Supplement to: 'Macitentan for the Treatment of Idiopathic Pulmonary Fibrosis: The Randomised Controlled MUSIC Trial'

Exclusion criteria

In addition to the criteria included in the main article, subjects meeting the following conditions were excluded from the Macitentan USe in an Idiopathic pulmonary fibrosis Clinical (MUSIC) trial: a documented sustained improvement in idiopathic pulmonary fibrosis (IPF) up to 12 months prior to randomisation; pulmonary or upper respiratory tract infection ≤4 weeks prior to randomisation; severe concomitant illness limiting life expectancy to <1 year; acute or chronic impairment (other than dyspnoea) limiting ability to comply with study requirements; chronic heart failure with New York Heart Association class III/IV or known left ventricular ejection fraction <25%; moderate-to-severe hepatic impairment (Child-Pugh Class B or C); estimated creatinine clearance <30 mL/min; serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5 times the upper limit of normal; haemoglobin <75% of the lower limit of the normal range; systolic blood pressure <100 mmHg; pregnant or breast-feeding; current drug or alcohol dependence; systemic treatment within 4 weeks prior to randomisation with cyclosporine A or tacrolimus, everolimus, sirolimus (calcineurin or mammalian target of rapamycin [mTOR] inhibitors) or CYP3A inducers; known hypersensitivity to endothelin receptor antagonists or any of their excipients in the investigational treatments; or, planned or already ongoing treatment with another investigational drug within 4 weeks of randomisation.

Assessment schedule

Subjects were assessed at baseline, every 4 months thereafter and at the end of the study. Screening assessments included demographics, medical history, vital signs, height, weight, concomitant medications, 12-lead electrocardiography, laboratory testing (haematology including haemoglobin, blood chemistry including liver function testing and serum pregnancy testing [for women of childbearing potential]), pulmonary function testing (total lung capacity, residual volume, forced expiratory volume in 1 second [FEV_1], vital capacity, forced vital capacity [FVC], diffusing capacity for carbon monoxide corrected for haemoglobin [DL_{CO}]), measurement of resting arterial blood gas, assessment of high-resolution computed tomography of the chest and histological analysis of surgical lung biopsy specimens.

At time of randomisation, subjects were assessed using the Baseline Dyspnoea Index [1], vital signs, weight, physical examination, concomitant medications, FEV_1, FVC, corrected DL_{CO}, laboratory tests, and the Short Form 36 (SF-36) health-related quality of life questionnaire (data on health-related quality of life are not reported) [2].

Thereafter, at monthly intervals, laboratory tests were performed. At 4-monthly intervals until the end of treatment, vital signs, weight, physical examination, concomitant medications, FEV_1, FVC, corrected DL_{CO}, transition dyspnoea index (TDI), laboratory tests, and subject-reported adverse events, serious adverse events and disease worsening events were recorded. In addition, TDI and SF-36 were assessed at Month 4 and Month 12, with 12-lead electrocardiography being performed at Month 12 and at the end of treatment visit. At the time of treatment discontinuation the Leicester Cough Questionnaire was completed (data on impact of cough are not reported) [3].

At a follow-up visit at least 28 days after treatment discontinuation, all adverse events, serious adverse events, medications prescribed for IPF, and results of laboratory tests (liver function testing and serum pregnancy testing [for women of childbearing potential]) and the Leicester Cough Questionnaire were documented. In cases of premature study treatment discontinuation, subjects could remain in the study and perform 4-monthly visits, where medications prescribed for IPF were recorded and FEV_1, FVC, corrected DL_{CO}, laboratory tests and subject-reported adverse events were assessed. Every attempt was made to obtain clinical status at end of study for all subjects who prematurely discontinued study treatment.

The end of study visit took place when the last randomised subject who did not discontinue therapy had completed Month 12. At this visit, concomitant medications prescribed for IPF were recorded and FEV_1, FVC, corrected DL_{CO}, TDI and disease worsening events were assessed.

Safety assessments – additional information

The median (95% confidence limit [CL]) change from baseline up to 28 days after treatment discontinuation in haemoglobin was −0.5 g/dL (−0.7 to −0.3) in the macitentan arm and −0.2 g/dL (−0.4 to 0.0) in the placebo arm.

