**VELETRI® (epoprostenol)**
**VELETRI - Treatment of PAH in the Pediatric Population via Intravenous Administration**

## SUMMARY


- The safety and efficacy of VELETRI in pediatric patients has not been established in randomized, controlled clinical trials. Please refer to your local labeling for the approved use of VELETRI.
- In the BREATHE-3 study, which investigated the pharmacokinetics, safety, and efficacy of bosentan in 19 pediatric patients ages 3-15 years with pulmonary arterial hypertension (PAH; idiopathic or secondary to congenital heart disease [CHD]), 10 of the patients were on stable VELETRI background therapy.[1]
- A prospective, multicenter, open-label study (N=3) was conducted to evaluate the effect of VELETRI on pulmonary vascular resistance index (PVRI) in Japanese children with idiopathic pulmonary arterial hypertension (IPAH; World Health Organization Functional Class [WHO FC] II-III), aged 8, 10, and 14 years. The mean±standard deviation (SD) change in PVRI from baseline to week 12 (primary endpoint) was -2.752±0.430 Wood units·m² (95% confidence limits [CL], -3.820 to -1.685). No adverse events leading to treatment discontinuation or dose reduction were reported.[2]
- A review of the published literature identified several studies of intravenous (IV) epoprostenol use in pediatric patients up to 22 years old. None of these articles refer to VELETRI for injection as the specific epoprostenol formulation administered.


## CLINICAL DATA

### Clinical Trials

#### *BREATHE-3*

BREATHE-3 was conducted to investigate the pharmacokinetics, safety, and efficacy of bosentan, a dual endothelin receptor antagonist, in 19 pediatric patients (aged 3 to 15 years) with PAH (idiopathic or secondary to CHD). More than half of these pediatric patients (n=10, 58%) were maintained on stable doses of VELETRI for at least 3 months prior to enrollment. Hemodynamic parameters were evaluated at week 12 in the whole cohort of patients and further in each group (bosentan monotherapy and combination with VELETRI).[1]

The mean changes from baseline to week 12 in the combination group for mean pulmonary arterial pressure (mPAP) were -6.5 mmHg (95% confidence interval [CI], -12.6 to -0.4 mmHg), for pulmonary vascular resistance index (PVRI) -39 $dyn \cdot s \cdot m^2/cm^5$ (95% CI, -413 to 334) and for cardiac index 0.41 $L \cdot min^{-1} \cdot m^{-2}$ (95% CI, -0.66 to 1.5).No statistically significant differences between the 2 groups were noted.[1]

The most frequently reported adverse events (AEs) for the whole cohort of patients were flushing (n=4), headache (n=3), and increased liver transaminase levels (n=3). There was no evidence of a drug-drug interaction between epoprostenol and bosentan.[1]

#### *Study AC-066A308 and AC-066A309*

Study AC-066A308 was a prospective, single-arm, multicenter, open-label study conducted to evaluate the efficacy, safety, and tolerability of VELETRI in Japanese children with PAH. VELETRI was administered by IV infusion for 12 weeks, starting from a dose of 0.5-2.0 ng/kg/min and increased in 0.5-2.0 ng/kg/min steps at intervals of 1-4 weeks to establish the optimal infusion rate while closely monitoring the patient's condition (including

PAH symptoms, blood pressure, heart rate, and hemodynamic parameters).[2] After completing the 12-week efficacy evaluation period, subjects were to participate in the long-term extension study (Study AC-066A309).[3] Safety at 52 weeks was also evaluated.[2]

Three pediatric patients with idiopathic PAH in WHO FC II and III, aged 8, 10, and 14 years, were enrolled. The mean±SD change in PVRI from baseline to week 12 (the primary endpoint), was -2.752±0.430 Wood units·$m^2$ (95% CL: -3.820 to -1.685). The changes in the three patients were -3.24, -2.59 and -2.43 Wood units·$m^2$. Mean right atrial pressure showed a mean±SD change of 1.7±1.5 mmHg [95% CL: -2.1 to 5.5] from baseline to week 12.[2]

All 3 patients had at least 1 AE (nasopharyngitis, diarrhea, decreased platelet count, contact dermatitis, pruritus, and headache), and 1 patient experienced serious adverse events (SAEs) of gastroenteritis and pneumonia. The treating physician assessed that neither SAE was related to the study drug. No adverse events leading to treatment discontinuation or dose reduction were reported.[2,3]

**Information From a Literature Search**

Several studies of IV epoprostenol use in pediatric patients were identified.

