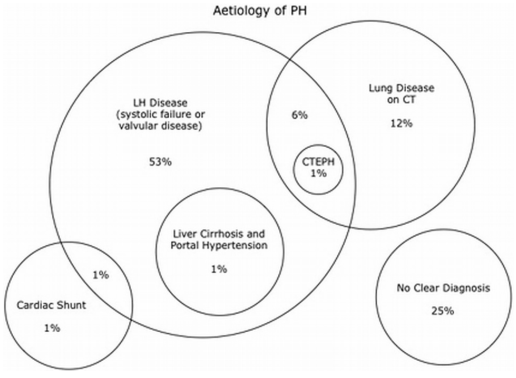

**Results:** Four patients died within 30 days of referral and before being assessed, 15 patients did not undergo cardiac catheterisation. 50% of those assessed had an associated connective tissue disease. 36 patients had resting pulmonary artery pressures <25mmHg, eleven with respiratory and ten with cardiac disease to explain their symptoms. 65 patients were diagnosed with pulmonary hypertension following invasive studies: 19 related to left heart disease, 7 related to chronic lung disease, 7 CTEPH, five mixed aetiology, and 27 PAH. Three patients with idiopathic PAH, one case associated with an atrial septal defect, 23 with connective tissue disease. Follow up log(10)NT-proBNP testing in 24 patients with PAH showed a significant reduction at 12 months (-0.21, $p<0.05$ students' t-test).
**Conclusion:** Pulmonary hypertension of all types may be present in older patients. Thorough assessment may provide insight into the drivers of symptoms in older patients and help to guide treatment, which can be successful.

**P936**
**Pulmonary hypertension in a district general hospital**
Yan-Pin Lin, Dominic Davenport, Natasha Shrikrishna, Abigail Cole, Harpreet Ranu. *Respiratory Department, St. Richard's Hospital, Western Sussex Hospitals NHS Trust, Chichester, United Kingdom*

**Introduction:** There is an increasing awareness to identify patients with pulmonary hypertension (PH). Classification of the underlying cause defines further management and referral to specialist centres.
**Aim:** To assess the burden of PH at St Richard's Hospital, which serves a population of 230,000.
**Methods:** All departmental transthoracic echocardiographs (TTEs) between 1st January 2009 and 30th June 2009 were reviewed using ERS suggested criteria to identify patients with possible PH and likely PH. Further investigations were reviewed to identify the underlying aetiology in those with likely PH.
**Results:** A total of 2038 TTEs were reviewed. 93 (5%) had likely PH with a pulmonary artery systolic pressure (PASP) of >50mmHg. 624 (31%) had possible PH with either the presence of additional echocardiographic variables suggestive of PH or a PASP 37-50mmHg.
Of those with likely PH, 48% were male and 52% were female. The median age was 85 years (range 52-98). The overall mortality rate was 39% at 1 year and 58% at 2 years. Only 13% had right heart catheterisation locally.

Further Investigations In Patients Without Significant Left Heart (LH) Disease on TTE

| | Percentage of Patients (%) |
|---|---|
| HRCT Chest | 17 |
| Other CT Chest | 23 |
| CTPA | 17 |
| V-Q Scan | 6 |
| Abdominal USS | 34 |




**Conclusions:** PH is associated with a poor prognosis. The most common cause in our population was LH disease. However in patients without LH disease, less than a quarter had further investigations to exclude potentially curable CTEPH.

## 103. Pulmonary circulation: clinical PAH, registries and treatments

**P935**
**Assessment of pulmonary hypertension in patients over 70**
Christopher Valerio[1], Benjamin Schreiber[1], Clive Handler[1], Christopher Denton[2], John Coghlan[1]. *[1]Pulmonary Hypertension, Royal Free Hospital, London, United Kingdom; [2]Rheumatology, Royal Free Hospital & UCL Medical School, London, United Kingdom*

**Background:** Recent registry data suggests that the average age of patients with PAH is rising. Pulmonary hypertension affects elderly people and there is increasing prevalence of cardiac and respiratory disease with age.
**Methods:** We report the findings for 120 consecutive patients aged over 70 referred to a tertiary service during 2008-09 for invasive haemodynamic studies to confirm or exclude a diagnosis of pulmonary hypertension.

**P937**

**Pulmonary arterial hypertension prototype for national protocol and registry**

Majid Malekmohammad[1], Fanak Fahimi[2], Babak Sharifkashani[3], Mohammad Reza Masjedi[1]. *[1]Pulmonology and Critical Care, National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran; [2]Clinical Pharmacy, National Research Institute of Tuberculosis and Lung Disease, Tehran, Islamic Republic of Iran*

**Background:** Pulmonary Hypertension (PH) has been defined as an increase in mean pulmonary arterial pressure (PAP) ≥ 25 mmHg at rest as assessed by right heart catheterization.
The idiopathic form so called idiopathic pulmonary arterial hypertension iPAH is a fatal disorder with a prevalence of 8.6 per million of population.
In the current report we introduced a registry site for iPAH patients, named www.pah.ir for better delivery of subsidized antihypertensive medications (now only Bosentan).
**Methods:** The registry was opened since November 2009. The first step of this action is to add iPAH patient's information with a username and password in the site. Data entry is only available to the physicians and healthcare organizations via internet that are given a personalized username & password for entry. Following the patient's profile submission in the site, a scientific committee composed of a cardiologist and a pulmonologist who are selected by Ministry of Health (MOH), would then evaluate the data. The eligibility of the patient to receive the medications is announced in the site after evaluation. If a patient is eligible, 82% of bosentan cost is paid by MOH.
**Results:** Till now, one hundred and sixteen patients (82 females, 34 males) are registered. Measured mean pulmonary artery pressure by right heart catheterization was 69.24±17 mmHg (ranging from 35 to 110 mmHg).
**Conclusion:** The first online Iranian registry program for iPAH patients has recently been started and it is believed that this national program will supply essential information for health care providers in the field.

