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## Results of the Fontan Udenafil Exercise Longitudinal (FUEL) Trial

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## Abstract

**Background:** The Fontan operation creates a total cavopulmonary connection, a circulation in which the importance of pulmonary vascular resistance is magnified. Over time, this circulation

leads to deterioration of cardiovascular efficiency associated with a decline in exercise performance. Rigorous clinical trials aimed at improving physiology and guiding pharmacotherapy are lacking.

**Methods:** The Fontan Udenafil Exercise Longitudinal (FUEL) Trial was a Phase III clinical trial conducted at 30 centers. Participants were randomly assigned udenafil, 87.5 mg twice daily, or placebo in a 1:1 ratio. The primary outcome was the between group difference in change in oxygen consumption at peak exercise. Secondary outcomes included between group differences in changes in sub-maximal exercise at the ventilatory anaerobic threshold (VAT), the myocardial performance index (MPI), the natural log of the reactive hyperemia index (lnRHI), and serum brain-type natriuretic peptide (BNP).

**Results:** Between 2017 and 2019, 30 clinical sites in North America and the Republic of Korea randomized 400 participants with Fontan physiology. The mean age at randomization was 15.5 ±2 years; 60% of participants were male and 81% were White. All 400 participants were included in the primary analysis with imputation of the 26-week endpoint for 21 participants with missing data (11 randomized to udenafil and 10 to placebo). Among randomized participants, peak oxygen consumption increased by 44 ±245 mL/min (2.8%) in the udenafil group and declined by 3.7 ±228 mL/min (-0.2%) in the placebo group (p=0.071). Analysis at VAT demonstrated improvements in the udenafil group versus the placebo group in oxygen consumption (+33 ±185 (3.2%) vs -9 ±193 (-0.9%) mL/min, p=0.012), ventilatory equivalents of carbon dioxide (-0.8 vs -0.06, p=0.014), and work rate (+3.8 vs +0.34 Watts, p=0.021). There was no difference in change of MPI, lnRHI, or serum BNP level.

**Conclusion:** In the FUEL trial, treatment with udenafil (87.5 mg twice daily) was not associated with an improvement in oxygen consumption at peak exercise but was associated with improvements in multiple measures of exercise performance at the ventilatory anaerobic threshold.

### Keywords

Fontan operation; phosphodiesterase type 5 inhibitor; congenital heart disease; exercise stress test

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Children born with single ventricle congenital heart disease (SV-CHD) require a series of surgical interventions for long-term survival. The Fontan operation, the final planned palliative procedure in this series, separates the systemic and pulmonary circulations by creating a total cavopulmonary connection<sup>1, 2</sup>. In the absence of a sub-pulmonary pump, however, the resultant Fontan circulation is characterized by passive pulmonary blood flow, chronically elevated central venous pressure, and low cardiac output<sup>3-6</sup>. Although Fontan physiology is often well tolerated during childhood, cardiovascular efficiency deteriorates through adolescence and into adulthood<sup>7-12</sup>. This deterioration correlates with a decline in exercise capacity and an increase in the prevalence of heart failure symptoms, hospitalizations, and mortality<sup>13-19</sup>.

After the Fontan operation, pulmonary blood flow is dependent on the relationship between central venous pressure, pulmonary vascular resistance, and systemic atrial pressure. In this construct, the role of pulmonary vascular resistance as a modulator of pulmonary blood flow and single ventricular preload is magnified and critical to circulatory efficiency<sup>3-6</sup>. Prior reports have explored the administration of pulmonary vasodilators, including

phosphodiesterase type 5 (PDE5) inhibitors, with mixed results<sup>20–29</sup>. A phase I/II study of udenafil (Mezzion Pharma Co. Ltd., Seoul, Republic of Korea), a long-acting PDE5 inhibitor, was previously completed in adolescents with Fontan physiology and demonstrated tolerability at all tested dosing regimens<sup>30</sup>. A dose of 87.5 mg twice daily was associated with the highest average serum concentration and was not associated with dose-limiting adverse events. In the Pediatric Heart Network's (PHN) Fontan Udenafil Exercise Longitudinal (FUEL) trial [], we evaluate the effect of udenafil on exercise performance and other cardiovascular and functional outcomes over a six-month period in adolescents who have undergone Fontan palliation.

## Methods

The FUEL trial was an international, multicenter, randomized, double-blind, placebo-controlled trial of udenafil, in addition to standard care, in adolescents with SV-CHD who had undergone Fontan palliation. The trial was supported by the National Heart, Lung, and Blood Institute (NHLBI)-funded PHN in partnership with the regulatory sponsor, Mezzion Pharma Co. Ltd., under a Special Protocol Assessment through the Food and Drug Administration. The FUEL protocol and consent forms and all subsequent amendments were approved by the DSMB, the institution review board or equivalent at each study center, and regulatory agencies from the United States, Canada, and the Republic of Korea. Consent was obtained from the study participant, or the legal guardian for those <18 years of age. Assent was obtained from participants <18 years of age. The trial design has been published previously<sup>31</sup> and the data that support the findings of this study are available from the corresponding author upon reasonable request.

