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BUILD-3: A Randomized, Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., MD[1]; Kevin K. Brown, MD[2]; Ganesh Raghu, MD[3]; Roland M. du Bois, MD[4]; David A Lynch, MB[5]; Fernando Martinez, MD[6]; Dominique Valeyre, MD[7]; Isabelle Leconte, PhD[8]; Adele Morganti, MSc[8]; Sébastien Roux, MD[8]; Juergen Behr, MD[9]

[1]Department of Medicine, University of California San Francisco, San Francisco, CA, United States; [2]Department of Medicine, National Jewish Health, Denver, CO, United States; [3]Division of Pulmonary and Critical Care Medicine, University of Washington, Seattle, WA, United States; [4]Imperial College, London, United Kingdom, [5]Division of Radiology, National Jewish Health, Denver, CO, United States; [6]Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, MI, United States; [7]Department of Pneumology, Avicenne Hospital, University of Paris, Bobigny, France; [8]Clinical Development, Actelion Pharmaceuticals Ltd, Allschwil, Switzerland; [9]Department of Respiratory and Critical Care Medicine, Ruhr-University, Bochum, Germany.

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Corresponding author and address for reprints:

Talmadge E. King, Jr., MD

Department of Medicine

University of California San Francisco

505 Parnassus Avenue, Box 0120

San Francisco, CA 94143–0120, United States

Tel: +1-415-476-0909;

Fax: +1-415-502-5869;

E-mail: tking@medicine.ucsf.edu

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At a glance commentary:

Scientific knowledge on the subject: Idiopathic pulmonary fibrosis (IPF) is a progressive, severe disease with limited therapeutic options. Patients with IPF exhibit an inexorable decline in pulmonary function that commonly leads to respiratory failure and death. Prognosis is poor; median survival after diagnosis is 2.5–3.5 years.

What this study adds to the field: The primary objective of this randomized, placebo-controlled trial of bosentan in IPF was not met. The safety profile for bosentan was similar to that observed in other clinical trials.

Abstract

Rationale: A previous trial of bosentan in idiopathic pulmonary fibrosis (IPF) showed a trend to delayed IPF worsening or death. Also, improvements in some measures of dyspnea and health-related quality of life were observed.

Objective: To demonstrate that bosentan delays IPF worsening or death.

Methods: Prospective, randomized (2:1), double-blind, placebo-controlled, event-driven, parallel-group, morbidity–mortality trial of bosentan in adults with IPF of <3 years duration, confirmed by surgical lung biopsy, and without extensive honeycombing on high-resolution computed tomography. The primary endpoint was time to IPF worsening (a confirmed decrease from baseline in forced vital capacity [FVC] ≥10% and diffusing capacity of the lung for carbon monoxide [DL_{CO}] ≥15%; or, acute exacerbation of IPF) or death up to End of Study. Effects of bosentan on health-related quality of life, dyspnea, and the safety and tolerability of bosentan, were investigated.

Measurements and Main Results: 616 patients were randomized to bosentan (n=407) or placebo (n=209). No significant difference between treatment groups was observed in the primary endpoint analysis (hazard ratio, 0.85; 95% confidence interval, 0.66 to 1.10; p=0.2110). No treatment effects were observed on health-related quality of life or dyspnea. Some effects of bosentan treatment were observed in changes from baseline to 1 year in FVC and DL_{CO}. The safety profile for bosentan was similar to that observed in other trials.

Conclusions: The primary objective in the BUILD-3 trial was not met. Bosentan was well tolerated.

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Key words (MeSH terms): Bosentan; Clinical Trial; Diffusing Capacity of the Lung for Carbon Monoxide (DL_{CO}); Endothelin Receptor Antagonism; Forced Vital Capacity (FVC); High Resolution Computed Tomography; Idiopathic Pulmonary Fibrosis; Morbidity; Mortality; Pulmonary Function Tests; Surgical Lung Biopsy.

Introduction

Idiopathic pulmonary fibrosis (IPF) is a progressive, severe, fibrosing lung disease that is usually fatal [1]. Symptoms of IPF at onset are non-specific, with the most prominent being dyspnea on exertion and non-productive cough [1, 2]. IPF patients are typically aged >50 years at time of diagnosis [1, 2] and the observed incidence of IPF is greater in men versus women and increases with advancing age [3]. Therapeutic options for patients with IPF are limited and the prognosis is poor: median survival after diagnosis is approximately 2.5–3.5 years [1, 4–6].

The pathogenesis of IPF is not completely understood. Evidence supports an evolving hypothesis in which a fibroproliferative disease process, suggesting abnormal wound repair, arises as a consequence of chronic and widespread injury to the alveolar epithelium [7]. A key mediator implicated in this fibroproliferative disease process is endothelin-1, which exerts pro-fibrotic effects that are understood to be deleterious in IPF (reviewed in [8]). The pro-fibrotic effects of endothelin-1 can be attenuated in animal models using bosentan, an oral antagonist of the A and B subtypes of the endothelin receptor [9].

When evaluated in the randomized, placebo-controlled, Bosentan Use in Interstitial Lung Disease (BUILD)-1 trial, bosentan treatment of IPF patients was not superior to placebo in the primary endpoint of change from baseline up to Month 12 in six-minute walk distance [10]. However, a trend in favor of bosentan was observed in the secondary endpoint of time to IPF worsening or death [10]. These effects were more pronounced in a subgroup of patients with IPF diagnosis confirmed by the presence of histological features of usual interstitial pneumonia in surgical lung biopsy specimens [10]. In addition, changes from baseline in some

measures of dyspnea and health-related quality of life favored bosentan treatment [10, 11].

The BUILD-3 trial was a randomized, double-blind, placebo-controlled, parallel group, event-driven, morbidity–mortality trial of bosentan that investigated the beneficial trends observed in the BUILD-1 trial in a homogenous subpopulation of IPF patients considered most likely to benefit from treatment. The primary objective was to demonstrate that bosentan delays IPF worsening or death. Secondary objectives were to assess the effects of bosentan on health-related quality of life, dyspnea, pulmonary function test (PFT) results, and the safety and tolerability of bosentan. Some results of the BUILD-3 trial have been reported previously in abstract form [12].

Methods

Study participants

BUILD-3 was a prospective, multicenter, randomized, double-blind, placebo-controlled, parallel group, event-driven, morbidity–mortality trial of bosentan conducted in teaching and community hospitals. Eligible patients were men and women aged ≥18 years with a proven diagnosis of IPF according to the American Thoracic Society/European Respiratory Society statement [1], of <3 years duration, and with diagnosis confirmed by surgical lung biopsy (additional detail provided online in Supplementary Methods, Section 1). Surgical lung biopsy was not performed for the sole reason of enabling participation in the trial.

Patients were excluded if they had extensive honeycombing on baseline high-resolution computed tomography (HRCT)—defined as >5% of the parenchyma in three or more out of six specified thoracic zones (additional detail provided online in Supplementary Methods, Section 2). Other exclusion criteria are described online in Supplementary Methods, Section 3.

The trial was registered at ClinicalTrials.gov (NCT00391443). Approval was obtained from all relevant ethics committees and institutional review boards prior to study start. All patients provided written, informed consent. Study management is described in Supplementary Methods, Section 4.

Study design

Within 4 weeks of screening, eligible patients were randomized 2:1 to receive oral bosentan or matching placebo, respectively. Patients received an initial dose of 62.5 mg twice daily, up-titrated after 4 weeks to a target dose of 125 mg twice daily (or remaining at 62.5 mg twice daily if body weight ≤40 kg). Patients unable to tolerate target dose could be maintained on initial dose. Randomization and concealment of treatment allocation is described online in Supplementary Methods Section 5.

Assessment schedule and outcome measures

A detailed assessment schedule is provided online (Supplementary Methods, Section 6). In brief, patients were assessed at baseline, at randomization, and every 4 months thereafter until BUILD-3 End of Study, which was scheduled to be declared when 202 primary endpoint events were confirmed. In cases of premature

discontinuation of study treatment, patients underwent an End of Study Treatment assessment, and remained in the trial until the BUILD-3 End of Study was declared.

The primary endpoint was time to IPF worsening or all-cause death up to End of Study. IPF worsening was defined as worsening PFT results (a decrease from baseline ≥10% in absolute forced vital capacity [FVC] and ≥15% in the absolute diffusing capacity of the lung for carbon monoxide [DL_{CO}], confirmed by two tests conducted ≥4 weeks apart) or acute exacerbation of IPF (Figure 1). Patients unable to perform PFTs at planned visits due to worsening IPF were considered to have worsening PFT results if the latter were not invalidated by a test at a follow-up visit. Patients with a documented disease worsening event had study treatment discontinued.

Secondary endpoints included: changes from baseline to 1 year in health-related quality of life assessed by the 36-item Short-Form questionnaire (SF-36; individual dimensions and raw transition item score) [13] and the EuroQol Group Five Dimension Self-Report Questionnaire (EQ-5D; health state score and visual analog score) [14]; transition dyspnea index (TDI) at 1 year [15]; time to occurrence of IPF worsening (excluding death) up to End of Study; and, time to death up to BUILD-3 End of Study. Exploratory measures included the change from baseline to 1 year in absolute FVC and DL_{CO}. A pre-specified subgroup analysis of the primary endpoint, which categorized patients by baseline demographics and clinical characteristics, was performed.

Safety was assessed on the basis of treatment-emergent adverse events, elevations of liver alanine or aspartate aminotransferases, and deaths occurring between randomization and up to 28 days after End of Study Treatment.