**P938**

**Pulmonary hypertension: The experience of a large UK district general hospital**

Sarah Clarke, Gemma Swarbrick, Sally Baddeley, Julie Chadwick, Tarek Saba. *Department of Respiratory Medicine, Blackpool Victoria Hospital, Blackpool, Lancashire, United Kingdom*

**Introduction:** Recent advances in therapy make early identification of patients with Pulmonary Hypertension (PH) important. The 2008 consensus statement reported an average UK treatment rate of 24.9 per million.(1)
**Aim:** Our institution is a District General Hospital serving a population of 330,000. Our aim was to compare our treatment rate to the national average since the appointment of a physician with an interest in PH.
**Method:** Retrospective casenote review of patients attending our monthly PH clinic since 2006.
**Results:** We identified 102 Outpatient and 35 Inpatient referrals. 28 went on to receive specialist treatment for PH; mean age 66 (range 36-85); 24 female 4 male. *Diagnoses:* Chronic thromboembolic 10, Idiopathic 8, Collagen vascular disease 5, Congenital left to right shunt 2, COPD 2 and Portal hypertension 1. *Haemodynamics (mean):* Cardiac catheter: mean Pulmonary Artery Pressure (PAP) 48mmHg (n=22, range 22-78), cardiac output 4.8 (n=21, range 2.5-7.7), cardiac index 2.83 (n=22, range 1.47-5.14) and pulmonary vascular resistance 760 (n=22, range 123-1600). Echocardiography: systolic PAP 66mmHg (n = 23, range 13.8-107). *Treatment:* Oral Monotherapy 11, Prostanoid Monotherapy 1, Combination therapy 10, Intolerant of therapy 1, Pulmonary Endarterectomy 6, Transplant referral 4, Shunt repair 1.
**Outcome:** 18 out of 28 patients survive on medical and surgical therapies. This is equivalent to 54 patients treated per million, considerably higher than the national average [1].
**Conclusion:** Diagnosis and treatment rates for PH in the UK can be substantially improved in many areas by developing local services with the support of the regional Specialist centre.
**Reference:**
[1] Thorax 2008;63(Suppl II):ii1-ii41.

**P939**

**Stability of a new formulation of intravenous epoprostenol sodium**

Olivier Lambert[1], Dirk Bandilla[2]. *[1]Technical Operations, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland; [2]Global Quality Management, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland*

Epoprostenol sodium with (undisclosed) excipients (epoprostenol XX) is a new formulation of epoprostenol, a pulmonary arterial hypertension treatment. This study assessed stability and determined shelf-life of epoprostenol XX. Stability of epoprostenol XX, either diluted for immediate use and tested at 25°C, 30°C and 40°C for up to 72 h, or following storage for up to 8 days at 5°C after reconstitution and immediate dilution with further exposure at 25°C and 30°C for up to 48 h, was assessed at 3,000, 15,000 and 60,000 ng/mL. Potency was measured by HPLC. The time period over which potency remained ≥90%, relative to 100% at time 0, determined shelf-life. Relative potency of diluted epoprostenol XX for immediate use was temperature-dependent and remained ≥90% after storage at 25°C, 30°C and 40°C for 48h, 24h and 8h, respectively (3,000 ng/mL); 48h, 24h and 12h, respectively (15,000 ng/mL); and 72h, 48h and 24h, respectively (60,000 ng/mL). The relative potency of reconstituted and immediately diluted epoprostenol XX after storage for 8 days at 5°C was ≥98% and remained ≥90% after further storage for 24-48h at 25°C or 30°C, depending on concentration. The table shows shelf-life of epoprostenol XX based on these results.

Table 1. Shelf-life of epoprostenol XX solutions for different conditions of use

| Concentration | Maximum shelf-life of diluted solution | |
|---|---|---|
| | Diluted solution for immediate administration | Diluted solution stored for ≤8 days at 5°C |
| ≥3,000 ng/mL and < 15,000ng/mL | 48h at 25°C / 24h at 30°C / 8h at 40°C | 24h at 25°C / 24h at 30°C |
| ≥15,000 ng/mL and < 60,000 ng/mL | 48h at 25°C / 24h at 30°C / 12h at 40°C | 48h at 25°C / 24h at 30°C |
| ≥60,000 ng/mL | 72h at 25°C / 48h at 30°C / 24h at 40°C | 48h at 25°C / 48h at 30°C |

**P940**

**Pulmonary arterial hypertension: Long term effects of oral ambrisentan on clinical status, exercise capacity and haemodynamics**

Michele D'Alto, Emanuele Romeo, Paola Argiento, Anna Correra, Berardo Sarubbi, Antonello D'Andrea, Antonietta Caronna, Maria Pignatiello, Nicola Grimaldi, Raffaele Calabrò, Maria Giovanna Russo. *Cardiology, Second University of Naples, Monaldi Hospital, Naples, Italy*

**Aim:** To evaluate the efficacy and safety of oral ambrisentan in adult patients with pulmonary arterial hypertension (PAH) by assessing its long term effects on clinical status, exercise capacity and cardiopulmonary haemodynamics.
**Methods:** This was a single-centre, open-label, single-arm, prospective study. Clinical status, resting transcutaneous oxygen saturation (SpO2), 6-minute walk distance, serology and RHC were assessed at baseline (before starting ambrisentan therapy) and at one year follow-up.
**Results:** Twenty-seven consecutive adult patients (18 female, age 51±11y) with PAH (15 with idiopathic, 7 with congenital heart disease-related and 5 with connective tissue-related PAH) were enrolled. No patient treated with ambrisentan developed aminotransferase concentrations >3 times the upper limit of normal. After 12±4 months of therapy, an improvement in clinical status, 6-minute walk distance, pro-brain natriuretic peptide and haemodynamics was observed.