**Rosenzweig et al**[4] performed an open-label, single center study to assess long-term prostacyclin ($PGI_2$) treatment in patients with PAH secondary to congenital heart defects. Fourteen out of 20 study participants were 12 years of age or younger. Although none of the patients acutely responded to $PGI_2$ administration, among the 16 patients who underwent repeat right heart catheterization after 1 year on continuous $PGI_2$, mPAP significantly decreased and cardiac index and pulmonary vascular resistance (PVR) significantly improved. Additionally, New York Heart Association (NYHA) functional class improved significantly on long-term $PGI_2$.

**Ivy et al**[5] reported on a cohort of 8 pediatric patients (aged 8 to 17 years) with idiopathic pulmonary arterial hypertension (IPAH) who were treated with epoprostenol for a mean duration of 7.6 years (SD 2.3 years). All patients received additional bosentan therapy with the aim of reducing the epoprostenol dose. In 7 out of the 8 children, concomitant use of bosentan allowed a reduction in the epoprostenol dose without deterioration of clinical and hemodynamic parameters.

**Eronen et al**[6] conducted a study in 8 newborns with persistent pulmonary hypertension of the newborn (PPHN) treated with $PGI_2$ infusion. The authors reported that these 8 patients subsequently recovered without the need for extracorporeal membrane oxygenation (ECMO).

A brief summary of studies (N>30) in pediatric patients receiving epoprostenol is presented in Table: Summary of Published Studies Evaluating IV Epoprostenol in Pediatric Patients.

**Summary of Published Studies Evaluating IV Epoprostenol in Pediatric Patients**

| Study Design and Patient Population | Drug Regimen(s) | Efficacy Results | Safety |
|---|---|---|---|
| **Haworth et al**[7]<br><br>Retrospective study of 216 children with PAH, including 6 patients with IPAH who were treated with EPO monotherapy and 22 patients with IPAH who were treated with EPO in combination with bosentan, sildenafil, or both.<br><br>Endpoint:<br>• Survival | IPAH EPO cohort:<br>• IV EPO initiated at 2 ng/kg/min and increased until a satisfactory clinical response was obtained, up to 60 ng/kg/min or more in some children.<br>• EPO was administered alone or in combination with bosentan, sildenafil, or both. | • Among 6 children with IPAH treated with EPO monotherapy, predicted survival was 3.25±0.84 years.<br>• Among 22 children with IPAH treated with EPO in combination with bosentan, sildenafil, or both, predicted survival was 4.61±0.25 years.<br>• Among children with IPAH treated with bosentan and EPO combination, predicted survival was 4.11±0.7 years with, out of a possible 5 years, 20% dying. | • Not reported. |
| **Rosenzweig et al**[8]<br>**Ivy et al**[9]<br><br>Observational retrospective study of 86 children (age 11±5 years) with IPAH/HPAH (n=36), PAH-CHD (n=48) and PAH-CTD (n=2).<br><br>Endpoints:<br>• Survival<br>• Changes in hemodynamics | • 42 bosentan monotherapy<br>• 44 concomitant bosentan-prostanoid therapy (36 EPO and 8 treprostinil) | • Median observation period: 39 months (range 2-60)<br>• EPO dose for the 36 children treated with pre-existing IV EPO decreased at bosentan initiation from 73±42 ng/kg/min to 68±43 ng/kg/min at data cutoff date, and to 46±45 ng/kg/min at end of data collection.<br>• Survival estimates for the whole cohort at 1, 2, 3, and 4 years were 98%, 90%, 87% and 86%, respectively.<br>• Survival estimates in the group receiving concomitant prostanoid therapy for 1 and 2 years were 98% and 89%, respectively.<br>• No significant changes from baseline in hemodynamics were observed in the concomitant prostanoid group. | • The most frequently reported AEs for the whole cohort: worsening peripheral edema (n=8) and systemic hypotension (n=4).<br>• Asymptomatic increases in liver transaminases (>2 × ULN) were reported in 10 (12%) patients and no patients reported symptomatic increases in liver transaminases.<br>• Three patients in the group starting bosentan with concomitant prostanoid therapy died during the study. |

