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BRIEF REPORT

Long-Term Safety, Tolerability and Survival in Patients with Pulmonary Arterial Hypertension Treated with Macitentan: Results from the SERAPHIN Open-Label Extension

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ABSTRACT

Introduction: In SERAPHIN, a long-term, event-driven, double-blind randomised controlled trial in pulmonary arterial hypertension (PAH), macitentan 10 mg significantly reduced the risk of morbidity/mortality compared with placebo. Its open-label extension study (SERAPHIN OL) further assessed long-term safety and tolerability of macitentan 10 mg in PAH patients.

Methods: Patients in SERAPHIN who completed the double-blind treatment period or experienced a morbidity event during the study could enter SERAPHIN OL. Patients received macitentan 10 mg once daily, and safety and survival were assessed until end of treatment (+ 28 days). Two overlapping sets were analysed

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for safety: (1) all patients in SERAPHIN OL (OL safety set); (2) patients randomised to macitentan 10 mg in SERAPHIN (long-term safety/survival set). Survival was evaluated as an exploratory endpoint in the latter set.

Results: Of 742 patients randomised in SERAPHIN, 550 (74.1%) entered SERAPHIN OL (OL safety set); 242 patients were randomised to macitentan 10 mg in SERAPHIN (long-term safety/survival set). Median (min, max) exposure to macitentan 10 mg was 40.1 (0.1, 130.5) months (2074.7 patient-years; OL safety set) and 54.7 (0.1, 141.3) months (1151.0 patient-years; long-term safety/survival set). Safety in both analysis sets was comparable to the known safety profile of macitentan. Kaplan-Meier survival estimates (95% CI) at 1, 5, 7 and 9 years were 95.0% (91.3, 97.1), 73.3% (66.6, 78.9), 62.6% (54.6, 69.6) and 52.7% (43.6, 61.0), respectively (long-term safety/survival set; median follow-up: 5.9 years).

Conclusions: This analysis provides the longest follow-up for safety and survival published to date for any PAH therapy. The safety profile of macitentan 10 mg over this extensive treatment period was in line with that observed in SERAPHIN. As the majority of patients were receiving other PAH therapy at macitentan initiation, our study provides additional insight into the long-term safety of macitentan, including as part of combination therapy.

Trial Registration: ClinicalTrials.gov Identifiers: NCT00660179 and NCT00667823.

Keywords: Endothelin receptor antagonist (ERA); Combination therapy; Long-term outcomes; Macitentan; Open-label extension; Pulmonary arterial hypertension (PAH); Safety; SERAPHIN; Survival; Tolerability

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Key Summary Points

Why carry out this study?

Long-term data from patients with this rare disease, pulmonary arterial hypertension (PAH), are sparse. The SERAPHIN open-label extension (OL) study provides data on long-term safety, tolerability and survival for patients with PAH treated with the endothelin receptor antagonist, macitentan.

What did the study ask?

SERAPHIN OL collected long-term data on adverse events (AEs) and laboratory tests, including haematology and liver function tests, in PAH patients treated with macitentan. Safety was analysed in two overlapping sets of patients: (1) all patients who received macitentan 10 mg in SERAPHIN OL (N = 550; OL safety set) regardless of their allocation in the SERAPHIN double-blind study; (2) all patients who were randomised to macitentan 10 mg in the SERAPHIN double-blind study (N = 242; long-term safety/survival set). Survival was assessed as an exploratory endpoint in the long-term safety/survival set.

What were the study outcomes/conclusions?

The median (min, max) exposure to macitentan 10 mg was 40.1 (0.1, 130.5) months in the OL safety set (N = 550), corresponding to a total of 2074.7 patient-years, and 54.7 (0.1, 141.3) months in the long-term safety/survival set (N = 242), corresponding to a total of 1151.0 patient-years. AEs reported in the study were in line with the known safety profile of macitentan and/or underlying disease. Kaplan-Meier estimates for survival (95% CI) in the long-term safety/survival set (N = 242) at 1, 5, 7 and 9 years were 95.0% (91.3, 97.1), 73.3% (66.6, 78.9) and 62.6% (54.6, 69.6), and 52.7% (43.6, 61.0), respectively.

What has been learned from the study?

These results provide extensive safety and tolerability data for macitentan, gathered over the longest follow-up period published to date for any PAH therapy. The long-term safety and tolerability profile of macitentan observed in this study was in line with that reported earlier, including both trial and real-world data.

INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare, progressive disease, which has a poor prognosis [1, 2]. However, over the past three decades a number of targeted therapies have become available and, together with better patient management, have contributed to improved outcomes [3]. Knowledge on the long-term safety and tolerability of individual PAH therapies is an important factor guiding treatment decisions.

Macitentan is an oral endothelin receptor antagonist (ERA) indicated for the treatment of PAH to reduce the risks of disease progression and hospitalisation for PAH [4, 5]. The efficacy and safety of macitentan were evaluated in the landmark trial, SERAPHIN, using a composite primary endpoint of morbidity and mortality; the findings from SERAPHIN were the first long-term outcome study results to be published in the field of PAH [6]. Prior to SERAPHIN, PAH therapies were generally investigated in short-term studies (12–16 weeks) with exercise capacity as the primary endpoint [7, 8]. In SERAPHIN, macitentan 10 mg was administered over a mean duration of 104 weeks and reduced the risk of morbidity and mortality events by 45% ($p < 0.001$) compared with placebo [6]. The open-label extension (OL) study of SERAPHIN collected further data on long-term safety, tolerability and survival for patients treated with macitentan. Here, we report an analysis of this long-term data from SERAPHIN and its OL extension study.

METHODS

The data sharing policy of the Sponsor is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to study data can be submitted through the Yale Open Data Access Project site at https://yoda.yale.edu.

Study Design

SERAPHIN (NCT00660179) was a global, multicentre, double-blind, randomised, placebo-controlled event-driven, phase 3 study, which assessed the safety and efficacy of macitentan in patients with PAH [6]. Patients were randomly assigned in a 1:1:1 ratio to receive placebo, macitentan 3 mg, or macitentan 10 mg once daily. Patients received double-blind treatment until occurrence of a primary endpoint event of morbidity or mortality, premature discontinuation or end of study, whichever occurred first. Components of the primary endpoint were worsening of PAH, initiation of treatment with intravenous or subcutaneous prostanoids, lung transplantation, atrial septostomy or death. Worsening of PAH was defined as the combination of a decrease in 6-min walk distance (6MWD) of at least 15% from baseline, worsening of PAH symptoms and the need for new PAH treatment(s). All primary endpoint events were independently adjudicated by a clinical event committee.

SERAPHIN OL (NCT00667823) (first patient, first visit: 17 October 2008; last patient, last visit: 7 December 2020) was a long-term, multicentre, single-arm, non-comparative OL study that evaluated long-term safety and tolerability of macitentan 10 mg in patients with symptomatic PAH (Supplementary Fig. 1). Patients enrolled in SERAPHIN could enter SERAPHIN OL either after completing the double-blind treatment period of SERAPHIN without experiencing a primary endpoint event or after experiencing a morbidity event during SERAPHIN.

Patients received macitentan 10 mg orally once daily in SERAPHIN OL until one of the following occurred: macitentan became commercially available in this indication in the patient's country, the sponsor decided to stop the study or the patient, investigator or study sponsor decided to discontinue macitentan. The end of SERAPHIN OL study treatment was followed by a post-treatment safety follow-up period of 28 days.

Ethics

SERAPHIN and SERAPHIN OL were conducted in accordance with the Declaration of Helsinki. The protocols were approved by the institutional review boards/independent ethics committees at each site (Supplementary Table 1). Written informed consent was obtained from all patients at entry into SERAPHIN and SERAPHIN OL.

Patient Population

The full inclusion/exclusion criteria for SERAPHIN have been described previously [6]. Briefly, patients enrolled were $\geq$ 12 years old with a right heart catheterisation-confirmed diagnosis of idiopathic PAH, 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 6MWD of $\geq$ 50 m and to be in World Health Organization functional class (WHO FC) II–IV. In SERAPHIN, concomitant treatment with oral phosphodiesterase type 5 inhibitors (PDE5i), oral or inhaled prostanoids, calcium channel blockers or L-arginine was permitted, if present for at least 3 months before randomisation at a stable dose. Patients receiving intravenous or subcutaneous prostanoids were excluded. In SERAPHIN OL, all concomitant PAH therapies were permitted, except for ERAs other than the study drug.

Study Endpoints and Assessments

Safety and tolerability endpoints included treatment-emergent adverse events (AEs), serious adverse events (SAEs), AEs leading to premature discontinuation of the study drug and clinical laboratory tests (including haematology

and liver function test abnormalities). Overall survival was evaluated as an exploratory endpoint.