Clinical and haemodynamic variables at baseline and after oral ambrisentan therapy

| | | Basal | Follow-up | p |
|---|---|---|---|---|
| | WHO FC | 2.8±0.4 | 2.5±0.5 | 0.0027 |
| | 6MWD (m) | 322±66 | 350±62 | 0.00005 |
| | proBNP (pg/ml) | 588±535 | 392±315 | 0.008 |
| Heart catheterization | mPAP (mmHg) | 50±17 | 49±16 | ns |
| | CI (L/m/m$^2$) | 2.4±0.5 | 2.7±0.4 | 0.0001 |
| | PVR (WU) | 10±6 | 8±4 | 0.007 |

FC, functional class; 6MWD, 6-minute walk distance; mPAP, mean pulmonary arterial pressure; CI, Cardiac Index; PVR, pulmonary vascular resistance.

**Conclusions:** Long term ambrisentan therapy is safe and well tolerated at 12-month follow-up, resulting in a significant improvement in clinical status, exercise capacity and cardiopulmonary heamodynamics.

**P941**

**Incidence of subdural hematoma in patients with pulmonary arterial hypertension (PAH) in two randomized controlled clinical trials**

Gerald Simonneau[1], Lie-Ju Hwang[3], Simon Teal[4], Nazzareno Galie[2]. *[1]Dept of Pneumology and ICU, Hopital Antoine Béclère, Paris, France; [2]Institute of Cardiology, University of Bologna, Italy; [3]Specialty Care Business Unit, Pfizer Inc., New York, United States*

**Background:** Recent reports have emerged of increased incidence of subdural haematoma in patients with PAH, a serious adverse event with high mortality and morbidity. We evaluate the event rate in two randomized controlled trials, SUPER-1/2 and PACES-1/2.
**Methods:** In SUPER-1, 277 patients (IPAH, CTD-, CHD-PAH, WHO FC II-IV, mean baseline PVR 952.0 dyne.s/cm*$^5$) naive to targeted therapy received placebo or sildenafil 20/40/80mg TID for 12 weeks. In the open-label extension (OLE) phase patients were up-titrated (as tolerated) to 80mg TID. In PACES-1, 267 patients (IPAH, CTD-PAH, WHO FC I-IV, mean baseline PVR 810.5 dyne.s/cm*$^5$) stable on IV epoprostenol received placebo or sildenafil (up-titrated to 80mg TID, as tolerated) for 16 weeks. Patients in both OLE trials received sildenafil for ≥3 years. Treatment with conventional agents (anticoagulants, diuretics, digoxin, oxygen, calcium-channel blockers) was permitted. We determined the annual event rate of subdural haematoma by treatment exposure in person-years. Patient days on therapy does not include days on placebo.
**Results:** 2 patients experienced subdural haematoma, both during OLE; one received placebo in PACES-1, one sildenafil 40mg TID in SUPER-1. Patients were

female, aged 58 and 62 years, diagnosed with IPAH, WHO FC III, mean PVR 557 (PACES-1) and 1073 dyne.s/cm*5 (SUPER-1) at baseline. Both patients received oral anticoagulants. In SUPER-1 and PACES-1, 73 and 82% of patients were on anticoagulants, respectively. Incidence of subdural haematoma in these 2 studies was 0.0015 events/patient-year.
**Conclusion:** Subdural haematoma is a rare event in PAH patients in these 2 randomized controlled trials.

**P942**
**Long-term bosentan therapy improves exercise capacity and hemodynamics in sarcoidosis-associated pulmonary hypertension**
Debbie Qua[1], Veronica Palmero[2], Roxana Sulica[1]. [1]*Division of Pulmonary, Critical Care and Sleep Medicine, Beth Israel Medical Center, New York, NY, United States;* [2]*Division of Pulmonary, Critical Care and Sleep Medicine, St. Luke's-Roosevelt Hospital Center, New York, NY, United States*

Introduction and Rationale
Therapeutic options in sarcoidosis-associated pulmonary hypertension (SPH) are limited. We evaluated the long-term efficacy of Bosentan in SPH.
**Methods:** Out of 60 consecutive patients with SPH retrospectively reviewed, 45 were eligible for Bosentan therapy and followed for 36 months. We recorded baseline characteristics, hemodynamics and 6-minute walk distance (6MWD) before/after treament, side effects, and vital status. Statistical analysis was perfomed using Student t-test and 1-way ANOVA.
**Results:** There were 66% Blacks, 64% women, with mean age of 53 years. Most patients (62%) had pulmonary fibrosis, and mean diffusing capacity was 37%. Additional SPH therapy was required in 45% cases; bosentan was discontinued in 5 patients due to liver abnormalities (incidence 11%). One- and 3-year survival rates were 73% and 48%. In 29 patients that remained on bosentan at three years, there were signficant improvements in the 6MWD (p=0.005) and hemodynamics.

