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ORIGINAL RESEARCH ARTICLE

# Evaluation of Macitentan in Patients With Eisenmenger Syndrome

## Results From the Randomized, Controlled MAESTRO Study

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**BACKGROUND:** Eisenmenger syndrome describes congenital heart disease-associated severe pulmonary hypertension accompanied by right-to-left shunting. The multicenter, double-blind, randomized, placebo-controlled, 16-week, phase III MAESTRO study (Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity) evaluated the efficacy and safety of the endothelin receptor antagonist macitentan in patients with Eisenmenger syndrome.

**METHODS:** Patients with Eisenmenger syndrome aged ≥12 years and in World Health Organization functional class II–III were randomized 1:1 to placebo or macitentan 10 mg once daily for 16 weeks. Patients with complex cardiac defects, Down syndrome and background PAH therapy were eligible. The primary end point was change from baseline to week 16 in 6-minute walk distance. Secondary end points included change from baseline to week 16 in World Health Organization functional class. Exploratory end points included NT-proBNP (N-terminal pro-B-type natriuretic peptide) at end of treatment expressed as a percentage of baseline. In a hemodynamic substudy, exploratory end points included pulmonary vascular resistance index (PVRi) at week 16 as a percentage of baseline.

**RESULTS:** Two hundred twenty six patients (macitentan n=114; placebo n=112) were randomized. At baseline, 60% of patients were in World Health Organization functional class II and 27% were receiving phosphodiesterase type-5 inhibitors. At week 16, the mean change from baseline in 6-minute walk distance was 18.3 m and 19.7 m in the macitentan and placebo groups (least-squares mean difference, -4.7 m; 95% confidence limit (CL), -22.8, 13.5; *P*=0.612). World Health Organization functional class improved from baseline to week 16 in 8.8% and 14.3% of patients in the macitentan and placebo groups (odds ratio, 0.53; 95% CL, 0.23, 1.24). NT-proBNP levels decreased with macitentan versus placebo (ratio of geometric means, 0.80; 95% CL, 0.68, 0.94). In the hemodynamic substudy (n=39 patients), macitentan decreased PVRi compared with placebo (ratio of geometric means, 0.87; 95% CL, 0.73, 1.03). The most common adverse events with macitentan versus placebo were headache (11.4 versus 4.5%) and upper respiratory tract infection (9.6 versus 6.3%); a hemoglobin decrease from baseline of ≥2 g/dL occurred in 36.0% versus 8.9% of patients. Five patients (3 macitentan; 2 placebo) prematurely discontinued treatment and 1 patient died (macitentan group).

**CONCLUSIONS:** Macitentan did not show superiority over placebo on the primary end point of change from baseline to week 16 in exercise capacity in patients with Eisenmenger syndrome.

**CLINICAL TRIAL REGISTRATION:** URL: https://www.clinicaltrials.gov. Unique identifier: NCT01743001.

*Drs Gatzoulis and Landzberg contributed equally.

**Key Words:** congenital heart disease ■ Down syndrome ■ Eisenmenger syndrome ■ endothelin receptor antagonist ■ macitentan ■ pulmonary arterial hypertension

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## Clinical Perspective

### What Is New?

- We report the results of the MAESTRO study (Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity) which investigated macitentan in patients with Eisenmenger syndrome (ES).
- MAESTRO is the second randomized, double-blind, placebo-controlled, multicenter study to investigate a pulmonary arterial hypertension therapy in ES patients.
- Macitentan did not show superiority over placebo on the primary end point of change from baseline to week 16 in exercise capacity; no relevant trends were observed for the secondary end points.
- Among the exploratory end points, macitentan reduced NT-proBNP (N-terminal pro-B-type natriuretic peptide) in the main cohort and improved pulmonary vascular resistance index and exercise capacity in the hemodynamic substudy.
- There were no specific safety concerns with macitentan use in ES patients.

### What Are the Clinical Implications?

- Compared with the previous BREATHE-5 study (which investigated bosentan in ES patients), MAESTRO enrolled a more heterogenous population, including patients with simple or complex cardiac defects, World Health Organization functional class II or III symptoms, and not restricting enrollment based on background therapy or presence of Down syndrome.
- MAESTRO therefore provides data on the use of pulmonary arterial hypertension therapy in ES patients with a wide range of real-world demographic characteristics.
- Furthermore, MAESTRO provides important insight into the conduct of future clinical studies of pulmonary arterial hypertension therapy in ES patients.

Eisenmenger syndrome (ES) is the most advanced form of uncorrected congenital heart disease-associated pulmonary arterial hypertension (PAH).[1] It can result from a wide range of congenital heart defects and is characterized by elevated pulmonary arterial pressure and resistance, and right-to-left intracardiac or intra-arterial shunting with cyanosis.[2,3] Patients with ES have multiorgan sequelae and significantly premature mortality.[3–8] For patients with ES who progress to World Health Organization (WHO) functional class (FC) III or above, disease progression is more rapid than for those in WHO FC II.[4,8]

A number of PAH therapies are used in clinical practice to treat patients with ES, including endothelin receptor antagonists (ERAs), phosphodiesterase type-5 (PDE-5) inhibitors and prostanoids.[9] However, the evidence supporting the use of these therapies in the ES population is limited, having been obtained from mostly small and uncontrolled or open-label studies.[10–13] To date, only the ERA bosentan has been investigated in a randomized, double-blind, placebo-controlled, multicenter study in patients with ES (BREATHE-5 [Bosentan Randomized Trial of Endothelin Antagonist Therapy-5]).[5] The study population consisted of 54 treatment-naive patients with ES whom, at enrollment, were restricted to WHO FC III, with anatomically-classified simple cardiac defects; bosentan was well tolerated and did not adversely affect oxygen saturation. Hemodynamics and exercise capacity were significantly improved by bosentan.[5] ES patients with Down syndrome, who represent more than 25% of adult ES cohorts,[14–16] and in whom data regarding efficacy of PAH therapy are particularly limited,[17–21] were not included in BREATHE-5. As such, there exists a gap in assessment of therapy for patients with ES with a fuller range of real-world demographic characteristics than previously studied in BREATHE-5.[5] The MAESTRO study (Macitentan in Eisenmenger Syndrome to Restore Exercise Capacity) was thus designed to address this need.

Macitentan, an ERA with sustained receptor binding,[22] delayed disease progression in patients with PAH in the long-term SERAPHIN study (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome), as well as improving exercise capacity.[23] SERAPHIN enrolled a broad range of PAH patients, including patients with repaired simple congenital systemic-to-pulmonary shunts at least 1 year postsurgical repair, but not patients with ES.[23] The aim of the MAESTRO study was to evaluate whether macitentan improves exercise capacity in patients with ES with typical demographic characteristics (inclusive of patients with anatomically classified simple and complex congenital heart disease, WHO FC II and III, and not restricting enrollment based on chronic background therapy with PDE-5i therapy or presence of Down syndrome).

