TRACLEER® (bosentan)
TRACLEER - Use in Pediatrics With PAH or Newborns With PPHN

SUMMARY

- BREATHE-3 was an open-label, prospective, non-controlled, single- and multiple-dose study to investigate the pharmacokinetics (PK) of bosentan in pediatric patients aged 3-15 years with pulmonary arterial hypertension (PAH). Bosentan was associated with significant improvements in mean pulmonary arterial pressure (mPAP) and pulmonary vascular resistance index (PVRI), however the improvement in cardiac index did not reach significance. The most frequent adverse events (AEs) were flushing, headache, edema, and elevated transaminase activity.[1]
- FUTURE-1 was an open-label, multicenter, single-arm, non-controlled, prospective study to assess whether at a selected dose, the exposure to bosentan in pediatric patients ages ≥2 and <12 years with idiopathic PAH (IPAH) or heritable PAH (HPAH) was similar to adults with PAH. The ratio of the geometric means for the area under the plasma concentration-time curve (AUC_t) between pediatric and adult patients was 0.54 (95% confidence interval [CI], 0.37-0.78), indicating that children had lower exposure to bosentan than adults. The most frequent (frequency >5%) AEs were abdominal pain, vomiting, upper abdominal pain, aggression, asthenia, bronchitis, chest pain, fatigue, flushing, headache, nasal congestion, pain in extremity, pulmonary hypertension, tonsillitis, and viral infection.[2]
- FUTURE-2 was a phase 3, open-label, long-term extension study of FUTURE-1.[3] Results of the study are summarized below.
- FUTURE-3 was an open-label, prospective, randomized, multicenter, multiple-dose, phase 3 study investigating whether increasing the TRACLEER dosing frequency from 2 mg/kg twice daily (BID) to 2 mg/kg three times daily (TID) in children with PAH (≥3 months to <12 years of age) would increase exposure. The geometric mean (95% CI) for $AUC_{0\text{-}24C}$ was 8535 h·ng/mL (6936-10,504) and 7275 h·ng/mL (5468-9679) for 2 mg/kg BID and TID, respectively (geometric mean ratio [95% CI] 0.85 [0.61-1.20]). The proportions of patients who experienced ≥1 AE were similar in the BID and TID groups and were comparable across age groups.[4] Fifty-eight patients who completed the end-of-study visit and were still receiving TRACLEER at week 24 of the core study were eligible for participation in the 48-week extension study. Results of the extension study are summarized below.[5]
- FUTURE-4 was a phase 3, multicenter, double-blind, placebo-controlled, randomized, prospective study to investigate TRACLEER as adjunctive therapy to inhaled nitric oxide in the management of persistent pulmonary hypertension of the newborn (PPHN) in neonates >34 weeks gestation and <7 days of age. This study has been terminated due to slow recruitment. Available results are summarized below.[6]
- A brief summary of published studies (N>50),[7-11] safety analyses,[12,13] and published studies (N<50)[14,15] in pediatrics and neonates are presented below.
- Additional case reports are included as citations in the REFERENCES section.[16-23]
- Please refer to your local labeling for the approved use of TRACLEER.

CLINICAL DATA

Clinical Trials

BREATHE-3

Design

Open-label, prospective, non-controlled, single- and multiple-dose study conducted over 12 weeks at 2 centers in the United States. A total of 19 patients, aged 3-15 years with IPAH or PAH related to congenital heart disease in WHO functional class (FC) II or III were stratified by weight and epoprostenol use to receive bosentan. The primary objective of this study was to investigate the PK of bosentan in pediatric patients with PAH. Exploratory measures included the efficacy, safety, and tolerability of bosentan in these patients.[1]

Dosing

BREATHE-3 utilized the available adult formulation of bosentan as the study drug. Patients weighing 10-20 kg, 20-40 kg, or >40 kg received bosentan 31.25 mg daily, 31.25 mg BID, or 62.5 mg BID, respectively for the first 4 weeks. The dose was then up titrated to the target dose (31.25 mg, 62.5 mg BID, or 125 mg BID) for the remainder of the study.