The FUEL protocol was primarily authored by the first and last authors with assistance from the protocol development committee, which consisted of at least one member from each PHN core institution, as well as representatives from Mezzion and the PHN leadership team. The data for this trial were collected by center investigators and analyzed by the data coordinating center (New England Research Institutes). An independent Medical Monitor adjudicated all serious adverse events and an independent Data and Safety Monitoring Board (DSMB), appointed by NHLBI, reviewed interim data, including safety data, at semi-annual DSMB meetings. The lead statistician (second author) vouches for the accuracy of the data and analyses, and all the authors vouch for the fidelity of this report to the trial protocol.

## Trial Population

Individuals between the ages of 12 and 18 years (inclusive) who had undergone the Fontan procedure, who were not receiving treatment with a PDE5 inhibitor, who were < 40 kg, and who met the minimum height requirement for cycle ergometry ( > 132 cm) were eligible for enrollment. To isolate the effect of udenafil on exercise performance, patients with severe ventricular dysfunction, severe atrioventricular valve insufficiency, or those with a prior clinical exercise test in which peak oxygen consumption was <50% of predicted for age and sex, were excluded. The full list of inclusion and exclusion criteria are listed in the study protocol.

## Randomization and Study Procedures

Enrolled participants were assigned to udenafil or placebo in a 1:1 ratio in a double-blind manner using randomly permuted blocks and stratified by ventricular morphology (left ventricle versus right ventricle or mixed). Randomization assignments were generated by a web-based algorithm after confirmation of trial eligibility and consent.

Baseline clinical testing completed before drug initiation included a blood draw to measure brain-type natriuretic peptide (BNP) level, a cardiopulmonary exercise test (CPET) using a standardized cycle ergometer ramp protocol (previously described in children and adolescents with Fontan physiology<sup>32</sup>), a standardized echocardiogram, and an assessment of peripheral vascular function using peripheral arterial tonometry (PAT) measured by finger cuff (EndoPAT; Itamar Medical, Israel). Participants who achieved maximal effort, defined as respiratory exchange ratio (RER)  $\geq 1.10$  at peak exercise during CPET, were eligible for randomization and study drug initiation. Participants who didn't achieve maximal effort were given a subsequent opportunity to repeat the exercise test within two weeks of the initial attempt. End-of-study clinical testing included repeat measurement of serum BNP, CPET, echocardiogram, and PAT.

## Primary and Secondary End Points

The primary aim was to determine the effect of udenafil on exercise capacity in adolescents with Fontan physiology over a six-month period. The primary outcome was the between group difference in the change in oxygen consumption at peak exercise (peak  $\text{VO}_2$ ) from baseline to the 26-week visit. Secondary exercise outcomes included between group differences in change in additional measures at maximal exertion, as well as change in measures of submaximal exercise at the ventilatory anaerobic threshold (VAT). All measurement of values for exercise testing were initially made by the exercise physiologists and physicians at the individual participating sites. These were subsequently reviewed for accuracy in a blinded fashion at each site by one of two trained reviewers (MGM, SMP) in conjunction with the sites' exercise teams prior to finalization. For both peak  $\text{VO}_2$  and  $\text{VO}_2$  at VAT, unindexed oxygen consumption was evaluated to avoid the introduction of confounding based on short-term change in body habitus. An analysis of oxygen consumption corrected for body weight is included as Supplemental Table 1.

The primary outcome for clinical secondary aims included the between group differences in change in myocardial performance index (MPI), an echocardiographically-derived measure of systolic and diastolic ventricular function, change in log-transformed reactive hyperemia index (lnRHI), a PAT-derived measure of peripheral vascular function, and change in log-transformed serum BNP level. Measurements for each of these secondary outcomes were performed at core labs. Safety was monitored through adverse event reports, which were collected according to a pre-specified protocol of study coordinator outreach, and through *ad hoc* patient and family communication with members of the study team at each site.

## Statistical Analysis

A sample size of 200 participants per arm was chosen to allow for 90% power to detect a mean treatment difference in change from baseline to 26-week testing in peak  $\text{VO}_2$  of 10% with a type 1 error of 0.05. We assumed a baseline standard deviation of 7.235 ml/kg/min, a correlation between peak  $\text{VO}_2$  measurements of 0.33, a drop-out and incomplete testing rate of 10%, and failure to reach maximal effort at the 26-week exercise testing in 15% of participants. These assumptions were based on historical data and reflect a conservative approach to assessing within-participant correlations and failure to reach maximal effort and the analysis was performed using a two-sample, independent means t-test. The primary analysis used the intention-to-treat population to evaluate the difference in the change in the primary outcome between treatment arms. This difference was assessed with an analysis of covariance (ANCOVA) with fixed factors for ventricular morphology (single left versus single right or mixed) and treatment group, with a continuous covariate of baseline peak  $\text{VO}_2$ . For those without data at the 26-week visit, this value was imputed as equal to the baseline value (no change). The alpha level was set at 0.05 with two-sided testing. All statistical analyses were performed using SAS statistical software 9.4 (SAS Institute, Inc., Cary, North Carolina). Secondary analyses included participants who successfully completed the protocol with measurable values at each of the secondary endpoints. Secondary outcomes of continuous data points were analyzed in the manner described for the primary outcome. In order to assess the generalizability of findings at the ventilatory anaerobic threshold, demographic and clinical characteristics were compared between participants without paired  $\text{VO}_2$  at VAT data and those comprising the remainder of the cohort using the Student's t-test and Fisher's exact test. Fisher's exact test was used to compare adverse events between the udenafil and placebo cohorts.