Statistical Analyses

All analyses were descriptive in nature. Two separate analysis sets were used for the safety analyses. The first analysis set (the OL safety set) included all patients who were enrolled in SERAPHIN OL and received at least one dose of macitentan 10 mg. The observation period for each patient was from first intake of macitentan 10 mg in SERAPHIN OL and continued up to end of treatment (EOT) plus 28 days. The second analysis set (the long-term safety/survival set) included all patients randomised to macitentan 10 mg in SERAPHIN, irrespective of whether they enrolled into SERAPHIN OL. This set was used for the analysis of additional long-term safety data as well as for the post-hoc analysis of survival. Use of this set for the survival analysis ensured a robust and non-biased approach, as treatment with macitentan had been initiated in all patients at the same time point. For this set, the observation period started from first intake of macitentan 10 mg in SERAPHIN and continued up to EOT plus 28 days (in either SERAPHIN or SERAPHIN OL). The Kaplan-Meier (KM) method was used to estimate time from macitentan initiation to death up to EOT plus 28 days; deaths that occurred up to study closure were also included if reported to the sponsor. Patients were censored at their last date of contact (in either SERAPHIN or SERAPHIN OL), which for most patients was EOT plus 28 days. Survival analyses were performed on all patients in the long-term safety/survival set as well as on patients grouped according to WHO FC at baseline (WHO FC I/II or WHO FC III/IV). Summary of study follow-up time (where patients who died before study closure were censored) was calculated using the reverse KM method [9].

RESULTS

Patient Characteristics

Of the 742 patients randomised in SERAPHIN, 550 (74.1%) were enrolled in SERAPHIN OL (OL safety set), including 182 (33.1%) originally randomised to macitentan 10 mg, 185 (33.6%) to macitentan 3 mg and 183 (33.3%) to placebo (Fig. 1). Of the 550 patients in the OL safety set,

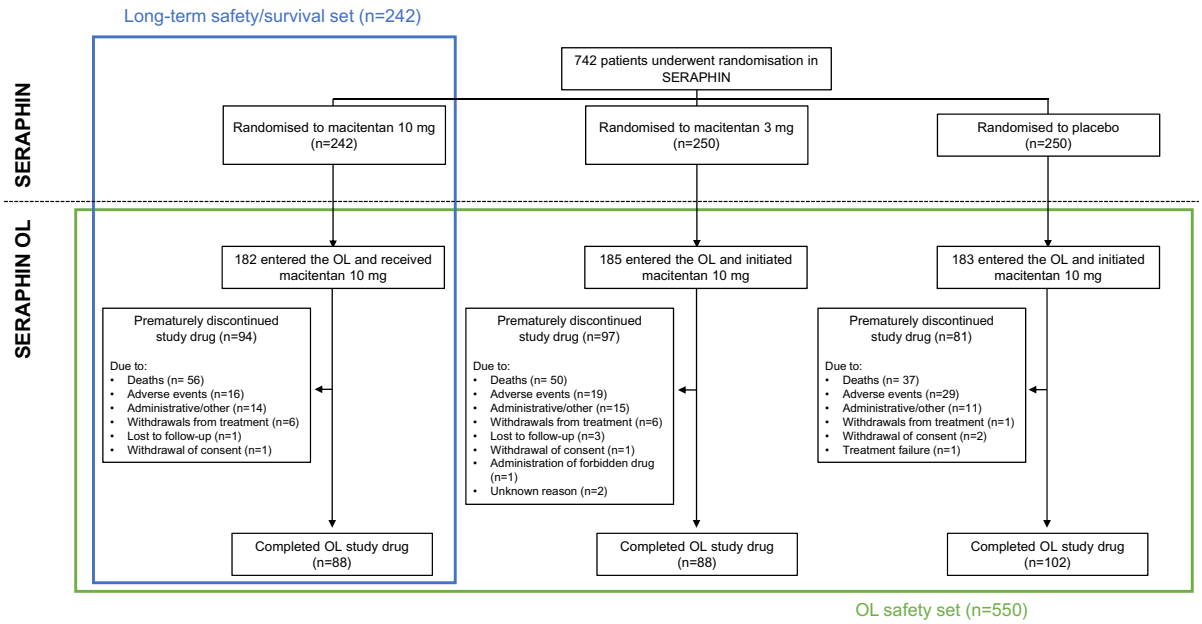

Fig. 1 Patient disposition in SERAPHIN and SERAPHIN OL. *OL* open-label

Table 1 Treatment disposition at end of SERAPHIN OL

	OL safety set (*N* = 550)	Long-term safety/survival set (*N* = 242)
Completed study treatment[a], *n* (%)	278 (50.5)	95 (39.3)
Discontinued study treatment, *n* (%)	272[b] (49.5)	147 (60.7)
Reason for discontinuation, *n* (%)[c]		
Death	143 (26.0)	66 (27.3)
Adverse event	64 (11.6)	38 (15.7)
Administrative/other	40 (7.3)	19 (7.9)
Withdrawal from treatment	13 (2.4)	18 (7.4)
Lost to follow-up	4 (0.7)	1 (0.4)
Other[d]	6 (1.1)	5 (2.1)