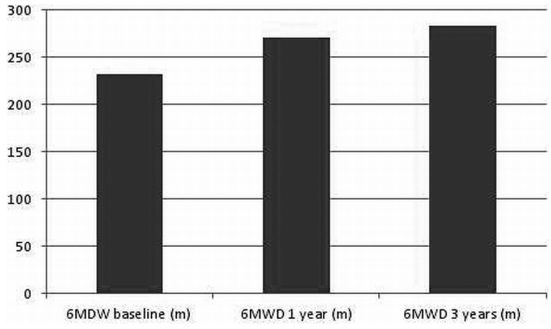



Table 1

| Variable | Baseline (mean (SE)) | Follow-up (mean (SE)) | Difference (mean (SE)) | p value |
|---|---|---|---|---|
| mPAP (mmHg) | 44.9 (2) | 37.1 (2) | 7.8 (2) | 0.005 |
| PVR (Wood units) | 8 (1.3) | 5.7 (0.8) | 2.3 (0.9) | 0.01 |

mPAP = mean pulmonary artery pressure; PVR = pulmonary vascular resistance; cardiac index and pulmonary artery saturation non-significant; trend for improvement right atrial pressure.

**Conclusions:** A subset of SPH patients may benefit from bosentan therapy.

**P943**
**First long-term experience with intravenous treprostinil administered by the implantable infusion pump LenusPro. A single-center pilot study**
Regina Steringer-Mascherbauer[1], Veronika Eder[1], Charlotte Huber[1], Susanne Wittrich[1], Reinhold Fuegger[2], Uwe Fröschl[2], Hans Joachim Nesser[1]. [1]*Department of Cardiology, Public Hospital Elisabethin Linz, Academic Teaching Center, Linz, Austria;* [2]*Department of Surgery, Public Hospital Elisabethinen Linz, Academic Teaching Center, Linz, Austria*

**Introduction:** Parenteral prostanoids are considered to be the most potent agents in the treatment of pulmonary arterial hypertension (PAH). However, administration of prostanoids with external pump systems is technically challenging and associated with side effects such as infusion site pain with subcutaneous (s.c.) and possibly life-threatening catheter-related infections with intravenous (i.v.) administration. The Lenus Pro implantable infusion pump was specifically developed to overcome the drawbacks of s.c. administration. In 2010, we reported the first implantation of a Lenus Pro pump with a filling interval of 28 days.
**Results:** Between September 2010 and October 2011, 14 patients underwent implantation at our center. All patients had previously shown significant clinical response to s.c. Treprostinil but suffered from site pain. Implantations were performed under general anesthesia. After preparation of the pump pocket in the abdominal wall the pump was connected to the central venous access. No intraoperative complications occurred. Postoperatively two patients developed a mild seroma. No other complications especially no infections were observed. Up to now more than 100 refill procedures were performed.
**Conclusions:** This first pilot study demonstrates that i.v. Treprostinil, delivered by the implantable pump Lenus Pro® is safe, effective and feasible in PAH patients transitioned from s.c. Treprostinil. Filling intervals of 28 days ensure optimal compliance and long-term patient management. The absence of side effects such as infusion site pain is associated with a dramatic increase in quality of life.

**P944**
**An international survey of current pulmonary arterial hypertension (PAH) management**
Ioana Preston[1], Barbara Hinzmann[2], Nicholas Bawden[3], Henning Tiede[4]. [1]*Pulmonary and Critical Care and Sleep Medicine Departments, Tufts University School of Medicine, Tufts Medical Center, Boston, United States;* [2]*Global Market Research Department, Bayer HealthCare Pharmaceuticals, Berlin, Germany;* [3]*Healthcare Department, Ipsos MORI, London, United Kingdom;* [4]*Medical Clinic 2, University of Giessen Lung Centre, Giessen, Germany*

**Background:** The therapeutic approach to PAH is evolving, multiple classes of agents are available and physicians from expert centres and the community treat PAH.
**Objectives:** To compare therapeutic management of PAH between countries and explore physicians' attitudes towards PAH-specific therapies.
**Methods:** Quantitative online survey conducted in 5 European countries, the US, and Canada during 2010. Physicians involved in PAH treatment decisions with experience in managing PAH for ≥2 years completed a perceptual questionnaire. Retrospective clinical records from last 5 patients (pts) seen by each physician were analysed.
**Results:** 472 physicians (43% cardiologists, 29% pulmonologists, 20% rheumatologists, and 8% internists), 62% based in pulmonary hypertension centres, entered data for 2360 pts. Among those, 51% had idiopathic PAH and 42% had PAH associated with other conditions; 38% had significant physical limitation (NYHA functional class III/IV) at diagnosis. US pts were more likely to be diagnosed in the community (40%) than pts in Europe (6%) and Canada (28%). Globally, 73% were on PAH-specific therapy, with PDE-5 inhibitors, endothelin receptor antagonists, and prostacyclins used in 57%, 54%, and 26%, respectively. Of pts treated, 29% were on combination therapies; highest usage was in the US (36%) and lowest in Italy (17%). For 95% of pts, their physicians were satisfied to some degree with the current treatment regimen. Main reasons for satisfaction included symptom control or improvement and stable disease condition.
**Conclusions:** This multinational survey highlights significant differences in PAH management between countries and illustrates physicians' perceptions of treating this condition.