Statistical analysis

The main analysis of the primary endpoint was performed on the All-Randomized Set, comprising all randomized patients. Treatment comparison was conducted using log-rank testing with asymptotic approximation to test the null hypothesis that there was no difference between treatment groups for the distribution of time to first occurrence of IPF worsening or death up to End of Study. The primary endpoint was described using Kaplan-Meier methods and the hazard ratio of bosentan-to-placebo from Cox modeling with its 95% two-sided confidence limits. The planned sample size was 600 patients, with 202 events needed to detect a 35% relative risk reduction in the primary endpoint (i.e., a hazard ratio for bosentan-to-placebo of 0.62 when the yearly event rate for placebo was 20% and hazards were proportional, adopting the asymptotic log-rank test for treatment comparison) with a study-wise type I error equal to 0.05 (two sided), O'Brien-Fleming's Test, and overall 90% power. No imputation method was used. Patients who underwent lung transplantation without a prior event of disease progression, who withdrew consent, or who were lost to follow-up, were censored at the date of last visit or transplant surgery, whichever was earlier.

Secondary and exploratory endpoints were evaluated in the All-Randomized Set. Safety analyses were performed on the Safety Set, which comprised all randomized patients who received study drug at least once and had at least one safety assessment post-baseline. Statistical methods for secondary, exploratory, and safety analyses are described online in Supplementary Methods Section 7; data were summarized descriptively.

Results

Patient population and study duration

In total, 616 adults with IPF were randomized to receive bosentan (n=407) or placebo (n=209) at 119 centers in 19 countries (Australia, Canada, Israel, Japan, South Korea, the United States, and 13 countries in Europe). The dates of randomization for the first and last patients were 27 February 2007 and 31 October 2008, respectively. BUILD-3 End of Study was declared on 30 November 2009 after 252 morbidity–mortality events. The last patient visits were on 11 February 2010. The mean duration of study participation (± standard deviation) was 19.9 ± 6.7 months in the bosentan group and 19.9 ± 6.0 months in the placebo group.

Patient disposition

Patient retention in the BUILD-3 trial

A total of 616 patients comprised the intent-to-treat population (Figure 2). Retention of patients in the trial was very good, with 383 patients randomized to bosentan (94.1%) and 207 patients randomized to placebo (99.0%) completing the trial as scheduled (i.e., up to an endpoint event or the sponsor-declared BUILD-3 End of Study). A total of 24 patients randomized to bosentan (5.9%) and 2 patients randomized to placebo (1.0%) discontinued participation the trial before the BUILD-3 End of Study due to withdrawal of consent.

Patient retention on study treatment

Retention of patients on study treatment was also good (Figure 3). A total of 332 bosentan-treated patients (81.8%) and 188 placebo recipients (90.0%) completed the treatment period up to an endpoint event or the sponsor-declared BUILD-3 End of Study.

The number of patients who discontinued study treatment before an endpoint event or the BUILD-3 End of Study was 74 (18.2%) in the bosentan group and 21 (10.0%) in the placebo group (Figure 3). Reasons for discontinuation comprised: adverse events (14.8% bosentan, 6.2% placebo), withdrawal of consent (2.5% bosentan, 1.0% placebo), investigator decision (0.7% bosentan, 1.0% placebo), or lung transplant (0.25% bosentan, 1.9% placebo).

Baseline demographics and clinical characteristics

Table 1 shows the baseline characteristics of the participants assigned to each treatment group. Most patients enrolled in the trial were men (69.6%) and there was a slight difference between treatment groups in gender. The presence of honeycombing on baseline HRCT was slightly more frequent in the placebo group. Five patients randomized to bosentan and three to placebo were listed for lung transplantation before study treatment initiation.

Efficacy

Primary endpoint analysis: Time to IPF worsening or death

No significant difference was observed between treatment groups in the primary endpoint of time to IPF worsening or death (hazard ratio, 0.85; 95% confidence

interval, 0.66 to 1.10; log rank p-value, 0.2110; Figure 4). A non-statistically significant trend in favor of bosentan was apparent.

In total, 252 morbidity–mortality events were observed (Supplementary Table E1, Figure 3), 158 in the bosentan group and 94 in the placebo group, representing 38.8% of patients randomized to bosentan and 45.0% of patients randomized to placebo. In both treatment groups, primary endpoint events were mainly cases of PFT/IPF worsening (128 events in the bosentan group [31.4% of patients randomized to bosentan], 82 events in the placebo group [39.2% of patients randomized to placebo]). Acute exacerbations of IPF accounted for 19 and 6 primary endpoint events in the bosentan and placebo groups, respectively (4.7% of patients randomized to bosentan and 2.9% of patients randomized to placebo). A total of 17 deaths were primary endpoint events (11 in the bosentan group [2.7%] and 6 in the placebo group [2.9%]).

In the pre-specified, exploratory subgroup analysis of the primary endpoint, in which patients were categorized by their demographics and clinical characteristics at baseline, results were generally similar to those observed in the overall study population (Figure 5).

Health-related quality of life

No treatment effects of bosentan were observed in changes from baseline to 1 year in the individual dimensions and raw transition item score of the SF-36 (Supplementary Table E2). No treatment effects of bosentan were observed on

changes from baseline to 1 year in the health state and visual analog scores of the EQ-5D (Supplementary Table E3).

Transition dyspnea index

No treatment effects of bosentan were observed in the change from baseline to 1 year in shortness of breath, as measured using the TDI (Supplementary Table E4).

Time to IPF worsening (excluding death) up to End of Study

A small, non-significant delay in the time to IPF worsening up to End of Study (excluding death) was observed among patients in the bosentan versus placebo groups (hazard ratio, 0.850; 95% confidence interval, 0.653 to 1.107).

Time to death up to BUILD-3 End of Study

The total number of deaths (all causes), assessed up to BUILD-3 End of Study (including patients who prematurely discontinued the study due to withdrawal of consent), was 58 (39 in the bosentan group versus 19 in the placebo group). No significant difference between treatment groups was observed in the time to death up to BUILD-3 End of Study (hazard ratio, 1.039; 95% confidence interval, 0.600 to 1.798).

Change from baseline to 1 year in pulmonary function test results

A median treatment effect favoring bosentan of 0.04 L (95% confidence interval, −0.01, 0.08) was observed in the change from baseline to 1 year in absolute FVC (Table 2). In the change from baseline to 1 year in DL_{CO}, a median treatment effect

favoring bosentan of 0.16 mmol·kPa^{-1}·min^{-1} (95% confidence interval, 0.03, 0.28) was observed (Table 2).

Safety

The Safety Set comprised 615 randomized patients who received at least one dose of study treatment and had at least one post-baseline safety assessment. Exposure to study treatment was similar in each treatment group, with a median (range) duration of 17.9 (0.3, 33.0) months in the bosentan group (n=406) and 19.9 (1.2, 32.3) months in the placebo group (n=209).

Among the study population, 396 patients (97.5%) who received bosentan and 203 patients (97.1%) who received placebo experienced at least one treatment-emergent adverse event (Supplementary Table E5). Adverse events observed in >10% of bosentan-treated patients were IPF worsening (32.8% bosentan, 36.4% placebo), upper respiratory tract infection (28.1% bosentan, 29.2% placebo), cough (19.5% bosentan, 24.9% placebo), dyspnea (15.5% bosentan, 11.5% placebo), bronchitis (11.3% bosentan, 14.8% placebo), fatigue (11.3% bosentan, 7.2% placebo), and headache (10.8% bosentan, 10.5% placebo).

A total of 190 bosentan-treated patients (46.8%) and 92 placebo recipients (44.0%) experienced at least one adverse event that led to study treatment discontinuation (Supplementary Table E6). Of these patients, 110 who were treated

with bosentan (27.1%) and 68 who received placebo (32.5%) discontinued treatment prematurely due to a per-protocol endpoint event. Serious adverse events (SAEs) up to end of treatment occurred in 129 bosentan-treated patients (31.8%) and 74 (35.4%) placebo recipients. The majority of SAEs were related to IPF worsening or respiratory in nature (Supplementary Table E7).

Elevations of liver alanine or aspartate aminotransferases greater than three times the upper limit of normal were observed in 59 bosentan-treated patients (14.7%) and 6 placebo recipients (2.9%).

In total, 17 patients (4.2%) treated with bosentan and 7 patients (3.3%) who received placebo died between treatment start and up to 28 days after End of Study Treatment. Twelve deaths were attributed to IPF worsening (9 in the bosentan group [2.2%], 3 in the placebo group [1.4%]) and 6 were attributed to respiratory failure (all in the bosentan group [1.5%]).

Discussion

The BUILD-3 trial was a prospective, randomized, double-blind, placebo-controlled, parallel group, event-driven, morbidity–mortality trial of bosentan in patients with IPF. The primary objective of the BUILD-3 trial, which was to demonstrate that bosentan delays IPF worsening or death, was not met. No differences were observed between treatment groups with respect to changes from baseline in health-related quality of life or dyspnea. A non-significant delay in the time to IPF worsening (excluding

death) up to End of Study, and treatment effects on changes from baseline to 1 year in FVC and DL_{CO}, were observed in bosentan-treated patients. Observations in the pre-specified exploratory subgroup analyses of the primary endpoint were generally similar to those of the main analysis. Bosentan was well tolerated in IPF patients, with a safety profile consistent with that observed in other patient populations [10, 16–18].

