**TRACLEER® (bosentan)**
**TRACLEER - Interstitial Lung Disease (ILD)**

## SUMMARY


- Three randomized, double-blind, placebo-controlled, multicenter phase 2/3 studies designed to assess the efficacy, safety, and tolerability of TRACLEER in patients with interstitial lung disease (ILD) did not meet their primary endpoints.[1-4]
- No unexpected adverse events (AEs) were reported in these 3 trials. The safety profile of TRACLEER was similar to what was observed in other trials. No new safety issues were identified in an open-label (OL) extension study with a mean duration of exposure to TRACLEER of 6.4 months.[1-5]


## CLINICAL DATA

### Phase 3 Study: BUILD-3

BUILD-3 was a multicenter, double-blind, randomized, placebo-controlled, parallel group, event-driven, group sequential, phase 3 study investigating the effects of TRACLEER on morbidity and mortality in patients with idiopathic pulmonary fibrosis (IPF).[1] The primary endpoint was time to disease worsening or death up to end of study. Secondary outcome objectives were to assess the effects of TRACLEER on health-related quality of life (QoL), dyspnea, pulmonary function test (PFT) results, and the safety and tolerability of TRACLEER. Please visit http://www.clinicaltrials.gov for more information on the inclusion and exclusion criteria of the BUILD-3 trial (identifier NCT00391443).[6]

A total of 616 patients randomized 2:1 to TRACLEER (n=407) or placebo (n=209). A total of 252 events were recorded in the study. The primary endpoint was not met (*P*=0.2110). No treatment effects were observed on health-related QoL or dyspnea. Some effects of TRACLEER treatment were observed in changes from baseline to 1 year in forced vital capacity (FVC) and a diffusing capacity of the lung for carbon monoxide ($DL_{CO}$). The safety profile for TRACLEER was similar to that observed in other trials.

Adverse events observed in more than 10% of TRACLEER-treated patients included IPF worsening, upper respiratory tract infection (URTI), cough, dyspnea, bronchitis, fatigue, and headache. Serious AEs occurred in 129 (31.8%) of TRACLEER patients and 74 (35.4%) of placebo patients. The majority of serious AEs (SAEs) were related to IPF worsening or respiratory in nature. Seventeen patients on TRACLEER died during the study (due to IPF worsening n=9; due to respiratory failure n=6). The cause of death was not provided in the publication for the other 2 TRACLEER-treated patients.[1]

### Phase 3 OL Extension: BUILD-3 OL

BUILD-3 OL was an open-label extension in patients who completed BUILD-3 to assess the long-term safety and tolerability of TRACLEER in patients with IPF. Endpoints included AEs and SAEs that lead to discontinuation of study treatment and increase in aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) >3 × upper limit of normal (ULN). Please visit http://www.clinicaltrials.gov for more information on the inclusion and exclusion criteria of the BUILD-3 OL trial (identifier NCT00631475).[7]

A total of 128 patients were transitioned into the extension study from the BUILD-3 study. The mean duration of exposure to OL TRACLEER during the extension was 6.4 months (range, 0.6 to 21.0 months), with ex-TRACLEER patients reaching a mean total exposure (in BUILD-3 and this extension combined) of 25.5 months (range, 14.0 to 33.3 months). During this extension study, 39.8% of patients had at least one SAE, which was most frequently respiratory, thoracic, and mediastinal disorders (24.2%, including worsening IPF in 18.0%), infections and infestations (11.7%, involving the pulmonary system in most cases), and cardiac disorders (5.5%). In 18 cases (14.1%), the event had a fatal outcome. All deaths were considered by the investigator to be unrelated to TRACLEER treatment.

Overall, 25.0% of patients (including the 18 patients who died) were discontinued prematurely because of one or more AEs. A liver-related event was observed in 5 patients (3.9%) overall. Three patients had an elevation in AST and/or ALT to > 8 × ULN, and 1 additional patient had an abnormal liver function test ≤ 3 × ULN reported as an AE. For these patients, the elevation resolved when TRACLEER was temporarily or permanently discontinued. The remaining patient had hepatic failure in association with severe and fatal cardiopulmonary failure while awaiting lung transplantation, and the events were judged by the investigator to be unrelated to TRACLEER treatment.[5]

**Phase 2/3 Study: BUILD-1**

BUILD-1 was a randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy, safety and tolerability of TRACLEER in patients with IPF.[2,4] The primary endpoint for the study was change in 6 minute walk distance (6MWD) at month 12 vs baseline. Secondary efficacy endpoints included time to death or disease progression, change in pulmonary function tests, change in Borg dyspnea index and QoL questionnaires. Key inclusion criteria included documented IPF. Key exclusion criteria included ILD due to conditions other than IPF. Please visit http://www.clinicaltrials.gov for more information on the inclusion and exclusion criteria of the BUILD-1 trial (identifier NCT00071461).[8]