## METHODS

The data, analytic methods, and study materials will be made available to other researchers for purposes of reproducing the results or replicating the procedure.[24]

### Study Design

The MAESTRO study (URL: www.clinicaltrials.gov. Unique identifier: NCT01743001) was a multicenter, double-blind, randomized, placebo-controlled, 16-week, phase III study. At certain centers, selected based on steering committee review of right heart catheterization expertise, patients were eligible to participate in a substudy that assessed exploratory hemodynamic end points by cardiac catheterization.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice as outlined in the International Conference of Harmonization. Ethical approval was obtained from the relevant Institutional Review Board or Independent Ethics Committee for each participating center (refer to the online-only Data Supplement for more information). Written informed consent was obtained from all patients or a parent/legal representative and from the caregiver, where applicable. Additionally, written assent was obtained from all patients with Down syndrome and pediatric patients who were unable to give written consent. The MAESTRO steering committee was involved in the design of the study, provided guidance on the study conduct, and members reviewed screening data including all echocardiographic and cardiac catheterization data to corroborate the diagnosis of ES and confirm patient eligibility. An independent data monitoring committee reviewed the data on a regular basis during the trial in order to ensure patient safety. All authors had full access to the study data and take responsibility for the integrity of the data and the accuracy of the data analyses. All authors were involved in the development and review of the manuscript.

## Selection of Patients

Patients with ES who were aged ≥12 years were eligible for the main study, including patients with Down syndrome and those with anatomically-classified complex cardiac defects (excluding conotruncal defects, which refer to ventricular outflow tract anomalies such as tetralogy of fallot, truncus arteriosus or transposition of great arteries). Enrollment into the hemodynamic substudy was restricted to patients aged ≥18 years, with ES and simple atrial septal defects or ventricular septal defects, without Down syndrome. For the main study and the hemodynamic substudy, ES was established by echocardiography showing a large or nonrestrictive open congenital defect at atrial, ventricular or arterial level (isolated defect or in combination) and right-to-left shunt or bidirectional shunt with prevalent right-to-left direction. Patients also had to have a resting oxygen saturation ($SpO_2$) ≤90% and >70% and hemodynamic measurements of mean resting pulmonary arterial pressure >25 mm Hg, pulmonary artery wedge pressure or mean left atrial pressure or left ventricular end diastolic pressure ≤15 mm Hg, and pulmonary vascular resistance (PVR) ≥800 dyn·sec/$cm^5$ (10 Wood units). Cardiac catheterization must have been performed within 5 years prior to randomization or during the screening period for the main study and within 30 days prior to randomization for the hemodynamic substudy.

For both the main study and the hemodynamic substudy, patients were required to have symptomatic PAH in WHO FC II to IV and a 6-minute walk distance (6MWD) of 50 to 450 m, documented by 2 tests that did not differ by more than 15% performed during the screening period. For patients who had not previously performed a 6-minute walk test (6MWT), a practice test was requested before the qualifying walk test for inclusion; for patients with Down syndrome, at least 2 practice tests were required. PDE-5 inhibitors were allowed if the dose was stable for at least 1 month prior to randomization. Stable background therapy for other cardiopulmonary diseases (eg, antiarrhythmics, oral anticoagulants, digoxin, supplemental oxygen) was also allowed. Diuretics were allowed if the dose was stable for at least 1 week prior to randomization. Iron supplementation was allowed if initiated at least 3 months prior to randomization.

Patients were excluded from both the main study and the hemodynamic substudy if they had significant left ventricular dysfunction (ejection fraction <45%), previously recognized moderate-to-severe lung disease, conotruncal heart defects, severe tricuspid regurgitation or greater than mild tricuspid stenosis (as determined by site principle investigator or steering committee review), serum aspartate transaminase or alanine transaminase greater than 3 times the upper limit of normal, iron deficiency (serum ferritin <10 μg/L), treatment by phlebotomy within 1 month prior to randomization, and treatment with ERAs or prostanoid(s) within 1 month prior to randomization. For the hemodynamic substudy, patients with certain congenital cardiac lesions (such as patent ductus arteriosus), where estimation of resting PVR was not readily possible or reproducible with standard techniques, were excluded.

## Study Procedures

Within 30 days of screening, eligible patients were randomly assigned in a 1:1 ratio to receive oral placebo or macitentan 10 mg once daily for 16 weeks. Patient allocation to treatment groups was initially stratified by location of the cardiac defect and participation in the hemodynamic substudy (n=87, 44 macitentan, 43 placebo). Following a global protocol amendment, patients were stratified by WHO FC (II versus III/IV), presence of Down syndrome (yes/no) and participation in the hemodynamic substudy (yes/no) (n=139; 70 macitentan, 69 placebo). Randomization was based on a prespecified randomization schedule using randomization lists generated by an independent Contract Research Organization (Almac Clinical Technologies) and their centralized randomization system, via an Interactive Voice Response System or Interactive Web Response System.

During the treatment period, patients were assessed at randomization, and at weeks 4, 8, 12 and 16. In the hemodynamic substudy, cardiac catheterization was performed at screening and at the end of treatment (EOT) visit. EOT was at week 16 for patients who did not prematurely discontinue study treatment. For patients who did prematurely discontinue study treatment, the EOT visit was performed whenever possible within 7 days after the last dose of study treatment; these patients also subsequently had a week 16 assessment. Adverse events were monitored throughout the treatment period and up to 30 days after EOT. Patients were considered to have completed the study if they completed the week 16 assessments, regardless of whether or not they prematurely discontinued study treatment. Patients who completed the study were eligible to participate in the long-term open-label extension study, MAESTRO-OL (MAESTRO open-label; unless they had discontinued treatment due to an adverse event considered related to the study drug or due to liver enzyme elevations); all patients received macitentan 10 mg once daily in MAESTRO-OL (URL: www.clinicaltrials.gov. Unique identifier: NCT01739400). Patients and sites remained blinded to their previous treatment allocation.

## Outcome Measures

The primary end point was change from baseline to week 16 in 6MWD. Secondary end points, listed in the order of the prespecified testing hierarchy, included the change from baseline to week 16 in WHO FC and Borg Dyspnea index. Exploratory end points included the NT-proBNP (N-terminal pro-B-type natriuretic peptide) level at EOT expressed as a percent of baseline and change in $SpO_2$ from baseline to week 16 (at rest and 0 minutes after performing a 6MWT). Safety end points included the evaluation of adverse events, laboratory abnormalities, and decreases from baseline in $SpO_2$ >10% at rest, up to 30 days after study treatment discontinuation.

In the hemodynamic substudy, the following exploratory end points were assessed: indexed pulmonary vascular resistance index (PVRi) at week 16 expressed as a percent of baseline and absolute change from baseline to week 16 in mean resting pulmonary arterial pressure, mean right atrial pressure, indexed pulmonary blood flow/indexed systemic blood flow ratio, systemic vascular resistance index, and PVRi/systemic vascular resistance index. Additionally, posthoc exploratory end points of absolute change from baseline to week 16 in indexed pulmonary blood flow, indexed systemic blood flow, and 6MWD were evaluated.