## Results

### Participants

From July 2016 to May 2018, 1376 patients at 30 centers were screened (Figure 1). Of these, 200 were randomly assigned to udenafil and 200 to placebo. Mean age at randomization was 15.5 years, mean height was 163.6 cm, and mean weight was 58.1 kg. Sixty percent of participants were male and 81% described their racial identity as white. Those in the placebo group were taller, compared to those in the udenafil group, but baseline characteristics were otherwise similar between groups (Table 1).

### Exercise measures

Resting, submaximal, and maximal exercise measures are presented in Table 2. Maximal exercise data were available for all participants at baseline testing, and for 379 participants at 26-week testing (189 in the udenafil group and 190 in the placebo group). Reasons for absence of data at 26-week testing included patient dropout or errors in data capture (n=14) and participant inability to generate an  $\text{RER} \geq 1.10$  (n=7). There was no difference in the change from baseline to 26-week testing in resting heart rate, respiratory rate, or systolic blood pressure between the udenafil and placebo groups. Peak minute ventilation at baseline (pre-drug exposure) was higher in the placebo group, but there was no difference in the

change in minute ventilation between groups. There was a small but statistically significant increase in resting oxygen saturation and a small but statistically significant decrease in diastolic blood pressure in the udenafil group.

Analysis at maximal exercise demonstrated an increase in peak  $\text{VO}_2$  of 44 mL/min (2.8%) in the udenafil group compared to a decline of 3.7 mL/min (-0.2%) in the placebo group, although the difference did not reach statistical significance (Figure 2,  $p=0.071$ ). Metabolic data for the calculation of  $\text{VO}_2$  at VAT were available for 317 participants; 155 in the udenafil group and 162 in the placebo group. There was no difference in the baseline demographic or clinical characteristics of this subgroup compared to the larger cohort (Supplemental Table 2). For those with paired  $\text{VO}_2$  at VAT data, there was a statistically significant improvement of 33 mL/min (3.2%) in the udenafil group compared to a decrease of 9 mL/min (-0.9%) in the placebo group (Figure 3,  $p=0.012$ ). Ventilatory equivalents of carbon dioxide measured at VAT ( $\text{VE}/\text{VCO}_2$ ) significantly decreased (improved ventilatory efficiency) by 0.8 in the udenafil group compared to 0.06 in the placebo group ( $p=0.014$ ), while the work rate significantly improved by 3.8 Watts (5.7%) in the udenafil group compared to 0.34 Watts (0.5%) in the placebo group (Figure 4,  $p=0.021$ ).

### Secondary aims

Paired echocardiographic data for the measure of MPI were available in 250 participants (63%); 122 in the udenafil group and 128 in the placebo group (Table 3). There were small, non-significant decreases (improvement) in MPI in both the udenafil and placebo groups (-0.02 vs -0.01,  $p=0.34$ ). Paired PAT-derived vascular function data were available in 328 participants (81%); 163 in the udenafil group and 165 in the placebo group. There were non-significant improvements in  $\ln\text{RHI}$  in both the udenafil and placebo groups (0.07 vs 0.05,  $p=0.59$ ). Paired measures of serum BNP level were available in 378 participants (95%); 187 in the udenafil group and 191 in the placebo group. The change in log serum BNP level was not different between groups ( $p=0.18$ ).

### Safety and tolerability

Udenafil and placebo were well tolerated by study participants. There were no deaths in the study cohort. A total of 24 participants (6%) experienced a serious adverse event; 14 in the udenafil group and 10 in the placebo group. There were 3 events in the udenafil group and 2 events in the placebo group that were thought to have a possible, probable, or definite relationship to study drug. Those that occurred in the udenafil group included unilateral retinal artery and vein thrombosis, transient lower extremity diplegia, and transient dyspnea. Frequent non-serious adverse events thought to have a possible, probable, or definite relationship to study drug are listed in Table 4. Headache, facial flushing, abdominal pain, epistaxis, and erection (male participants) were more common in the udenafil group. There were no reported episodes of priapism. All other adverse events occurred with similar frequency between the groups.

## Discussion

We report the results of the FUEL trial, a phase III clinical trial of udenafil in children with SV-CHD who have undergone the Fontan operation. Although the relative improvement in peak  $\text{VO}_2$  in the udenafil group did not reach statistical significance when compared between treatment arms, treatment with udenafil did lead to statistically significant improvements in pre-specified secondary outcome measures of sub-maximal exercise. Participants randomized to udenafil had superior gains in oxygen consumption, work rate, and ventilatory efficiency at the anaerobic threshold. We did not see a relative improvement in the myocardial performance index or in the PAT-derived reactive hyperemia index. Overall, udenafil was well tolerated with few serious adverse events and side effects limited to those known to be associated with PDE5 inhibitor therapy<sup>21, 33, 34</sup>.