| Study Design and Patient Population | Drug Regimen(s) | Efficacy Results | Safety |
|---|---|---|---|
| **Siehr et al**[10]<br><br>Observational retrospective study of 77 children (mean age ± SD, 7.7±5.2 years) with PAH (IPAH, n=47; CHD-related PAH, n=24; other forms of WHO Group 1 IPAH, n=6)<br><br>Endpoint:<br>• Changes in hemodynamics<br>• Survival | • Initial therapy with IV EPO (n=37), initial therapy with IV or SC treprostinil (n=20), or IV or SC treprostinil following transition from IV EPO (n=20).<br>• Target dose of EPO: 30-50 ng/kg/min; target dose of treprostinil: 50-70 ng/kg/min. | • Mean follow-up of 4.3±3.4 years.<br>• With both EPO and treprostinil, an initial improvement in mean Rp/Rs was observed after 1-2 years but was not sustained.<br>• Similar changes were observed for PVR index and mPAP with both treatments.<br>• Among 7 evaluable patients who transitioned from EPO to treprostinil, mean Rp/Rs increased from 0.6 to 0.8 at 9 to 15 months, respectively, after transition.<br>• Overall, 5-year transplant-free survival for entire cohort was 70%. | • Sixteen patients died and 5 patients received a heart-lung transplant. |
| **Yung et al**[11]<br>**Barst et al**[12]<br><br>Observational retrospective/prospective study of 77 children (mean age ± SD, 7±4 years) with IPAH, including 35 who received EPO.<br><br>Endpoints:<br>• Survival<br>• Treatment success (freedom from death, transplantation, or atrial septostomy)<br>• Changes in hemodynamics | EPO cohort:<br>• IV EPO (specific regimen not reported). | Among 35 patients treated with EPO:<br>• Survival at 1, 5, and 10 years was 94%, 81%, and 61%, respectively.<br>• Mean survival time was 84±6 months.<br>• Treatment success at 1, 3, 5, and 10 years was 83%, 66%, 57%, and 37%, respectively.<br>• After a mean follow-up of 53±28 months (n=31), significant improvements in mPAP, cardiac index, PVR, and mixed venous saturation were noted (all $P<0.05$). | • Not reported. |

| Study Design and Patient Population | Drug Regimen(s) | Efficacy Results | Safety |
|---|---|---|---|
| **Lammers et al**[13]<br><br>Prospective study of 39 children (median age, 5.4 years; range, 4 months to 7 years) with severe PAH (IPAH, n=25; PAH associated with CHD, connective tissue disease, chronic lung disease, or HIV, n=14).<br><br>Endpoints:<br>• Survival<br>• Changes in WHO FC, weight, 6MWD | • IV EPO:<br>2 ng/kg/min, with increasing rate based on disease severity, clinical response, and development of AEs.<br>• Mean dose:<br>29.6±15.2 ng/kg/min (range, 6-63 ng/kg/min). | • Median follow-up of 27±21 months (range, 1-90 months).<br>• Cumulative survival at 1, 2, and 3 years was 94%, 90%, and 84%, respectively.<br>• Mean WHO FC significantly improved during first year of therapy (from baseline of 3.6 to 2.6, $P<0.001$) and remained stable throughout 3 years of treatment.<br>• Mean z-score for weight increased significantly during follow-up ($P<0.03$).<br>• Mean 6MWD increased significantly after a mean follow-up of 11.4±7.1 months ($P<0.003$). | • Hickman line replacement in 15/39 patients.<br>• Antibiotics required on 43 occasions, primarily due to local site infections. |
| **Nakayama et al**[14]<br><br>Retrospective study of 31 children (mean age±SD, 10.7±3.5 years) with IPAH<br><br>Endpoints:<br>• Survival<br>• Changes in WHO FC, 6MWD, hemodynamics | • IV EPO initiated at 0.5-2 ng/kg/min and increased by 0.5-1 ng/kg/min every 2 to 4 weeks until CI increased to 3.5 L/min/$m^2$ or Rp/Rs dropped below 0.5 in combination with supportive measures[a] | • Mean follow-up of 3.4 years (range, 1.2-6.1 years).<br>• Among 27 patients who received long-term EPO therapy, the event-free rate from death or lung transplantation after 1, 2, and 3 years was 100%, 96.3%, and 79.4%, respectively.<br>• Among 22 survivors, 18 improved from WHO FC III/IV to II and 4 remained in WHO FC III.<br>• 6MWD improved significantly from baseline at 3 years (to 524.3±85.7 m, $P<0.05$) and 4 years (to 530±70.8 m, $P<0.05$)<br>• After 2 years, mPAP and Rp/Rs remained elevated in the majority (n=13, 72%) of patients.<br>• Cardiac index increased significantly after 3 months and improved to a maximum of 58% in the fourth year. | • Four patients died and 1 patient underwent a living donor lobar lung transplantation. |