## Statistical Analysis

A sample size of 196 patients (98 per treatment group) had 90% power to detect a treatment difference in 6MWD between placebo and macitentan of 35 m with a standard deviation for the primary end point of 75 m, based on a 2-sided significance level of 5% using the Student *t* test. It was planned to randomize 220 patients allowing for approximately 10% early drop out. Given the uncertainty of the variability for the primary end point in this patient population, an interim monitoring conducted on blinded data was planned and performed by the sponsor to check the assumptions of the sample size calculations. A blinded sample size re-estimation was performed, and it was recommended not to increase the sample size. Analyses for all efficacy end points were based on all randomized patients (full analysis set). Hemodynamic substudy analyses were performed on all patients in the full analysis set who participated in the hemodynamic substudy. Safety analyses were performed on all patients who received at least 1 dose of study treatment (safety analysis set).

For the analyses of 6MWD, the latest valid assessment from the 2 screening tests and the randomization test was taken as the baseline value. All available measurements at week 16 were used, irrespective of whether or not treatment was prematurely discontinued prior to week 16. The primary end point was analyzed by means of an analysis of covariance (ANCOVA), including treatment group, Down syndrome (yes/no), baseline WHO FC (II versus III/IV) and baseline 6MWD as covariates. Least-squares means and 2-sided 95% confidence limits (CLs) for the treatment effect between placebo and macitentan were estimated from the model. Prespecified and posthoc subgroup analyses were performed on the primary end point of change in 6MWD using interaction tests to investigate heterogeneity of treatment effects across subgroups. To control for multiplicity, secondary end points were tested hierarchically according to a prespecified sequence. Improvement in WHO FC from baseline to week 16 was analyzed by means of a logistic regression model, including the treatment group and location of cardiac defect as covariates. NT-proBNP was analyzed by means of an ANCOVA model on the log transformed ratio EOT/baseline, including treatment group, location of cardiac defect and NT-proBNP baseline value (natural log scale) as covariates. $SpO_2$ was analyzed descriptively. For the hemodynamic substudy, PVRi was analyzed by means of an ANCOVA model on the log transformed ratio week 16/baseline, including treatment group, location of cardiac defect and baseline value (natural log scale) as covariates. Other hemodynamic parameters were analyzed by means of an ANCOVA model including the treatment group, location of cardiac defect and respective baseline value as covariates. The 6MWD in the hemodynamic substudy was analyzed posthoc by means of an ANCOVA model including the treatment group and baseline 6MWD as covariates.

Missing 6MWD values at week 16 were imputed as 0 m in the case of death. Otherwise, imputation of the missing week 16 value was performed in 2 steps: first, the predicted probability of a missing value at each visit was estimated; then, the available 6MWD value at the prior visit was adjusted with this estimation. Imputation rules for all end points are provided in the online-only Data Supplement.

SAS® software, version 9.3 (SAS Institute, Cary, NC, USA) was used for the statistical analysis and the reporting of clinical data.

# RESULTS

Patients were screened in 71 centers across 26 countries. The number of patients enrolled at each center is provided in Table I in the online-only Data Supplement. The first patient visit was in April 2013 and the last patient visit was in December 2016. In total, 226 patients were randomized to macitentan (n=114) or placebo (n=112), including 20 patients with Down syndrome (10 per treatment group). Overall, 221 patients completed 16 weeks of treatment (macitentan n=111; placebo n=110) (Figure 1). In the hemodynamic substudy, 39 patients were randomized to macitentan (n=20) or placebo (n=19), all of whom completed the substudy (Figure I in the online-only Data Supplement).

In the overall study, the baseline characteristics were generally well matched between the treatment groups (Table 1). The majority of patients were from Asia-Pacific nations or Eastern Europe (40.3% and 23.0%, respectively). There was an imbalance between treatment groups in age distribution, with a higher percentage of patients in both the older (≥56 years) and younger (12–17 years) age categories in the macitentan group (9.6 and 11.4%, respectively) as compared with placebo (4.5 and 1.8%, respectively). The majority of patients were in WHO FC II (59.7%) and the remaining patients (40.3%) were in WHO FC III. Most patients had post-tricuspid defects (78.3%) and the majority of patients had isolated ventricular septal defects

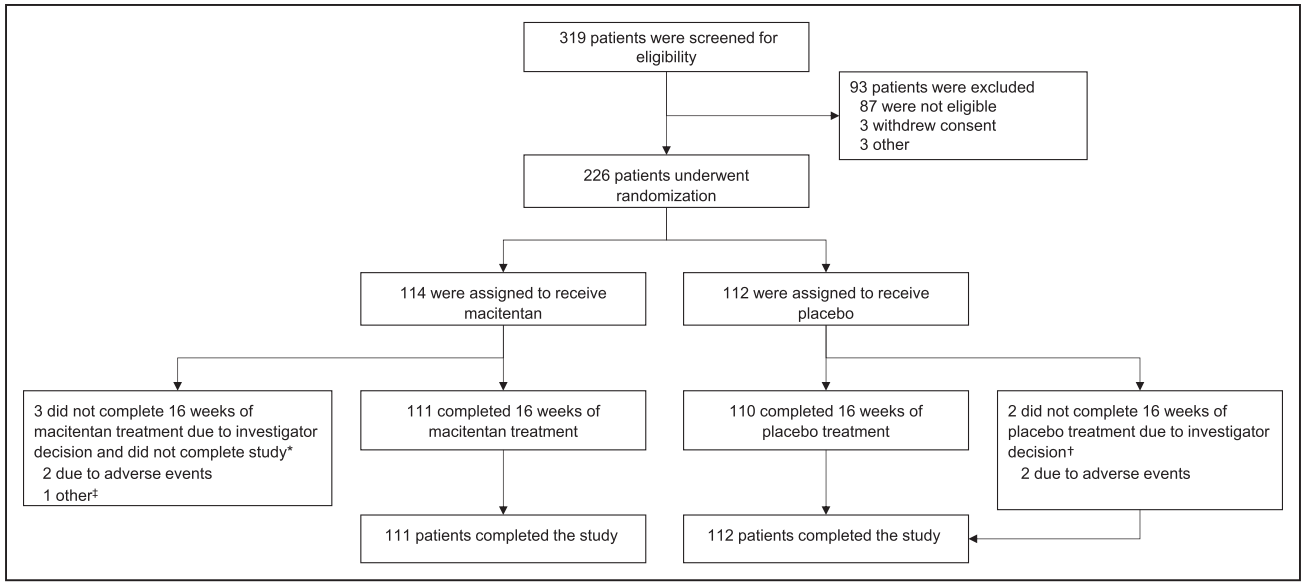


**Figure 1. Patient disposition.**
Patients were considered to have completed the study if they completed the 30-day safety follow-up period and Week 16 assessments, regardless of premature study treatment discontinuation. *The 3 patients who discontinued macitentan treatment prior to week 16 did not complete the study. †The 2 patients who discontinued placebo treatment prior to week 16 did complete the study. ‡The patient did not fulfill the inclusion criteria.

