Introduction

Pulmonary arterial hypertension (PAH) is a fatal and progressive condition characterized by the presence of precapillary pulmonary hypertension at right heart catheterization (mean pulmonary arterial pressure \( \geq 25 \text{ mmHg at rest} \) and wedge pressure \( \leq 15 \text{ mmHg} \)) and high pulmonary vascular resistance (>3 Wood units) in the absence of other causes of precapillary pulmonary hypertension, like lung disease or chronic thromboembolic pulmonary hypertension.\(^4\) PAH is the first group of the pulmonary hypertension classification\(^1\) (Table 1). In the idiopathic form, no etiology is found. In the heritable form there is a context of familial history or a genetic mutation. Other forms are associated with drugs and toxins, connective tissue diseases, liver disease, human immunodeficiency virus (HIV), congenital heart disease or schistosomiasis.

PAH is a rare disease, defined by a prevalence lower than 1/2000 in Europe or fewer than 200,000 people at any given time in the United States (US) but is being increasingly recognized. Recent large multicenter registries have provided low estimates of PAH prevalence of 15 cases/million inhabitants and incidence of 2.4 cases/million adult inhabitants/year in France, and 10.6 and 2 respectively in the US.\(^2,3\)
Table 1. Clinical classification of pulmonary hypertension.¹

| Group 1. Pulmonary arterial hypertension |
|----------------------------------------|
| 1.1 Idiopathic PAH                       |
| 1.2 Heritable PAH                        |
| 1.2.1 BMPR2 mutation                    |
| 1.2.2 Other mutations                   |
| 1.3 Drug and toxin induced              |
| 1.4 Associated with                     |
| 1.4.1 Connective tissue disease         |
| 1.4.2 HIV infection                     |
| 1.4.3 Portal hypertension               |
| 1.4.4 Congenital heart diseases         |
| 1.4.5 Schistosomiasis                   |
| Group 1’. Pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis |
| Group 1”. Persistent pulmonary hypertension of the newborn |
| Group 2. Pulmonary hypertension due to left heart disease |
| 2.1 Left ventricular systolic dysfunction |
| 2.2 Left ventricular diastolic dysfunction |
| 2.3 Valvular disease                    |
| 2.4 Congenital/acquired left heart inflow/outflow tract obstructions and congenital cardiomyopathies |
| 2.5 Congenital/acquired pulmonary veins stenosis |
| Group 3. Pulmonary hypertension due to lung diseases or hypoxia |
| 3.1 Chronic obstructive pulmonary disease |
| 3.2 Interstitial lung disease           |
| 3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern |
| 3.4 Sleep-disordered breathing          |
| 3.5 Alveolar hypoventilation disorders  |
| 3.6 Chronic exposure to high altitude  |
| 3.7 Developmental lung diseases         |
| Group 4. Chronic thromboembolic pulmonary hypertension and other pulmonary artery obstructions |
| 4.1 Chronic thromboembolic pulmonary hypertension |
| 4.2 Other pulmonary artery obstructions |
| 4.2.1 Angiosarcoma                      |
Remodeling of the pulmonary vasculature is responsible for an increase in pulmonary vascular resistance leading to progressive right heart failure and ultimately death. It is partially explained by an imbalance between three main pathways, the prostacyclin, the nitric oxide and the endothelin pathways. Current treatments aim to re-establish the balance between the vasoactive and vasodilatory capacities in the lung vasculature.

**Endothelin and the pulmonary circulation**

Increased levels of endothelin (ET)-1 have been observed in the plasma and pulmonary vascular endothelium of patients with pulmonary hypertension and increased plasma levels were also observed in experimental animal models of PAH. ET-1 is the principal isofrom in the cardiovascular system, and it is one of the most potent vasoconstrictors. The activity of ET-1 is mediated through two distinct receptors: ETA and ETB. In physiological conditions vasoconstriction is essentially mediated by ETA receptors which predominate on vascular smooth muscle cells (SMCs). ETB receptors are mainly expressed on the vascular endothelium and mediate vasodilation. This is the reason why theoretically it was thought that selective ETA inhibition may be more efficient. However, in pathological conditions like PAH, ETB receptors are upregulated on SMCs and downregulated on endothelial cells, suggesting that dual endothelin receptor antagonism (ERA) may be better than ETA Selective inhibition. There is however no clinical evidence of improved efficacy of one or the other type of ERA.