The median (95% CL) change from baseline in heart rate was 1 bpm (−2 to 3) in the macitentan treatment group and 2 bpm (−2 to 4) in the placebo arm. The median (95% CL) changes from baseline up to 28 days after study drug discontinuation in QTc interval (Fredericia's formula) were 5.3 ms (−0.7 to 8.9) in the macitentan treatment group and −0.5 ms (−6.9 to 6.9) in the placebo group.

The median (95% CL) change from baseline in systolic blood pressure was −8 mmHg (−11 to −5) in the macitentan arm and 0 mmHg (−3 to 4) in the placebo arm. The median (95% CL) change from baseline in diastolic blood pressure was −6 mmHg (−10 to −4) in the macitentan arm and 0 mmHg (−5 to 2) in the placebo arm.

Suppl. Table 1. Change from baseline up to Month 12 in mean absolute forced vital capacity

	Macitentan 10 mg (n=119)	Placebo (n=59)
Baseline		
- Mean FVC ± SD, L	2.88 ± 0.834	2.79 ± 0.776
- Lower quartile (Q1), upper quartile (Q3)	2.19, 3.48	2.19, 3.43
- Minimum, maximum	1.24, 5.42	1.36, 4.61
Up to Month 12		
- Mean FVC ± SD, L	2.56 ± 1.012	2.45 ± 0.918
- Lower quartile (Q1), upper quartile (Q3)	2.01, 3.30	1.92, 3.03
- Minimum, maximum	0.00, 5.16	0.00, 4.67
Change from baseline		
- Mean FVC ± SD, L	−0.32 ± 0.538	−0.34 ± 0.708
- Lower quartile (Q1), upper quartile (Q3)	−0.41, −0.06	−0.40, −0.08
- Minimum, maximum	−2.86, 0.42	−4.12, 0.62
Mean treatment effect (95% CL), L	0.02 (−0.17 to 0.21)	

Data from subjects in the all-randomised set.
95% CL, 95% confidence limits; FVC, forced vital capacity; SD, standard deviation
For this analysis, 8 (6.8%) subjects in the macitentan group had no post-baseline data: for 4 (3.4%) subjects the worst values were imputed and for 4 (3.4%) subjects the mean percentage change was imputed. In subjects with post-baseline data, 5 (4.2%) macitentan-treated subjects and 4 (6.8%) placebo recipients had data carried forward and 3 (2.5%) macitentan-treated subjects and 2 (3.4%) placebo recipients had worst values substituted for missing data.

Suppl. Table 2. Kaplan–Meier estimates for time to first event of idiopathic pulmonary fibrosis worsening or death at Months 4, 8, 12, 20 and 28

	Macitentan 10 mg (n=119)	Placebo (n=59)
Month 4		
- Kaplan–Meier estimate (95% CL)	92.4 (86.0 to 96.0)	98.3 (88.6 to 99.8)
- Subjects at risk	112	59
- Subjects censored	0	0
- Subjects with event	9	1
Month 8		
- Kaplan–Meier estimate (95% CL)	85.6 (77.8 to 90.8)	94.9 (85.1 to 98.3)
- Subjects at risk	103	57
- Subjects censored	3	0
- Subjects with event	17	3
Month 12		
- Kaplan–Meier estimate (95% CL)	77.4 (68.6 to 84.0)	83.9 (71.3 to 91.3)
- Subjects at risk	81	44
- Subjects censored	19	9
- Subjects with event	26	9
Month 20		
- Kaplan–Meier estimate (95% CL)	59.9 (45.5 to 71.7)	65.9 (49.5 to 78.1)
- Subjects at risk	14	8
- Subjects censored	74	35
- Subjects with event	35	16
Month 28		
- Kaplan–Meier estimate (95% CL)	59.9 (45.5 to 71.7)	57.7 (36.0 to 74.3)
- Subjects at risk	–	–
- Subjects censored	84	42
- Subjects with event	35	17
Treatment difference up to Month 12*		
- Hazard ratio	1.562	
- 95% CL of hazard ratio	0.732 to 3.334	
- Log-rank p-value	0.2428	

Data from subjects in the all-randomised set.
95% CL, 95% confidence limits.
*Due to violation of proportionality of hazard by treatments violation, the hazard ratio of macitentan versus placebo and the log-rank test up to Month 12 (i.e. censoring before Kaplan–Meier curves cross at Month 12) are presented *post hoc*.