(52.7%). Complex cardiac defects were present in 24.3% of patients, with 40% of these having isolated patent ductus arteriosus and 27.3% having a partial/complete atrioventricular septal defect. At baseline, 27.4% of patients were taking PDE-5 inhibitors and had been receiving these for a median duration of 12.6 months. Baseline characteristics of patients in the hemodynamic substudy were generally comparable to those in the overall study. Exceptions include differences in age (with the substudy only enrolling patients aged ≥18 years), geographical region and defect complexity and the exclusion of patients with Down syndrome from the substudy (Table II in the online-only Data Supplement).

## Primary End Point

At week 16, the 6MWD had increased from baseline by a mean±SD of 18.3±84.4 m in the macitentan group and 19.7±53.0 m in the placebo group. The least-squares mean difference (95% CL) for the change from baseline to week 16 between macitentan and placebo was -4.7 m (-22.8, 13.5; *P*=0.612) (Table 2 and Figure 2). The proportion of patients with an improvement in 6MWD at week 16 (change from baseline >0 m) was 72.8% in the macitentan group and 65.2% in the placebo group. The difference in exercise capacity between treatment groups was consistent in all prespecified subgroups, as indicated by nonsignificant *P* values for interaction (Figure II in the online-only Data Supplement). Posthoc analyses showed that the difference between treatment groups was also consistent regardless of whether patients had simple or complex cardiac defects (*P* value for interaction 0.89). The treatment effect was also consistent across gender subcategories (*P* value for interaction 0.788) (posthoc analysis) (Figure III in the online-only Data Supplement). A posthoc analysis showed that the treatment effect of macitentan on change from baseline to week 16 in 6MWD was similar for patients with and without a hemoglobin decrease of ≥ 2 g/dL from baseline to EOT (Table III in the online-only Data Supplement).

## Secondary and Exploratory End Points

WHO FC improved from baseline to week 16 in 8.8% and 14.3% of patients in the macitentan and placebo groups, respectively (odds ratio, 0.53; 95% CL, 0.23, 1.24) (Table 2). Worsening of WHO FC from baseline to week 16 was reported for 1 patient in each treatment group. There were no relevant trends in change from baseline to week 16 in the Borg dyspnea index between the macitentan and placebo groups. At baseline, the mean±SD NT-proBNP level was 693±1135.5 pg/mL and 893±2320.8 pg/mL in the macitentan and placebo groups, respectively. At end of treatment, the geometric mean (95% CL) NT-proBNP level decreased to 88.7% (80.0, 98.3) of the baseline value (mean decrease from baseline of 88 pg/mL) in the macitentan group and increased to 109.2% (96.5, 123.6) of the baseline value (mean increase from baseline of 72 pg/mL) in the placebo group (ratio of geometric means, 0.80; 95% CL, 0.68, 0.94) (Table 2). The placebo-corrected mean (95% CL) treatment effect of macitentan on $SpO_2$ at rest was 0.8% (-0.3, 2.0). $SpO_2$ was also measured immediately after completion of the 6MWD; at this timepoint, the placebo-corrected mean (95% CL) treatment effect of macitentan was 2.0% (-0.7, 4.7) (Table 2).

**Table 1. Patient Characteristics at Baseline***

| Characteristic | Macitentan n=114 | Placebo n=112 | All patients N=226 |
|---|---|---|---|
| Female, n (%) | 82 (71.9) | 68 (60.7) | 150 (66.4) |
| Age, y | | | |
| Median (range) | 33 (12, 82) | 31 (13, 62) | 32 (12, 82) |
| Distribution, n (%) | | | |
| 12–17 | 13 (11.4) | 2 (1.8) | 15 (6.6) |
| 18–55 | 90 (78.9) | 105 (93.8) | 195 (86.3) |
| ≥56 | 11 (9.6) | 5 (4.5) | 16 (7.1) |
| Geographic region, n (%) | | | |
| Asia-Pacific | 47 (41.2) | 44 (39.3) | 91 (40.3) |
| Eastern Europe | 25 (21.9) | 27 (24.1) | 52 (23.0) |
| Western Europe-Israel | 21 (18.4) | 18 (16.1) | 39 (17.3) |
| Latin America | 19 (16.7) | 18 (16.1) | 37 (16.4) |
| North America | 2 (1.8) | 5 (4.5) | 7 (3.1) |
| Time from ES diagnosis, y, median (range) | 5.28 (0.0, 59.4) | 4.02 (0.0, 51.2) | 4.65 (0.0, 59.4) |
| Down syndrome, n (%) | 10 (8.8) | 10 (8.9) | 20 (8.8) |
| WHO functional class, n (%)† | | | |
| II | 69 (60.5) | 66 (58.9) | 135 (59.7) |
| III | 45 (39.5) | 46 (41.1) | 91 (40.3) |
| 6-minute walk distance, meters | 368.7±74.5 | 380.3±76.3 | 374.5±75.4 |
| $SpO_2$ at rest, % | 84.4±5.6 | 85.2±5.1 | 84.8±5.4 |
| PDE-5 inhibitors | | | |
| n (%) | 35 (30.7) | 27 (24.1) | 62 (27.4) |
| Time from initiation, months, median (range) | 12.8 (1.1, 79.3) | 11.3 (1.0, 101.4) | 12.6 (1.0, 101.4) |
| Location of cardiac defect, n (%) | | | |
| Pretricuspid | 29 (25.4) | 20 (17.9) | 49 (21.7) |
| Posttricuspid | 85 (74.6) | 92 (82.1) | 177 (78.3) |
| Simple cardiac defect, n (%) | 91 (79.8) | 80 (71.4) | 171 (75.7) |
| Complex cardiac defect, n (%)‡ | 23 (20.2) | 32 (28.6) | 55 (24.3) |
| Right heart catheterization | | | |
| Mean PAP, mm Hg | 77.4±15.1 | 79.9±17.3 | 78.7±16.2 |
| Mean RAP, mm Hg | 7.9±5.2 | 7.7±4.5 | 7.8±4.9 |
| Mean PVR, dyn·sec/$cm^5$ | 1807.5±792.8 | 1828.1±937.4 | 1817.7±865.9 |
| Mean LAP, LVEDP or mean PAWP, mm Hg§ | 8.9±3.6 | 9.4±3.8 | 9.2±3.7 |
| Hemoglobin, g/dL | 18.5±2.83 | 19.0±2.66 | 18.7±2.75 |

ES indicates Eisenmenger syndrome; LAP, left atrial pressure; LVEDP, left ventricular end diastolic pressure; PAWP, pulmonary artery wedge pressure; PAP, mean pulmonary arterial pressure; PDE-5, phosphodiesterase type-5; PVR, pulmonary vascular resistance; RAP, right atrial pressure; $SpO_2$, oxygen saturation; and WHO, World Health Organization.

*Plus–minus values are mean±standard deviation.

For time from ES diagnosis, data were missing for 2 patients in the macitentan group and 3 in the placebo group (a total of 5 patients with missing data). For mean PAP, PVR, and mean LAP/LVEDP/mean PAWP, data were missing for 2 patients in the macitentan group and 1 in the placebo group (a total of 3 patients with missing data). For mean RAP, data were missing for 11 patients in the macitentan group and 11 in the placebo group (a total of 22 patients with missing data).

