Initial combination therapy of macitentan and tadalafil in pulmonary arterial hypertension

To the Editor:

Initial combination therapy plays a central role in managing pulmonary arterial hypertension (PAH) [1–4]. Patients with low- or intermediate-risk of 1-year mortality at diagnosis should be treated with initial combination therapy with an endothelin receptor antagonist (ERA) and phosphodiesterase type-5 inhibitor (PDE5i) [2–4]. Benefits of initial therapy with the ERA ambrisentan and PDE5i tadalafil were demonstrated in AMBITION [1]; prospective evidence for other treatment combinations within these drug classes is needed.

In SERAPHIN, macitentan, a dual ERA, improved long-term outcomes in PAH patients [5], including those receiving background treatment (predominantly PDE5i) [5, 6]. OPTIMA (NCT02968901) was a prospective, multicentre, single-arm, open-label, phase IV study that explored the efficacy and safety of macitentan administered as initial oral combination therapy with tadalafil, in newly diagnosed, treatment-naïve PAH patients.

Treatment-naïve adult patients diagnosed with PAH within the previous 6 months were eligible if they had idiopathic, heritable or associated PAH (drug/toxin-induced, connective tissue disease (CTD), HIV, corrected congenital heart disease). Patients were World Health Organization functional class (FC) II to III, with 6-min walk distance (6MWD) $\geqslant$50 m and the following haemodynamics at screening: resting mean pulmonary arterial pressure (mPAP) $\geqslant$25 mmHg, pulmonary arterial wedge pressure (PAWP) or left ventricular end diastolic pressure $\leqslant$15 mmHg, and pulmonary vascular resistance (PVR) $\geqslant$5 Wood units if PAWP was <12 mmHg, or PVR $\geqslant$6.25 Wood units if PAWP was 12–15 mmHg. Written informed consent was obtained from all patients and the study conducted in accordance with the Declaration of Helsinki and Good Clinical Practice.

The study included a 16-week period during which efficacy and safety were assessed followed by an optional extension period assessing safety. Within 28 days of screening, macitentan 10 mg once daily and tadalafil 20 mg once daily were initiated; at day 8±3, the tadalafil dose was increased to 40 mg once daily. The dose of tadalafil could be decreased for tolerability reasons. Study treatment continued until week 16, or until PAH progression required administration of other PAH drugs. Patients who completed 16 weeks of treatment could enter an extension period with macitentan, tadalafil or both drugs until the sponsor stopped the trial, or patient/investigator decision to discontinue both treatments. Patients who discontinued both treatments had an end-of-treatment safety visit within 7 days. All patients had an end-of-study safety visit 30 days after the end of treatment.

Clinical assessments and right heart catheterisation (RHC) were performed at baseline and at week 16. Safety laboratory testing was performed monthly during the first 6 months, after which it was recommended monthly and performed at the discretion of the treating physician. Adverse events were monitored until 30 days after the end of treatment. The primary end-point was the ratio of week 16 to baseline PVR assessed by RHC. Secondary end-points were: percentage of patients with PVR decrease $\geqslant$30% from baseline to week 16; change from baseline to week 16 in mean right atrial pressure, mPAP, cardiac index, total pulmonary resistance, mixed venous oxygen saturation, 6MWD, FC and N-terminal pro-brain natriuretic peptide (NT-proBNP); and percentage of patients with improvement/worsening FC from baseline to week 16. A pre-specified exploratory end-point was the number of low-risk criteria at

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TABLE 1 Haemodynamic parameters, 6-min walk distance (6MWD), N-terminal pro-brain natriuretic peptide (NT-proBNP) concentrations, World Health Organization functional class (FC) and low-risk criteria