The dual ERA bosentan was approved as the first oral therapy for PAH, based on two randomized controlled trials (RCTs) showing improvements in exercise capacity, hemodynamic parameters and time to clinical worsening. However, the treatment was associated with an increased, dose-dependent, incidence of elevated liver transaminases, and an increase in plasma bile salts and alkaline phosphatases attributed to inhibition of the bile salt export pump by bosentan and its metabolites. Peripheral edema was also observed with bosentan. An extensive drug discovery program was then started to maximize the inhibition of the ET receptors and minimize the risk of elevated liver enzymes and fluid retention.

**Macitentan pharmacology**

Macitentan is the result of this optimization program. It is a dual ERA with enhanced tissue penetration (related to greater lipophilicity) and receptor binding properties, and superior efficacy in animal models. The structure of macitentan is derived from the structure of bosentan. Increased receptor affinity and increased lipophilicity was obtained by replacing the sulfonamide moiety present in bosentan with a sulfamide moiety. Macitentan has a compact conformation facilitating deep penetration into the receptor and allowing precise occupation of a hydrophobic pocket in the ETA receptor. ET1 acts as a tissular (paracrine or autocrine) factor, therefore an ERA that can easily penetrate tissue is more potent to increase ET receptor blockade. Optimization of the ability to target the tissue has been achieved by optimization of physiochemical properties of the molecule. This was achieved by increasing the pKa value (6.2 for macitentan compared with 5.1 for bosentan and 3.5 for ambrisentan) and by increasing the distribution coefficient leading to increased affinity for the tissue (800:1, lipid phase: aqueous phase for macitentan compared...
with 20:1 for bosentan whereas 1:20.5 for ambrisentan which has more affinity for the aqueous milieu than for lipids). Macitentan also binds longer to the receptor (receptor occupancy half-time \( \approx 1020 \text{ s} \) for macitentan, \( \approx 70 \text{ s} \) for bosentan and \( \approx 40 \text{ s} \) for ambrisentan) resulting in a better blockade of ET signaling and making it possible to have a once daily dosing.\(^{14,19,20,22}\)

Macitentan does not inhibit bile salt transport.\(^{23}\) Macitentan also shows a favorable drug–drug interaction profile.\(^{24}\) Concomitant use of rifampicin, which reduces macitentan exposure, should be avoided.\(^{25}\)

**Macitentan: clinical evidence**

The effects of macitentan have been extensively investigated in 15 phase I studies in more than 300 subjects,\(^{14}\) a phase II study (in patients with idiopathic pulmonary fibrosis)\(^{26}\) and the pivotal phase III study with an ERA in PAH to improve clinical outcome (SERAPHIN trial\(^{27}\)). Specific efficacy aspects have been detailed in many more publications (effect on hospitalizations,\(^{28}\) on prevalent and incident patients,\(^{29}\) on hemodynamic parameters,\(^{30}\) on health-related quality of life,\(^{31}\) and on the relationships between the 6 minute walking distance (6MWD) and long-term outcomes,\(^{32}\) between morbidity and mortality,\(^{33}\) and between pharmacokinetics and hemodynamic efficacy\(^{34}\)). New studies have also been dedicated to different pulmonary hypertension (PH) groups (inoperable chronic thromboembolic pulmonary hypertension\(^{35}\) and pulmonary hypertension due to left ventricular dysfunction\(^{36}\)), to exploratory end-points (Table 2), and to real-life experience (Table 2).

The SERAPHIN trial evaluated the efficacy and safety of two doses of macitentan (3 and 10 mg once a day) by using a composite primary endpoint of time to first morbidity and (all-cause) mortality event in 742 patients with symptomatic PAH in a randomized, double-blind, multicenter, placebo-controlled, event-driven trial. After randomization, 250 patients received placebo, 250 received macitentan 3 mg and 242 received macitentan 10 mg.

Eligible patients were aged \( \geq 12 \text{ years} \) with confirmed PAH diagnosis (idiopathic or heritable PAH, PAH associated with connective tissue disease, repaired congenital systemic-to-pulmonary shunts, HIV infection, drug use or toxin exposure). Patients were required to have a 6MWD \( \geq 50 \text{ m} \) and a World Health Organization (WHO) functional class (FC) II, III or IV. Patients naïve to PAH treatment or those receiving a phosphodiesterase type 5 inhibitor (PDE5i), oral or inhaled prostanoids, calcium channel blockers or L-arginine at stable doses for at least 3 months could be included. Patients treated with intravenous or subcutaneous prostanoids or ERAs were excluded.