†The WHO functional class ranges from I to IV, with higher numbers indicating greater functional limitations. There were no patients in WHO functional class I or IV enrolled in the study.

‡Twenty-two patients with an isolated patent ductus arteriosus, 15 patients with a partial/complete atrioventricular septal defect, 4 patients with an atrial septal defect and partial or total anomalous venous return, 14 patients classified as "other" (defined as isolated aortopulmonary window and combinations of other cardiac lesions, eg, ventricular septal defect plus patent ductus arteriosus).

§If more than 1 parameter was measured in the same patient, only 1 is displayed using the following order: mean LAP > LVEDP > mean PAWP.

**Table 2. Primary, Secondary and Exploratory Efficacy End Points***

| Endpoints | Macitentan | | | Placebo | | | Treatment effect (95% CL) |
|---|---|---|---|---|---|---|---|
| | Baseline n=114 | Postbaseline n=114 | Change | Baseline n=112 | Postbaseline n=112 | Change | |
| Primary end point | | | | | | | |
| 6-minute walk distance, m† | 368.7±74.5 (155 – 523) | 387.1±101.8 (0 – 547) | 18.3±84.4 | 380.3±76.3 (90 – 501) | 399.9±79.5 (57 – 534) | 19.7±53.0 | -4.7 (-22.8, 13.5) *P*=0.612 |
| Secondary end points | | | | | | | |
| WHO FC, n (%)‡ | | | | | | | |
| I | - | 3 (2.6) | Improved: 10 (8.8) | - | 1 (0.9) | Improved: 16 (14.3) | 0.53 (0.23, 1.24) |
| II | 69 (60.5) | 72 (63.2) | | 66 (58.9) | 79 (70.5) | | |
| III | 45 (39.5) | 38 (33.3) | | 46 (41.1) | 32 (28.6) | | |
| IV | - | 1 (0.9) | | - | - | | |
| Exploratory end points | | | | | | | |
| NT-proBNP, pg/mL§# | 693±1135.5 | 605±994.5 | -88±537.2 88.7 (57.7)‖ | 893±2320.8 | 965±1951.6 | 72±1253.5 109.2 (70.5)‖ | 0.80 (0.68, 0.94) |
| $SpO_2$ at rest, %**†† | 84.3±5.6 | 85.4±5.8 | 1.1±4.0 | 85.2±5.1 | 85.4±5.6 | 0.2±4.5 | 0.8 (-0.3, 2.0) |
| $SpO_2$ at 0 mins after 6-minute walk test, %**‡‡ | 68.1±13.1 | 69.2±12.4 | 1.1±9.4 | 70.9±10.3 | 70.0±12.3 | -0.9±10.7 | 2.0 (-0.7, 4.7) |

CL indicates confidence limit; NT-proBNP, N-terminal pro-B-type natriuretic peptide; $SpO_2$, oxygen saturation; and WHO FC, World Health Organization functional class.

*Plus–minus values are mean±standard deviation. Post-baseline values were collected at end of treatment for NT-proBNP and at week 16 for all other endpoints. No imputation rules were planned for exploratory efficacy endpoints of the overall study; patients with missing values at baseline or week 16/end of treatment are excluded from these analyses.

†The primary end point was analyzed in the intention-to-treat population. Missing values were imputed for three patients at week 16 (all in the macitentan arm). The range in 6MWD values is reported in parentheses at baseline and week 16. The treatment effect expressed as the least-squares mean difference (macitentan minus placebo) for the change from baseline to week 16 in 6MWD was calculated by analysis of covariance, including treatment group, Down syndrome status, baseline WHO functional class and baseline 6MWD as covariates.

‡The treatment effect expressed as the odds ratio (macitentan:placebo) at week 16 was calculated using logistic regression, including treatment group and location of cardiac defect as covariates. Missing values were imputed for 2 patients.

§The treatment effect expressed as the ratio (macitentan:placebo) of geometric means was calculated by analysis of covariance on the log transformed ratio (end of treatment/baseline), including treatment group, location of cardiac defect and log transformed baseline values as covariates.

#Data were missing for 8 patients in the macitentan group and 8 patients in the placebo group.

‖For NT-proBNP, changes were expressed as a percentage of the baseline value (geometric mean [geometric coefficient of variation]).

**The treatment effect is expressed as mean (95% CL).

††Data were missing for 2 patients in the macitentan group.

‡‡Data were missing for 4 patients in the macitentan group and 1 patient in the placebo group.

## Exploratory End Points in the Hemodynamic Substudy

At week 16, the geometric mean PVRi decreased to 85.3% of the baseline value in the macitentan group (corresponding to a mean decrease from baseline of 410 dyn·sec/$cm^5/m^2$) and increased to 101.1% of the baseline value in the placebo group (corresponding to a mean increase from baseline of 79 dyn·sec/$cm^5/m^2$) (ratio of geometric means, 0.87; 95% CL, 0.73, 1.03) (Table 3, Figure 3). At week 16, the mean±SD systemic vascular resistance index decreased from baseline by 376±910.4 dyn·sec/$cm^5/m^2$ in the macitentan group and increased from baseline by 11±1119.1 dyn·sec/$cm^5/m^2$ in the placebo group (least-squares mean difference, -410 dyn·sec/$cm^5/m^2$; 95% CL, -953, 133). For all other cardiac hemodynamic parameters measured, there were no differences between treatment groups in the change from baseline to week 16 (Table 3). Posthoc analysis of the 6MWD for patients enrolled in the hemodynamic substudy showed a mean increase from baseline to week 16 of 34.1 m in the macitentan group and 3.5 m in the placebo group (least-squares mean difference, 24.9 m; 95% CL, -9.1, 59.0) (Table 3 and Figure 3). The proportion of patients in the hemodynamic substudy with an improvement in 6MWD at week 16 (change from baseline >0 m) was 85.0% in the macitentan group and 57.9% in the placebo group.

## Safety

An overview of adverse events is presented in Table 4. Two patients in each treatment group had at least 1 adverse event that led to premature discontinuation of study treatment. Treatment-emergent serious adverse events were reported in 7 macitentan-treated patients (6.1%) and 2 placebo-treated patients (1.8%). Eight patients were hospitalized due to serious adverse events in the study: 6 in the macitentan group (1 for a nervous system disorder, 3 for cardiac disorders, and 2 for infection) and 2 in the placebo group (both for cardiac disorders). One patient died (in the macitentan group); this death was due to respiratory failure and was considered unrelated to the study treatment.