While the Fontan operation and its modifications have led to the survival of a generation of patients with otherwise terminal SV-CHD, the circulation created by that procedure suffers from inherent physiologic flaws: central venous pressure is chronically elevated and cardiac output is chronically diminished<sup>3-5</sup>. Fundamental limitations to cardiovascular efficiency in the Fontan circulation are many, and commonly include abnormalities in pulmonary vascular resistance, single ventricular diastolic function, systemic and pulmonary vascular endothelial dysfunction, pathologic vascular remodeling, and others<sup>4, 35-40</sup>. Although each pathologic feature of the circulation may represent a potential therapeutic target, pharmacotherapy with agents designed to lower pulmonary vascular resistance make intuitive sense given their broad tolerability, their efficacy for the treatment of pulmonary hypertension, and the unique role of pulmonary vascular resistance as a modulator of cardiac output after Fontan<sup>4</sup>.

Despite the inherent appeal of pulmonary vasodilators, prior studies in those with the Fontan circulation have been equivocal<sup>20-29</sup>. A number of small, single-site studies across a range of classes of pulmonary vasodilators have demonstrated an acute improvement after a single dose, but these did not look at sustained effect or chronic usage<sup>24, 26, 27, 29</sup>. There have been two moderate-sized studies that have evaluated the use of endothelin-receptor antagonists in adolescents and adults after Fontan, but these two trials demonstrated conflicting results and did not undergo phase I testing in this cohort<sup>22, 25</sup>. Furthermore, in the study that was suggestive of a benefit, this benefit was associated with a drop in hemoglobin level, a side effect that is likely to offset the presumed benefit of the drug<sup>22</sup>. The FUEL trial is the first large-scale, multi-institutional study to suggest a physiologic benefit associated with the use of a specific pulmonary vasodilator at a dose determined by phase I clinical testing in adolescents with SV-CHD following Fontan palliation.

The challenges of living with Fontan physiology are well demonstrated by evaluations of exercise performance. Adolescents with Fontan physiology have diminished exercise capacity relative to healthy peers, a difference that is accentuated over time and associated with an increased rate of hospitalization and heart failure symptoms<sup>8-14, 18, 19</sup>. Exercise capacity below 50% predicted for age and sex is the approximate threshold beyond which circulation-associated morbidities become common and typically occurs during the third decade of life, but may occur earlier<sup>14</sup>. The ability to improve exercise capacity, as a marker of improved circulatory function more generally, is likely to be critical to the long-term



health of those who have undergone the Fontan procedure. This trial suggests that udenafil may help to improve key measures of exercise capacity following pharmacologic intervention in Fontan patients.

The FUEL trial was powered to detect a change in peak  $\text{VO}_2$  because it is relatively easy to measure and because it has been used in previous trials as an accepted surrogate for cardiac events<sup>41–44</sup>. However, while peak  $\text{VO}_2$  may be useful as a surrogate for many cardiovascular disease states, it may not be as relevant an endpoint after the Fontan operation. In this unique physiology, central venous pressure rather than right ventricular contraction is the primary driver of transpulmonary blood flow and, therefore, cardiac output<sup>3–6</sup>. As the demand for cardiac output increases with exertion, central venous pressure in the Fontan circulation must rise to meet that demand, but eventually reaches a critical ceiling beyond which it can rise no further<sup>45</sup>. At submaximal exertion, the elevation in central venous pressure does not reach the physiologic ceiling and thus outcomes at this level of exercise may be more sensitive to pharmacologic manipulation of the pulmonary vasculature. This is demonstrated by the relatively high ratio of both oxygen consumption and work rate at the anaerobic threshold compared to peak exercise, and is different from the physiology for those with a sub-pulmonary ventricle in whom central venous pressure changes very little during exercise and for whom trends in improvement or decline in  $\text{VO}_2$  at VAT and peak  $\text{VO}_2$  are usually equivalent.

Despite the importance of the findings reported here, there are limitations to this trial. First, to minimize burden to participants, the study design did not include detailed measures of hemodynamics such as might be obtained with cardiac magnetic resonance imaging or invasive catheterization study. Additionally, evaluation of the primary echocardiographic and PAT outcomes did not reveal a benefit to udenafil over placebo. Further interrogation of the multiple measures provided by these studies was not performed in this initial analysis but will be the subject of future analyses. Finally, the duration of the FUEL trial precluded a long-term assessment of safety, although this is being addressed by the ongoing FUEL open-label extension study.