OL open-label

[a]Completed study treatment in SERAPHIN or SERAPHIN OL: Patients who received study treatment as per protocol and did not prematurely discontinue study treatment

[b]Includes two patients who discontinued but did not have a reason for discontinuation recorded; these two patients and their time on treatment are excluded from the premature study drug discontinuation incidence rate

[c]Percentages are calculated out of the total number of patients included in each set

[d]Includes withdrawal of consent, administration of forbidden drug and treatment failure

278 (50.5%) completed study treatment without premature discontinuation (Table 1).

At enrolment in SERAPHIN OL, patients in the OL safety set (*N* = 550) had a mean (SD) age of 47.7 (15.7) years. Most patients were female (80.0%) and in WHO FC II (45.1%) or III (31.5%); 67.5% of patients were receiving background PAH therapy, with the majority (65.1%) receiving a PDE5i (Table 2).

Table 2 Demographics and clinical characteristics at time of macitentan (10 mg) initiation in SERAPHIN OL

Characteristic	OL safety set (*N* = 550)
Female, *n* (%)	440 (80.0)
Age, years, mean ± SD	47.7 ± 15.7
Time from diagnosis of PAH[a], years, mean ± SD	4.9 ± 4.1
PAH classification, *n* (%)	
Idiopathic PAH	306 (55.6)
Heritable PAH	12 (2.2)
Associated with connective tissue disease	175 (31.8)
Associated with congenital heart disease	39 (7.1)
Associated with HIV	5 (0.9)
Drug or toxin induced	13 (2.4)
6MWD, *m*, mean ± SD[b]	331.5 ± 150.2
WHO FC, *n* (%)[b]	
I	25 (4.5)
II	248 (45.1)
III	173 (31.5)
IV	104 (18.9)
Background PAH therapy, *n* (%)	371 (67.5)
PDE5i[c]	358 (65.1)
Oral or inhaled prostanoids[c]	55 (10.0)
Combination therapy	46 (8.4)
None	179 (32.5)
Randomisation arm in SERAPHIN, *n* (%)	
Placebo	183 (33.3)
Macitentan 3 mg	185 (33.6)
Macitentan 10 mg	182 (33.1)

Assessments are presented for start of SERAPHIN OL unless otherwise stated

6MWD 6-min walk distance, *EOT* end of treatment, *HIV* human immunodeficiency virus, *OL* open-label, *PAH* pulmonary arterial hypertension, *PDE5i* phosphodiesterase 5 inhibitor, *SD* standard deviation, *WHO FC* World Health Organization functional class

[a]Confirmed by right heart catheterisation before SERAPHIN start

[b]Evaluated at EOT in SERAPHIN

[c]Patients on combination therapy (i.e. PDE5i and oral/inhaled prostanoids) are counted several times—in each respective category

The 242 patients randomised to macitentan 10 mg in SERAPHIN comprised the long-term safety/survival set. Of these, 182 (75%) entered SERAPHIN OL and were also included in the OL safety set (Fig. 1).

The baseline characteristics for the long-term safety/survival set ($N = 242$) have been previously described [6]. Briefly, at macitentan 10 mg initiation in SERAPHIN, the mean (SD) age was 45.5 (15.0) years. Most patients were female (80.2%) and in WHO FC II (49.6%) or III (47.9%); 63.6% of patients were receiving background PAH therapy, with the majority (62.0%) receiving a PDE5i [6].