**P945**
**Comparison of the pharmacokinetic, pharmacodynamic, and safety profiles of three different formulations of intravenous epoprostenol sodium**
Laurent Nicolas, Marcelo Gutierrez, Jasper Dingemanse. *Clinical Pharmacology, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland*

A change in excipient of epoprostenol sodium, an i.v. pulmonary arterial hypertension treatment, from glycine-mannitol (epoprostenol GM; Flolan®) to arginine-mannitol (epoprostenol AM; Veletri®) or to undisclosed excipients (epoprostenol XX) has led to improvements in stability of the latter two formulations.
The pharmacokinetic (PK), haemodynamic, safety, and tolerability profiles of these formulations were compared in this 2-part study. 20 healthy males in Part 1 and 20 different subjects in Part 2 received epoprostenol AM and epoprostenol XX, and epoprostenol GM and epoprostenol XX, respectively, in a crossover design, in sequential 2h i.v. infusions of 2, 4, 6 and 8 ng/kg/min.
PK profiles were assessed by analysing plasma concentration-time curves of the primary epoprostenol metabolites 6-keto-prostacyclin F1α (kPF) and 6,15-diketo-13,14-dihydro-prostacyclin F1α (ddPF) obtained after treatment with the different epoprostenol formulations. For Part 1, the ratio of the geometric means (90% CI) of $AUC_{0-\infty}$ calculated after epoprostenol AM and epoprostenol XX treatment was 0.91 (0.88–0.95) for kPF and 0.88 (0.84–0.92) for ddPF. For Part 2, the ratio of $AUC_{0-\infty}$ determined after epoprostenol GM and epoprostenol XX treatment was 0.97 (0.91–1.03) for kPF and 1.08 (1.02–1.14) for ddPF. Haemodynamic variables, assessed by echocardiography, showed similar increases in cardiac output, cardiac index, and heart rate for all formulations with maximum values attained after 6–8h. Almost all subjects reported ≤1 adverse event.
These results suggest the 3 formulations of i.v. epoprostenol sodium have the same PK, haemodynamic, safety, and tolerability profiles.

**P946**
**Lack of relevant pharmacokinetic interactions between the new dual endothelin receptor antagonist macitentan and sildenafil in healthy subjects**
Patricia Sidharta[1], Paul van Giersbergen[1], Michael Wolzt[2], Jasper Dingemanse[1]. [1]*Clinical Pharmacology, Actelion Pharmaceuticals Ltd., Allschwil, Switzerland;* [2]*Clinical Pharmacology, Medical University of Vienna, Austria*

Macitentan, a new potent, dual endothelin receptor antagonist (ERA), is a potential treatment for pulmonary arterial hypertension (PAH). As PAH treatment may involve combination therapy of an ERA with sildenafil, the mutual pharmacokinetic (PK) interactions were investigated using a randomised, 3-way crossover study

design (AC-055-106). Twelve healthy male subjects were treated as follows: A) macitentan alone for 4 days (loading dose of 30 mg, thereafter 10 mg o.d.), B) sildenafil alone for 4 days (20 mg t.i.d. on Days 1–3 and 20 mg o.d. on Day 4), C) treatments A and B combined. Plasma concentrations of macitentan and its pharmacologically active metabolite ACT-132577 (A and C) and sildenafil and its N-desmethyl metabolite (B and C) were measured on Day 4. Tolerability was also assessed. The PK of macitentan was not affected (geometric mean ratios for $C_{max}$ and $AUC_{\tau}$ close to 1.0 with 90% confidence intervals within 0.8–1.25 bioequivalence limits) by sildenafil while the exposure to ACT-132577 decreased ($C_{max}$ 0.82 [0.76–0.89]; $AUC_{\tau}$ 0.85[0.80–0.91]). Exposure to sildenafil increased in the presence of macitentan ($C_{max}$ 1.26 [1.07–0.89]; $AUC_{\tau}$ 1.15 [0.94–1.41]), while that to N-desmethylsildenafil was unaffected. All treatments were well tolerated but combined treatment resulted in a higher incidence of adverse events (most commonly headache) and decreased diastolic blood pressure. As no clinically relevant PK interactions were observed between macitentan and sildenafil, dose adjustment of either compound is not necessary during combined treatment.

**P947**

**EPITOME-2: Evaluation of a new formulation of epoprostenol sodium in pulmonary arterial hypertension patients switched from an originally approved formulation**

Olivier Sitbon[1], Marion Delcroix[2], Emmanuel Bergot[3], Anco Boonstra[4], Pilar Escribano Subias[5], Nazzareno Galiè[6], John Granton[7], David Langleben[8], Thomas Pfister[9], Jean-Christophe Lemarié[10], Gérald Simonneau[1]. *[1]Service de Pneumologie, Hôpital Universitaire de Bicêtre, Université Paris-Sud, Le Kremlin Bicêtre, France; [2]Pneumology, Academic Hospital Gasthuisberg, Leuven, Belgium; [3]Service de Pneumologie, Hôpital Côte de Nacre-CHU, Caen, France; [4]Pulmonology, VU University Medical Center, Amsterdam, Netherlands; [5]Servicio de Cardiología, Hospital Universitario 12 de Octubre, Madrid, Spain; [6]Institute of Cardiology, University of Bologna, Italy; [7]Pulmonary Hypertension Programme, Toronto General Hospital, Toronto, Canada; [8]Jewish General Hospital, McGill University, Montreal, Canada; [9]Global Medical Science, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; [10]Effi-Stat, Effi-stat, Paris, France*