A total of 158 patients were randomized to TRACLEER (n=74) or placebo (n=84). TRACLEER showed no superiority over placebo on change in 6MWD up to month 12, the primary efficacy endpoint. No unexpected AEs were reported. Elevations in ALT were observed in 20.5% of TRACLEER-treated patients. All cases resolved without sequelae after no change, a decrease in dose or discontinuation of treatment. Nine TRACLEER-treated patients discontinued treatment due to elevations in ALT. Three deaths occurred in each group, the majority of which were due to IPF. A trend in delayed time to death or disease progression, and improvement in QoL, was observed with TRACLEER.[2,4]

**Phase 2/3 Study: BUILD-2**

BUILD-2 was a prospective, double-blind, randomized, placebo-controlled, multicenter, parallel group study to assess the efficacy, safety and tolerability of TRACLEER in patients with ILD/systemic sclerosis (SSc) for 12 months.[3] The primary endpoint for the study was change in 6MWD from baseline to month 12. Secondary outcome parameters included time to death (all cause) or worsening of PFTs and changes in PFTs compared to baseline. Please visit http://www.clinicaltrials.gov for information on the inclusion and exclusion criteria of the BUILD-2 trial (identifier NCT00070590).[9]

A total of 163 patients were randomized to TRACLEER (n=77) or placebo (n=86). No significant difference was observed between the treatment groups for change in 6MWD up to month 12. TRACLEER had no effect on time to death or worsening PFTs. Clinically significant worsening of PFTs occurred in 25.6% of placebo patients and 22.5% of TRACLEER patients (*P*=non-significant [NS]). No significant effect was observed for other exploratory endpoints.

Overall, the incidence of AEs was similar for both groups. The most commonly reported AEs (each occurring in >10% of TRACLEER patients) included skin ulcers, worsening PFT scores, fatigue, URTI, cough, arthralgia, peripheral edema, diarrhea, bronchitis, sinusitis and anemia. Elevations in ALT or AST >3 × ULN were observed in 11.3% of patients in the TRACLEER group versus 1.2% in the placebo group. Serious AEs were observed in 21.1% of TRACLEER-treated patients versus 18.6% of patients in the placebo group. No deaths occurred during this study.

Patients that completed the BUILD-2 study were eligible to enroll into a long-term OL extension. For more information on this extension study, please visit http://www.clinicaltrials.gov (identifier NCT00319033).[10]

### Pilot Safety Study in IPF[11]

Protocol AC-052-221 was an OL study conducted to evaluate the safety and tolerability of TRACLEER (62.5 and 125 mg twice a day [BID]) in patients with mild to moderate IPF. The primary objective of the study was to assess the effect of TRACLEER on standard deviation of perfusion (Q) and ventilation (V) and/or the perfusion of low ventilation perfusion ratio (V/Q) areas (day 1 only), oxygen saturation, and minute ventilation up to the end of period 2 (weeks 1 and 2).

A total of 12 patients with mild to moderate IPF and a FVC between 50% and 90%, a ≥10% decline in FVC during the previous year, $DL_{CO}$ >35% of predicted, and a $PaO_2$ >55 mmHg were enrolled in the study. During the acute testing on day 1, only 1 of the 12 patients was prematurely withdrawn from the study due to signs of an increase in V/Q mismatch (increase in low V/Q area from 0 to 22.2%) with TRACLEER, which was asymptomatic. Mean changes in cardiac output, minute ventilation, and oxygen saturation were small and not significant.

Three patients experienced a serious AE (2 with pneumonia, both of whom died and 1 respiratory tract infection). The deaths were considered by the investigator to be unrelated to TRACLEER. Two patients had an elevation in ALT levels to >3 × ULN, 1 on the last day of the treatment period and one whose values decreased with a temporary interruption of treatment.

A statistically significant 12.1% reduction in mean pulmonary arterial pressure (mPAP; *P*=0.0032) and an 8.8% reduction in pulmonary vascular resistance (PVR) were observed 4 hours after a single dose of TRACLEER accompanied by a small significant decrease in heart rate. No significant changes in mean right atrial pressure (mRAP), cardiac index, cardiac output, or oxygen saturation were observed. The diffusion capacity remained relatively stable over the 12-week treatment period, and no improvement was observed in pulmonary function or exercise capacity.

### BPHIT Study[12]

A 16-week, randomized, double-blind, placebo-controlled multicenter trial was conducted to evaluate the use of TRACLEER in patients with fibrotic idiopathic interstitial pneumonia (IIP, including IPF and nonspecific interstitial pneumonia [NSIP]) and pulmonary hypertension (PH). The primary endpoint was a fall in PVR index ≥20% over 16 weeks. Secondary endpoints included changes in pulmonary hemodynamics, 6MWD, World Health Organization (WHO) FC, QoL, lung function, oxygen saturation at rest, brain natriuretic peptide (BNP) concentrations, echocardiographic parameters, and disease progression.

