VELETRI® (epoprostenol)
Use of VELETRI in Pediatric Patients

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 PAH (idiopathic or secondary to congenital heart disease [CHD]), 10 of the patients were on stable VELETRI background therapy.[1]
- A small (N=3) prospective, multicenter, open-label, phase 3 study was designed with the primary objective to evaluate the effect of VELETRI on pulmonary vascular resistance index (PVRI) in Japanese children with PAH (WHO Functional Class [FC] II and III, aged 8, 10 and 14 years). The mean change in PVRI from baseline to week 12 (the primary endpoint), was –2.75 Wood units·m^2 (95% CI: –3.82, –1.69). No unexpected safety or tolerability concerns 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·s·m^2/cm^5 (95% CI, -413 to 334) and for cardiac index 0.41 L·min^{-1}·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 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

Study AC-066A308 was a small prospective, single-arm, multicenter, open-label phase 3 study 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 low dose (0.5-2.0 ng/kg/min) and increasing by 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). Further dose escalation was stopped upon development of prostacyclin-associated adverse events (eg,

flushing, headache, nausea), even if mild (excluding mild flushing), and the dosing rate was reduced by 0.5-2.0 ng/kg/min if these symptoms persisted. Three pediatric patients with idiopathic PAH in WHO FC II and III, aged 8, 10 and 14 years were enrolled.[2]

The mean±standard deviation (SD) duration of study treatment was 12.48±0.30 weeks (87.3±2.1 days), with a mean±SD infusion rate of 11.35±4.44 ng/kg/min (initiated at 0.5-1.0 ng/kg/min, up to 12.91-22.44 ng/kg/min at Week 12). No patient discontinued, interrupted, or decreased dose at any time during the treatment period.[2]

The mean change in PVRI from baseline to week 12 (the primary endpoint), was -2.75 Wood units·m^2 (95% CI: –3.82, –1.69). 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 increase from baseline to week 12 (1.7 mmHg [95% CI: –2.1, 5.5]).[2]

All 3 patients had at least 1 adverse event (AE), and 1 serious AE (SAE) was reported (gastritis, moderate in intensity). No unexpected safety or tolerability concerns were reported.[2]

Information From a Literature Search

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

Rosenzweig et al[3] 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[4] 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[5] conducted a study in 8 newborns with persistent pulmonary hypertension of the newborn (PPHN) treated with prostacyclin 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 below.