In this study, the 31.25 mg dose was obtained by cutting a 62.5 mg tablet into 2 halves using a tablet cutter provided with the study medication. The protocol recommended that the cutting of the tablets be performed only on the day of use.[1]

Outcome

Bosentan showed a PK profile similar to that in healthy adults. Concomitant administration of epoprostenol, body weight, gender, and age, had no significant effect on the PK of bosentan. Bosentan was associated with significant improvements in mPAP and PVRI, however the improvement in cardiac index did not reach significance. At week 12, mPAP decreased by 8.0 mmHg (95% CI, -12.2 to -3.7 mmHg; $P<0.05$), and PVRI decreased by 300 dyn·s·m^2/cm^5 (95% CI, -576 to -24; $P<0.05$). Further evaluation of hemodynamic parameters noted no statistically significant differences in patients who received concomitant epoprostenol compared to bosentan alone. There was no significant difference from baseline to week 12 in the exercise capacity of pediatric patients aged ≥8 years (n=12) in terms of peak oxygen consumption or mean walk distance. By week 12, 5 of 18 patients who completed the study had improved by one WHO FC (3 from FC III to II and 2 from FC II to I), with only 1 child deteriorating from FC II to III.[1]

Safety

The most frequent AEs were flushing (21%, n=4), headache, edema, and elevated transaminase activity (16%, n=3 in each). Small decreases in systemic blood pressure were also observed at week 12, although symptomatic hypotension was not observed in any patient. Two patients had serious AEs: tachycardia, systemic hypertension, tremor and dizziness in 1 patient and a marked increase in alanine aminotransferase (ALT) level in another patient who was subsequently diagnosed with ulcerative colitis and associated sclerosing cholangitis. In another patient, elevated ALT levels (>3 × upper limit of normal [ULN]) was observed at week 12, which resolved after discontinuation of bosentan. There was no evidence of drug-drug interactions with concomitant epoprostenol and no deaths were reported.[1]

FUTURE-1

Design

Open-label, multicenter, single-arm, non-controlled, prospective study conducted over 12 weeks at 11 centers in 7 countries. A total of 36 pediatric patients ≥2 and <12 years old with IPAH or HPAH in WHO FC II or III. The primary objective of this study was to demonstrate that, at a selected dose, the exposure to bosentan in pediatric patients with IPAH or HPAH was similar to adults with PAH (historical control). In addition, the efficacy, safety, and tolerability of the pediatric formulation were explored.[2]

Dosing

Patients with a body weight <30 kg were treated for 4 weeks with 2 mg/kg BID of the pediatric formulation of bosentan, then up titrated to the maintenance dose of 4 mg/kg BID for the remainder of the study. Patients with a body weight ≥30 kg received 64 mg BID of the pediatric formulation of bosentan for 4 weeks and then 120 mg BID as the maintenance dose. The oral, dispersible, pediatric formulation of bosentan utilized in FUTURE-1 is not available in the United States.[2]

Outcome

The ratio of the geometric means for the AUC_t between pediatric and adult patients was 0.54 (95% CI, 0.37 to 0.78), indicating that children had lower exposure to bosentan than adults. Bosentan exposure was similar in patients receiving either bosentan 2 or 4 mg/kg BID. Similar to BREATHE-3, age, gender, FC, background epoprostenol therapy, or previous exposure to bosentan had no effect on the PK of bosentan. Exploratory efficacy using WHO FC and quality-of-life analyses indicated that most patients remained unchanged from baseline to end of study. Improvements in WHO FC occurred mainly in bosentan-naïve patients (2/23 patients improved from FC II to I; 3/12 from FC III to II; 20/23 remained stable at FC II and 9/12 at FC III). Rare worsening occurred mainly in patients already on bosentan prior to study initiation.[2]