	Baseline	Week 16[#]	Change from baseline to week 16[#]	
			Mean (95% CI)	p-value
Subjects n	46	46		
Pulmonary vascular resistance Wood units	11.7±4.7	6.5±3.6	0.53 (0.47 to 0.59)[¶]	<0.0001
			47% reduction from baseline	
Mean pulmonary arterial pressure mmHg	50.0±12.3	42.2±14.7	−7.83 (−11.71 to −3.94)	0.0002
mRAP mmHg	8.1±4.7	7.8±5.3	−0.28 (−1.94 to 1.37)	0.7321
Cardiac index L·min^{-1}·m^{-2}	2.2±0.6	3.1±0.8	0.91 (0.71 to 1.11)	<0.0001
Total pulmonary resistance Wood units	13.9±5.3	8.5±4.3	−5.4 (−6.5 to −4.3)	<0.0001
Mixed venous oxygen saturation[+] %	63.0±7.1	68.2±7.2	5.53 (2.80 to 8.27)	0.0003
6MWD m	352.2±134.9	388.1±142.1	35.8 (15.8 to 55.9)	0.0008
NT-proBNP[§] ng·L^{-1}	1456.8	404.2	0.32 (0.23 to 0.44)[¶]	<0.0001
	(646.6 to 2119.5)[f]	(147.5 to 873.7)[f]	68% reduction from baseline	
FC: patients n (%)	FC I: 0 (0)	FC I: 9 (19.6)	Improved: 29 (63.0)	NA
	FC II: 10 (21.7)	FC II: 23 (50.0)	Worsened: 0 (0)	
	FC III: 36 (78.3)	FC III: 14 (30.4)	No change: 17 (37.0)	
Number of low-risk criteria: patients n (%)[##]				
Low-risk criteria: invasive and non-invasive variables defined as FC I/II, 6MWD >440 m, mRAP <8 mmHg, and cardiac index >2.5 L·min^{-1}·m^{-2} [7]	0 criteria: 11 (23.9)	0 criteria: 5 (10.9)	Increased: 34 (73.9)	NA
	1 criterion: 20 (43.5)	1 criterion: 8 (17.4)	Decreased: 8 (17.4)	
	2 criteria: 7 (15.2)	2 criteria: 9 (19.6)	No change: 4 (8.7)	
	3 criteria: 5 (10.9)	3 criteria: 16 (34.8)		
	4 criteria: 3 (6.5)	4 criteria: 8 (17.4)		
Low-risk criteria: non-invasive variables defined as FC I/II, 6MWD >440 m, and NT-proBNP <300 ng·L^{-1} [7]	0 criteria: 29 (63.0)	0 criteria: 10 (21.7)	Increased: 30 (65.2)	NA
	1 criterion: 7 (15.2)	1 criterion: 8 (17.4)	Decreased: 2 (4.3)	
	2 criteria: 9 (19.6)	2 criteria: 21 (45.7)	No change: 14 (30.4)	
	3 criteria: 1 (2.2)	3 criteria: 7 (15.2)		

Data are presented as mean±SD, unless otherwise stated. [#]: at week 16, missing data were imputed: two patients for pulmonary vascular resistance (baseline value carried forward); two patients for mean pulmonary arterial pressure, mean right atrial pressure (mRAP), cardiac index, total pulmonary resistance and FC (baseline value carried forward); five patients for mixed venous oxygen saturation (baseline value carried forward for four patients; for one patient who died the day after week 16, the value imputed at week 16 was calculated from baseline using the worst evolution between baseline and week 16 in the analysed population); three patients for 6MWD (baseline value carried forward for two patients; for one patient who died the day after week 16, the value imputed at week 16 was calculated from baseline using the worst evolution between baseline and week 16 in the analysed population); six patients for NT-proBNP (last observation carried forward); for risk assessment, missing parameters were considered "not low risk". [¶]: change expressed as the ratio of week 16 *versus* baseline (geometric mean and 95% confidence interval). [+]: n=29 at baseline, n=33 at week 16, n=29 for change from baseline. [§]: n=43. [f]: median (interquartile range); [##]: percentages may not add to 100% due to rounding. NA: not applicable.

baseline and week 16. Two sets of parameters were assessed and the thresholds used to define low-risk were updated *post hoc* to align with those recommended in the European Society of Cardiology (ESC)/European Respiratory Society (ERS) guidelines [2, 3] and validated in a French registry analysis [7]. For PVR and NT-proBNP, ratios of week 16 *versus* baseline were log-transformed and the geometric mean of the ratio and its 95% two-sided confidence interval obtained by exponentiation. Other parameters were summarised descriptively.