The aim of the BUILD-3 trial was to investigate observations from the randomized, double-blind, placebo-controlled BUILD-1 trial of bosentan in IPF. In the BUILD-1 trial, no difference was observed between bosentan versus placebo in the primary efficacy endpoint of change from baseline up to Month 12 in six-minute walk distance. However, a trend in the secondary endpoint of delayed IPF worsening or death up to Month 12, and improvements in some measures of dyspnea and health-related quality of life, were observed in IPF patients treated with bosentan [10, 11]. Notably, the observed effects of bosentan on the endpoint of delayed IPF worsening or death up to Month 12 were more pronounced in a post-hoc analysis of a prespecified subpopulation of interest: patients who underwent SLB to confirm their diagnosis of IPF [10, 11]. Based on these observations, the population studied in the present trial—a homogeneous subpopulation of IPF patients with baseline FVC ≥50% and DL_{CO} ≥30% of predicted values, diagnosed using surgical lung biopsy, and without extensive honeycombing on baseline HRCT—was selected, as they were considered most likely to respond to treatment. In clinical practice, for some patients, recourse to surgical lung biopsy is necessary in order to achieve a confident diagnosis of IPF [2]. Consequently, the requirement for all patients in the BUILD-3 trial to have undergone both HRCT and surgical lung biopsy to confirm diagnosis of

IPF is unique among major trials in IPF, and this led to a well-defined patient population with confirmed, mild-to-moderate IPF. This cohort exhibited comparable demographics and clinical characteristics at baseline to patients enrolled in other recent trials in IPF [10, 19, 20]. However, as with any clinical trial scenario, the observed results may apply only to the trial participants and may not relate to the general IPF patient population.

The results of the BUILD-1 trial also suggested that a minimum treatment period of 1 year was needed to investigate a delay in IPF worsening or death [10]. An event-driven design that provided a time-to-event approach to the analysis of the primary endpoint, with a variable treatment period and expected treatment duration of approximately 1.5 years, was therefore considered most appropriate for the present trial.

The primary endpoint of the BUILD-3 trial was the time to occurrence of IPF worsening or death up to End of Study. IPF worsening was defined as either a worsening of pulmonary function tests (a combined decrease from baseline in FVC of ≥10% and in DL_{CO} of ≥15%, confirmed by two tests ≥4 weeks apart) or acute exacerbation of IPF. This unique endpoint was selected due to the high clinical relevance of such changes at these orders of magnitude. Data have shown that longitudinal changes ≥10% in FVC [21] or ≥15% in DL_{CO} [6] are important predictors of survival in patients with IPF. Acute exacerbation of IPF is also considered to have a high mortality rate [22]. In comparison with other recent studies in IPF, which assessed the effects of investigational treatments on changes from baseline in FVC alone, the primary endpoint of the BUILD-3 trial was therefore uniquely demanding [19, 23, 24]. In particular, the requirement that any combined

decreases in both FVC and DL_{CO} be confirmed by two tests ≥4 weeks apart, in order to qualify as an event, underscored this rigor. It is therefore important to recognize that the criteria used to assess treatment responses in the primary endpoint of the BUILD-3 trial were challenging.

Besides the uniquely demanding primary endpoint, there are other possible reasons why the primary objective of the BUILD-3 trial was not met. While treatment groups were well matched for demographics and most clinical characteristics at baseline, one cannot rule out unexpected influences arising from any observed differences. In addition, the BUILD-3 trial was designed to confirm the results of the BUILD-1 trial, the most pronounced of which were observed in a post-hoc subgroup analysis. It is possible that the effects of bosentan in IPF are sufficiently slight that a significant treatment effect may only be discerned with an even larger patient population, a greater number of events, or a less demanding primary endpoint. We consider that the absence of a significant treatment effect of bosentan cannot be ascribed to shortcomings in patient retention in the trial, as this was very good. The trial was not powered for statistical analysis of secondary and exploratory endpoints.

Longitudinal changes observed in FVC and DL_{CO} in the placebo group were comparable with those reported in other recent trials in IPF patients [10, 23, 25]. The incidence of acute exacerbation, counted as primary endpoint events, observed in bosentan and placebo patients (4.7% and 2.9%, respectively) in the BUILD-3 trial was low compared with other studies in IPF. While the exact incidence of acute exacerbation in IPF is not known, it is estimated to be in the range of 5–19% of patients per year [22].

The incidence of death observed in the BUILD-3 patient population was lower versus those reported from older trials in IPF [26, 27], although it was similar to incidences observed in trials conducted more recently [10, 23]. Given these differences in the estimated incidences of death, and the strict inclusion criteria used in the BUILD-3 trial that led to enrollment of a well-defined patient population with confirmed, mild-to-moderate IPF, it is possible these differences have arisen as a result of a broader, albeit, subtle evolution in the natural history of IPF and a likely greater proportion of incident versus prevalent disease in the BUILD-3 cohort.

While the prognostic significance of each primary endpoint component is established, a possible inherent limitation in the BUILD-3 trial may have been the endpoint requirement for a combined and sustained decrease from baseline in FVC by ≥10% and in DL_{CO} by ≥15%. During therapeutic studies of IPF, the likelihood of decreases from baseline in FVC ≥10% is usually modest [10, 23, 25], and data suggest that 'marginal', longitudinal reductions in FVC, i.e., decreases from baseline to Month 6 of 5–10%, retain prognostic value [21, 28, 29]. While several studies in IPF have investigated decreases from baseline in FVC ≥10% or DL_{CO} ≥15% in isolation [6, 21, 30, 31], only the BUILD-3 trial required changes in both parameters to be observed together and to be confirmed after ≥4 weeks.

The requirement for patients to have a confirmed IPF diagnosis following surgical lung biopsy represents both a strength and limitation of the BUILD-3 trial. Based on the observations from BUILD-1, this patient subpopulation was considered most likely to respond to bosentan treatment. This requirement led to a uniform, well-defined patient population with confirmed IPF.

In conclusion, the primary objective in the BUILD-3 trial was not met. No effects of bosentan were observed in changes from baseline to 1 year in measures of health-related quality of life or dyspnea. A small and non-significant delay in the time to IPF worsening (excluding death) up to End of Study was observed, as were small differences favoring the bosentan treatment group in changes from baseline to 1 year in absolute FVC and DL_{CO}. Bosentan was well tolerated, with a safety profile consistent with that observed in previous clinical trials.

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References

1. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS) and the European Respiratory Society (ERS). *Am J Respir Crit Care Med* 2000;161:646–664.

2. American Thoracic Society. American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias. *Am J Respir Crit Care Med* 2002;165:277–304.

3. Raghu G, Weycker D, Edelsberg J, Bradford WZ, Oster G. Incidence and prevalence of idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2006;174:810–816.

4. Bjoraker JA, Ryu JH, Edwin MK, Myers JL, Tazelaar HD, Schroeder DR, Offord KP. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 1998;157:199–203.

5. King TE Jr, Tooze JA, Schwarz MI, Brown KR, Cherniack RM. Predicting survival in idiopathic pulmonary fibrosis: scoring system and survival model. *Am J Respir Crit Care Med* 2001;164:1171–1181.

6. Latsi PI, du Bois RM, Nicholson AG, Colby TV, Bisirtzoglou D, Nikolakopoulou A, Veeraraghavan S, Hansell DM, Wells AU. Fibrotic idiopathic interstitial pneumonia: the prognostic value of longitudinal functional trends. *Am J Respir Crit Care Med* 2003;168:531–537.

7. Selman M, King TE, Pardo A; American Thoracic Society; European Respiratory Society; American College of Chest Physicians. Idiopathic pulmonary fibrosis:

prevailing and evolving hypotheses about its pathogenesis and implications for therapy. *Ann Intern Med* 2001;134:136–151.

8. Ross B, D'Orléans-Juste P, Giaid A. Potential role of endothelin-1 in pulmonary fibrosis: from the bench to the clinic. *Am J Respir Cell Mol Biol* 2010;42:16–20.

9. Park S-H, Saleh D, Giaid A, Michel RP. Increased endothelin-1 in bleomycin-induced pulmonary fibrosis and the effect of an endothelin receptor antagonist. *Am J Respir Crit Care Med* 1997;156:600–608.

10. King TE Jr, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, Stähler G, Leconte I, Roux S, Raghu G. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008;177:75–81.

11. Raghu G, King TE Jr, Behr J, Brown KK, du Bois RM, Leconte I, Roux S, Swigris J. Quality of life and dyspnoea in patients treated with bosentan for idiopathic pulmonary fibrosis (BUILD-1). *Eur Respir J* 2010;35:118–123.

12. King TE Jr, Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez FJ, Valeyre D, Leconte I, Morganti A, Roux S, Behr J. The BUILD-3 trial: a prospective, randomized, double-blind, placebo-controlled study of bosentan in idiopathic pulmonary fibrosis [abstract]. *Am J Respir Crit Care Med* 2010;181:A6838.

13. SF-36v2™ Health Survey© 2000, 2002 by Medical Outcomes Trust and Quality Metric Incorporated.

14. EuroQoL Group: EuroQoL – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.

15. 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.

16. Rubin LJ, Badesch DB, Barst RJ, Galie N, Black CM, Keogh A, Pulido T, Frost A, Roux S, Leconte I, Landzberg M, Simonneau G. Bosentan therapy for pulmonary arterial hypertension. *N Engl J Med* 2002;346:896–903.

17. Humbert M, Segal ES, Kiely DG, Carlsen J, Schwierin B, Hoeper MM. Results of European post-marketing surveillance of bosentan in pulmonary hypertension. *Eur Respir J* 2007;30:338–344.

18. Galiè N, Rubin LJ, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic A, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomised controlled trial. *Lancet* 2008;371:2093–2100.