Safety

The pediatric formulation was well-tolerated. When compared with adult patients, no new safety findings were observed. One child discontinued because of 'bad' taste of the medication and 1 child died. A total of 22 patients (61%) experienced at least 1 AE. The most frequent (frequency >5%) individual AEs were abdominal pain (11.1%, n=4), vomiting (8.3%, n=3), upper abdominal pain, aggression, asthenia, bronchitis, chest pain, fatigue, flushing, headache, nasal congestion, pain in extremity, pulmonary hypertension, tonsillitis, and viral infection (5.6%, n=2 each). Overall, 4 patients (11.1%) experienced 8 serious adverse events, all requiring hospitalization. One death occurred 1 day after discontinuation of treatment, considered by the investigator to be unrelated to study treatment. Worsening of pulmonary hypertension occurring in 1 patient was the only event judged as related to study treatment by the investigator. No patients experienced transaminase elevations over the course of this study.[2]

FUTURE-2

FUTURE-2 was a phase 3, open-label, long-term extension study of FUTURE-1. Children who completed 12-week treatment in FUTURE-1 and for whom TRACLEER was considered beneficial were enrolled in FUTURE-2. The main objective of FUTURE-2 was to assess the long-term safety and tolerability of the pediatric formulation of TRACLEER via

treatment-emergent AEs, serious AEs, growth, and laboratory measurements. Exploratory efficacy endpoints included time to PAH worsening and long-term survival.[3]

Of the 36 patients enrolled in FUTURE-1, 33 continued to FUTURE-2 (2 did not complete FUTURE-1 and 1 elected to not enroll in FUTURE-2). The overall median (range) duration of exposure to TRACLEER during the study (from study treatment start date in FUTURE-1 to study treatment end in FUTURE-2) was 27.7 (1.9-59.6) months. Treatment-emergent AEs occurred in 32 (88.9%) patients and AEs considered TRACLEER-related occurred in 15 (41.7%) patients. Overall, the most common AEs were abdominal pain (n=7; 19.4%) and nasopharyngitis (n=7; 19.4%). Fifty-one serious AEs occurred in 18 (50%) patients, 3 were considered treatment-related: 2 incidences of reported PAH worsening and 1 of autoimmune hepatitis. Six deaths occurred during the study period, and all were reported as unrelated to TRACLEER. Measurements of laboratory abnormalities, body weight, height, and vital signs did not reveal new safety concerns with TRACLEER. Kaplan-Meier event-free estimates of PAH worsening were 78.9% (95% CI, 60.7-89.3%) and 73.6% (95% CI, 53.1-86.2%) at 2 and 4 years, respectively. Estimated long-term survival at 2 and 4 years after start of treatment in FUTURE-1 were 91.2% (95% CI, 75.0-97.1%) and 84.0% (95% CI, 65.5-93.1%), respectively.[3]

FUTURE-3

FUTURE-3 was an open-label, prospective, randomized, multicenter, multiple-dose, phase 3 study investigating whether increasing the TRACLEER dosing frequency from 2 mg/kg BID to 2 mg/kg TID in children with PAH (from ≥3 months to <12 years of age) would increase exposure. Overall, 64 patients were randomized 1:1 to receive oral doses of TRACLEER 2 mg/kg BID (n=33) or TID (n=31). The main PK endpoint was the daily exposure to TRACLEER over 24 h corrected to the 2 mg/kg dose ($AUC_{0\text{-}24C}$). The maximum plasma concentration corrected to the 2 mg/kg dose (C_{maxC}), the time to reach the maximum plasma concentration (t_{max}), and safety endpoints were also assessed.[4]