In conclusion, treatment with udenafil (87.5 mg twice daily), in addition to standard therapy, was not associated with a statistically significant improvement in oxygen consumption at peak exercise but did demonstrate statistically significant improvements in multiple measures of exercise performance at the ventilatory anaerobic threshold. As the first large, multicenter, placebo-controlled, randomized trial to demonstrate a measurable physiologic benefit for Fontan patients, the FUEL trial represents a milestone in the nearly 50-year experience with the Fontan circulation and serves as a model of how public-private partnership can advance science in congenital heart disease. Further study is warranted to determine if udenafil is selectively beneficial for subpopulations within the larger cohort with SV-CHD, and to evaluate the long-term tolerability and safety of treatment.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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## Non-Standard Abbreviations and Acronyms

|                            |   |
|----------------------------|---|
| <b>SV-CHD</b>              | single ventricle congenital heart disease   |
| <b>PDE5</b>                | phosphodiesterase type 5                    |
| <b>PHN</b>                 | Pediatric Heart Network                     |
| <b>FUEL</b>                | Fontan Udenafil Exercise Longitudinal Trial |
| <b>NHLBI</b>               | National Heart, Lung, and Blood Institute   |
| <b>DSMB</b>                | Data and Safety Monitoring Board            |
| <b>BNP</b>                 | brain natriuretic peptide                   |
| <b>CPET</b>                | cardiopulmonary exercise test               |
| <b>PAT</b>                 | peripheral arterial tonometry               |
| <b>RER</b>                 | respiratory exchange ratio                  |
| <b>Peak VO<sub>2</sub></b> | oxygen consumption at peak exercise         |
| <b>VAT</b>                 | ventilatory anaerobic threshold             |
| <b>lnRHI</b>               | natural log of the reactive hyperemia index |

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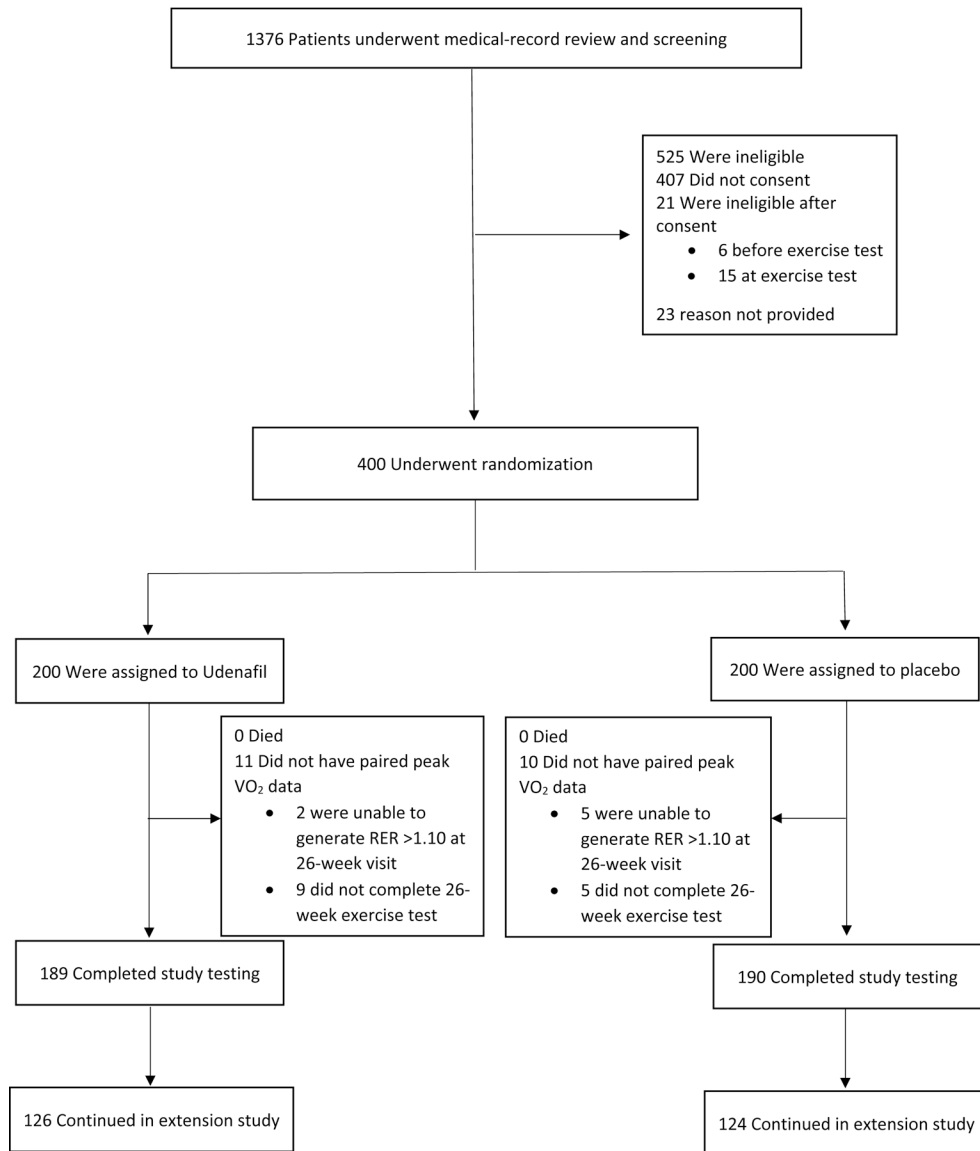
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**Clinical Perspective:****What is New?**