Sixty patients were recruited for the study with no difference detected between the TRACLEER and placebo groups for the primary endpoint. No significant differences were seen in secondary endpoints between the groups. During the study, the most frequent serious AEs were chest infection (n=8) and heart failure (n=3). Six patients (3 in each group) died during the study and 5 of these deaths were attributed to disease progression.

### Information From a Literature Search

Tanaka et al looked at the potential benefit of TRACLEER therapy in borderline or less severe PH secondary to IPF.[13] Romaniello et al looked at TRACLEER for digital ulcers prevention in SSc patients with ILD.[14]

Additional case reports are included in the REFERENCES section for your review.[15-17]

## LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, Derwent® (and/or other resources, including internal/external databases) was conducted on 4 March 2024.

## REFERENCES


1. Jr. King TE, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011;184(1):92-99.

2. Jr. King TE, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2008;177(1):75-81.

3. Seibold JR, Denton CP, Furst DE, et al. Randomized, prospective, placebo-controlled trial of bosentan in interstitial lung disease secondary to systemic sclerosis. *Arthritis Rheum*. 2010;62(7):2101-2108.

4. Raghu G, Jr. King TE, Behr J, et al. Quality of life and dyspnoea in patients treated with bosentan for idiopathic pulmonary fibrosis (BUILD-1). *Eur Respir J*. 2010;35(1):118-123.

5. Ltd Actelion. Trial Registry Study ID: AC-052-322. 2012.

6. Actelion Ltd. BUILD 3: bosentan use in interstitial lung disease. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017]. Available from: http://clinicaltrials.gov/ct2/show/NCT00391443 NLM Identifier: NCT00391443.

7. Actelion Ltd. Open label extension study in patients with idiopathic pulmonary fibrosis who completed protocol AC-052-321/BUILD 3/NCT00391443 (BUILD OL). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017]. Available from: http://clinicaltrials.gov/ct2/show/NCT00631475 NLM identifier: NCT00631475.

8. Actelion Ltd. Efficacy and safety of oral bosentan in patients with idiopathic pulmonary fibrosis (BUILD 1). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017]. Available from: http://clinicaltrials.gov/ct2/show/NCT00071461 NLM Identifier: NCT00071461.

9. Actelion Ltd. Efficacy and safety of oral bosentan in pulmonary fibrosis associated with scleroderma. In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017]. Available from: http://clinicaltrials.gov/ct2/show/NCT00070590 NLM Identifier: NCT00070590.

10. Actelion Ltd. Open-label study with bosentan in interstitial lung disease (BUILD 2 OL). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2000- [cited 2017]. Available from: http://clinicaltrials.gov/ct2/show/NCT00319033 NLM Identifier: NCT00319033.

11. Data on File. Bosentan. 4th Development Safety Update Report for Bosentan (TRACLEER). Janssen Scientific Affairs, LLC.; 2021.

12. Corte TJ, Keir GJ, Dimopoulos K, et al. Bosentan in pulmonary hypertension associated with fibrotic idiopathic interstitial pneumonia. *Am J Respir Crit Care Med*. 2014;190(2):208-217.

13. Tanaka Y, Hino M, Gemma A. Potential benefit of bosentan therapy in borderline or less severe pulmonary hypertension secondary to idiopathic pulmonary fibrosis-an interim analysis of results from a prospective, single-center, randomized, parallel-group study. *BMC Pulm Med*. 2017;17(1):200.

14. Romaniello A, Gigante A, Paolo MD, et al. Bosentan for digital ulcers prevention does not worsen cardiopulmonary exercise test parameters in SSc patients with interstitial lung disease. *Int J Cardiol*. 2016;223:113-115.

15. Sandamali S, Munidasa D. An unusual presentation of mixed connective tissue disease: a case of chronic pulmonary thromboembolism and nephrotic range proteinuria [abstract]. *Indian J Rheumatol*. 2023;18(Suppl. 2):S304-S305.

16. Gil-Calderon D, Galindo JLP, Arteaga C, et al. An unusual case of blue finger syndrome and interstitial lung disease secondary anti-PL7 antibody positive antisynthetase syndrome [abstract]. *Am J Respir Crit Care Med*. 2023;207(1):A6326.

17. Morren MA, Marchal O, Koryllou A, et al. Treatment of atypical cutaneous ulcers in a pediatric mixed connective tissue disease [abstract]. *Pediatr Dermatol*. 2023;40(Suppl. 2):54.