Safety and Tolerability of Macitentan 10 mg in SERAPHIN OL

In the OL safety set ($N = 550$), the median (min, max) exposure to macitentan from first intake of macitentan 10 mg in SERAPHIN OL to EOT was 40.1 (0.1, 130.5) months (Table 3), corresponding to a total of 2074.7 patient-years. In this set, macitentan 10 mg was received for at least 5 years by 172 (31.3%) patients, for at least 7 years by 62 (11.3%) patients and for at least 9 years by 13 (2.4%) patients. Ninety-three (16.9%) patients initiated a new class of concomitant PAH therapy, where the concomitant period corresponded to the exposure period plus 28 days. The most common were a PDE5i ($n = 50$; 9.1%) and prostacyclin or its analogue ($n = 43$; 7.8%). However, 89.6% of the macitentan exposure occurred without or prior to the addition of any new PAH therapies during the study.

In the OL safety set, the most frequently reported AEs were PAH worsening (28.5%), upper respiratory tract infection (23.1%), peripheral oedema (19.5%) and nasopharyngitis (19.1%) (Table 3). Forty-five (8.2%) patients experienced an increase in alanine aminotransferase (ALT) or aspartate aminotransferase (AST) to $> 3 \times$ upper limit of normal (ULN), corresponding to an incidence rate of 2.2 per 100 patient-years. Eight (1.5%) patients experienced an increase in ALT or AST to $> 3 \times$ ULN and in bilirubin to $> 2 \times$ ULN (incidence rate of 0.4 per 100 patient-years). Most of these cases were observed in the setting of worsening of the underlying or concomitant disease or in the presence of other confounding factors. Haemoglobin levels ≤ 8 g/dl were experienced by 33 (6.0%) patients (incidence rate of 1.7 per 100 patient-years).

There were 62 (11.3%) patients who experienced an AE leading to OL treatment discontinuation, with an incidence rate of 3.0 AEs per 100 patient-years (Table 3). The most common AEs leading to discontinuation (non-mutually exclusive and occurring in $\geq 1\%$ of patients) were PAH worsening (2.4%), right ventricular failure (1.8%) and lung transplant (1.1%).

During SERAPHIN OL, 175 (31.8%) patients had died by EOT (plus 28 days). The most common reasons for death (occurring in $\geq 2\%$ of patients) were PAH worsening (10.5%), right ventricular failure (6.4%) and sudden death (2.0%).

Safety and Tolerability of Macitentan 10 mg in SERAPHIN and SERAPHIN OL

In the long-term safety/survival set ($N = 242$), the median (min, max) exposure to macitentan (from first intake of macitentan 10 mg in SERAPHIN up to EOT) was 54.7 (0.1, 141.3) months (Table 3), corresponding to a total of 1151.0 patient-years. In this set, macitentan 10 mg was received for at least 5 years by 104 (43.0%) patients, for at least 7 years by 69 (28.5%) patients and for at least 9 years by 22 (9.1%) patients. Fifteen (6.2%) patients initiated a new class of concomitant PAH therapy (where the concomitant period corresponded to the exposure period plus 28 days). The most common were a PDE5i ($n = 8$; 3.3%) and a prostacyclin or its analogue ($n = 7$; 2.9%). However, 96.2% of the macitentan exposure was accumulated without or prior to the addition of any new PAH therapies during the study.

In the long-term safety/survival set, the most frequently reported AEs were PAH worsening (35.5%), peripheral oedema (26.0%), upper respiratory tract infection (25.6%) and nasopharyngitis (21.5%) (Table 3). Twenty-one (8.7%) patients experienced an increase in ALT or AST to $> 3 \times$ ULN (incidence rate of 1.9 per