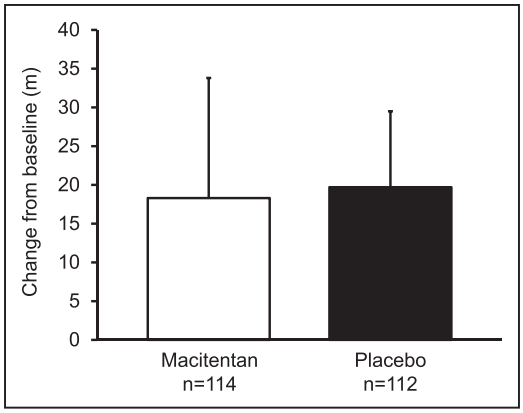


**Figure 2. Primary end point of change from baseline to week 16 in 6-minute walk distance.**
6MWD indicates 6-minute walk distance; and CL, confidence limit. Mean (plus 95% CL) change from baseline to week 16 in 6MWD is shown for macitentan and placebo in the intention-to-treat population with missing values imputed. The 6MWD increased from baseline by a mean of 18.3 m in the macitentan group and 19.7 m in the placebo group. The macitentan minus placebo least-squares mean difference (treatment effect) was -4.7 m (95% CL -22.8 to 13.5; *P*=0.612) calculated using an analysis of covariance model including the treatment group, Down syndrome (yes/no), WHO functional class at baseline (II versus III/IV), and baseline 6MWD as covariates. Missing values were imputed for 3 patients.

A mean decrease in hemoglobin of -1.04 g/dL from baseline up to week 16/EOT was observed in the macitentan group, which occurred primarily within the first 4 weeks of treatment and was maintained thereafter (Table 4). In the placebo group, hemoglobin values remained stable from baseline up to week 16/EOT (mean change of 0.12 g/dL). One patient in each treatment group had an increase in alanine transaminase or aspartate transaminase above 3 times the upper limit of normal, and this led to treatment discontinuation in the placebo group. The increase in the macitentan group was confirmed to be a false-positive signal by the central laboratory and treatment was continued. A decrease of more than 10% in $SpO_2$ at any time from baseline up to 30 days after study treatment discontinuation was reported for 6 patients (5.3%) in the macitentan group and 10 patients (8.9%) in the placebo group.

## Open-Label Extension Study

A total of 217 patients (97% of the patients who completed the double-blind study) entered the open-label extension study; 202 had an assessment at month 6 (data collected up to 7th June 2017). In an analysis of these 202 patients (n=100 for macitentan, n=102 for placebo/macitentan) from this open-label study, which is based on observed data only, patients who received double-blind placebo followed by open-label macitentan had a mean±SD improvement in 6MWD of 27.1±43.4 m from baseline to month 6. This improvement was maintained at month 12, with a mean±SD increase in 6MWD of 24.5±55.6 m from the open-label baseline. Patients who received macitentan in the double-blind study followed by open-label macitentan had a mean±SD improvement in 6MWD of 6.0±55.8 m from baseline in the open-label extension to month 12.

**Table 3. Exploratory Hemodynamic End Points and 6MWD in the Hemodynamic Substudy***

| Endpoints | Macitentan | | | | Placebo | | | | Treatment effect (95% CL) |
|---|---|---|---|---|---|---|---|---|---|
| | n | Baseline | Week 16 | Change | n | Baseline | Week 16 | Change | |
| mPAP, mm Hg† | 19 | 77.5±11.6 | 71.1±13.6 | -6.4±8.2 | 17 | 79.0±15.8 | 75.5±16.3 | -3.5±9.6 | -3.0 (-8.8, 2.7) |
| mRAP, mm Hg† | 19 | 6.1±3.8 | 7.2±4.5 | 1.1±4.2 | 16 | 6.7±3.8 | 6.7±3.6 | 0.0±3.6 | 0.8 (-1.7, 3.3) |
| Qpi, L/min/m²†‡ | 18 | 2.3±0.88 | 2.4±0.61 | 0.09±0.88 | 17 | 2.4±0.65 | 2.2±0.68 | -0.12±0.32 | 0.17 (-0.19, 0.53) |
| Qsi, L/min/m²†‡ | 16 | 2.6±0.58 | 2.7±0.54 | 0.15±0.74 | 17 | 2.8±1.47 | 2.5±1.03 | -0.31±1.67 | 0.25 (-0.36, 0.85) |
| Qpi/Qsi ratio† | 16 | 0.98±0.73 | 0.94±0.32 | -0.05±0.80 | 17 | 0.98±0.46 | 1.01±0.50 | 0.04±0.35 | -0.09 (-0.38, 0.20) |
| PVRi, dyn·sec/cm⁵/m²§ | 20 | 2821±1321 | 2411±1011 | -410±752<br>85 (36)‖ | 19 | 2776±1455 | 2855±1515 | 79±491<br>101 (21)‖ | 0.87 (0.73, 1.03) |
| SVRi, dyn·sec/cm⁵/m²† | 16 | 2757±889.4 | 2381±524.2 | -376±910.4 | 16 | 2789±1229.1 | 2801±1010.2 | 11±1119.1 | -410 (-953, 133) |
| PVRi/SVRi† | 16 | 1.08±0.56 | 1.05±0.73 | -0.03±0.49 | 16 | 1.08±0.65 | 1.06±0.64 | -0.03±0.83 | 0.01 (-0.44, 0.46) |
| 6WMD, m#‡ | 20 | 359.0±69.8<br>(170 – 484) | 393.1±60.7<br>(300 – 510) | 34.1±57.4 | 19 | 382.9±91.5<br>(90 – 501) | 386.4±96.6<br>(57 – 482) | 3.5±51.6 | 24.9 (–9.1, 59.0) |

6WMD indicates 6-minute walk distance; CL, confidence limit; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; PVRi, pulmonary vascular resistance index; Qpi, pulmonary flow index; Qsi, systemic flow index and SVRi, systemic vascular resistance index.

*Plus–minus values are mean±standard deviation. No imputation rules were planned for hemodynamic parameters other than PVRi in the substudy. Patients with missing values at baseline or week 16/end of treatment were excluded from the analyses.

†The treatment effect expressed as the least-squares mean difference (macitentan minus placebo) was calculated by analysis of covariance, including treatment group, location of cardiac defect and baseline value as covariates.

‡Posthoc analyses.

§The treatment effect expressed as the ratio (macitentan:placebo) of geometric means was calculated by analysis of covariance on the log transformed ratio (week 16/baseline), including treatment group, location of cardiac defect and log transformed baseline value as covariates.

‖For PVRi, changes were expressed as a percentage of the baseline value (geometric mean [geometric coefficient of variation]).

#The treatment effect is the least-squares mean difference (macitentan minus placebo) calculated by analysis of covariance, including treatment group and baseline 6MWD as covariates. The range in 6MWD values is reported in parentheses at baseline and week 16. There were no patients with missing 6MWD data at week 16 in the hemodynamic substudy.