Summary of Published Studies Evaluating IV Epoprostenol in Pediatric Patients

Study Design and Patient Population	Drug Regimen(s)	Efficacy Results	Safety
Haworth et al[6] Retrospective study of 216 children with PAH, including 6 patients with IPAH who were treated with epoprostenol monotherapy and 22 patients with IPAH who were treated with epoprostenol in combination with bosentan, sildenafil, or both. Endpoint: • Survival	IPAH epoprostenol cohort: • IV epoprostenol 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. • Epoprostenol was administered alone or in combination with bosentan, sildenafil, or both.	• Among 6 children with IPAH treated with epoprostenol monotherapy, predicted survival was 3.25±0.84 years. • Among 22 children with IPAH treated with epoprostenol in combination with bosentan, sildenafil, or both, predicted survival was 4.61±0.25 years. • Among children with APAH treated with bosentan and epoprostenol combination, predicted survival was 4.11±0.7 years with, out of a possible 5 years, 20% dying.	• Not reported.
Rosenzweig et al[7] **Ivy et al**[8] Observational retrospective study of 86 children (age 11±5 years) with IPAH/HPAH (n=36), PAH-CHD (n=48) and PAH-CTD (n=2). Endpoints: • Survival • Changes in hemodynamics	• 42 bosentan monotherapy • 44 concomitant bosentan -prostanoid therapy (36 epoprostenol and 8 treprostinil)	• Median observation period: 39 months (range 2-60) • Epoprostenol dose for the 36 children treated with pre-existing intravenous epoprostenol 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. • Survival estimates for the whole cohort at 1, 2, 3, and 4 years were 98%, 90%, 87% and 86%, respectively. • Survival estimates in the group receiving concomitant prostanoid therapy at 1 and 2 years were 98% and 89%, respectively. • 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). • Asymptomatic increases in liver transaminases (>2 × ULN) were reported in 10 (12%) patients and no patients reported symptomatic increases in liver transaminases. • 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[9] 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) Endpoint: • Changes in hemodynamics • Survival	• Initial therapy with IV epoprostenol (n=37), initial therapy with IV or SC treprostinil (n=20), or IV or SC treprostinil following transition from IV epoprostenol (n=20). • Target dose of epoprostenol: 30-50 ng/kg/min; target dose of treprostinil: 50-70 ng/kg/min.	• Mean follow-up of 4.3±3.4 years. • With both epoprostenol and treprostinil, an initial improvement in mean Rp/Rs was observed after 1-2 years but was not sustained. • Similar changes were observed for PVR index and mPAP with both treatments. • Among 7 evaluable patients who transitioned from epoprostenol to treprostinil, mean Rp/Rs increased from 0.6 to 0.8 at 9 to 15 months, respectively, after transition. • 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[10] **Barst et al**[11] Observational retrospective/prospective study of 77 children (mean age ± SD, 7±4 years) with IPAH, including 35 who received epoprostenol. Endpoints: • Survival • Treatment success (freedom from death, transplantation, or atrial septostomy) • Changes in hemodynamics	Epoprostenol cohort: • IV epoprostenol (specific regimen not reported).	Among 35 patients treated with epoprostenol: • Survival at 1, 5, and 10 years was 94%, 81%, and 61%, respectively. • Mean survival time was 84±6 months. • Treatment success at 1, 3, 5, and 10 years was 83%, 66%, 57%, and 37%, respectively. • 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[12] 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). Endpoints: • Survival • Changes in WHO FC, weight, 6MWD	• IV epoprostenol 2 ng/kg/min, with increasing rate based on disease severity, clinical response, and development of AEs. • Mean dose: 29.6±15.2 ng/kg/min (range, 6-63 ng/kg/min).	• Median follow-up of 27±21 months (range, 1-90 months). • Cumulative survival at 1, 2, and 3 years was 94%, 90%, and 84%, respectively. • 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. • Mean z-score for weight increased significantly during follow-up ($P<0.03$). • 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. • Antibiotics required on 43 occasions, primarily due to local site infections.
Nakayama et al[13] Retrospective study of 31 children (mean age ± SD, 10.7±3.5 years) with IPAH Endpoints: • Survival • Changes in WHO FC, 6MWD, hemodynamics	• IV epoprostenol 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). • Among 27 patients who received long-term epoprostenol therapy, the event-free rate from death or lung transplantation after 1, 2, and 3 years was 100%, 96.3%, and 79.4%, respectively. • Among 22 survivors, 18 improved from WHO FC III/IV to II and 4 remained in WHO FC III. • 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, $P<0.05$) • After 2 years, mPAP and Rp/Rs remained elevated in the majority (n=13, 72%) of patients. • 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[14] Retrospective cohort study of children with PH between January 2001 and August 2015 at a single center (median age at prostacyclin start was 2.6 years) Endpoints: • Clinical and echocardiographic parameters of PH and RV function	• IV epoprostenol, IV/SC treprostinil, or inhaled treprostinil (specific regimen not reported)	• Participants received IV epoprostenol (14%) and IV/SC (67%) or inhaled (18%) treprostinil. • Prostacyclin analogues 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). • 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). • 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[15] Observational, retrospective multicenter study of data from 280 PAH patients in the Pediatric Health Information System (PHIS) in the US (2004-2014) Mean±SD age at epoprostenol initiation: 10.4±5.4 years Mean±SD age at treprostinil initiation: 10.9±6.0 years	• IV epoprostenol or treprostinil	• Epoprostenol predominated in the earlier years of the analysis (97% of initiations in 2005), treprostinil predominated in more recent years (52-67% of initiations/year). • Children initiated on treprostinil vs epoprostenol (median [IQR], unless otherwise stated: shorter 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
Tella et al[16] Observational, retrospective cohort study of data from 31 pediatric patients with PAH (April 1999-April 2019) Endpoints: • Clinical and hemodynamic response	• IV epoprostenol (n=9) or treprostinil (n=13), or epoprostenol transitioned to treprostinil (n=9) • Generally, the dose was slowly increased with a goal of ~75–100 ng/kg/min for epoprostenol 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 epoprostenol and 11.1 months (median, 6.1 months; range, 3-54.9 months) for treprostinil. • Average dose level at the first hemodynamic finding of ≥25% reduction in mPAP: 28.5±10.0 ng/kg/min for epoprostenol and 88.1±18.9 ng/kg/min for treprostinil. • Doses of epoprostenol greater than ~60 ng/kg/min (~100 ng/kg/min for treprostinil) were not associated with lower mPAP. • No association was observed between cardiac index and dose (P=0.431) with treprostinil; for epoprostenol, 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). • 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. • 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%]).

Abbreviations: 6MWD, 6-minute walking distance; ACE, angiotensin-converting enzyme; AE, adverse event; CHD, congenital heart disease; CI, confidence interval; FC, functional class; HIV, human immunodeficiency virus; HPAH, heritable pulmonary arterial hypertension; IV, intravenous; IPAH, idiopathic pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; Rp/Rs, pulmonary-to-systemic vascular resistance ratio; RV, right ventricular; SC, subcutaneous; ULN, upper limit of normal; 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 adverse event (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 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 adverse events and 140 total adverse events.[17]

The search also identified several case reports describing epoprostenol as mono- or combined therapy for neonates or pediatric patients with various PAH etiologies: PAH associated to CHD,[18,19] portopulmonary hypertension (PoPH),[20-23] IPAH or hereditary PAH,[24-28] PAH associated with multisystemic disorder,[29] persistent pulmonary hypertension associated with preterm refractory shock,[30] systemic sclerosis sine scleroderma with PAH,[31] pulmonary hypertension crisis,[32] and refractory pulmonary hypertension associated with alveolar capillary dysplasia.[33,34]

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.[35-48] 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 5 April 2024.

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