The geometric mean (95% CI) for $AUC_{0\text{-}24C}$ was 8535 h·ng/mL (6936, 10,504) and 7275 h·ng/mL (5468, 9679) for 2 mg/kg BID and TID, respectively (geometric mean ratio [95% CI] 0.85 [0.61, 1.20]). The geometric mean (95% CI) for C_{maxC} was 743 ng/mL (573-963) and 528 ng/mL (386-722) for 2 mg/kg BID and TID, respectively (geometric mean ratio [95% CI] 0.71 [0.48-1.05]). The median (range) for t_{max} was 3.0 h (0.0-7.5) and 3.0 h (1.0-8.0) for 2 mg/kg BID and TID, respectively. The proportions of patients who experienced ≥1 AE were similar in the BID (66.7%) and TID (67.7%) groups and were comparable across age groups. Overall, there was a slightly higher proportion of serious adverse events (SAEs) in the TID dosing regimen (19.4%) compared with BID (12.1%) and all SAEs were assessed by the investigator as unrelated to study drug administration.[4]

48-Week Extension Study

Patients who completed the end-of-study visit and were still receiving TRACLEER at week 24 of the core study were eligible for participation in the 48-week extension study; 58 patients (90.6%) continued to the extension study and 45 patients completed the full extension study for a total of 72 weeks of treatment.[5]

In this exploratory post-hoc analysis, associations of worsening from baseline to week 24 were observed in echocardiographic parameters, such as systolic left ventricular eccentricity index and E/A ratio mitral valve flow, which were associated with outcomes in time to death and time to PAH worsening. At Week 72, WHO FC was stable for 50 patients (78.1%), worsened for 8 patients (12.5%), and improved for 6 patients (9.4%). By end of treatment plus 7 days, PAH worsened for 15 patients (23.4%). This included 11 patients (17.2%) who had new or worsening right-sided heart failure, 10 patients (15.6%) who died, 7 patients

(10.9%) who were hospitalized due to PAH progression, and 4 patients (6.3%) who began new therapy for PAH.[5]

FUTURE-4

FUTURE-4 was a phase 3, multicenter, double-blind, placebo-controlled, randomized, prospective study to investigate TRACLEER as adjunctive therapy to inhaled nitric oxide in the management of PPHN.[6] This study has been terminated due to slow recruitment. Eligible patients were >34 weeks gestation, <7 days of age, with persistent respiratory failure (defined as oxygenation index [OI] ≥12) despite at least 4 hours of inhaled nitrous oxide (iNO) treatment, and PPHN confirmed by echocardiography. During the 2-year study period, 21 eligible neonates (13 TRACLEER, 8 placebo) received TRACLEER 2 mg/kg or matching placebo by nasogastric tube BID for at least 48 hours, up to 1 day after iNO weaning, and a maximum duration of 14 days. The groups had similar gestational age, weight, and sex distribution. On day 1, TRACLEER concentrations were low and highly variable. Steady-state conditions comparable to those observed in adult PAH patients were achieved by Day 5. Treatment time (mean days ± standard deviation [SD]) was 5.0 ± 2.6 for the TRACLEER arm and 4.3 ± 1.3 for the placebo arm. Time to weaning from iNO (median days, 95% CI) was 3.7 (1.17-6.95) and 2.9 (1.26-4.23) for the TRACLEER and placebo groups, respectively, while the corresponding values for time to weaning from mechanical ventilation were 10.8 (3.21-12.21) and 8.6 (3.71-9.66). One patient in the TRACLEER arm required extracorporeal membrane oxygenation (ECMO), compared with none in the placebo arm. TRACLEER was well tolerated and did not adversely affect systemic blood pressure or hepatic transaminases. Blood transfusions were performed in 4/13 patients on TRACLEER compared with 1/8 patients on placebo. AEs of anemia (3/13 TRACLEER vs 1/8 placebo) and edema were more frequent in the TRACLEER group (3/13 TRACLEER vs 0/8 placebo). The authors concluded that the study results did not indicate any additional benefit of TRACLEER on top of iNO in this population. Note that these results are not consistent with those presented by Mohamed et al (see Table: Summary of Published Studies and Reviews With TRACLEER in Neonates With PPHN below).[15]

Information From a Literature Search

Several additional studies of TRACLEER administration in pediatric patients with PAH and neonates with PPHN were identified. These studies are briefly summarized in the tables below.