Table 3 Safety and exposure

Macitentan exposure	**OL safety set (*N* = 550)**		**Long-term safety/survival set (*N* = 242)**	
Median (min, max), months	40.1 (0.1, 130.5)		54.7 (0.1, 141.3)	
Mean ± SD, years	3.8 ± 2.5		4.8 ± 3.1	
Adverse events	***n* (%)**	**Incidence rate per 100 patient-years[a]**	***n* (%)**	**Incidence rate per 100 patient-years[a]**
Patients with ≥ 1 adverse event	527 (95.8)	144.3	235 (97.1)	180.5
Patients with ≥ 1 serious adverse event	354 (64.4)	25.5	167 (69.0)	24.1
Patients with ≥ 1 adverse event leading to macitentan discontinuation[b]	62 (11.3)[c]	3.0	39 (16.1)[d]	3.4
Most frequent[e] adverse events	***n* (%)**	**Incidence rate per 100 patient-years[a]**	***n* (%)**	**Incidence rate per 100 patient-years[a]**
PAH worsening	157 (28.5)	8.7	86 (35.5)	9.4
Upper respiratory tract infection	127 (23.1)	7.6	62 (25.6)	6.8
Peripheral oedema	107 (19.5)	5.8	63 (26.0)	6.7
Nasopharyngitis	105 (19.1)	6.2	52 (21.5)	5.7
Anaemia	97 (17.6)	5.4	47 (19.4)	4.7
Bronchitis	86 (15.6)	4.7	45 (18.6)	4.6
Right ventricular failure	86 (15.6)	4.4	47 (19.4)	4.5
Cough	74 (13.5)	3.9	33 (13.6)	3.1
Dyspnoea	67 (12.2)	3.5	40 (16.5)	3.8
Headache	65 (11.8)	3.5	47 (19.4)	4.8
Pneumonia	61 (11.1)	3.1	28 (11.6)	2.6
Diarrhoea	60 (10.9)	3.1	39 (16.1)	3.8
Dizziness	56 (10.2)	2.9	39 (16.1)	3.9
Urinary tract infection	48 (8.7)	2.5	29 (12.0)	2.8
Chest pain	44 (8.0)	2.3	30 (12.4)	2.8
Laboratory abnormality	***n* (%)**	**Incidence rate per total 100 patient-years[a]**	***n* (%)**	**Incidence rate per 100 patient-years[a]**
Alanine aminotransferase or aspartate aminotransferase > 3 × ULN	45 (8.2)	2.2	21 (8.7)	1.9
Alanine aminotransferase or aspartate aminotransferase > 3 × ULN and bilirubin > 2 × ULN	8 (1.5)	0.4	9 (3.7)	0.8

Table 3 continued

Laboratory abnormality	*n* (%)	Incidence rate per total 100 patient-years[a]	*n* (%)	Incidence rate per 100 patient-years[a]
Haemoglobin ≤ 8 g/dl	33 (6.0)	1.7	15 (6.2)	1.4

AE adverse event, *EOT* end of treatment, *OL* open-label, *PAH* pulmonary arterial hypertension, *SD* standard deviation, *ULN* upper limit of normal

[a]For the patients with an event, the time up to first event is counted; otherwise, the time is censored up to EOT

[b]All adverse events leading to discontinuation of macitentan are reported here and not only those considered the primary reason for discontinuation as presented in Table 1

[c]Sixty-four patients had AE listed as their reason for discontinuation (Table 1) but two of these patients are excluded here as they did not have any respective AEs reported as leading to discontinuation

[d]Thirty-eight patients had AE listed as their reason for discontinuation (Table 1). Here, one additional patient is included who discontinued treatment in SERAPHIN due to an AE but died during SERAPHIN OL and had "death" recorded as the reason for discontinuation in Table 1

[e]Occurring in ≥ 10% of patients in either set

100 patient-years). Nine (3.7%) patients experienced an increase in ALT or AST to > 3 × ULN and in bilirubin to > 2 × ULN (incidence rate of 0.8 per 100 patient-years). Most of these cases were observed in the setting of worsening of the underlying or concomitant disease or in the presence of other confounding factors. Haemoglobin levels ≤ 8 g/dl were experienced by 15 (6.2%) patients (incidence rate of 1.4 per 100 patient-years).

Thirty-nine (16.1%) patients experienced an AE leading to treatment discontinuation, with an incidence rate of 3.4 AEs per 100 patient-years (Table 3). The most common AEs leading to discontinuation (non-mutually exclusive and occurring in ≥ 1% of patients) were PAH worsening (2.1%), right ventricular failure (1.7%), increased aspartate aminotransferase (1.7%), increased liver function test (1.2%), increased alanine aminotransferase (1.2%) and headache (1.2%).

In the long-term safety/survival set, 78 (32.2%) patients had died by EOT (plus 28 days). The most common reasons for death (occurring in ≥ 2% patients) were PAH worsening (9.1%), right ventricular failure (6.2%) and sudden death (2.9%).

Survival

The median survival follow-up for the long-term safety/survival set was 5.9 (95% CI 5.2, 7.4) years. KM estimates for survival (95% CI) at 1, 3, 5, 7 and 9 years were 95.0% (91.3, 97.1), 84.0% (78.6, 88.2), 73.3% (66.6, 78.9), 62.6% (54.6, 69.6) and 52.7% (43.6, 61.0), respectively (Fig. 2).