**Morbidity and mortality**

Macitentan 3 and 10 mg daily was effective in delaying the disease progression, reducing the risk of a morbidity or mortality event by 45\% (10 mg) and by 30\% (3 mg) over the treatment time as compared with placebo.\(^{27}\)

Macitentan treatment also significantly reduced the composite secondary endpoint of death due to PAH or hospitalization for PAH by 50\% (10 mg versus placebo, \( p < 0.001 \)). The risk of hospitalization for PAH in the group treated with 10 mg of macitentan was reduced by 51.6\% compared with the placebo group (\( p < 0.0001 \)), the rate of hospitalization for PAH by 49.8\% (\( p < 0.0001 \)), and the number of hospital days by 52.3\% (\( p = 0.0003 \)).\(^{28}\)

The incidence of all-cause death and death due to PAH did not differ significantly between the macitentan and placebo group. However, as PAH is a progressive disease, clinical deterioration is likely to precede death which is rarely the first recorded event.\(^{27}\)

To overcome the hurdle of evaluating survival benefits in rare diseases the use of real-world observational data has been proposed to complement RCT data. To this end, a prediction model based on the US REVEAL registry data has been used to further explore the effect of macitentan on mortality. This analysis suggested that, over 3 years, the risk of mortality with macitentan 10 mg was 31\% lower than that predicted from the model (\( p = 0.033 \)).\(^{37}\)

It is noteworthy that the patients enrolled in the SERAPHIN trial were younger than currently observed in the western countries; the mean age of PAH patients at diagnosis averaging 50 \( \pm 14 \) and 65 \( \pm 15 \) years in recent registries (French, COMPERA and US REVEAL registries).\(^{38}\) The
Table 2. Clinical trials with macitentan in pulmonary arterial hypertension.

| Trial          | Number of patients | Time frame | Design                          | Primary endpoint                                                                 | Status | Conclusion                      |
|----------------|--------------------|------------|---------------------------------|----------------------------------------------------------------------------------|--------|---------------------------------|
| SERAPHIN       | 742                | 36 months  | Interventional randomized       | Time to first confirmed morbidity or mortality event up to end of treatment       | completed | primary endpoint reached        |
| NCT00660179   | IPAH, PAH-CTD, PAH-CHD closed defect morbi-mortality |            | double-blind placebo-controlled parallel assignment phase III |                                                                    |        |                                 |
| MAESTRO        | 266                | 16 weeks   | Interventional randomized       | Change from baseline to week 16 in exercise capacity as measured by 6-minute walk distance | completed | primary endpoint not met        |
| NCT01743001   | PAH-CHD            |            | double-blind placebo-controlled parallel assignment phase III |                                                                    |        |                                 |
| MAESTRO-OL     | 220                | 3 years    | Interventional open label       | Treatment-emergent serious adverse events up to 30 days after study drug discontinuation Treatment-emergent marked lab abnormalities Proportion of patients with treatment-emergent ALT or AST abnormality | completed | NA                              |
| NCT01739400   | PAH-CHD            |            | single arm phase III            |                                                                    |        |                                 |
| OPTIMA         | 60 (estimated)     | 16 weeks   | Interventional open label       | Change from baseline to Week 16 in % of patients with clinically meaningful improvement of PVR (decrease of 30% from baseline to Week 16) combination therapy with tadalafil | recruiting | NA                              |
| NCT02968901   | PAH right heart cath |            | single arm phase IV             |                                                                    |        |                                 |
| OPUS           | 5000               | 1 year     | Interventional open label       | To estimate incidence rates for specified outcomes Liver test, hepatic and any other adverse events Discontinuation, hospitalization and death | recruiting | NA                              |
| NCT02126943   | PAH safety         |            | single arm phase IV             |                                                                    |        |                                 |
| ORCHESTRA      | 160                | 16 weeks   | Interventional open label       | To evaluate the psychometric characteristics of reliability and construct validity of the French, Italian and Spanish versions of the PAH-SYMPACT™ | completed | NA                              |
| NCT02081690   | PAH* PRO           |            | single arm phase III            |                                                                    |        |                                 |