Summary of Published Studies (N>50) With TRACLEER in Pediatric Patients With PAH

Study Design and Population	Drug Regimen	Observations	Safety
Miyamoto et al (2021)[7] Retrospective, nationwide, multicenter, cohort study of 91 pediatric patients with PAH (45% female, median age at diagnosis 8 years [IQR, 4 to 11 years]) Fifteen patients were NYHA FC I, 39 were NYHA FC II, 31 were NYHA FC III, and 1 was NYHA FC IV at the time of diagnosis. Objective: • To investigate clinical outcomes and risk factors for poor prognosis in Japanese pediatric patients with IPAH. Death or lung transplantation were the primary endpoints.	• Ninety-two percent of patients received targeted therapy for PAH. Therapy for PAH included PDE-5 inhibitors (n=62, 68%), endothelin receptor antagonists (n=55, 60%), epoprostenol infusion (n=49, 53%), oral prostacyclin (n=42, 46%), and calcium blockers (n=12, 13%). Forty-seven patients received TRACLEER (51%). Monotherapy, double therapy, and triple therapy were used by 19 (20%), 30 (33%), and 38 (41%) of patients, respectively.	• The AUC for mPAP was 0.66 and the discriminating threshold was 52 mmHg (Youden index: 0.37; 100% sensitivity; 37% specificity). • Patients with a mPAP ≥52 mmHg at cardiac catheterization, a cardiothoracic ratio ≥55%, or a BNP level ≥300 pg/mL during follow-up were more likely to experience the primary endpoint (death or lung transplantation) than those without these parameters.	• Sixteen patients died. Causes of death included: pulmonary hypertensive crisis (n=5), respiratory failure (n=4), heart failure (n=2), ventricular tachycardia (n=1), sudden death (n=1), and other causes (n=3). Three patients underwent lung transplantation; 1 patient died due to associated complications.

Study Design and Population	Drug Regimen	Observations	Safety
Hislop et al (2011)[8] Retrospective, observational study of 101 pediatric patients with IPAH or CHD-APAH (mean age 9.7±5.5 years) treated with TRACLEER as monotherapy or in combination therapy. Objective: • Assess the efficacy and safety of TRACLEER in the management of children with PAH.	• Therapeutic regimen was tailored to the needs of each child and adjusted to response. • Target dose of TRACLEER was 31.5-125 mg BID according to weight. • 15 mg BID for children weighing <10 kg. • Addition of sildenafil or epoprostenol if patients deteriorated on TRACLEER monotherapy. • Median duration of treatment: 31.5 months (range 6-73).	• Height and weight z-scores did not change significantly during follow-up. • Initial improvement in WHO FC and maintained for up to 3 years. • 6MWD increased significantly from baseline at 6 months and maintained for up to 3 years. • Repeat cardiac catheterization after a median of 17 months (range 8-33) revealed no significant change in either mPAP or PVRI. • After 3 years, TRACLEER continued as monotherapy in only 21% of patients with IPAH, 69% of repaired cases, and 56% with ES. • Survival estimates: 95%, 89%, 83% and 60% at 1, 2, 3, and 5 years.	• Discontinuation of treatment in 7 patients: elevated alanine transaminase >3 × ULN (n=1), mild systemic hypotension (n=1), successfully weaned off (n=1), repeatedly refused to have liver function tests (n=4). • Fourteen patients with IPAH started on monotherapy (58%) required additional therapy for worsening of symptoms. • Sixteen patients with CHD-APAH started on monotherapy (37%) needed additional medication. • Seven patients underwent transplantation. • Twenty-one patients died.
Ivy et al (2010)[9] Retrospective cohort study of 86 consecutive pediatric (≤18 years of age) patients with IPAH or HPAH and CHD-APAH or CTD-APAH treated with TRACLEER with or without pre-existing IV epoprostenol or subcutaneous treprostinil. Objective: • Analyze long-term outcomes.	• TRACLEER as monotherapy (n=42) or as add-on to pre-existing continuous IV epoprostenol or subcutaneous treprostinil (n=44). • Median observation period: 39 months (range 2-60).	• WHO FC improvement in 24 patients (31%); worsening in 21 patients (27%). • WHO FC improvement in 44% of patients with IPAH/HPAH and in 20% of patients with CHD-APAH. • At 4 years, estimates of disease progression in patients while on TRACLEER: 54% (7 patients at risk) with a survival estimate of 82% (16 patients at risk). • Risk factors significantly associated with survival: WHO FC and indexed pulmonary vascular resistance.	• Worsening peripheral edema in 8 patients (9%) and systemic hypotension in 4 patients (5%). • Increases in liver transaminase levels (>3 × ULN) reported for 6 patients (7%), resulting in TRACLEER discontinuation in 4 patients. • At the end of data collection: 25 patients (29%) remained on TRACLEER, 43 (50%) had stopped TRACLEER, 11 (13%) had died while on TRACLEER, 2 had died after discontinuation of TRACLEER, and 7 were lost to follow-up.