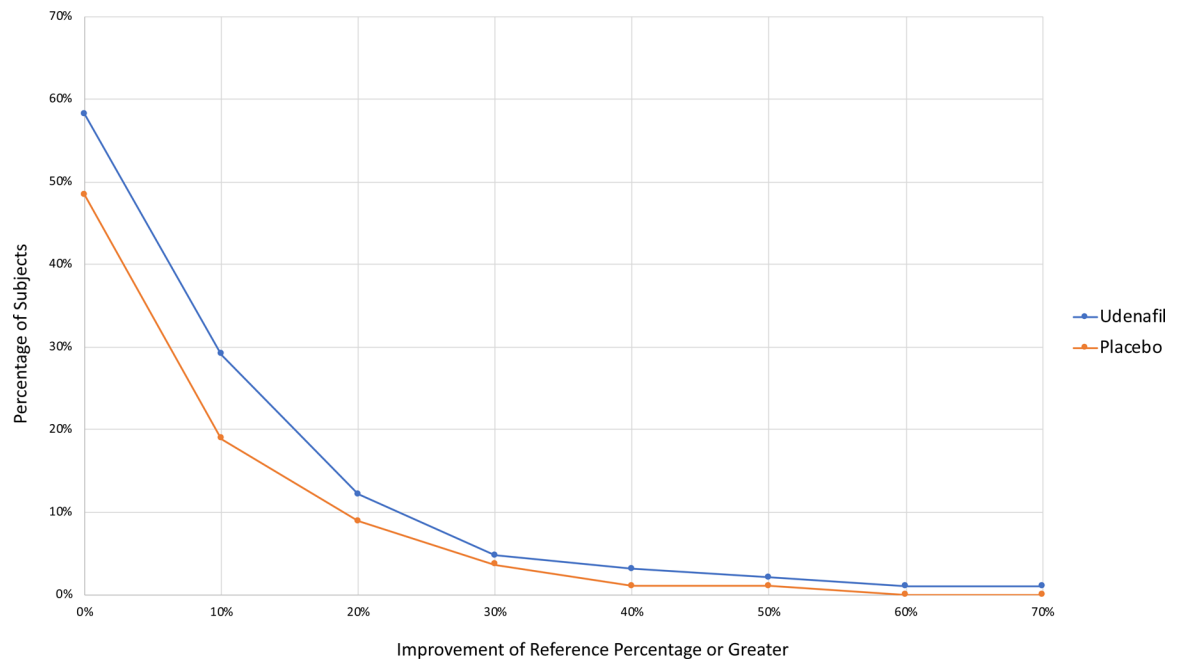
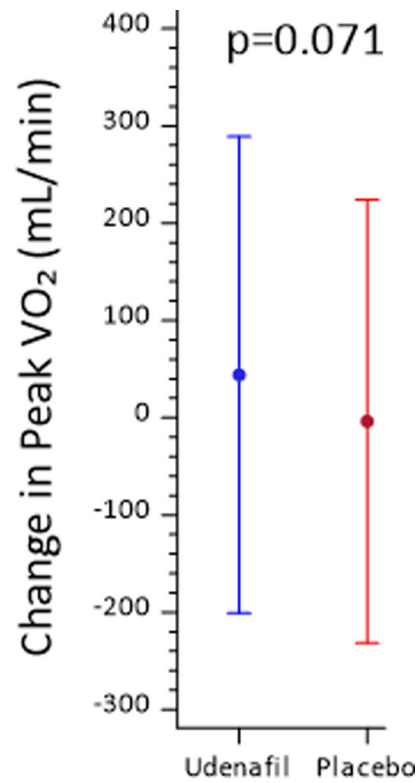
- Treatment with udenafil did not result in an increase in peak oxygen consumption, but did result in improvements in measures of exercise performance at the anaerobic threshold.
- Udenafil was well tolerated with side effects limited to those previously known to be associated with phosphodiesterase type 5 inhibitors.

**What are the Clinical Implications?**

- Although udenafil was not shown to improve peak oxygen consumption, this study was the first large-scale, phase III clinical trial to demonstrate a positive effect on measures of exercise performance in adolescents after Fontan palliation.
- These findings indicate that therapy with udenafil improves cardiovascular physiology at moderate levels of exercise in the cohort of patients who have undergone a total cavopulmonary connection.
- Ongoing surveillance is needed to determine the effect of chronic treatment with udenafil on the long-term clinical course of those living with single ventricle congenital heart disease.