(Continued)
| Trial | Number of patients | target population | Time frame | Design | Primary endpoint | Status | Conclusion |
|-------|--------------------|-------------------|------------|--------|-----------------|--------|------------|
| ORCHESTRA extension NCT02112487 | 160 (estimated) | PAH* safety | 6 months | Interventional open label single arm phase III | To assess the long-term safety of macitentan in patients with pulmonary arterial hypertension | active not recruiting | NA |
| PORTICO NCT02382016 | 84 (estimated) | POPH RHC | 12 weeks | Interventional randomized double-blind placebo-controlled parallel assignment phase IV | Relative change from baseline to week 12 in PVR | active not recruiting | primary endpoint reached (unpublished) |
| REPAIR NCT02310672 | 100 (estimated) | PAH# MRI | 52 weeks | Interventional open label single arm phase IV | Change in RV stroke volume and ratio of week 26 to baseline PVR | recruiting | NA |
| RUBATO NCT03153137 | 134 (estimated) | Fontan-palliated CPET | 16 weeks | Interventional randomized double-blind placebo-controlled parallel assignment phase III | Change in peak VO₂ (oxygen uptake) | recruiting | NA |
| SERAPHIN-OL NCT00667823 | 550 | PAH | 55 months | Interventional open label single arm phase IV | Number of patients with treatment-emergent adverse events and serious adverse events | active not recruiting | NA |
| TOMORROW NCT02932410 | 300 (estimated) | pediatric PAH disease progression | 6 years | Interventional open label parallel assignment phase IV | Time to the first disease progression event in children | recruiting | NA |

ALT, Alanine aminotransferase; AST, Aspartate aminotransferase; CHD, congenital heart disease; CPET, cardiopulmonary testing; CTD, connective tissue disease; HIV, human immunodeficiency virus; IPAH, idiopathic pulmonary arterial hypertension; lab, laboratory; NA, not applicable; NCT, National Clinical Trials identifier; POPH, portopulmonary hypertension; PRO, patient-related outcome; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricle. PAH*: IPAH, heritable PAH, drug or toxin-induced PAH, PAH associated with CTD or with CHD with simple systemic-to-pulmonary shunt at least 1 year after surgical repair or with HIV. PAH#: IPAH, heritable PAH, drug or toxin-induced PAH, PAH associated with CHD [only simple atrial septal defect, ventricular septal defect, patent ductus arteriosus] congenital systemic-to-pulmonary shunts at least 2 year post-surgical repair.
geographical distribution of the included patients was heterogeneous. While in the placebo arm patients were mainly European or Asian, in the macitentan arms patients came mainly from Eastern Europe or Asia. Patients from North America were underrepresented in all arms. Therefore, the real-world effects of macitentan on morbi-mortality may be different from a clinical trial.

The strengths of the SERAPHIN trial are the large number of included patients and the prolonged observation time of the trial. It is also the first study in PAH powered for a robust clinical endpoint (morbidity and mortality) instead of a change in 6MWD.

Functional class and exercise capacity
The WHO FC at 6 months improved in a higher percentage of patients receiving 10 mg of macitentan \( (p = 0.006) \), and the treatment effect on the 6MWD with 10 mg dose versus placebo was 22.0 m [97.5% confidence interval (CI), 3.2–40.8; \( p = 0.008 \)].

Interestingly, a post hoc analysis of the SERAPHIN trial showed that patients with higher absolute values of the 6MWD at baseline or at month 6 had better prognosis but that the magnitude of change in 6MWD was not associated with long-term clinical outcomes. This confirms that establishing absolute thresholds of 6MWD as treatment goals in daily clinical practice make sense. Similarly a meta-analysis of 22 short-term RCTs in PAH (including 3112 patients), showed that improvements in the 6MWD did not reflect the benefit in clinical outcomes, such as death, hospitalization for PAH and initiation of PAH rescue therapy.