| Study Design and Patient Population | Drug Regimen(s) | Efficacy Results | Safety |
|---|---|---|---|
| **Hopper et al**[15]<br><br>Retrospective cohort study of children with PH between January 2001 and August 2015 at a single center (median age at $PGI_2$ start was 2.6 years)<br><br>Endpoints:<br>• Clinical and echocardiographic parameters of PH and RV function. | • IV EPO, IV/SC treprostinil, or inhaled treprostinil (specific regimen not reported) | • Participants received IV EPO (14%) and IV/SC (67%) or inhaled (18%) treprostinil.<br>• $PGI_2$ analogs were associated with improvement in qualitative RV function ($P$=0.037) by echocardiogram, and BNP ($P$<0.001), functional class ($P$=0.047) and 6MWD ($P$=0.001).<br>• The proportion of participants with moderate or severely diminished RV function decreased from 41% to 17% over the course of the study period ($P$=0.037).<br>• RV strain was abnormally low at baseline (-13.6%) and significantly improved over the study period ($P$<0.001). | • At last known follow-up, 16% patients had died or undergone lung transplantation. |
| **Hart et al**[16]<br><br>Observational, retrospective multicenter study of data from 280 PAH patients in the PHIS in the US (2004-2014)<br><br>Mean±SD age at EPO initiation: 10.4±5.4 years<br><br>Mean±SD age at treprostinil initiation: 10.9±6.0 years | • IV EPO or treprostinil | • EPO predominated in earlier years of the analysis (97% of initiations in 2005), treprostinil predominated in more recent years (52-67% of initiations/year).<br>• Children initiated on treprostinil vs EPO (median [IQR], unless otherwise stated: shorter intensive care unit (ICU) stays (1 [0-4] vs 4 [0-10] days, $P$<0.001), shorter total lengths of stay (4 [2-9] vs 8 [4-18] days, $P$=0.001), lower in-hospital mortality (1 vs 12%, $P$=0.001) (no out of hospital mortality data were available), lower intensive care utilization (62% vs 74%, $P$=0.05), no difference in 30-day, 90-day or 1 year readmission rates, no difference in the use of right heart catheterization, no difference in medical or surgical complications. | • Not reported |

| Study Design and Patient Population | Drug Regimen(s) | Efficacy Results | Safety |
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| **Tella et al**[17]<br><br>Observational, retrospective cohort study of data from 31 pediatric patients with PAH (April 1999-April 2019)<br><br>Endpoints:<br>• Clinical and hemodynamic response | • IV EPO (n=9) or treprostinil (n=13), or EPO transitioned to treprostinil (n=9)<br>• Generally, the dose was slowly increased with a goal of ~75-100 ng/kg/min for EPO and ~125-150 ng/kg/min for treprostinil | • Mean time to first follow-up: 14.1 months (median, 9 months; range, 3.5-81.4 months) for EPO and 11.1 months (median, 6.1 months; range, 3-54.9 months) for treprostinil.<br>• Average dose level at the first hemodynamic finding of ≥25% reduction in mPAP: 28.5±10.0 ng/kg/min for EPO and 88.1±18.9 ng/kg/min for treprostinil.<br>• Doses of EPO greater than ~60 ng/kg/min (~100 ng/kg/min for treprostinil) were not associated with lower mPAP.<br>• No association was observed between cardiac index and dose (*P*=0.431) with treprostinil; for EPO, there was an increase in cardiac index of 0.14 L/min/$m^2$ (95% CI: 0.02-0.26) with each additional 10 ng/kg/min (*P*=0.011).<br>• Cardiac index >41/min/$m^2$ was observed with modest and higher doses of prostanoid. | • Not reported by treatment; 13 patients (41.9%) had ≥1 AE; patients had a total of 29 AEs.<br>• The first AEs included listing for lung transplant (7 patients [22.6%]), death without lung transplant (3 patients [9.7%]), and balloon atrial septostomy (3 patients [9.7%]). |