Study Design and Population	Drug Regimen	Observations	Safety
Beghetti et al (2008)[10] Non-interventional, prospective, internet-based post marketing surveillance data analysis of 146 TRACLEER-naïve pediatric patients with PAH aged 2-11 years compared with the TRACLEER-naïve adult (≥12 years of age) patients (n=4443) in the database. Objective: • Investigate the safety profile of TRACLEER in pediatric patients compared to that in adolescent/adult patients.	• During the 30-month reporting period, 146 patients had initiated TRACLEER treatment in 13 countries under clinical practice conditions. • Approximately one-third of the patients (30.8%) received combination therapy with prostanoids and/or sildenafil.	• Median exposure to TRACLEER in pediatric patients: 29.1 weeks (range 0.1-119.6), similar to the 29.7 weeks (range 0.0-135.1) in patients ≥12 years.	• Elevated transaminase levels reported in 2.7% of pediatric patients vs 7.8% of patients ≥12 years. • Discontinuation rate was 14.4% in pediatric patients vs 28.1% in patients ≥12 years. • Most common reasons for discontinuation: death (7.5% in pediatric patients vs. 9.0% in adults), hospitalization (4.1% vs 3.8%, respectively), and AEs (2.7% vs 3.6%, respectively). • Other reasons for discontinuation: need for IV prostacyclin (0.7% in pediatric patients vs 2.0% in adults), need for transplantation or atrial septostomy (0.7% vs 1.0%). • AEs leading to discontinuation in pediatric patients: aggravated cardiac failure, pulmonary hypertension, cardiomyopathy, intracardiac thrombus; 1 AE was not specified.

Study Design and Population	Drug Regimen	Observations	Safety
Rosenzweig et al (2005)[11] Retrospective study of 86 pediatric patients (under 18 years of age) with IPAH, CHD-APAH, or CTD-APAH, in WHO FC I to IV treated with TRACLEER with or without concomitant IV epoprostenol or subcutaneous treprostinil. Objective: • Investigate the long-term outcome of children with PAH treated with TRACLEER.	TRACLEER target doses: • 31.25 mg BID for children weighing 10-20 kg • 62.5 mg BID for patients weighing 20-40 kg • 125 mg BID for patients weighing >40 kg • 15.6 mg BID for patients weighing <10 kg (n=3 in study) • Half target dose during the first 4 weeks and increased to target dose if well tolerated • Addition of IV epoprostenol or subcutaneous treprostinil when clinically significant deterioration occurred despite treatment with TRACLEER; dose according to investigator's judgment.	• Median exposure to TRACLEER: 14 months (range 2 to 28 months). • WHO FC improvement in 46% of patients (P<0.001), no change in 44%, and worsening by one class in 10% of patients on TRACLEER. • Decrease in mean pulmonary artery pressure (64±3 mmHg to 57±3 mmHg, P=0.005) and pulmonary vascular resistance (20±2 U·m^2 to 15±2 U·m^2, P=0.01) (n=49). • Survival estimates at 1 and 2 years: 98% and 91%, respectively. • Risk for worsening PAH was lower in patients in WHO FC I/II compared with patients in FC III/IV at TRACLEER initiation.	• Most frequent AE: peripheral edema (n=7, 8%). • Systemic hypotension reported in 3 patients (3%) • Fatigue leading to discontinuation in 2 patients (2%) 9 and 11 months after starting TRACLEER, which resolved after discontinuation • Two patients (2%) with unrepaired CHD discontinued TRACLEER 5 and 7 months after starting due to systemic arterial oxygen desaturation. • Asymptomatic increases in transaminase levels (>2 × ULN) reported in 10 patients (12%). • Five patients died during the study. All deaths considered to be due to clinical progression of PAH.