Furthermore, the MAESTRO study conducted in patients with PAH associated with Eisenmenger syndrome, did not reach its primary endpoint of change in 6MWD from baseline to week 16 of treatment, while macitentan reduced the exploratory endpoint N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in the global cohort and improved pulmonary vascular resistance index and exercise capacity in the hemodynamic substudy. The results of this RCT are difficult to interpret as there was an unexpected improvement in the placebo arm, which had not been observed in a previous study conducted with bosentan, and significantly contribute to the failure to achieve the primary endpoint in the MAESTRO trial. Of note, this study, as opposed to the bosentan study in Eisenmenger patients, included a significant proportion of patients with Down’s syndrome and patients with complex cardiac defects. The long-term open-label trial in Eisenmenger patients (MAESTRO-OL; ClinicalTrials.gov identifier: NCT01739400) is also completed but results are not yet available (Table 2).

Hemodynamics
A subset of 187 patients in the SERAPHIN trial (68 randomized to placebo, 62 to macitentan 3 mg and 57 to macitentan 10 mg) underwent right heart catheterization at baseline and after 6 months \( (n = 147) \) of treatment. Cardiopulmonary hemodynamic parameters and NT-proBNP were assessed. The baseline characteristics of the patients in the hemodynamic substudy were similar to the total SERAPHIN population and balanced between the different treatment groups. Both doses of macitentan significantly reduced pulmonary vascular resistance (PVR) and increased cardiac index, as compared with the placebo group. Absolute levels of cardiac index, right atrial pressure (RAP), and NT-proBNP at baseline and after 6 months of treatment, but not their changes, were associated with morbidity or mortality events. Lower risk for morbidity or mortality was observed in patients with cardiac index > 2.5 l/min/m², RAP < 8 mmHg, or NT-proBNP < 750 fmol/ml after 6 months of treatment [hazard ratio (HR) 0.49, 95% CI 0.28–0.86; HR 0.72, 95% CI 0.42–1.22 and HR 0.22, 95% CI 0.15–0.33, respectively]. Reaching threshold values of cardiac index, RAP and NT-proBNP should thus lower the risk of morbidity or mortality in PAH patients. Interestingly the findings of the SERAPHIN trial confirm the original findings of the National Institutes of Health registry where baseline cardiac index and RAP were the most predictive hemodynamic parameters of survival. Moreover, the SERAPHIN trial also shows the predictive value of these variables at the 6-month follow up, offering indirect validation of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS) risk stratification at baseline and during follow up. The fact that changes in some hemodynamic parameters are not associated with a better outcome can be partly explained by patient baseline condition (a
low-risk patient with small improvement after treatment may have a better outcome).

The mechanism of action by which macitentan influences hemodynamic parameters will be studied in the ongoing REPAIR (right ventricular remodeling in pulmonary arterial hypertension) trial evaluating the effects of macitentan on right ventricle remodeling in PAH assessed by cardiac magnetic resonance imaging (ClinicalTrials.gov Identifier: NCT02310672) (Table 2).

**Quality of life**

Macitentan (10 mg) improved seven to eight domains of the short form health survey (SF-36) questionnaire assessing health-related quality of life (HRQoL) and reduced significantly the risk of a three-point or greater deterioration in physical component summary score (HR 0.60; 95% CI, 0.47–0.76; \( p < 0.0001 \)) and mental component summary score (HR 0.76; 95% CI, 0.61–0.95; \( p = 0.0173 \)) until end of treatment. Patients with a HRQoL at baseline greater than the median baseline value had improved long-term outcomes. Potential limitation of these analyses is that the SF-36 questionnaire is a generic measure tool of HRQoL and is not created to specifically assess quality of life in PAH patients. Also, the long-term effect is difficult to evaluate due to missing data: at 6 months HRQoL was not available for 134 (18.9%) of patients and imputation for missing data was used. At 12 months 30% of data were missing making it impossible to analyze.

Of note, a disease-specific patient-reported outcome (PRO) instrument, the Pulmonary Arterial Hypertension-Symptoms and Impact (PAH-SYMPECT®) questionnaire, has been recently finalized and validated using data from the SYMPHONY trial which included 278 US patients with PAH treated with macitentan.

**Tolerability and safety**

Macitentan was generally well tolerated in the SERAPHIN study. Similar rates of adverse events were reported in the three study arms: 96% in patients treated with macitentan 3 mg daily, 94.6% in patients treated with macitentan 10 mg daily and 96.4% in patients from the placebo group. Serious adverse events were similarly reported in the three groups: 52% with macitentan 3 mg daily, 45% with macitentan 10 mg daily and 55% with placebo. There was no difference in incidence of edema, a well-known adverse event of ERAs, between the placebo and the macitentan arms (18.1% versus 18.2%).