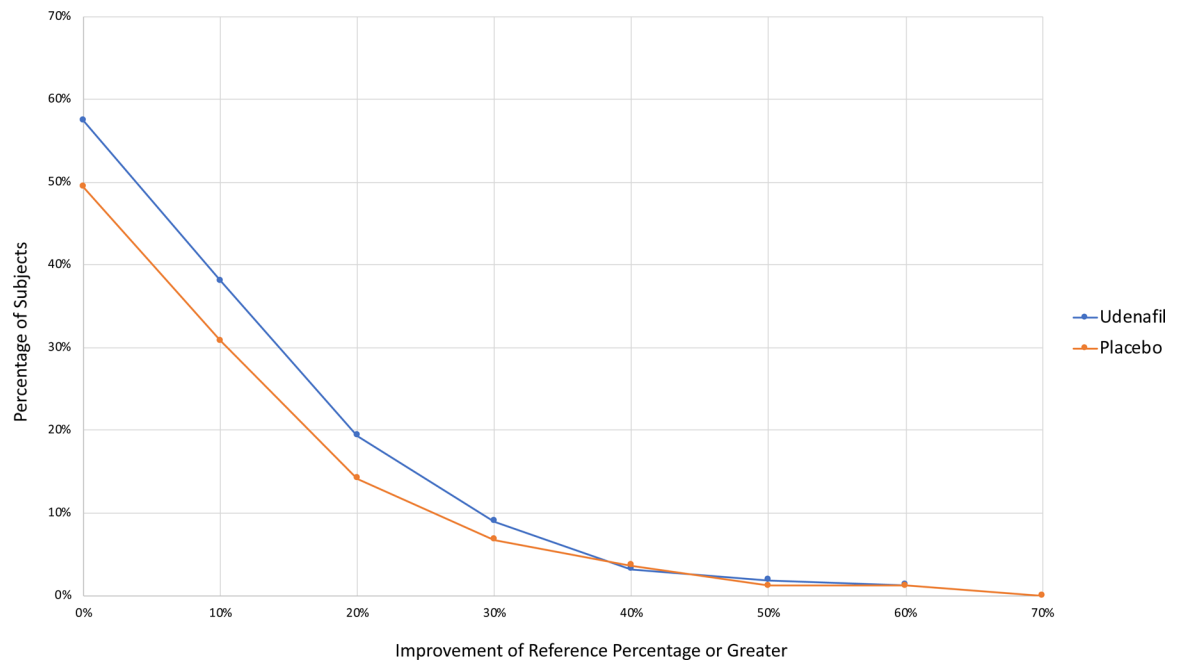
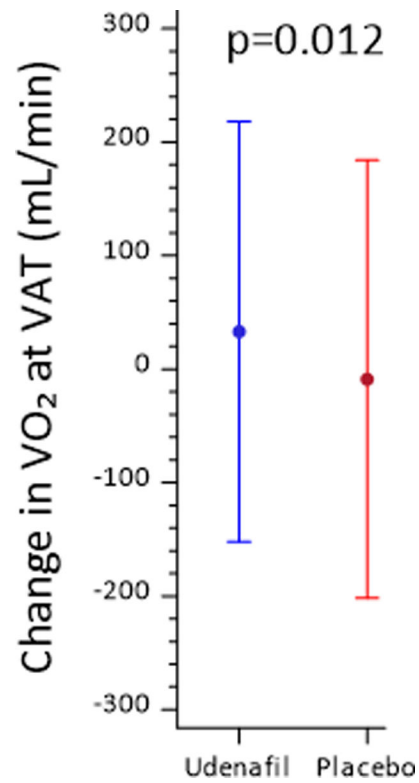


**Figure 1.** Randomization and Treatment of FUEL Participants. Peak  $VO_2$  denotes oxygen consumption at peak exercise. RER denotes respiratory exchange ratio.



**Figure 2.** Oxygen consumption at peak exercise. Panel A demonstrates the difference in the change in mean peak  $\text{VO}_2$  from Baseline to Week 26 along with the standard deviation for each treatment arm. Panel B demonstrates the percentage of participants (y axis) who demonstrated improvement in peak  $\text{VO}_2$  by the reference percentage or greater (x axis).





**Figure 3.**

Oxygen consumption at the ventilatory anaerobic threshold. Panel A demonstrates the difference in the change in mean  $\text{VO}_2$  at VAT from Baseline to Week 26 along with the standard deviation for each treatment arm. Panel B demonstrates the percentage of

participants (y axis) who demonstrated improvement in  $\text{VO}_2$  at VAT by the reference percentage or greater (x axis).