Abbreviations: 6MWD, 6-minute walk distance; AE, adverse event; AUC, area under the curve; BID, twice daily; CHD-APAH, pulmonary arterial hypertension associated with congenital heart disease; BNP, brain natriuretic peptide; FC, functional class; CTD-APAH, pulmonary arterial hypertension associated with connective tissue disease; ES, Eisenmenger syndrome; IPAH, idiopathic pulmonary arterial hypertension; IQR, interquartile range; mPAP, mean pulmonary arterial pressure; NYHA/WHO FC, New York Heart Association/World Health Organization functional class; PAH, pulmonary arterial hypertension associated with systemic sclerosis; PDE-5, phosphodiesterase; PH, pulmonary hypertension; PVRI, pulmonary vascular resistance index; ULN, upper limit of normal.

Summary of Retrospective, Safety Only Analyses With TRACLEER in Pediatrics With PAH

Study Design and Population	Drug Regimen	Observations	Safety
Roldan et al (2014)[12] Retrospective, longitudinal, observational study on 63 pediatric patients undergoing treatment with pulmonary targeted therapies (51% male, median age 3.4 years [IQR, 3.6 months to 10 years], median weight 13 kg [IQR, 6 to 30 kg]) Congenital heart disease was the etiology of pulmonary hypertension in the majority of cases (n=33) and 28 patients were in NYHA FC III/IV. Objective: Evaluate the safety and tolerability of the pharmacological treatment of PH in pediatric patients.	The most commonly used drug was sildenafil (n=79, 56%), followed by TRACLEER (n=27, 23%), and a combination of both (n=14, 41%).	• See safety.	• Thirty-four patients (54%) had adverse reactions with an incidence rate of 1.02 per patient per year. • The most commonly reported reactions were gastrointestinal symptoms (22%) and spontaneous erections (22%) in males. • Nine severe adverse reactions (10%) occurred, requiring 8 treatment withdrawals and one hospital admission. • Severe ADRs were uncommon both in monotherapy and in combination of therapy.
Maxey et al (2013)[13] • Retrospective review of 588 pediatric AE reports (death in 257 cases) for the 3 most commonly used therapies: TRACLEER, epoprostenol, and sildenafil between November 1997 and December 2009. The FDA postmarket records for PH medications in pediatric patients show a significant number of AEs.	TRACLEER, epoprostenol, and sildenafil.	• See safety.	• AEs occurring in more than 5% of events for each drug were assumed to be associated with the targeted PH medication. • A total of 342 AEs were reported for 326 patients receiving TRACLEER. • Liver function test abnormality (n=202, 62%) • Cardiac failure (n=37, 11%) • Syncope (n=28, 8.6%) • Bilirubin increased (n=24, 7.4%) • Thrombocytopenia (n=17, 5.5%), not been described previously in the pediatric literature. • Death was reported for 121 patients and clinical worsening for 68 patients. • It is not possible to discern whether these reported events were related to TRACLEER or the disease process.

Abbreviations: AE, adverse event; ADR, adverse drug reaction; IQR, interquartile range; NYHA FC, New York Heart Association functional class; PH, pulmonary hypertension.