Treatment with ERAs, especially with bosentan, has been associated with increased levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) due to inhibition of the bile salt transport. In the SERAPHIN trial, 3.4% of patients with macitentan compared with 4.5% of patients in the placebo group developed ALT or AST levels >3 times the upper limit of normal (ULN) and bilirubin levels >2 times the ULN. Severe anemia (hemoglobin ≤ 8 g/dl) was observed more frequently in the macitentan group (10 mg) compared with the placebo group (4.3% versus 0.4%).

Anemia, nasopharyngitis, bronchitis and headache were reported more frequently (delta>3%) in the group treated with macitentan 10 mg compared with the placebo group. Of note, the SERAPHIN trial was underpowered for the identification of rare severe side effects.

Although the trough plasma concentration of macitentan and its active metabolite was about two-fold higher in PAH patients from the SERAPHIN trial than in healthy people, this did not translate to a significant difference in exposure expressed as maximum plasma concentration (Cmax) or area under the plasma concentration–time curve (AUC) over a dosing interval.

**Dosage and (contra)indications**

Macitentan (10 mg once daily orally) was approved in 2013 by the United States Food and Drug Administration (US FDA) and European Medicines Agency for the treatment of PAH to delay disease progression and to reduce hospitalizations (US, https://opsumit.com/opsumit-prescribing-information.pdf) and for the long-term treatment of adults with PAH functioning in New York Heart Association class II–III (Europe, https://www.actelion.com/documents/en-rebranded/our-products/opsumit-smpc.pdf), in monotherapy or in combination therapy.

Teratogenicity is a well-known side effect shared by all ERAs. Macitentan is therefore contraindicated in pregnant women (US and Europe). In Europe its use is also contraindicated in breastfeeding women and in women of childbearing potential who are not using reliable contraception (however
reliable contraception is recommended in all women of childbearing potential with PAH because of the negative prognosis of pregnancy).

Clinical experience with macitentan

The place of macitentan in the therapeutic algorithm

The most recent treatment algorithm for PAH (2015 ESC/ERS guidelines,1) gives macitentan a I-B recommendation for monotherapy or sequential combination therapy in patients functioning in WHO FC II–III, based on a single RCT with time to clinical worsening as primary endpoint, and a IIa-C recommendation for initial combination therapy with PDE5i in patients functioning in WHO FC II–III.

There are no head-to-head comparisons of macitentan and other drugs approved for PAH treatment making it difficult to recommend one agent above another. All of the ERAs have shown clear clinical benefit in double-blind, randomized, placebo-controlled trials but as the trials have a different design it is difficult to compare one ERA with another. Comparative studies would be needed to demonstrate the incremental value of macitentan in the treatment of PAH.

However, since the SERAPHIN trial included a large number of patients already treated with PAH therapy (mostly PDE5 inhibitors) and since patients with and without background therapy were prespecified subgroups for analysis, combination therapy has been evaluated (although this was not the primary endpoint of the trial) in a post hoc analysis.45 The risk of morbidity/mortality was reduced by 38% in patients on macitentan and background therapy compared with those on background therapy alone. Also, the risk of being hospitalized for PAH was reduced by 37.4% compared with patients receiving background therapy alone. Macitentan treatment in combination with background therapy was associated with improvements in exercise capacity, functional class, cardiopulmonary hemodynamics and HRQoL compared with background therapy alone.

Since the publication of the AMBITION trial (initial use of ambrisentan plus tadalafil in PAH46), which showed a significantly lower risk of clinical failure ($p < 0.01$) in patients receiving initial bi-therapy with ambrisentan and tadalafil compared with patients treated with ambrisentan or tadalafil in monotherapy, there is a growing interest for initial combination therapy. Actually, it is not known if these results can be extended to other drugs from the same classes. Used in combination, there is clear pharmacokinetic distinction between the three ERAs. In healthy volunteers the concomitant administration of bosentan and sildenafil showed a decrease in the AUC of sildenafil by 62.6% and an increase in the AUC of bosentan by 49.8%.47 The concomitant administration of bosentan and tadalafil decreased the AUC of tadalafil with 41.5% and slightly increased the AUC of bosentan by <20%.48 There were no significant interactions between ambrisentan and sildenafil,49 ambrisentan and tadalafil,50 and macitentan and sildenafil51 in healthy volunteers.