19. Noble P, Albera C, Bradford W, Costabel U, Kardatzke D, King TE Jr., Sahn S, Szwarcberg J, Valeyre D, du Bois RM. The CAPACITY (CAP) trials: randomized, double-blind, placebo-controlled, phase III trials of pirfenidone (PFD) in patients with idiopathic pulmonary fibrosis (IPF) [abstract]. *Am J Respir Crit Care Med* 2009;179:A1129.

20. King TE Jr, Albera C, Bradford WZ, Costabel U, Hormel P, Lancaster L, Noble PW, Sahn SA, Szwarcberg J, Thomeer M, Valeyre D, du Bois RM; INSPIRE Study Group. Effect of interferon gamma-1b on survival in patients with idiopathic pulmonary fibrosis (INSPIRE): a multicentre, randomised, placebo-controlled trial. *Lancet* 2009;374:222–228.

21. Collard HR, King TE Jr, Bartelson BB, Vourlekis JS, Schwarz MI, Brown KK. Changes in clinical and physiologic variables predict survival in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2003;168:538–542.

22. Hyzy R, Huang S, Myers J, Flaherty K, Martinez F. Acute exacerbation of idiopathic pulmonary fibrosis. *Chest* 2007;132:1652–1658.

23. Raghu G, Brown KK, Costabel U, Cottin V, du Bois RM, Lasky JA, Thomeer M, Utz JP, Khandker RK, McDermott L, Fatenejad S. Treatment of idiopathic pulmonary fibrosis with etanercept: an exploratory, placebo-controlled trial. *Am J Respir Crit Care Med* 2008;178:948–955.

24. Taniguchi H, Ebina M, Kondoh Y, Ogura T, Azuma A, Suga M, Taguchi Y, Takahashi H, Nakata K, Sato A, Takeuchi M, Raghu G, Kudoh S, Nukiwa T; Pirfenidone Clinical Study Group in Japan. Pirfenidone in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;35:821–829.

25. Martinez FJ, Safrin S, Weycker D, Starko KM, Bradford WZ, King TE Jr, Flaherty KR, Schwartz DA, Noble PW, Raghu G, Brown KK; IPF Study Group. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med* 2005;142:963–967.

26. Raghu G, Brown KK, Bradford WZ, Starko K, Noble PW, Schwartz DA, King TE Jr; Idiopathic Pulmonary Fibrosis Study Group. A placebo-controlled trial of interferon gamma-1b in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2004;350:125–133.

27. Demedts M, Behr J, Buhl R, Costabel U, Dekhuijzen R, Jansen HM, MacNee W, Thomeer M, Wallaert B, Laurent F, Nicholson AG, Verbeken EK, Verschakelen J,

Flower CD, Capron F, Petruzzelli S, De Vuyst P, van den Bosch JM, Rodriguez-Becerra E, Corvasce G, Lankhorst I, Sardina M, Montanari M; IFIGENIA Study Group. High-dose acetylcysteine in idiopathic pulmonary fibrosis. *N Engl J Med* 2005;353:2229–2242.

28. Zappala CJ, Latsi PI, Nicholson AG, Colby TV, Cramer D, Renzoni EA, Hansell DM, du Bois RM, Wells AU. Marginal decline in forced vital capacity is associated with a poor outcome in idiopathic pulmonary fibrosis. *Eur Respir J* 2010;35:830–836.

29. du Bois RM, Albera C, Bradford WZ, Costabel U, Kartashov A, Noble PW, Raghu G, Szwarcberg J, Thomeer M, Valeyre D, Weycker D, King TE Jr. Ascertainment of individual risk of mortality for patients with idiopathic pulmonary fibrosis (IPF) [abstract]. *Am J Respir Crit Care Med* 2010;181:A2499.

30. Flaherty KR, Mumford JA, Murray S, Kazerooni EA, Gross BH, Colby TV, Travis WD, Flint A, Toews GB, Lynch JP 3rd, Martinez FJ. Prognostic implications of physiologic and radiographic changes in idiopathic interstitial pneumonia. *Am J Respir Crit Care Med* 2003;168:543–548.

31. King TE Jr, Safrin S, Starko KM, Brown KK, Noble PW, Raghu G, Schwartz DA. Analyses of efficacy end points in a controlled trial of interferon-gamma1b for idiopathic pulmonary fibrosis. *Chest* 2005;127:171–177.

Figure legends

Figure 1. Components of the primary efficacy endpoint

*Combined decrease, confirmed by two tests at least 4 weeks apart.

Figure 2. Enrollment, randomization, and retention of patients in the BUILD-3 trial

*Following the screening visit, investigators used inclusion and exclusion criteria to determine the eligibility of each patient for enrollment into the trial.

Figure 3. Patient retention on study treatment in the BUILD-3 trial

*For a total of 48 bosentan-treated patients (11.8%) and 26 placebo recipients (12.4%), a per-protocol (endpoint event) did not coincide with a premature discontinuation from treatment period (i.e., the event occurred while the patient was no longer receiving study treatment or the event coincided with the BUILD-3 End of Study visit).

Figure 4. Kaplan–Meier survival estimate for each treatment group

Figure 5. Subgroup analysis of the time to IPF worsening or death

n_B, number of exposed patients in bosentan group; n_P, number of exposed patients in placebo group; CI, confidence interval; HR, hazard ratio; Data from All-Randomized Set.

Tables

Table 1. Demographics and clinical characteristics at baseline

	Bosentan (N=407)	**Placebo** (N=209)
Location, n (%)		
United States	185 (45.5)	99 (47.4)
Japan and South Korea	49 (12.0)	23 (11.0)
Other	173 (42.5)	87 (41.6)
Age, years		
Mean ± SD	63.8 ± 8.4	63.2 ± 9.1
Median (range)	64.0 (28.0, 82.0)	63.0 (34.0, 85.0)
Gender, men (%)	296 (72.7)	133 (63.6)
Median duration of symptoms (range), years	2.00 (0.11, 13.30)	2.07 (0.18, 14.84)
Median time since diagnosis* (range), years	0.48 (0.05, 4.72)[†]	0.50 (0.05, 4.72)[†]
Smoking history, n (%)		
Ever smoked (current/former)	252 (61.9)	142 (67.9)
Never smoked	155 (38.1)	67 (32.1)
Pulmonary function tests, % of predicted		
Mean FVC ± SD	74.9 ± 14.8	73.1 ± 15.3
Mean DL_{CO} ± SD	47.7 ± 11.9	47.9 ± 12.7
Blood oxygenation, mean ± SD		
PaO_2 at rest, mmHg	81.1 ± 12.2[‡]	80.3 ± 11.6[§]
$AaPO_2$ at rest, mmHg	17.8 ± 11.4[‡]	17.7 ± 10.4[§]
Digital clubbing, n (%)		
Yes	105 (25.8)	49 (23.4)

No	302 (74.2)	160 (76.6)
Corticosteroid use[‖], n (%)	60 (14.7)	36 (17.2)
Presence of honeycombing, n (%)**		
Yes	157 (38.8)[††]	98 (46.9)
No	248 (61.2)[††]	111 (53.1)
Baseline dyspnea index, mean total score	7.9 (2.5)[‡‡]	7.6 (2.5)[§§]
Health-related quality of life		
SF-36 (health transition score)	3.3 ± 0.8[‖‖]	3.4 ± 0.8***
EQ-5D (visual analog score)	70.4 ± 18.7[‖‖]	69.5 ± 19.4***
Use of supplemental oxygen, n (%)	50 (12.3)	23 (11.0)

*Time from surgical lung biopsy to randomization; [†]Includes 9 patients per treatment group who deviated from entry criteria of proven diagnosis of IPF of <3 years with surgical lung biopsy; [‡]n=393; [§]n=204; [‖]≤20 mg/day prednisone or equivalent; **honeycombing considered 'present' if >5% on HRCT in three or more out of six thoracic zones (see Supplementary Methods, Section 2); [††]n=405; [‡‡]n=400; [§§]n=202; [‖‖]n=379; ***n=196.

Abbreviations: $AaPO_2$, alveolar–arterial oxygen gradient; DL_{CO}, carbon monoxide diffusing capacity; EQ-5D, EuroQol Group 5 Dimension Self-Report Questionnaire; FVC, forced vital capacity; HRCT, high-resolution computed tomography; mmHg, millimeters of mercury; PaO_2, arterial oxygen pressure; SD, standard deviation; SF-36, 36-item Short-Form questionnaire.