Suppl. Table 3. Causes of first occurrences of idiopathic pulmonary fibrosis worsening and death up to Month 12 and up to end of study

	Macitentan 10 mg (n=119)	Placebo (n=59)
Up to Month 12, n (%)		
- Total subjects with at least one cause	26 (21.8%)	9 (15.3%)
o Death	3 (2.5%)	1 (1.7%)
o PFT/IPF worsening	16 (13.4%)	7 (11.9%)
▪ Confirmed	13 (10.9%)	6 (10.2%)
▪ Substituted	3 (2.5%)	1 (1.7%)
o Acute respiratory decompensation of IPF	7 (5.9%)	1 (1.7%)
End of study, n (%)		
- Total subjects with at least one cause	35 (29.4%)	17 (28.8%)
o Death	3 (2.5%)	2 (3.4%)
o PFT/IPF worsening	25 (21.0%)	14 (23.7%)
▪ Confirmed	17 (14.3%)	12 (20.3%)
▪ Substituted	8 (6.7%)	2 (3.4%)
o Acute respiratory decompensation of IPF	7 (5.9%)	1 (1.7%)

Data from subjects in the all-randomised set. PFT, pulmonary function test.

Suppl. Table 4. Change from baseline up to Month 12 in mean absolute forced expiratory volume in 1 second and in corrected diffusing capacity for carbon monoxide

	Macitentan 10 mg (n=119)	**Placebo (n=59)**
Mean FEV_1 ± SD, L*		
- Baseline	2.35 ± 0.664	2.26 ± 0.623
- Up to Month 12	2.10 ± 0.803	2.01 ± 0.734
- Change from baseline	−0.25 ± 0.438	−0.25 ± 0.587
- Treatment effect	−0.01 ± 0.494	
Mean corrected DL_{CO} ± SD, $mol \cdot kPa^{-1} \cdot min^{-1}$*		
- Baseline	4.60 ± 1.491	4.35 ± 1.316
- Up to Month 12	3.99 ± 1.846	3.74 ± 1.528
- Change from baseline	−0.61 ± 1.041	−0.61 ± 0.968
- Treatment effect	0.00 ± 1.017	

Data from subjects in the all-treated set.

DL_{CO}, corrected diffusing capacity for carbon monoxide; FEV_1, forced expiratory volume in 1 second; SD, standard deviation.

*n=115 in macitentan treatment arm; for the FEV_1 analysis, 6 (5.2%) subjects in the macitentan group had no post-baseline data and the worst values were imputed. In subjects with post-baseline data, 3 (2.6%) macitentan-treated subjects and 4 (6.8%) placebo recipients had data carried forward and 3 (2.6%) macitentan-treated subjects and 2 (3.4%) placebo recipients had worst values substituted for missing data. For the DL_{CO} analysis, 4 (3.5%) subjects in the macitentan group had no post-baseline data and the worst value was imputed. In subjects with post-baseline data, 6 (5.2%) macitentan-treated subjects and 4 (6.8%) placebo recipients had data carried forward and 4 (3.5%) macitentan-treated subjects and 3 (5.1%) placebo recipients had worst values substituted for missing data.

References

1. Mahler DA, Weinberg DH, Wells CK, Feinstein AR. The measurement of dyspnea. Contents, interobserver agreement, and physiologic correlates of two new clinical indexes. *Chest* 1984; 85: 751–758.
2. SF-36v2™ Health Survey© 2000, 2002 by Medical Outcomes Trust and Quality Metric Incorporated.
3. Birring SS, Prudon B, Carr AJ, Singh SJ, Morgan MD, Pavord ID. Development of a symptom specific health status measure for patients with chronic cough: Leicester Cough Questionnaire (LCQ). *Thorax* 2003; 58: 339–343.