A small trial evaluating the effects of first-line oral combination therapy of macitentan and tadalafil in patients with newly diagnosed PAH is currently recruiting (OPTIMA; ClinicalTrials.gov Identifier: NCT02968901, Table 2), and will give better insights in the place of macitentan in PAH treatment.

Moreover, as combination dual therapy strategies are becoming more and more standard of care, the question of initial triple therapy led to the initiation of the TRITON trial evaluating initial triple (tadalafil, macitentan and selexipag) versus dual oral therapy (tadalafil, macitentan and placebo) (ClinicalTrials.gov Identifier: NCT02558231).

Macitentan in daily practice: the post-marketing experience

Although there was no difference in incidence of elevated hepatic transaminases between the placebo and the macitentan arms in the SERAPHIN trial,27 a first case of fulminant liver failure, with a probable autoimmune origin, was recently reported in a patient treated with macitentan,52 prompting a modification to the US-approved labeling for macitentan. The European label was unchanged but already mentioned that liver enzymes should be measured before starting treatment by macitentan and monthly monitoring of AST and ALT was recommended. If sustained, unexplained clinically relevant increases in aminotransferases occurred or if these elevations are accompanied with a more than two-fold ULN
values of bilirubin or with a clinical symptoms of liver injury, macitentan should be discontinued. Once transaminase levels had normalized, re-introduction of macitentan could be considered in patients without clinical symptoms of liver injury (https://www.actelion.com/documents/en-rebranded/our-products/opsumit-smpc.pdf). The US FDA also mandated a long-term surveillance program, the OPUS registry (ClinicalTrials.gov Identifier: NCT02126943), which was initiated in 2014 to characterize the safety profile of macitentan and to describe clinical characteristics and outcomes of 5000 patients treated with macitentan in a real-world, post-marketing setting.

In the context of ERA hepatotoxicity, great caution has been applied to their use in patients with portopulmonary hypertension due to end-stage liver disease. However, small case series reported favorable results with bosentan and ambrisentan.53,54 The PORtopenlmonary Hypertension Treatment wIth macitentan, a randOmized clinical trial (PORTICO study; ClinicalTrials.gov Identifier: NCT02382016) that was presented at the 2018 ERS annual meeting, included 84 patients with mild-to-moderate hepatic impairment and showed a significant improvement in the primary endpoint of PVR without safety issues.55

As ERA therapy can cause anemia (also reported for macitentan), hemoglobin levels should be measured before starting treatment and macitentan should not be administrated in patients with severe anemia (https://www.actelion.com/documents/en-rebranded/our-products/opsumit-smpc.pdf). Hemoglobin measurements should be repeated during treatment as clinically indicated.

Drug interactions occur with strong CYP3A4-inducers or inhibitors resulting in reduced (CYP3A4 inducers such as rifampicin, carbamazepine, phenytoin) or increased (CYP3A4 inhibitors such as ketoconazole, itraconazole, ritonavir) plasma concentrations of macitentan. However, macitentan seems to have less drug interactions compared with other ERAs24 but this should be confirmed in larger populations in clinical practice.

Perspectives
Macitentan has been the first drug demonstrating an effect on long-term outcome in PAH in addition to improvements in functional class and exercise capacity. Multiple publications (from basic science to RCT) have illustrated and enforced the evidence on efficacy and safety of this drug. Some uncertainties still exist regarding the effects in children (TOMORROW study; ClinicalTrials.gov Identifier: NCT02932410), and the long-term effects in Eisenmenger patients (MAESTRO-OL trial; Table 2). In the absence of head-to-head comparison of the different ERAs it is obvious that hepatotoxicity is reduced in comparison with bosentan and that edema is less frequent than with bosentan and ambrisentan.

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M. Delcroix is an investigator, speaker, consultant or steering committee member for Actelion, Bayer AG, Bellerophon, Eli Lilly, GSK, MSD, Pfizer and Reata; and has received an institutional research grant from Actelion C. Belge is an investigator, speaker or consultant for Actelion, Bayer and GSK.

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