Table 2. Change from baseline to 1 year in absolute forced vital capacity and carbon monoxide diffusing capacity

	Bosentan (N=407)	**Placebo (N=209)**	**Treatment effect**
	Median (range)	Median (range)	Median (95% CI)
FVC, L			
Baseline	2.84 (1.32, 6.12)*	2.66 (1.23, 5.24)†	
1 year	2.63 (0.00, 6.02)*	2.43 (0.00, 5.25)†	
Change from baseline	−0.14 (−4.21, 0.76)*	−0.18 (−4.89, 0.62)†	0.04 (−0.01, 0.08)
DL_{CO}, mmol·kPa^{-1}·min^{-1}			
Baseline	4.56 (2.04, 9.76)‡	4.28 (2.14, 8.94)†	
1 year	4.24 (0.00, 10.04)‡	3.70 (0.00, 9.11)†	
Change from baseline	−0.33 (−5.08, 2.00)‡	−0.51 (−8.76, 1.23)†	0.16 (0.03, 0.28)

*n=403; †n=208; ‡n=402; CI, confidence interval

Figures

Figure 1

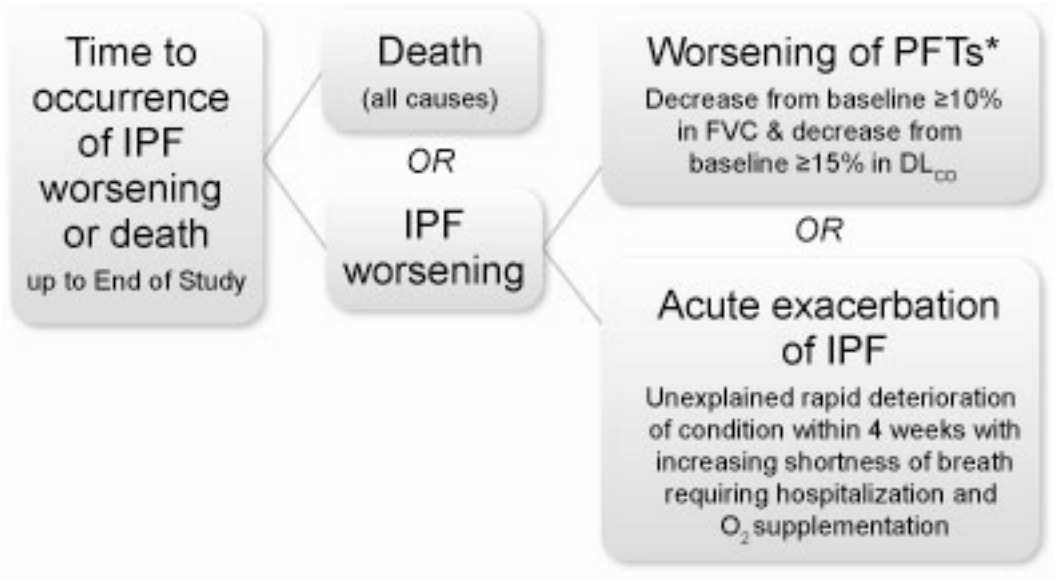


Figure 2

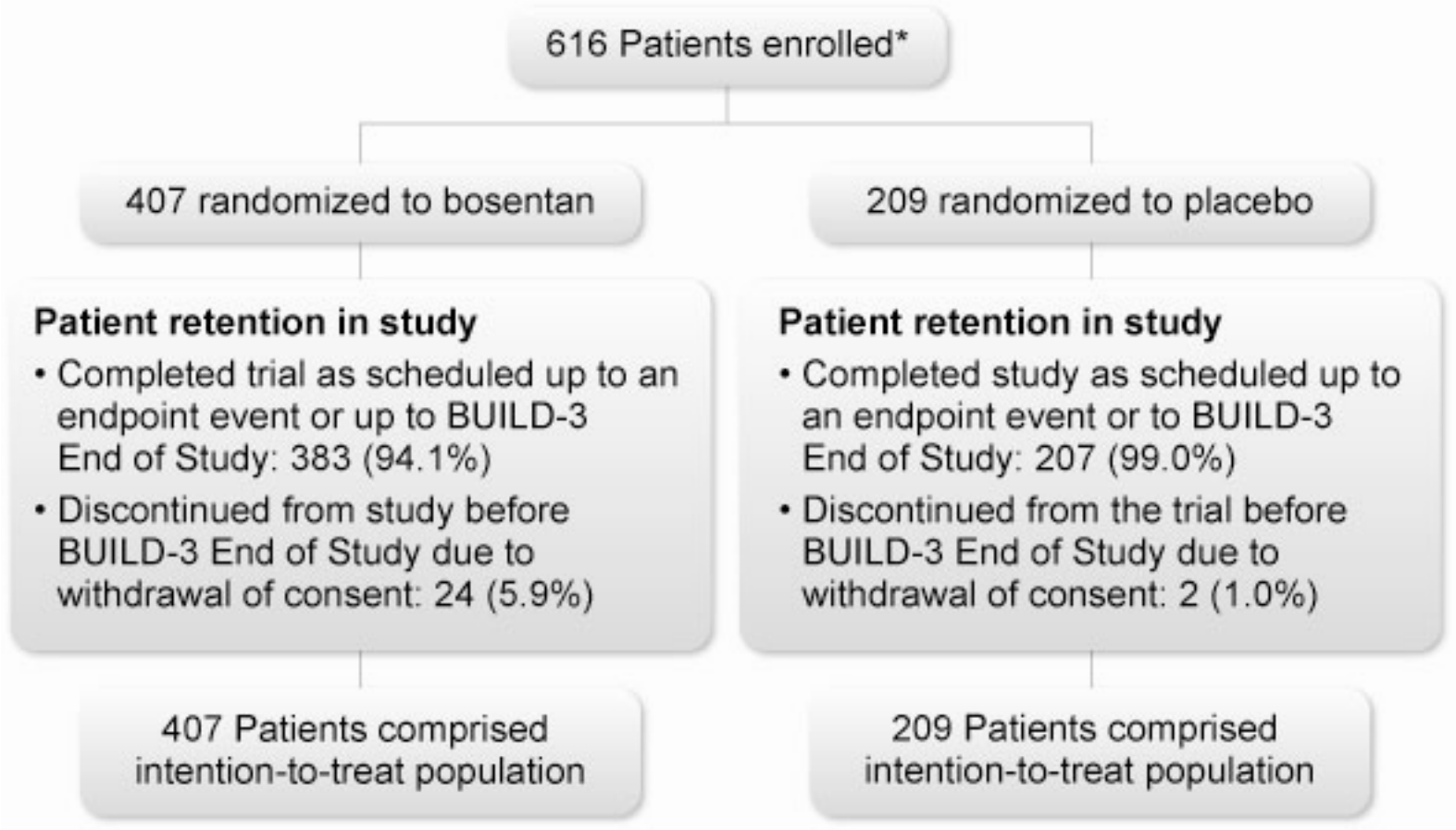

616 Patients enrolled*
407 randomized to bosentan
209 randomized to placebo
Patient retention in study
• Completed trial as scheduled up to an endpoint event or up to BUILD-3 End of Study: 383 (94.1%)
• Discontinued from study before BUILD-3 End of Study due to withdrawal of consent: 24 (5.9%)
Patient retention in study
• Completed study as scheduled up to an endpoint event or to BUILD-3 End of Study: 207 (99.0%)
• Discontinued from the trial before BUILD-3 End of Study due to withdrawal of consent: 2 (1.0%)
407 Patients comprised intention-to-treat population
209 Patients comprised intention-to-treat population