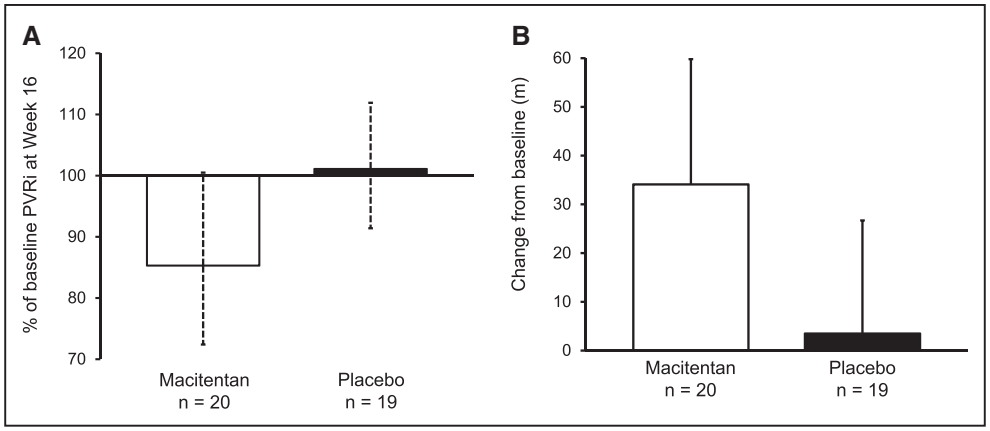


**Figure 3. Percent of baseline PVRi at Week 16 and change in 6MWD from baseline to week 16 in the hemodynamic substudy.**
6MWD indicates 6-minute walk distance; PVRi, pulmonary vascular resistance index; and CL, confidence limit. **A**, Unadjusted geometric mean PVRi (95% CL) at week 16, expressed as a percentage of baseline, is shown for the macitentan and placebo groups in the intention-to-treat population with missing values imputed. The geometric mean PVRi decreased to 85.3% of the baseline value in the macitentan group and increased to 101.1% of the baseline value in the placebo group. The macitentan:placebo ratio of geometric means (treatment effect) was 0.87 (95% CL, 0.73–1.03) calculated using an analysis of covariance model on the log transformed ratio (week 16/baseline), including the treatment group, location of cardiac defect and PVRi at baseline as covariates. Missing values were imputed for 4 patients. **B**, Mean (plus 95% CL) change from baseline to week 16 in 6MWD in the hemodynamic study (posthoc analysis) is shown for the macitentan and placebo groups in the intention-to-treat population. There were no patients with missing data. The 6MWD increased from baseline by a mean of 34.1 m in the macitentan group and 3.5 m in the placebo group. The macitentan minus placebo least-squares mean difference (treatment effect) was 24.9 m (95% CL, -9.1 to 59.0) calculated using an analysis of covariance model, including treatment group and baseline 6MWD as covariates.

## DISCUSSION

In the MAESTRO study, macitentan did not have an effect on the primary end point of change from baseline to week 16 in 6MWD compared with placebo in patients with ES. In addition, no relevant trends with macitentan were observed for the secondary end points. Among the exploratory end points, macitentan reduced NT-proBNP levels in the main study cohort and improved PVRi and 6MWD in the hemodynamic substudy. There were no specific safety concerns with the use of macitentan in patients with ES; the safety profile was consistent with that in other PAH etiologies.[23]

In contrast to results from the BREATHE-5 study,[5] ES patients treated with an ERA in MAESTRO had less robust improvement in 6MWD; furthermore, a large improvement was seen in placebo-treated patients, limiting the overall treatment effect of macitentan. The placebo effect was consistent across all prespecified subgroups and was unexpected, given that the MAESTRO population was predominantly untreated. This placebo effect also runs contrary to results from most randomized controlled trials of targeted therapies in PAH,[5,23,25–38] regardless of concomitant disease state or WHO FC. The reasons for the large placebo effect, and the overall lack of treatment effect of macitentan on the primary end point, are not clear, but a number of factors were considered and are discussed below.

In MAESTRO, enrollment of patients with complex cardiac defects, WHO FC II, Down syndrome and PDE-5i therapy at baseline resulted in a more heterogeneous population compared with BREATHE-5.[5] In the latter trial, all patients had simple cardiac defects, WHO FC III, were treatment-naive and did not have Down syndrome.[5] Of note, mortality rates for WHO FC II patients with ES are considerable[8] and therefore their inclusion in MAESTRO is of fundamental importance. We explored whether these population differences influenced the treatment effect on the primary end point in MAESTRO. With regards to the inclusion of patients receiving PDE-5i, PAH studies have demonstrated that the presence of background therapy can attenuate the treatment effect on exercise capacity.[39] In MAESTRO, however, the difference in exercise capacity between treatment groups was consistent across subgroups defined according to background therapy. In relation to the inclusion of patients with Down syndrome, the beneficial effects of PAH-specific therapy on 6MWD may be less pronounced in this population,[40] and their cooperation during exercise testing may not be consistent. As enrollment of Down syndrome patients may affect assessment of exercise capacity, their inclusion in the study was extensively discussed by the steering committee, and efforts were made to adapt the standard 6MWT procedures and familiarization components to the needs of the Down syndrome patient. Although the sample size was small for Down syndrome patients, the data indicate that including these patients did not compromise the primary end point result. Similar consistency in results was noted between the subset of patients with WHO FC II as compared with WHO FC III.

We investigated whether there was variability in the performance of the 6MWT and if this impacted the primary end point result. In our study, patients with variance in screening 6MWD >15% were excluded,

**Table 4. Summary of Adverse Events and Abnormal Laboratory Findings***

| | Macitentan N=114 | Placebo N=112 |
|---|---|---|
| Patients with ≥1 treatment-emergent AE, n (%) | 76 (66.7) | 70 (62.5) |
| Patients with ≥1 treatment-emergent SAE, n (%) | 7 (6.1) | 2 (1.8) |
| Patients with ≥1 AE leading to discontinuation of study treatment, n (%) | 2 (1.8) | 2 (1.8) |
| Adverse event, n (%)† | | |
| Headache | 13 (11.4) | 5 (4.5) |
| Upper respiratory tract infection | 11 (9.6) | 7 (6.3) |
| Bronchitis | 6 (5.3) | 3 (2.7) |
| Dizziness | 6 (5.3) | 3 (2.7) |
| Edema peripheral | 5 (4.4) | 4 (3.6) |
| Right ventricular failure | 4 (3.5) | 1 (0.9) |
| Fatigue | 4 (3.5) | 1 (0.9) |
| Erythema | 4 (3.5) | 0 |
| Serious adverse events, n (%) | | |
| Right ventricular failure | 3 (2.6) | 0 |
| Pneumonia | 2 (1.8) | 0 |
| Acute kidney injury | 1 (0.9) | 0 |
| Atrial fibrillation | 1 (0.9) | 1 (0.9) |
| Dizziness | 1 (0.9) | 0 |
| Endocarditis | 1 (0.9) | 0 |
| Respiratory failure | 1 (0.9) | 0 |
| Septic shock | 1 (0.9) | 0 |
| Transient ischemic attack | 1 (0.9) | 0 |
| Chronic cardiac failure | 0 | 1 (0.9) |
| Other AEs of interest, n (%)‡ | | |
| AEs related to anemia | 6 (5.3) | 1 (0.9) |
| AEs related to edema and fluid overload | 8 (7.0) | 6 (5.4) |
| AEs related to hypotension | 3 (2.6) | 3 (2.7) |
| Laboratory findings of interest§ | | |
| Change from baseline to week 16/ end of treatment in hemoglobin, g/dL, mean±SD | -1.04±1.37‖ | 0.12±1.22‖ |
| Hemoglobin decrease from baseline ≥2 g/dL | 41 (36.0) | 10 (8.9) |
| ALT or AST ≥3 x ULN | 1 (0.9) | 1 (0.9) |
| $SpO_2$ decrease from baseline >10%, n (%) | 6 (5.3) | 10 (8.9) |

AE indicates adverse event; ALT, alanine transaminase; AST, aspartate transaminase; SAE, serious adverse event; SD, standard deviation; $SpO_2$, oxygen saturation; and ULN, upper limit of normal.