| Study Design and Patient Population | Drug Regimen(s) | Efficacy Results | Safety |
|---|---|---|---|
| **Date N et al**[18]<br><br>Retrospective, nonrandomized, single-center study of 37 patients who underwent lung transplantation for PAH between June 2008 and July 2022. | • Preoperative IV EPO<br>• Of the 37 patients included in the study, 26 received IV EPO therapy<br>• Median EPO dose in the EPO group was 63 ng/kg/min (range, 3.5-200 ng/kg/min) | • Preoperative platelet counts were lower in the EPO group (127,000/μL) compared with the no-EPO group (176,000/μL).<br>• Platelet counts increased from 127,000/μL to 298,000/μL in the EPO group ($P$<0.001) and 176,000/μL to 284,000/μL in the no-EPO group ($P$=0.020) within 1 month after transplant.<br>• Median follow-up period was 51 months (IQR, 33-84 months).<br>• In a subgroup analysis of 24 patients with IPAH treated with EPO, 20 patients (83.3%) developed thrombocytopenia (54.1% mild, 25.0% moderate, 5.4% severe); preoperative characteristics, postoperative outcomes, and survival were comparable across severity groups, with no in-hospital deaths and 1- and 3-year survival rates of 100% in patients with normal or moderate/severe thrombocytopenia and 100% and 91.7%, respectively, in those with mild thrombocytopenia. | • The incidence of acute AEs during the early post-transplant period was comparable between the EPO and no-EPO groups.<br>• During observation period, 3 deaths occurred in the EPO group and 2 in the no-EPO group.<br>• 1- and 3-year survival rates were 96.0% and 91.4% in the EPO group respectively, and 80.8% at both time points in the no-EPO group. |

| Study Design and Patient Population | Drug Regimen(s) | Efficacy Results | Safety |
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| **Shah NR et al**[19]<br><br>Single-center, retrospective chart review of 57 neonates with CDH who required ECLS between January 1, 2013, and December 31, 2023. | • IV EPO<br>• Of the 57 patients, 40 received IV EPO during hospitalization, while 17 did not.<br>• IV EPO was initiated at 1-2 ng/kg/min and uptitrated in increments of 1-2 ng/kg/min every 6-8 hours to a target dose of 10-20 ng/kg/min, based on individual clinical status and response. | • Infants receiving EPO had more severe prenatal disease, with lower MRI O/E TFLV (20% vs 26.2%; *P*=0.042), higher rates of liver-up position (90% vs 64.7%; *P*=0.023), and greater prenatal classification as severe CDH (67.5% vs 35.3%; *P*=0.007).<br>• Among infants receiving EPO, prenatal prognostic indicators were similar between survivors and nonsurvivors.<br>• Most hernia defects were classified as type C/D (80%), and 68% of the hernia defects were repaired early (in <72 hours) during ECLS course with a patch or muscle flap.<br>• The median age at initiation of EPO was day of life 6 (IQR, 4-7) in survivors and day of life 8 (IQR, 7-16) in nonsurvivors (*P*=0.012).<br>• Survivors had a shorter duration of ECLS compared with nonsurvivors (11 vs 20 days; *P*=0.049) and significantly more ventilator-free days in the first 60 days of life (18 vs 0; *P*<0.05). | • Survival to hospital discharge was comparable between infants treated with EPO and those not treated (60% vs 64.7%; *P*=0.234).<br>• Refractory PH was the cause of death in 81% (13/16) of nonsurvivors. |
| **Garcia RU et al**[20]<br><br>Single-center, retrospective study of 24 CICU admissions of patients aged 0-18 years with PH between January 2012 and March 2022.<br>• The mean age of patients was 3.1 years (range, 0-16.6 years). | • IV EPO, IV/SC treprostinil | • $PGI_2$ therapy included IV EPO in 12 (50%) patients, IV treprostinil in 6 (25%) patients, and SC treprostinil in 6 (25%) patients.<br>• The mean initial $PGI_2$ dose was 2.79 ng/kg/min (SD, 2.68), with a mean maximum dose of 18.75 ng/kg/min (SD, 17.99); mean treatment duration of $PGI_2$ in CICU was 38.5 days (SD, 89.4).<br>• At $PGI_2$ initiation, 21 (87.5%) of patients were receiving vasoactive infusions, 19 (79.2%) were mechanically ventilated, and 6 (25%) were on VA-ECMO. | • Mean CICU length of stay was 41.8 days (SD, 43.7), and mean hospital length of stay was 54.6 days (SD, 52.3).<br>• In-hospital mortality was 37.5% (n=9).<br>• Mechanical ventilation and VA-ECMO support were associated with a higher risk of mortality (*P*=0.04 and *P*<0.01, respectively). |

| Study Design and Patient Population | Drug Regimen(s) | Efficacy Results | Safety |
|---|---|---|---|