Figure 3

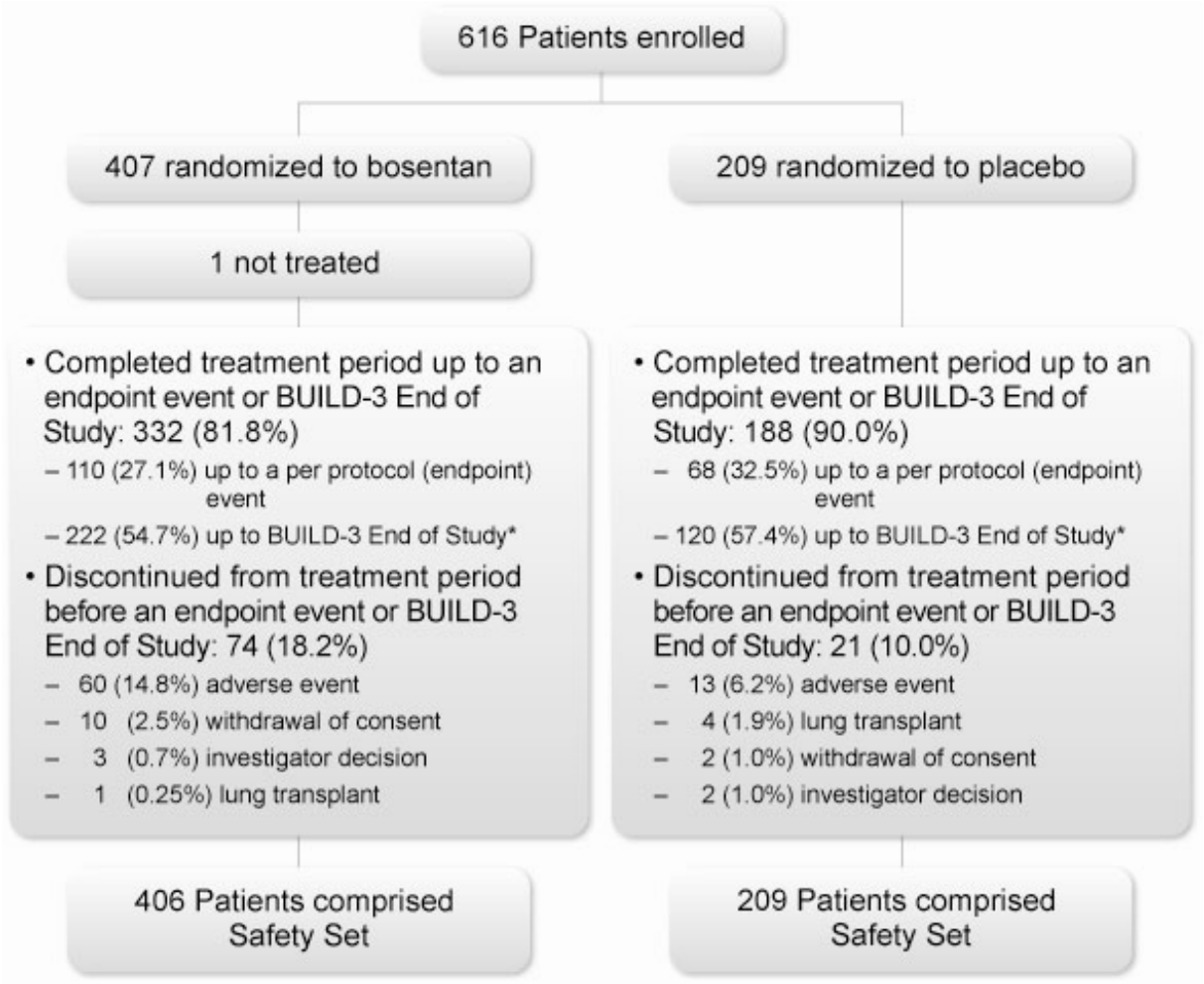

616 Patients enrolled
407 randomized to bosentan
209 randomized to placebo
1 not treated
• Completed treatment period up to an endpoint event or BUILD-3 End of Study: 332 (81.8%)
– 110 (27.1%) up to a per protocol (endpoint) event
– 222 (54.7%) up to BUILD-3 End of Study*
• Discontinued from treatment period before an endpoint event or BUILD-3 End of Study: 74 (18.2%)
– 60 (14.8%) adverse event
– 10 (2.5%) withdrawal of consent
– 3 (0.7%) investigator decision
– 1 (0.25%) lung transplant
• Completed treatment period up to an endpoint event or BUILD-3 End of Study: 188 (90.0%)
– 68 (32.5%) up to a per protocol (endpoint) event
– 120 (57.4%) up to BUILD-3 End of Study*
• Discontinued from treatment period before an endpoint event or BUILD-3 End of Study: 21 (10.0%)
– 13 (6.2%) adverse event
– 4 (1.9%) lung transplant
– 2 (1.0%) withdrawal of consent
– 2 (1.0%) investigator decision
406 Patients comprised Safety Set
209 Patients comprised Safety Set

Figure 4

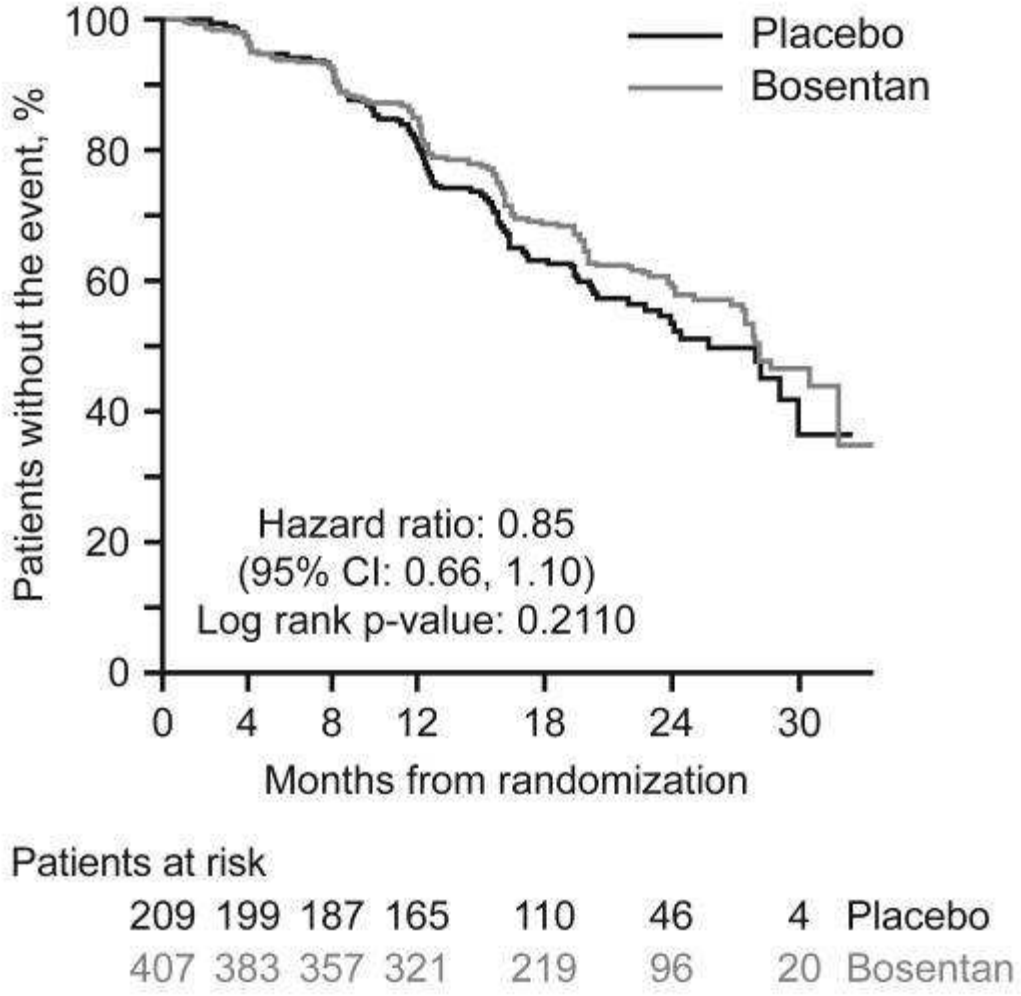
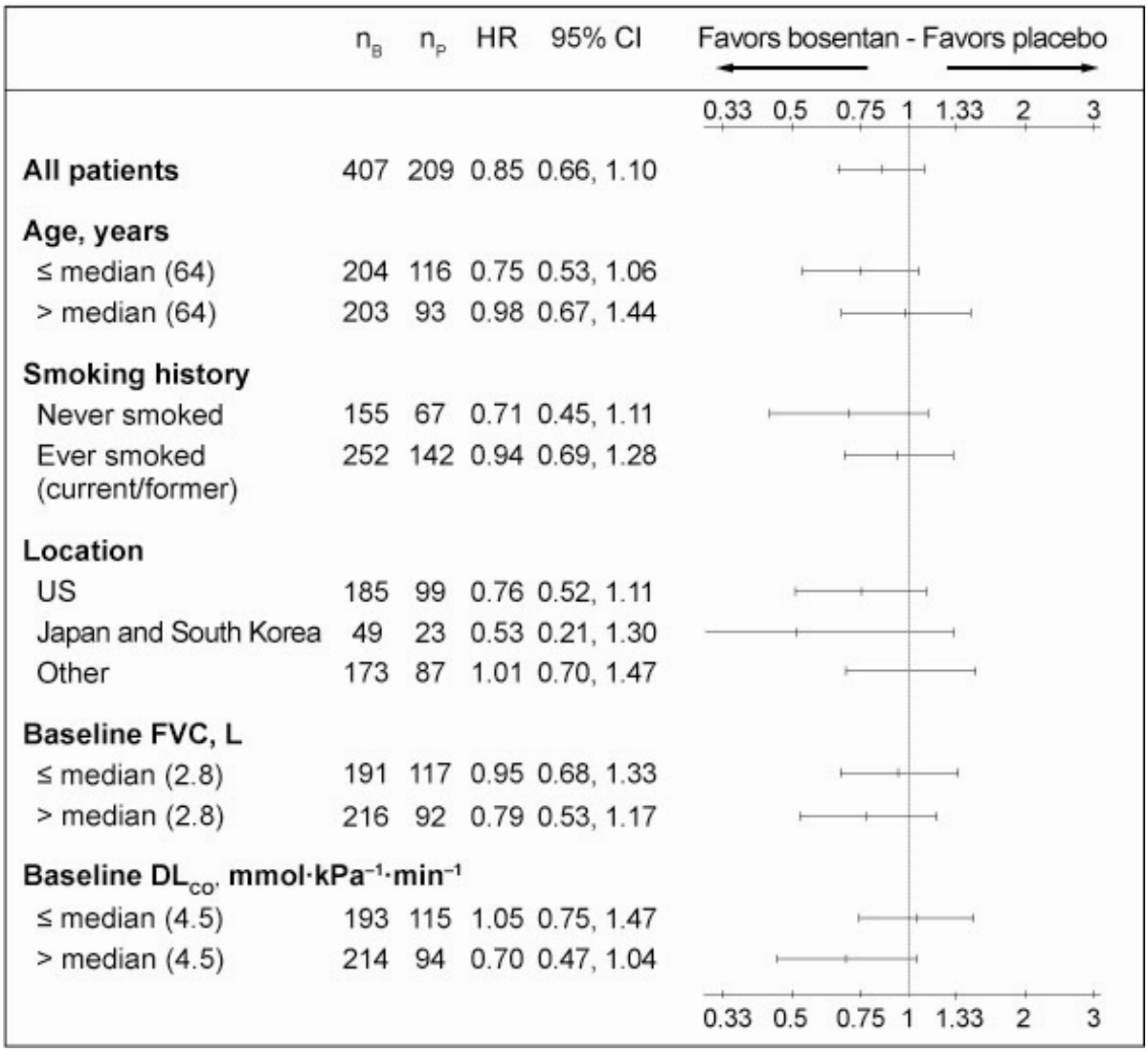

Placebo
Bosentan
Patients without the event, %
100
80
60
40
20
0
Hazard ratio: 0.85
(95% CI: 0.66, 1.10)
Log rank p-value: 0.2110
0
4
8
12
18
24
30
Months from randomization
Patients at risk
209 199 187 165 110 46 4 Placebo
407 383 357 321 219 96 20 Bosentan