Additional survival analyses were performed on the long-term safety/survival set grouped according to WHO FC at randomisation (Supplementary Fig. 2). Patients in WHO FC I/II (n = 121) had an estimated survival KM (95% CI) of 97.5% (92.5, 99.2), 89.0% (81.8, 93.5), 83.3% (74.6, 89.2), 77.1% (66.7, 84.6) and 65.2% (52.3, 75.5) at 1, 3, 5, 7 and 9 years, respectively. Patients in WHO FC III/IV (n = 121) had an estimated survival KM (95% CI) of 92.4% (85.9, 96.0), 78.9% (70.1, 85.4), 62.7% (52.1, 71.5), 46.7% (34.8, 57.7) and 38.8% (26.3, 51.1) at 1, 3, 5, 7 years and 9 years, respectively.

DISCUSSION

This article summarises the long-term safety, tolerability and survival data of PAH patients treated with macitentan 10 mg in SERAPHIN and/or its open-label extension study (SERAPHIN OL) over an observation period of up to 9 years. The results of this analysis complement and are reflective of the safety profile of macitentan as reported previously in SERAPHIN

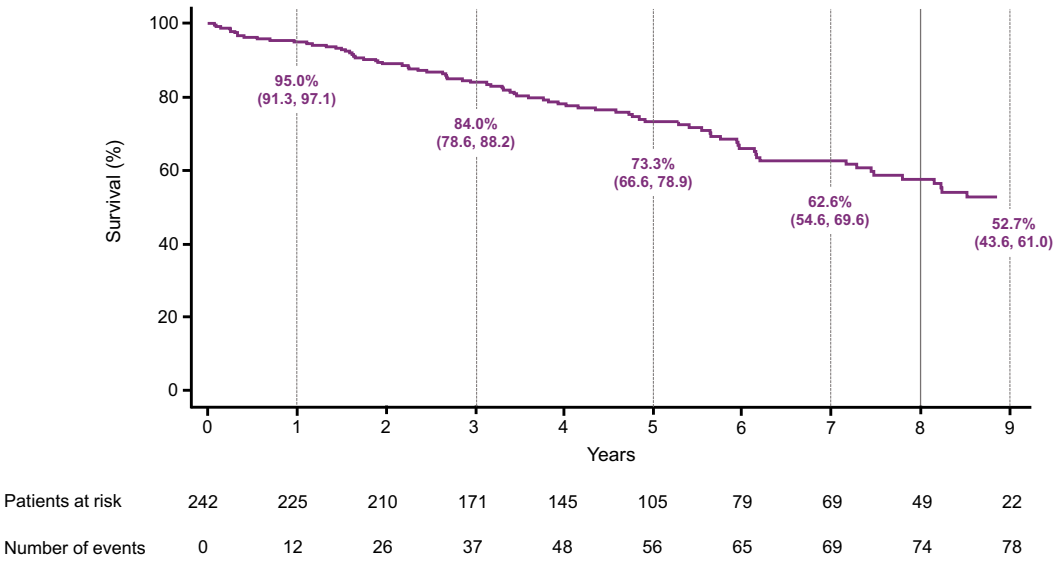

Fig. 2 Survival in patients randomised to macitentan 10 mg (long-term safety/survival set; $N = 242$). Kaplan-Meier curve for time to death. Observation period was from first intake of macitentan 10 mg in SERAPHIN up to EOT plus 28 days, but deaths that occurred up to study closure were included if reported to the sponsor. The survival analysis included 82 deaths (78 occurred up to EOT plus 28 days and 4 additional deaths occurred after that time period). The Kaplan-Meier curve is truncated at 9 years (4 deaths occurred after this time point). Patients were censored at their last date of contact, which for most patients was EOT plus 28 days. The reference line at 8 years corresponds to the time point when at least 10% of patients are still at risk in accordance with the Pocock's stopping rule [23]. The survival estimates at 9 years should be interpreted with caution, as only 9% of patients were ongoing in the study at that time. *EOT* end of treatment

and REPAIR [6, 10] and also in a real-world clinical setting [11].

Two partially overlapping sets were included in the analysis of safety and tolerability. The first one comprised all patients who were treated with macitentan 10 mg in SERAPHIN OL regardless of treatment assignment in SERAPHIN (OL safety set, $N = 550$). With 550 patients and a total of 2047.7 patient-years, this analysis set provided long-term safety data on a large PAH population, especially given the rarity of PAH. For the OL safety set, the observation period began from the start of OL, and as such two thirds of patients had already received macitentan 3 mg or 10 mg in the double-blind study. The second set comprised all patients who were randomised to macitentan 10 mg in SERAPHIN (long-term safety/survival set, $N = 242$), with the observation period starting at randomisation. Encompassing both SERAPHIN and its OL, this analysis set, although smaller, provided safety data on a population that was naïve to macitentan at the start of the observation period and hence a more homogeneous population. For this same reason, it also allowed for a robust and non-biased analysis of survival, providing data for the longest follow-up period published to date for a PAH therapy.