*Patients could have >1 event. Adverse events and serious adverse events were reported from study drug initiation until 30 days after study drug discontinuation, and were reported at the discretion of the investigator.

†Adverse events are listed for those that occurred in more than 3 patients in the macitentan group.

‡AEs of special interest related to anemia, edema and fluid overload, and hypotension were predefined in the analysis plan.

§Data are n (%) unless otherwise indicated.

‖Data were missing for 1 patient in the macitentan group and 3 patients in the placebo group (a total of 4 patients with missing data).

with intent to minimize variability in 6MWT performance. Surprisingly, 36% of patients had a 6MWD at randomization that was lower (in some cases by more than 30 m) than the mean of their 2 screening tests. While site-specific variance in 6MWD testing was not noted among the larger study sites, we cannot exclude the possibility that the involvement of less-experienced centers may have impacted the performance of the 6MWT. Interestingly, in the hemodynamic substudy (in which only participating centers with greater adult congenital heart disease catheterization experience were included) a favorable treatment effect on 6MWD and PVR was observed in the macitentan-treated group, whereas no placebo effect was detected; this suggests potential effects of improved adherence to anatomic and physiological entry criteria by substudy sites, refinement of diagnosis by hemodynamic assessment within 30 days of trial enrollment in the substudy as contrasted to a 5-year window for such within the main study, or that the 6MWT might have been performed in a more standard fashion in the substudy. However, it should be noted that the proportion of patients with a 6MWD at randomization that was lower than the mean of their 2 screening 6MWTs was comparable between the overall study and the substudy.

We also investigated whether the decrease in hemoglobin for macitentan-treated patients affected the primary end point result, given that reduced hemoglobin levels are associated with impaired exercise capacity.[41] However, posthoc analysis demonstrated that the treatment effect of macitentan on 6MWD was comparable between patients with and without a hemoglobin decrease of ≥2 g/dL. In addition, there was no decrease in mean $SpO_2$ following macitentan treatment. Given that the ratio of pulmonary blood flow (indexed pulmonary blood flow) to systemic blood flow (indexed systemic blood flow) also did not change with macitentan (ie, the intravascular shunt remained unchanged), the lack of fall in the systemic oxygen saturation (as reflected by the mean $SpO_2$) does not lend support to an effect of hemoglobin on the primary end point result.

The large effect in the placebo arm on exercise capacity contributed significantly to the failure to achieve the primary end point in MAESTRO. During the study, gains in 6MWD may have resulted from familiarization with the 6MWT in a supervised clinical setting, or from adaptation to exercise and improved muscle strength. As ES patients are traditionally restricted from exercising, due to the risk of systemic vasodilatation in the context of markedly reduced pulmonary vasodilator reserve, training-related improvements in exercise capacity may be particularly pronounced in this population. It is important to note that the resulting increase in exercise capacity would occur equally in both treatment arms, contributing to the observed

effect in the placebo arm and potentially masking the treatment effect of macitentan in the active arm; an additive effect of drug therapy on top of the increased function resulting from physical conditioning or familiarization with the 6MWT would not be expected during the 16-week study period. This is particularly true in the ES population, as PAH therapies have systemic vasodilator potential, which may increase right-to-left shunting and exaggerate cyanosis, hampering an additional increase in function due to therapy. We recognize that other factors may have contributed to the increased functional ability of patients with ES in our study; trial enrollment and clinical care within the study centers alone may also have improved care. Of note (and recognizing their limitations), a number of posthoc analyses were performed and all failed to demonstrate meaningful differences in the treatment effect between the patient subgroups tested. It is possible that certain physiological and clinical findings, including decrease in NT-proBNP in macitentan-treated patients in the main MAESTRO study, decrease in PVR and increase in 6MWD in macitentan-treated patients in the hemodynamic substudy, and the improvement in placebo-treated patients switched to macitentan in the open-label extension study, may help shed light on disease mechanisms in ES.

The safety and tolerability of macitentan in patients with ES was congruent with the known safety profile of macitentan in patients with PAH.[23,42] This included a higher incidence of headaches with macitentan versus placebo and a comparable low incidence of edema between the treatment arms. In addition, the observed decrease in hemoglobin following macitentan treatment is consistent with the previously reported safety profile of the drug. Similar to the BREATHE-5 study with bosentan,[5] treatment with macitentan did not adversely affect $SpO_2$. As previously discussed, this can be explained by the fact that macitentan had a similar effect on both the systemic and pulmonary circulations and, therefore, a limited impact on the net right-to-left shunt.

In conclusion, macitentan did not show superiority over placebo on the primary end point of change from baseline to week 16 in exercise capacity in patients with ES. There were no safety concerns with the use of macitentan in patients with ES. There were several novel elements to the study, including the enrollment of patients with Down syndrome and anatomically-classified complex cardiac defects. MAESTRO may serve as a reference for future trials in patients with Eisenmenger syndrome.

## ARTICLE INFORMATION

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### Disclosures

Dr Gatzoulis is a steering committee member for Actelion Pharmaceuticals and has received unrestricted educational grants from Actelion Pharmaceuticals, Pfizer and GlaxoSmithKline. Dr Landzberg is a steering committee member for Actelion Pharmaceuticals. Dr Beghetti is a steering committee member for Actelion Pharmaceuticals; has received nonfinancial support, grant support and personal fees from Actelion Pharmaceuticals; has received personal fees from GlaxoSmithKline, Eli Lilly and Pfizer; and has received grant support and personal fees from Bayer Healthcare. Dr Berger is a steering committee member for Actelion Pharmaceuticals and has received nonfinancial support from Actelion Pharmaceuticals; in addition, the University Medical Center Groningen has contracted with and received fees from Actelion Pharmaceuticals, Lilly, GlaxoSmithKline, Pfizer and Bayer Healthcare for Dr Berger to be a consultant. Ms Efficace and Dr Gesang are employees of Actelion Pharmaceuticals. Dr Papadakis is an employee of Actelion Pharmaceuticals. Dr Pulido has served on advisory boards of Actelion Pharmaceuticals, Bayer Healthcare, and GlaxoSmithKline, has received grant support through institutional funds from Actelion Pharmaceuticals, Bayer HealthCare, BristolMyersSquibb, United Therapeutics, GlaxoSmithKline, and Eli Lilly & Company; and has received consultancy honoraria from Actelion Pharmaceuticals, GlaxoSmithKline and Bayer HealthCare. Dr Galiè is a steering committee member for Actelion Pharmaceuticals; has received grant support, personal fees and nonfinancial support from Actelion Pharmaceuticals; and has received grant support and personal fees from Bayer Healthcare, Pfizer and GlaxoSmithKline. Dr He has no conflicts of interest to disclose.

## APPENDIX

Please see the online-only Data Supplement for a list of the MAESTRO Study Investigators.

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