Figure 5


n_B n_P HR 95% CI
Favors bosentan - Favors placebo
0.33 0.5 0.75 1 1.33 2 3
All patients 407 209 0.85 0.66, 1.10
Age, years
≤ median (64) 204 116 0.75 0.53, 1.06
> median (64) 203 93 0.98 0.67, 1.44
Smoking history
Never smoked 155 67 0.71 0.45, 1.11
Ever smoked (current/former) 252 142 0.94 0.69, 1.28
Location
US 185 99 0.76 0.52, 1.11
Japan and South Korea 49 23 0.53 0.21, 1.30
Other 173 87 1.01 0.70, 1.47
Baseline FVC, L
≤ median (2.8) 191 117 0.95 0.68, 1.33
> median (2.8) 216 92 0.79 0.53, 1.17
Baseline DL_{CO}, mmol·kPa^{-1}·min^{-1}
≤ median (4.5) 193 115 1.05 0.75, 1.47
> median (4.5) 214 94 0.70 0.47, 1.04
0.33 0.5 0.75 1 1.33 2 3

BUILD-3: A Randomized, Controlled Trial of Bosentan in Idiopathic Pulmonary Fibrosis

Talmadge E. King, Jr., MD; Kevin K. Brown, MD; Ganesh Raghu, MD; Roland M. du Bois, MD; David Lynch, MD; Fernando Martinez, MD; Dominique Valeyre, MD; Isabelle Leconte, PhD; Adele Morganti, MSc; Sébastien Roux, MD; Juergen Behr, MD

Online Data Supplement

Supplementary Methods, Section 1

Central reading of surgical lung biopsy slides

Surgical lung biopsy slides were assessed at each investigational site or, upon investigator request, by a central reader at a core (central) laboratory before randomization. After randomization of the first two patients at each investigational site, the surgical lung biopsy slides from these patients were reviewed by a central reader at a core (central) laboratory to ensure that each site was enrolling patients with a proven diagnosis of IPF (i.e., by the identification of the pattern of usual interstitial pneumonia [UIP]).

Supplementary Methods, Section 2

Quantification of honeycombing on high resolution computed tomography

Quantification of honeycombing on high resolution computed tomography (HRCT) was assessed by: (i) a radiologist and a pulmonologist at each site, (ii) two radiologists at each site, or (iii) by a central reader at a core (central) laboratory

upon investigator request and before randomization. The radiologists reviewed the HRCT scan images and quantitated the amount of honeycombing at three levels by comparison with a set of standards provided for this study. Extensive honeycombing was defined as that involving >5% of the parenchyma in three or more out of six thoracic zones:

- Left lung viewed at the levels of tracheal carina, inferior pulmonary veins, and 1 cm above the dome of the diaphragm
- Right lung viewed at the levels of tracheal carina, inferior pulmonary veins, and 1 cm above the dome of the diaphragm

After randomization of the first two patients at each investigational site, the HRCT images from these patients were reviewed by a central reader at a core (central) laboratory to ensure that each site was enrolling patients within the defined extent of honeycombing.

Supplementary Methods, Section 3

Exclusion criteria

Patients were not enrolled in the BUILD-3 trial if they exhibited severe concomitant illness limiting life expectancy (<1 year); severe restrictive lung disease (forced vital capacity [FVC] <50% of predicted or <1.2 L [formula reported in {E1}], diffusing capacity for carbon monoxide [DL_{CO}] <30% of predicted [formula reported in {E2}], or residual volume [RV] ≥120% of predicted [formula reported in {E3}]); obstructive lung disease (forced expiratory volume in 1 second [FEV_1] ÷ FVC <0.65); a documented, sustained improvement in IPF up to 12 months prior to randomization;

recent pulmonary or upper respiratory tract infection (≤4 weeks prior to randomization); acute or chronic impairment (other than dyspnea) limiting ability to comply with study requirements; chronic heart failure; serum levels of alanine aminotransferase or aspartate aminotransferase >1.5 × upper limit of normal; moderate-to-severe hepatic impairment; and, serum creatinine ≥2.5 $mg \cdot dL^{-1}$.

In addition, patients were not enrolled if, within 4 weeks preceding randomization, they received chronic treatment for IPF with: oral corticosteroids (>20 mg per day prednisone or equivalent), immunosuppressive or cytotoxic drugs, antifibrotic drugs, or N-acetylcysteine. Patients treated using glibenclamide (glyburide) and calcineurin inhibitors within 1 week preceding randomization were also not enrolled.

Supplementary Methods, Section 4

Study management

The BUILD-3 trial was conducted in accordance with the Declaration of Helsinki and its amendments, and applicable regulations and laws. Approval was obtained from all relevant ethics committees and institutional review boards prior to study start. All patients provided written, informed consent. All authors had full access to data and vouch for the accuracy and completeness of data and analyses reported here.

A Steering Committee comprising eight academic researchers oversaw trial design, study conduct, approval of statistical analyses, review and interpretation of data, the writing and the decision to publish this manuscript. The BUILD-3 trial had a group sequential design with two interim analyses for superiority and futility,

conducted when 50% and 75% of events were observed. Monitoring of safety data and conduct of planned interim analyses were performed by an independent Data Safety and Monitoring Board. At all safety interim analyses and at both efficacy interim analyses, continuation of the trial was recommended by the Data Safety Monitoring Board.

Supplementary Methods, Section 5

Randomization and concealment of treatment allocation

Patients were assigned a unique randomization number via a centralized Interactive Randomization System (Cenduit/Fisher Clinical Services AG, Allschwil, Switzerland), which designated which study treatment was to be dispensed at randomization, at each patient visit to the site, and each time a patient's dose was adjusted. The randomization code was generated using Visual Basic 6.0 (Microsoft, Redmond, WA, United States). The investigators, study staff, patients, monitors, and study sponsor remained blinded to treatment assignment until study database closure.

Supplementary Methods, Section 6

Detailed schedule of assessments

At baseline, assessments included medical history, physical examination, electrocardiogram, vital signs, height, body weight, complete laboratory tests, PFT results and measurement of resting arterial blood gas. At randomization, assessments included medical history, physical examination, concomitant

medications, FVC, DL_{CO}, health-related quality of life using 36-item Short-Form questionnaire (SF-36v2™) [E4] and the EuroQol Group 5 Dimension Self-Report Questionnaire (EQ-5D) [E5], and baseline dyspnea index [E6]. At monthly intervals, liver function tests were performed as well as 2 weeks after each up-titration of study treatment. Every 4 months, assessments of concomitant medications, vital signs, body weight, FVC, and DL_{CO} were performed until End of Study. At Month 12, assessments of SF 36, EQ-5D, and transition dyspnea index (TDI) [E6] were performed. At each patient's individual End of Study visit (or End of Study Treatment visit in cases of premature discontinuation) assessments included vital signs, body weight, FVC, DL_{CO}, SF 36, EQ-5D, and TDI. Clinical status at BUILD-3 End of Study was obtained for all patients who did not complete the study due to withdrawal of consent.

Supplementary Methods, Section 7

Statistical methods for analyses of secondary, exploratory, and safety measures

Secondary and exploratory endpoints were evaluated in the All-Randomized Set and summarized descriptively. Treatment comparisons were carried out at the nominal two-sided 0.05 type I error. Dichotomous variables were analyzed using the Fisher exact test. Continuous variables were assessed using the Wilcoxon rank-sum test with asymptotic approximation. Time-to-event variables were analyzed using log-rank testing with asymptotic approximation. No correction for multiple testing was performed.

No imputation methods were applied to the proportion of patients who experienced IPF worsening or death at 1 year, at End of Study, or to the time to IPF worsening up to End of Study excluding death, and the time to death up to End of Study. Censoring for time to death up to End of Study in patients without an event was performed using the latest available measurements (i.e., from the date of last contact or End of Study visit). For other endpoints, the last post-baseline observation carried forward was used for all patients except in cases of IPF worsening or death. In cases of IPF worsening or death, the worst post-baseline value derived or observed at 1 year was used for changes from baseline to 1 year in health-related quality of life and forced vital capacity. For TDI and changes in DL_{CO} at 1 year the fixed values (−9 for TDI, 1 $mmol \cdot kPa^{-1} \cdot min^{-1}$ for DL_{CO}) were used.

Safety analyses were performed on the Safety Set, which comprised all randomized patients who received study drug at least once and had at least one safety assessment post baseline. Data were summarized descriptively.

Table E1

Events contributing to IPF worsening or death up to End of Study

	Bosentan (N=407)	**Placebo** (N=209)
Events contributing to primary endpoint, n (%)	**158 (38.8)**	**94 (45.0)**
Death (Primary endpoint, all causes)	11 (2.7)	6 (2.9)
Acute exacerbation of IPF	19 (4.7)	6 (2.9)
PFT/IPF worsening	128 (31.4)	82 (39.2)
– Confirmed	120 (29.5)	71 (34.0)
– Substituted*	8 (2.0)	11 (5.3)

*PFT/IPF worsening events with missing confirmation

Table E2

Changes from baseline to 1 year in health-related quality of life measured using the individual domains and health transition score of the SF-36 questionnaire

	Bosentan (N=407) Mean ± SD	**Placebo** (N=209) Mean ± SD	**Treatment effect** (95% CI)
Physical functioning			
Baseline	61.1 ± 25.4*	58.2 ± 24.9†	0.0
1 year	55.7 ± 28.9*	52.8 ± 27.6†	(−3.9, 3.9)
Role-physical			
Baseline	63.1 ± 30.0‡	59.2 ± 29.0†	−2.8
1 year	58.5 ± 32.4‡	57.4 ± 30.9†	(−7.7, 2.2)
Pain index			
Baseline	69.9 ± 26.5‡	68.4 ± 27.8†	0.7
1 year	64.3 ± 31.1‡	62.0 ± 30.0†	(−4.2, 5.7)
General health perceptions			
Baseline	52.1 ± 21.5‖	48.7 ± 20.0§	−2.9
1 year	47.4 ± 24.1‖	46.9 ± 22.9§	(−6.5, 0.6)
Vitality			
Baseline	55.5 ± 21.9‡	52.3 ± 22.4§	−1.6
1 year	51.6 ± 24.4‡	50.0 ± 24.1§	(−5.4, 2.1)
Social functioning			
Baseline	77.6 ± 24.3**	72.5 ± 27.1§	−1.5
1 year	72.9 ± 30.5**	69.3 ± 29.7§	(−6.4, 3.4)