**Introduction:** Epoprostenol sodium originally approved with glycine-mannitol excipients (epoprostenol GM; Flolan®) is an i.v. pulmonary arterial hypertension (PAH) treatment. Epoprostenol sodium with undisclosed excipients (epoprostenol XX) is a new formulation with improved room temperature stability and simplified storage requirements. EPITOME-2 is an ongoing PAH study evaluating switch from epoprostenol GM to epoprostenol XX.
**Methods:** Adult PAH patients treated with epoprostenol GM for ≥12 months and on a stable dose for the last 3 months were switched to epoprostenol XX. Changes from baseline to 3 months were evaluated for cardiac haemodynamic and clinical parameters, including pulmonary vascular resistance (PVR) and WHO functional class (FC). Safety and tolerability were also evaluated.
**Results:** Of the 42 patients enrolled, data are available for the first 10 completers. Mean (range) age was 45 (25–78) years and 5 were female. Mean (range) time from diagnosis was 10.57 (1.6–37.1) years. Following switch, patients remained on a stable epoprostenol XX dose at 3 months. There was no change from baseline to Month 3 in haemodynamics or WHO FC (table). Most AEs were typical of epoprostenol therapy.

Epoprostenol XX dose, haemodynamics and WHO FC

| Parameter | Baseline | Month 3 |
|---|---|---|
| Dose, ng/kg/min | 25.1 (7–58) | 25.4 (7–58) |
| PVR, dyn.sec/cm$^5$ | 666 (455–1164) | 685 (356–1327) |
| mPAP, mmHg | 54.7 (42–65) | 55.0 (37–73) |
| CO, L/min | 5.7 (4.3–6.7) | 5.7 (3.6–7.4) |
| WHO FC I, II, III (n) | 1,5,4 | 1,6,3 |

**Conclusions:** There are no indications thus far of unexpected safety, tolerability, efficacy or dosing issues arising from switching patients to epoprostenol XX.

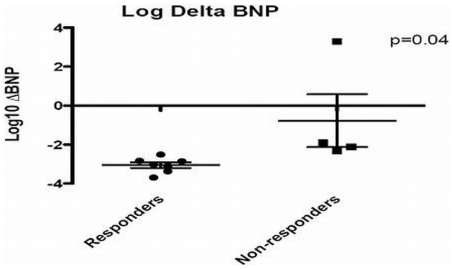
**P948**

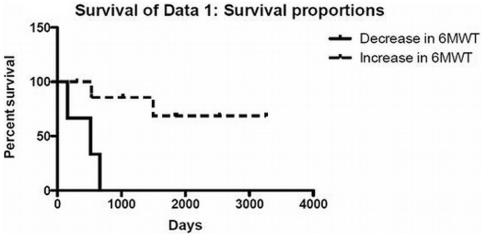
**Outcomes from use of targeted therapy in pulmonary hypertension associated with sarcoidosis (PHAS)**

John Cannon, Colm McCabe, Joanna Pepke-Zaba, Karen Sheares. *Pulmonary Vascular Disease Unit, Papworth Hospital, Cambridge, United Kingdom*

Pulmonary hypertension is a recognised complication of sarcoidosis and may arise from several aetiological pathways. We report our experience of patients with PHAS-GroupV on targeted treatment.
Retrospective study of patient outcomes with PHAS. All patients underwent right heart catheterisation satisfying criteria for diagnosis of PAH. We reviewed 16 patients, 10 of whom died in mean f/u 32m. Patients dichotomised into 2 groups (responders and non-responders) based on improvement in log ntproBNP and 6MWD within 6 months of therapy initiation.
Treatment response was associated with a reduced risk of death. Cohort phenotypes suggest that treatment response may not be predicted from sarcoid stage, functional class, FVC or presence of extrapulmonary features. However elevation in PVR may possibly be associated with a favourable response. An RCT is indicated to evaluate a larger cohort.

| | Responders (n=8) | Non-responders (n=5) | p value |
|---|---|---|---|
| Age, y | 60.8 | 58.8 | 0.71 |
| Gender, M:F | 4:4 | 3:2 | |
| Follow up, m | 54.8 | 17.4 | 0.02 |
| Sarcoid stage III/IV | 3:5 | 1:4 | 0.66 |
| NYHA Functional Class | 7:1 | 5:1 | 0.81 |
| mPAP | 52.6 | 45.4 | 0.11 |
| CI | 1.85 | 1.64 | 0.20 |
| PVR, dyn | 1001 | 648 | 0.046 |
| FVC, % | 61 | 66 | 0.61 |
| KCO, % | 50 | 53 | 0.79 |
| 6MWD, Δm | +78 | –52 | 0.004 |