From November 2015 to December 2017, 50 patients were screened at 15 sites in France. 46 patients were enrolled and 44 completed 16 weeks of treatment (two discontinued both drugs due to: aetiology revision, n=1; adverse event and suspicion of veno-occlusive disease, n=1). 44 patients entered the extension period and 39 completed the study (five discontinued both drugs due to: adverse event and aetiology revision, n=1; adverse event and death, n=1; death, n=2; patient decision, n=1). Patients were predominantly female (65.2%) with idiopathic (63.0%) or CTD-associated (19.6%) PAH, and were FC II (21.7%) or III (78.3%), with a mean±SD 6MWD of 352.2±134.9 m. Mean±SD age was 57.4±14.9 years and time from PAH diagnosis was 29.6±55.2 days (n=45). All patients were titrated to tadalafil 40 mg once daily, the majority within 8±3 days. Tadalafil dose reductions to 20 mg once daily occurred in two patients, both between day 15 and week 16.

The geometric mean ratio of week 16 to baseline PVR was 0.53 (95% CI 0.47–0.59), representing a 47% reduction (table 1). A ⩾30% decrease in PVR between baseline and week 16 occurred in 87.0% (95% CI 73.7–95.1) of patients. Changes in other haemodynamic parameters, 6MWD, NT-proBNP concentration, FC, and the number of low-risk criteria are shown in table 1.

Median (interquartile range) exposure to macitentan and tadalafil was 86.5 (53.0–115.1) weeks. At least one adverse event was reported in 43 (93.5%) patients and serious adverse events were reported in 13 (28.3%) patients. Three (6.5%) patients had an adverse event leading to study treatment discontinuation (both study drugs) (one adverse event of lack of efficacy before week 16, one of treatment inefficiency after week 16, and one of PAH worsening after week 16). Most frequent adverse events were peripheral oedema (28.3%), headache (23.9%), diarrhoea (19.6%), dyspnoea (15.2%), anaemia (13.0%) and asthenia (13.0%). Haemoglobin decreases to >8 and $\leqslant$10 g·dL^{-1} were reported for five (10.9%) patients (who had baseline values ranging from 10.9 to 13.4 g·dL^{-1}), with no decreases to $\leqslant$8 g·dL^{-1}. No patients discontinued study treatment due to decreased haemoglobin. Aspartate aminotransferase levels above three times the upper limit of normal (ULN) without bilirubin elevation above double the ULN were reported in one patient but did not lead to treatment discontinuation. Three patients died (one due to multiorgan failure on day 764 and two due to underlying disease, on days 127 and 588). Kaplan–Meier survival estimates were 97.7% (95% CI 84.9%–99.7%) at 12 months, 93.7% (95% CI 75.7%–98.5%) at 24 months and 87.8% (95% CI 64.5%–96.2%) at end of study (2.7 years).

Our findings are aligned with those from previous randomised controlled trials and real-world studies where haemodynamic and functional improvement was observed following initial ERA and PDE5i combination therapy [1, 8–12]. Safety and tolerability were generally consistent with previous data for macitentan in combination with PDE5i [5, 6, 13]. The main limitations of our study were the open-label uncontrolled nature of the design and the small sample size.

Overall, in the prospective OPTIMA study, initial double combination therapy with macitentan and tadalafil led to a significant improvement, from baseline to week 16, in cardiopulmonary haemodynamics, functional parameters, NT-proBNP and risk profile in newly diagnosed, treatment-naïve patients with PAH. There were no unexpected safety findings during long-term follow-up. In line with recommendations in the ESC/ERS guidelines [2, 3] and proceedings from the 6th World Symposium on Pulmonary Hypertension [4], the data presented here support early use of double oral combination therapy with an ERA and PDE5i to optimally manage PAH.

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