Role-emotional			
Baseline	79.3 ± 26.2[‡]	74.7 ± 29.0[†]	−3.2
1 year	73.4 ± 31.6[‡]	71.9 ± 31.2[†]	(−8.6, 2.2)
Mental health index			
Baseline	73.6 ± 20.1[‡]	71.3 ± 21.0[§]	−1.6
1 year	71.1 ± 22.9[‡]	70.4 ± 23.5[§]	(−5.3, 2.2)
Health transition score			
Baseline	3.3 ± 0.8*	3.4 ± 0.8[§]	0.0
1 year	3.1 ± 1.0*	3.2 ± 1.0[§]	(−0.2, 0.2)

*n=379; [†]n=195; [‡]n=377; [§]n=196; [‖]n=376; **n=378; CI, confidence interval

Table E3

Changes from baseline to 1 year in health-related quality of life measured using the health state score and visual analog score of the EuroQoL EQ-5D questionnaire

	Bosentan (N=407) Mean ± SD	**Placebo** (N=209) Mean ± SD	**Treatment effect** (95% CI)
Health state score			
Baseline	0.758 ± 0.185*	0.718 ± 0.242[†]	−0.035
1 year	0.660 ± 0.386*	0.656 ± 0.366[†]	(−0.098, 0.027)
Visual analog score			
Baseline	70.4 ± 18.7[‡]	69.5 ± 19.4[§]	−1.5
1 year	65.9 ± 24.0[‡]	66.4 ± 23.2[§]	(−5.4, 2.4)

*n=381; [†]n=200; [‡]n=374; [§]n=199; CI, confidence interval

Table E4

Baseline dyspnea index and transition dyspnea index at 1 year

	Bosentan (N=407) Mean ± SD	**Placebo** (N=209) Mean ± SD	**Treatment effect** (95% CI)
Baseline dyspnea index			
Functional impairment	2.8 ± 1.0*	2.7 ± 0.9[†]	
Magnitude of task	2.6 ± 0.9[‡]	2.5 ± 0.9[†]	-
Magnitude of effort	2.5 ± 0.9*	2.4 ± 0.9[§]	
Mean total score	**7.9 ± 2.5**[‖]	**7.6 ± 2.5****	
Transition dyspnea index	−1.7 ± 3.5[††]	−1.7 ± 3.6[‡‡]	0.1 (−0.5, 0.7)

*n=402; [†]n=205; [‡]n=403; [§]n=206; [‖]n=400; **n=202; [††]n=383; [‡‡]n=199; CI, confidence interval

Table E5

Treatment-emergent adverse events observed in ≥5% of bosentan-treated patients

	Bosentan (N=406) n (%)	**Placebo** (N=209) n (%)
Total patients with at least one adverse event	396 (97.5%)	203 (97.1%)
Total number of adverse events	2297	1223
Worsening idiopathic pulmonary fibrosis	133 (32.8%)	76 (36.4%)
Upper respiratory tract infection	114 (28.1%)	61 (29.2%)
Cough	79 (19.5%)	52 (24.9%)
Dyspnea	63 (15.5%)	24 (11.5%)
Bronchitis	46 (11.3%)	31 (14.8%)
Fatigue	46 (11.3%)	15 (7.2%)
Headache	44 (10.8%)	22 (10.5%)
Nasopharyngitis	40 (9.9%)	22 (10.5%)
Sinusitis	38 (9.4%)	18 (8.6%)
Edema peripheral	37 (9.1%)	23 (11.0%)
Lower respiratory tract infection	33 (8.1%)	21 (10.0%)
Arthralgia	31 (7.6%)	17 (8.1%)
Liver function test abnormal	30 (7.4%)	0 (0.0%)
Back pain	27 (6.7%)	19 (9.1%)
Nausea	27 (6.7%)	15 (7.2%)
Alanine aminotransferase increased	27 (6.7%)	7 (3.3%)
Dizziness	25 (6.2%)	17 (8.1%)
Chest pain	25 (6.2%)	14 (6.7%)
Pneumonia	23 (5.7%)	12 (5.7%)

Aspartate aminotransferase increased	23 (5.7%)	6 (2.9%)

Table E6

Treatment-emergent adverse events leading to discontinuation of study treatment

	Bosentan (N=406) n (%)	**Placebo** (N=209) n (%)
Total patients with at least one adverse event*	190 (46.8%)	92 (44.0%)
Total number of adverse events*	215	96
Worsening idiopathic pulmonary fibrosis	121 (29.8%)	76 (36.4%)
Liver function test abnormal	18 (4.4%)	0 (0.0%)
Alanine aminotransferase increased	15 (3.7%)	1 (0.5%)
Aspartate aminotransferase increased	15 (3.7%)	1 (0.5%)
Pulmonary function test decreased	6 (1.5%)	4 (1.9%)
Hepatic enzyme increased	5 (1.2%)	0 (0.0%)
Dyspnea	4 (1.0%)	0 (0.0%)
Pneumonia	3 (0.7%)	2 (1.0%)
Respiratory failure	3 (0.7%)	0 (0.0%)
Transaminases increased	2 (0.5%)	0 (0.0%)
Myocardial infarction	1 (0.2%)	1 (0.5%)
Acute respiratory distress syndrome	1 (0.2%)	0 (0.0%)
Allergic edema	1 (0.2%)	0 (0.0%)
Anemia	1 (0.2%)	0 (0.0%)
Angina unstable	1 (0.2%)	0 (0.0%)
Bilirubin conjugated increased	1 (0.2%)	0 (0.0%)
Blood alkaline phosphatase increased	1 (0.2%)	0 (0.0%)
Blood bilirubin increased	1 (0.2%)	0 (0.0%)
Cardiac arrest	1 (0.2%)	0 (0.0%)

Cerebral hemorrhage	1 (0.2%)	0 (0.0%)
Drug hypersensitivity	1 (0.2%)	0 (0.0%)
Fluid retention	1 (0.2%)	0 (0.0%)
General physical health deterioration	1 (0.2%)	0 (0.0%)
Hepatic cirrhosis	1 (0.2%)	0 (0.0%)
Hepatic function abnormal	1 (0.2%)	0 (0.0%)
Hepatitis acute	1 (0.2%)	0 (0.0%)
Lower respiratory tract infection	1 (0.2%)	0 (0.0%)
Lung adenocarcinoma	1 (0.2%)	0 (0.0%)
Lymphadenopathy	1 (0.2%)	0 (0.0%)
Pancytopenia	1 (0.2%)	0 (0.0%)
Pruritus allergic	1 (0.2%)	0 (0.0%)
Sjögren's syndrome	1 (0.2%)	0 (0.0%)
Urosepsis	1 (0.2%)	0 (0.0%)
Clostridium difficile colitis	0 (0.0%)	1 (0.5%)
Computerized tomogram abnormal	0 (0.0%)	1 (0.5%)
Cough	0 (0.0%)	1 (0.5%)
Dementia	0 (0.0%)	1 (0.5%)
Hypoxia	0 (0.0%)	1 (0.5%)
Lobar pneumonia	0 (0.0%)	1 (0.5%)
Lung transplant	0 (0.0%)	1 (0.5%)
Memory impairment	0 (0.0%)	1 (0.5%)
Mesenteric arteriosclerosis	0 (0.0%)	1 (0.5%)
Upper respiratory tract infection	0 (0.0%)	1 (0.5%)
Vasculitis	0 (0.0%)	1 (0.5%)

*Leading to discontinuation of study treatment. Note: The discontinuation of study

treatment could have been reported at BUILD-3 End of Study, and would not therefore be considered a premature discontinuation of study treatment.

Table E7

Treatment-emergent serious adverse events with frequency >1.5% in bosentan-treated patients

	Bosentan (N=406) n (%)	**Placebo** (N=209) n (%)
Total patients with at least one serious adverse event	129 (31.8%)	74 (35.4%)
Total number of severe adverse events	199	117
Worsening idiopathic pulmonary fibrosis	41 (10.1%)	17 (8.1%)
Pneumonia	16 (3.9%)	10 (4.8%)
Lower respiratory tract infection	7 (1.7%)	5 (2.4%)
Coronary artery disease	6 (1.5%)	1 (0.5%)
Dyspnea	6 (1.5%)	0 (0.0%)

References

E1. Morris JF, Koski A, Johnson LC. Spirometric standards for healthy nonsmoking adults. *Am Rev Respir Dis* 1971;103:57–67.

E2. Crapo RO, Morris AH. Standardized single breath normal values for carbon monoxide diffusing capacity. *Am Rev Respir Dis* 1981;123:185–189.

E3. Crapo RO, Morris AH, Clayton PD, Nixon CR. Lung volumes in healthy nonsmoking adults. *Bull Eur Physiopathol Respir* 1982;18:419–425.

E4. SF-36v2™ Health Survey© 2000, 2002 by Medical Outcomes Trust and Quality Metric Incorporated.

E5. EuroQoL Group: EuroQoL – a new facility for the measurement of health-related quality of life. *Health Policy* 1990;16:199–208.

E6. 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.