**P949**

**Ambrisentan for therapy of portopulmonary hypertension (POPH): Update on safety and efficacy**

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**Aim:** To present an update of the long-term hemodynamic response and clinical outcomes of POPH patients treated with ambrisentan.
**Methods:** Observational study of POPH patients from 01/2007 to 12/2011 treated with ambrisentan. Clinical data, baseline and follow up transthoracic echocardiograms (TTE) and right heart catheterizations (RHC) were accomplished and compared.
**Results:** A total of 27 patients with POPH were started on ambrisentan (female=15). Median age (IQR) was 56 (53-60). Median follow up 874 days (472-1548). Median time on ambrisentan 391 days (259-839). Ten patients underwent liver transplantation successfully. Nine out of 27 patients died, 7 deaths due to complications of chronic liver disease, one patient of sepsis, and one died of an acute coronary syndrome. Follow up RHC data were available in 20 patients. Mean pulmonary artery pressure (mPAP) improved from 42 mmHg (35-57) to 38.5 (28-43.5), p= 0.001; pulmonary vascular resistance (PVR) improved from 434 dynes*s/cm−5 (311-611) to 228 (154-361), p=0.001; and cardiac output increased from 6 L/min (5-7.4) to 7.9 (6.4-9.2), p=0.005. TTE data showed that RV size and function improved in 19 and 18 patients respectively. Ambrisentan was well tolerated in all but one patient who developed severe edema and required discontinuation after 2 weeks of initiation. No significant elevation of transaminases requiring discontinuation of the medication was identified.
**Conclusion:** In this cohort of patients with POPH, ambrisentan proved to be safe and efficacious for the therapy of POPH patients. Ambrisentan resulted in significant improvement in hemodynamics and normalization of RV size, function and PVR in the majority of the patients.

**P950**

**Lack of relevant pharmacokinetic and pharmacodynamic interactions between the new dual endothelin receptor antagonist macitentan and warfarin in healthy subjects**

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Macitentan, a new, potent, dual endothelin receptor antagonist (ERA), is a potential treatment for pulmonary arterial hypertension (PAH). In this study (AC-055-105),

the effect of macitentan on the pharmacokinetics (PK) and pharmacodynamics (PD) of a single dose of warfarin was investigated in 14 healthy male subjects. Subjects received treatment sequence A/B or B/A separated by a 2-week washout. Treatment A: macitentan for 8 days (loading dose of 30 mg, thereafter 10 mg o.d.). On Day 4, a single dose of 25 mg warfarin was given with macitentan. Treatment B: A single dose of 25 mg warfarin on Day 1. Blood samples were assessed for warfarin PK (R- and S-warfarin) and PD (INR and Factor VII). Plasma trough levels of macitentan and its active metabolite, ACT-132577, were determined. Twelve subjects were included in the PK/PD analysis. The plasma concentration-time profiles of R- and S-Warfarin (Figure 1) and PD parameters of INR and Factor VII were comparable between treatments.

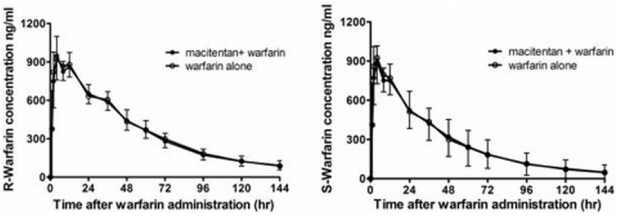


Figure 1. Plasma concentration-time profile of R- and S-warfarin with and without macitentan (mean ± SD, n=12).

Warfarin did not impact the trough levels of macitentan and ACT-132577. Both treatments were well tolerated. Based on these results, no dose correction of macitentan or warfarin is needed when using these drugs together.

**P951**

**Absorption behavior of riociguat (BAY 63-2521): Bioavailability, food effects, and dose-proportionality**

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**Introduction:** Riociguat, an oral soluble guanylate cyclase (sGC) stimulator, is currently investigated in the treatment of PH. Riociguat increases cGMP production through a novel dual mode of action: direct NO-independent sGC stimulation and increasing sGC sensitivity to low NO levels.
**Aim:** To characterize the biopharmaceutic properties of riociguat including absolute bioavailability (BA), interaction with food, and dose-proportionality.
**Methods:** Pharmacokinetics (PK) following IV and oral administration of immediate release tablets were characterized in 3 open-label, randomized, crossover studies in healthy male subjects: absolute BA (n=22), food effect at 2.5 mg (n=24), and dose-proportionality over 0.5–2.5 mg (n=24). Safety and tolerability were also assessed.
**Results:** Absolute BA was 94% (90% CI: 83–107). A high-fat breakfast delayed absorption with little effect on the extent of riociguat absorption (ratio $AUC_{fed}/AUC_{fasted}$ 88% CI: 82–95). PK were dose-proportional over 0.5–2.5 mg (common slope of AUC 1.09 [90%CI: 1.04–1.14]; $C_{max}$ 0.98 [90% CI: 0.93–1.04]). Intra-individual variability was low (G-CV AUC, $C_{max}$ <20%); inter-individual variability was moderate-to-high (G-CV AUC 30%, $C_{max}$ G-CV 65%). Riociguat was well tolerated in all studies. Adverse events were as expected from the mode of action.
**Conclusion:** Riociguat shows complete oral absorption, and no clinically relevant food effect. At 0.5–2.5 mg, riociguat systemic exposure increased dose-proportionately with moderate-to-high inter-individual and low intra-individual variability. Results support the suitability of the individualized dose titration concept investigated in Phase 3 PAH and CTEPH studies.

**P952**

**Effect of ambrisentan, bosentan and macitentan on human hepatic uptake and efflux transporters**

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**Background:** The putative mechanism for hepatic adverse reactions observed with bosentan, an endothelin receptor antagonist (ERA), is inhibition of the hepatic transport of bile salts (Fattinger K.2001). The ERA ambrisentan has a low risk of hepatic adverse reactions.
**Objective:** Bosentan, ambrisentan and macitentan, an experimental ERA in clinical development, were tested for inhibition of hepatic transporters in vitro.
**Methods:** Inhibition constants (IC50) were measured for human BSEP, sodium taurocholate cotransporting polypeptide (NTCP), multidrug resistance protein 2 (MRP2), P-glycoprotein (Pgp), breast cancer resistance protein (BCRP), organic anion-transporting polypeptide 1B1 (OATP1B1), and OATP1B3 in transfected cell-lines. Known inhibitors were used as positive controls.
**Results:** The most potent inhibition observed was for OATP1B1 (range 2 μM to 47 μM). Ambrisentan had no measurable effect on BSEP and NTCP while inhibition was observed for bosentan and macitentan. The most potent inhibition of these transporters was observed for macitentan with IC50 values of 12 and 8 μM for BSEP and NTCP, respectively.