**Abbreviations**: 6MWD, 6-minute walking distance; ACE, angiotensin-converting enzyme; AE, adverse event; CDH, congenital diaphragmatic hernia; CHD, congenital heart disease; CICU, cardiac intensive care unit; CI, confidence interval; CTD, Connective tissue disorder; ECLS, extracorporeal life support; EPO, epoprostenol; FC, functional class; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; IQR, interquartile range; IV, intravenous; IPAH, idiopathic pulmonary hypertension; mPAP, mean pulmonary artery pressure; MRI, magnetic resonance imaging; O/E TFLV, observed/expected total fetal lung volume; PAH, pulmonary arterial hypertension; $PGI_2$, prostacyclin; PH, pulmonary hypertension; PHIS, Pediatric Health Information System; PVR, pulmonary vascular resistance; Rp/Rs, pulmonary-to-systemic vascular resistance ratio; RV, right ventricular; SC, subcutaneous; SD, standard deviation; ULN, upper limit of normal; US, United States; VA-ECMO, venoarterial extracorporeal membrane oxygenation; WHO, World Health Organization.

[a]Prior to 2003, supportive measures included catecholamine or phosphodiesterase-III inhibitors (for WHO FC IV patients), oxygen therapy, warfarin, diuretics, digoxin, and ACE inhibitors; after July 2003, sildenafil added as additional therapy (n=16).

One article which reviewed postmarketing AE reports associated with current PAH therapies is summarized below.

A publication reviewed postmarketing AE reports associated with current therapies in pediatric pulmonary hypertension, requested from the Food and Drug Administration (FDA) in January 2010. A total of 157 AEs were reported for 175 patients (aged 0 to 18 years) receiving epoprostenol. Of these, 108 reports listed death as the outcome. As reported, 10 AEs were present in more than 5% of the records, including pulmonary hemorrhage (n=23, 13.1%), cardiac failure (n=17, 9.7%), hemoptysis (n=14, 8%), right ventricular failure (n=14, 8%), cardiac arrest (n=13, 7.4%), dyspnea (n=11, 6.3%), cyanosis (n=9, 5%), hypoxia (n=9, 5%), oxygen saturation decrease (n=9, 5%), and pneumonia (n=9, 5%). Clinical worsening was noted in 21 patients. A total of 132 patients receiving epoprostenol monotherapy reported 78 unique AEs and 140 total AEs.[21]

The search also identified several case reports describing the use of epoprostenol as monotherapy or combined therapy in neonates or pediatric patients with various PAH etiologies: PAH associated with CHD,[22,23] portopulmonary hypertension (PoPH),[24-27] IPAH or hereditary PAH,[28-33] PAH associated with incontinentia pigmenti,[34] PAH of unknown etiology,[35] persistent pulmonary hypertension associated with preterm refractory shock,[36] systemic sclerosis sine scleroderma with PAH,[37] pulmonary hypertension crisis,[38] refractory pulmonary hypertension associated with alveolar capillary dysplasia[39,40], pulmonary hypertension associated with pediatric heart transplantation,[41] pulmonary hypertension associated with neuroblastoma,[42] Bone morphogenetic protein receptor type 2 (BMPR2) variant-associated PAH,[43] and PoPH with secondary pulmonary hypertension.[44]

In addition, there are a limited number of publications describing epoprostenol background therapy before switching to other PAH specific medications or mentioning pediatric patients among the adult patient cohort cited.[45-58] The amount of data pertaining to epoprostenol is limited.

It should be noted that the references mentioned should not be interpreted as a comprehensive review of all literature on this subject. Please also note that none of these articles refer to VELETRI for injection as the specific epoprostenol formulation administered. All publications should be consulted for full information.

## LITERATURE SEARCH

A literature search of MEDLINE®, EMBASE®, BIOSIS Previews®, DERWENT® (and/or other resources, including internal/external databases) was conducted on 11 March 2026.

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