The two analysis sets provided complementary data on the safety of macitentan in PAH and showed that macitentan 10 mg was well tolerated by PAH patients. There were proportionally more patients with severe disease in the OL safety set at baseline (19% of patients were in WHO FC IV) compared with the long-term safety/survival set (2% in WHO FC IV) [6]. This was to be expected as the OL safety set includes patients that were enrolled following a disease progression event during the double-blind study. As safety and tolerability were consistent between the two sets, these results provide evidence on the safety of macitentan, including in

a patient population with more advanced disease.

Overall, the safety profile of macitentan in the two analysis sets was in line with that observed in previous studies [6, 10–15]. As previously observed in SERAPHIN [6], the three most common AEs reported here were PAH worsening, upper respiratory tract infection and peripheral oedema. Compared with a mean duration of exposure to macitentan 10 mg of 2 years in SERAPHIN [6], the OL safety set and the long-term safety/survival set in this analysis had considerably longer exposure times of 3.8 and 4.8 years, respectively. Considering these differences, the proportion of patients who discontinued macitentan 10 mg because of an AE was similar between the OL safety set (11.6%), the long-term safety/survival set (15.7%) and SERAPHIN (10.7%) [6].

Hepatic toxicity has been previously linked to other ERAs, and although there was no clear indication of hepatic toxicity from macitentan in SERAPHIN, this was further monitored in SERAPHIN OL. Due to the longer treatment period in the current analysis, the percentage of patients with liver test abnormalities is slightly higher than that in SERAPHIN [6]; however, the exposure-adjusted incidence rate reported here suggests that the overall hepatic safety profile is consistent with previous observations [6, 10, 11]. In SERAPHIN, a small group of patients treated with macitentan 10 mg (4.3%) experienced a decrease in haemoglobin levels $\leq$ 8 g/dl [6]. Considering the longer exposure in the two cohorts presented here, the incidence of such decreases (approximately 6% in both cohorts) was comparable to that observed in SERAPHIN [6]. Given the long observation periods, these results provide further evidence for the long-term safety and tolerability of macitentan in PAH patients. Furthermore, the majority of patients in both analysis sets were on background therapy at macitentan initiation, demonstrating good tolerability for macitentan as part of a combination therapy regimen.

Generally, long-term outcome data on PAH patients are limited [1, 2, 16]. Previous OL studies in PAH have typically provided only 2–3-year survival estimates [17–20]. An exception is the recently published analysis on GRIPHON and its OL, which provided 7-year survival estimates in a large PAH population treated with selexipag (N = 574) [21]. The analysis of SERAPHIN and its OL extension reported here includes survival estimates of up to 9 years and thus provides the longest follow-up period to date for PAH patients treated with PAH therapy. Our results suggest that patients in WHO FC I/II who are treated with macitentan have good long-term survival, with a 5-year estimated survival rate of 83.3%. In line with previous observations [1, 22], our data also show that patients in WHO FC I/II at baseline have a better prognosis than those in WHO FC III/IV. Of note, given the long observation period in SERAPHIN OL, the proportion of patients who had their treatment regimen escalated to include a new class of concomitant PAH therapy during the study was low.

The main limitation of this analysis is that the data are uncontrolled and descriptive in nature, inherent to OL extension studies. Another limitation is a loss to follow-up of some patients that switched to commercial macitentan once it became available in their country, causing a possible bias. For the OL safety set, the observation period began at the start of SERAPHIN OL and does not include safety events that occurred during the double-blind study, and prior treatment with macitentan may have impacted tolerability reporting in the OL set. To address these limitations, the long-term safety/survival set was included in the safety analysis to assess all AEs from the start of macitentan 10 mg treatment in SERAPHIN.

CONCLUSIONS

These analyses provide important clinical insights into the long-term safety and tolerability for PAH patients receiving macitentan 10 mg, with a follow-up period of up to 9 years. The safety profile of macitentan was consistent with that observed during SERAPHIN. As most patients were receiving background therapy at the time of macitentan initiation, these analyses help to further our understanding of the long-term benefit-risk ratio of using macitentan

combination therapy and provide survival estimates for the longest follow-up period to date for PAH patients treated with PAH therapy.

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Data Availability. The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

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