Effect of ERAs on hepatic uptake and efflux transporters

| Transporter | IC50 (μM) | | |
|---|---|---|---|
| | Ambrisentan | Bosentan | Macitentan |
| BSEP | >100 | 54.4 | 12 |
| NTCP | >100 | 36.5 | 8 |
| MRP2 | ~ 75 | >100 | >100 |
| Pgp | >100 | >100 | 64±15 |
| BCRP | >100 | >100 | 75±37 |
| OATP1B1 | 47.0±21.3 | 5.0±2.0 | 2.0±0.3 |
| OAT1B3 | 44.6±23.8 | 5.2±2.1 | 2.1±0.3 |

**Conclusions:** Macitentan inhibited hepatic transporters the greatest whilst ambrisentan showed little or no effect.

**P953**

**Bosentan influence on catecholamines levels in patients with idiopathic arterial pulmonary hypertenson**

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**Aim:** To assess the influence of endothelin receptor antagonist Bosentan on catecholamines levels in pts with idiopathic pulmonary arterial hypertension (IPAH).
**Methods:** In the single-center comparative study we included 35 pts aged 35,2±9,6ys with IPAH confirmed by RHC (WHO Functional Class (FC) II-IV)without systemic inflammation signs. On top of stable therapy with anticoagulants, diuretics, glycosides, calcium antagonists for at least 3 months, Bosentan therapy was started 62,5 mg twice daily for 4 wks.At wk4 the pts were randomized 1:1 by the envelope method to bosentan 125 or 250 mg/day.At baseline, at wk3 and wk12 visits the pts underwent the clinical and lab assessment, including catecholamines (HPLC).
**Results:** At baseline IPAH groups were comparable by age, sex, disease duration, hemodynamic parameters. In both groups the levels of norepinephrine were significantly higher than normal values (139,9±1,2). Otherwise the epinephrine levels were decreased as compared with controls (69,4±1,2).
**Conclusion:** In IPAH pts Bosentan therapy influenced on catecholanines levels by significant reduction of initially increased norepinephrine levels.This effect was more pronounced in Pts treated with Bosentan 125mg daily.

**P954**

**Endothelin-1 downregulates BMP signaling in pulmonary artery smooth muscle cells**

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Increased endothelin-1 (ET-1) and decreased bone morphogenetic protein (BMP) receptor type 2 (BMPR2) signaling pathways have been shown to be implicated in the pathogenesis of pulmonary arterial hypertension (PAH). However, little is known about the interaction between these two signaling pathways and its implication in the generation of altered pulmonary artery smooth muscle cell (PA-SMC) phenotype in PAH.
We further explored BMP signaling in PA-SMCs isolated from PAH patients and the effects of ET-1 treatment on the expressions of BMPR2, BMP agonists (BMP4) and antagonists (gremlin-1, gremlin-2 and noggin) in PA-SMCs.
We therefore quantified, by RTQ-PCR, the gene expressions of BMPR2, BMP agonists and antagonists in primary cultures of PA-SMCs isolated from PAH patients (n=4) and controls (n=9). We evaluated the effects of increasing concentrations of

**Abstract P953** – Table 1

| Parameter | Group 1 (bosentan 125mg) | | | Group 2 (bosentan 250mg) | | |
|---|---|---|---|---|---|---|
| | Baseline | Wk3 | Wk12 | Baseline | Wk3 | Wk12 |
| Norepinephrine (pg/ml) | 679,7 [297,1; 1019,2] | 524,8 [202,5; 721,7]* | 153,6 [109,5; 294,9]* | 384,6 [257,7; 888,3] | 428,0±288,9 354,8 [206,9; 625,3]* | 248,1 [154,3; 475,8]* |
| Epinephrine (pg/ml) | 45,8 [40,5; 60,5] | 39,80 [38,1; 46,7] | 27,1 [25,1; 44,4] | 29,9 [17,1; 40,9]# | 29,1 [26,1; 54,3] | 34,3 [26,2; 48,7] |

*p<0,05 vs baseline, #p<0,05 group 1 vs group 2.

ET-1 (10-6M and 10-7M) on the expression of these BMP signaling members in control PA-SMCs.
PA-SMCs isolated from PAH patients presented with decreased BMPR2 gene expression, while gene expressions of gremlin-1, gremlin-2 and noggin increased in PA-SMCs isolated from PAH patients compared to controls. BMP4 gene expression increased in PA-SMCs isolated from PAH patients. Stimulation of control PA-SMCs with ET-1 induced an increase in mRNA encoding BMP antagonists (gremlin-1, gremlin-2 and noggin), while BMPR2 gene expression decreased dose-dependently. However, in ET-1-treated PA-SMCs, BMP4 expression did not change. After ET-1 treatment, levels of BMPR2 and BMP antagonists were similar as those observed in PA-SMCs isolated from PAH patients.
Endothelium-derived ET-1 seems to contribute to altered BMPR2 signaling observed in PAH patients.