Summary of Published Studies With TRACLEER in Neonates With PPHN

Study Design and Population	Drug Regimen	Observations	Safety
Maneenil et al (2017)[14] Retrospective medical records review of 40 neonates (gestational ages 36.8-40 weeks and OI of 29.2 [IQR, 13.4-40.1]) who received oral TRACLEER as an adjunctive therapy for treatment of PPHN (21 received iNO and TRACLEER and 19 received TRACLEER alone). Objective: Efficacy and safety of TRACLEER on oxygenation and hemodynamic status over 72 h period.	• TRACLEER 125 mg tablet crushed and dissolved in 5 mL of sterile water. • 1 mg/kg administered BID via orogastric tube. • Mean (SD) duration of therapy and number of doses of TRACLEER given to patients were 6.2 (3.1) days and 12.1 (6.8) doses, respectively.	• Significant improvement of OI, $AaDO_2$ and SpO_2 at 2 h after treatment (P=0.002, P=0.01 and P<0.001, respectively). • In the 21 (52.5%) neonates who received iNO and TRACLEER, the median OI was 34.2 (IQR, 29.0-42.6) with a significant decrease of OI at 6 h (P=0.005) after treatment. • In 19 (47.5%) neonates who received TRACLEER alone, the median OI was 13.0 (IQR, 9.8-30.9) with a significant decrease of OI in 2 h (P=0.01) after treatment.	• The blood pressures before and after TRACLEER treatment were not significantly different. • No adverse events observed except 1 patient with systemic hypotension shortly after TRACLEER initiation which required inotropic support. • Nineteen (47.5%) neonates needed new additional inotropic medications within 24 h of TRACLEER treatment. • Three neonates died in the iNO + TRACLEER group and 2 in the TRACLEER alone group.

Study Design and Population	Drug Regimen	Observations	Safety
Mohamed et al (2012)[15] Randomized, double-blind, placebo-controlled, prospective study of 47 neonates (gestational ages ≥34 weeks and <7 postnatal days of age) with PPHN (24 treated with TRACLEER, 23 with placebo). Objective: • Assess the efficacy and safety of TRACLEER as adjuvant therapy in PPHN.	• TRACLEER 125 mg tablet crushed to one-fourth and dissolved in 10 mL sterile water (3 mg in 1 mL). • 1 mg/kg administered BID or same volume of placebo via orogastric tube followed by administration of 1 mL sterile water. • Patients in the TRACLEER group were treated with study therapy for a mean 4.8±1.1 days (median 5 days; range 3-7)	• Favorable response in 87.5% of patients treated with TRACLEER compared with 20% of those treated with placebo (P<0.0001). • Significant improvement in OI and SpO_2 (P<0.05) in the TRACLEER group compared with the baseline and with the placebo group at 6 hours after initiation and thereafter. • Duration of mechanical ventilation in the TRACLEER group was significantly lower than that of placebo group (4.3±0.9 days, 11.5±0.6 days, respectively, P<0.001).	• Well tolerated. • No drug-related clinical or laboratory adverse events in patients treated with TRACLEER. • Overall PPHN major sequelae significantly lower in the TRACLEER vs the placebo group (P=0.0008). • One infant died in the TRACLEER group and 3 in the placebo group (P=0.14). • Normal neurologic assessment in all infants in the TRACLEER group; neurological sequelae in 28.5% of infants in the placebo group (P=0.01).

Abbreviations: $AaDO_2$, alveolar-arterial oxygen difference; BID, twice daily; iNO, inhaled nitric oxide; IQR, interquartile range; OI, oxygenation index; PPHN, persistent pulmonary hypertension of the newborn; SD, standard deviation; SpO_2, pulse oxygen saturation.

LITERATURE SEARCH

A literature search of MEDLINE®, Embase®, BIOSIS Previews®, and Derwent Drug File (and/or other resources, including internal/external databases) pertaining to this topic was conducted on 27 February 2025.

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