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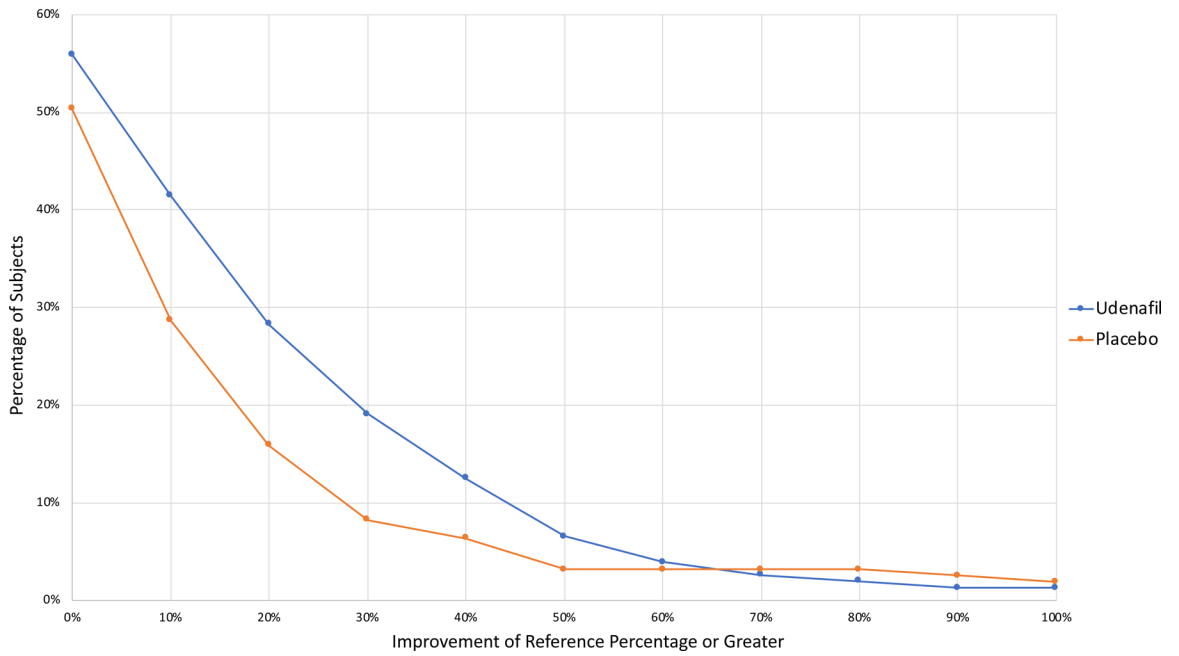
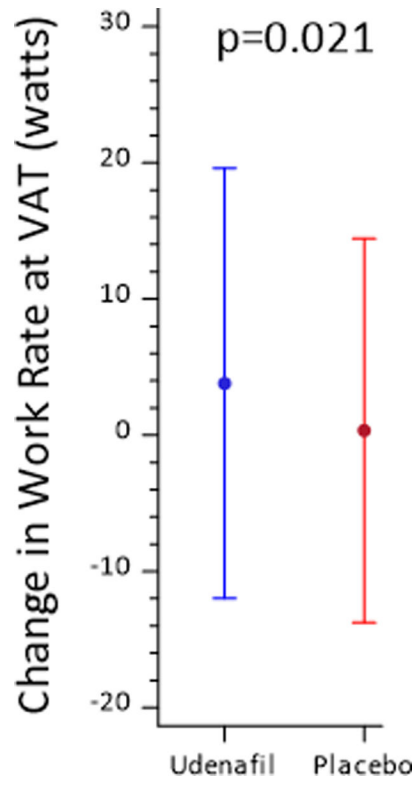
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**Figure 4.** Work at the ventilatory anaerobic threshold. Panel A demonstrates the difference in the change in mean work rate at VAT from Baseline to Week 26 along with the standard deviation for each treatment arm. Panel B demonstrates the percentage of participants (y

axis) who demonstrated improvement in work rate by the reference percentage or greater (x axis).

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Demographic and clinical baseline characteristics for the 400 participants randomized to a treatment arm; summaries presented as mean (standard deviation) unless otherwise noted as n (%).

**Table 1:**

|  | Total (n=400) | Udenafil (n=200) | Placebo (n=200) |
|--|---------------|------------------|-----------------|
| Age, years                                     | 15.5 (2.0)    | 15.4 (2.0)       | 15.6 (2.0)      |
| Female, n (%)                                  | 161 (40.3)    | 89 (44.5)        | 72 (36.0)       |
| Race, n (%)                                    |               |                  |                 |
| White  | 324 (81.0)    | 169 (84.5)       | 155 (77.5)      |
| Asian  | 38 (9.5)      | 17 (8.5)         | 21 (10.5)       |
| Black  | 23 (5.8)      | 10 (5.0)         | 13 (6.5)        |
| Other  | 15 (3.8)      | 4 (2.0)          | 11 (5.5)        |
| Predominant Ventricular morphology, n (%)      |               |                  |                 |
| Right  | 176 (44.0)    | 89 (44.5)        | 87 (43.5)       |
| Left   | 189 (47.3)    | 94 (47.0)        | 95 (47.5)       |
| Other (indeterminant and biventricular)        | 35 (8.8)      | 17 (8.5)         | 18 (9.0)        |
| Participants with a patent fenestration, n (%) | 131 (32.8)    | 73 (36.5)        | 58 (29.0)       |
| Height, cm                                     | 163.6 (9.6)   | 162.5 (10.4)     | 164.7 (8.7)     |
| Weight, kg                                     | 58.1 (13.6)   | 57.1 (13.9)      | 59.0 (13.2)     |
| Body mass index, kg/m <sup>2</sup>             | 21.6 (4.1)    | 21.5 (3.9)       | 21.7 (4.2)      |

Resting data and measures of exercise performance with comparison based on treatment arm. Summaries presented as mean  $\pm$  standard deviation (n).

**Table 2:**

| <i>Resting data</i>             | Udenafil               |                        | Placebo                |                        | <i>p</i> value                        |              |
|---------------------------------|------------------------|------------------------|------------------------|------------------------|---------------------------------------|--------------|
|                                 | Baseline               | 26-week                | Baseline               | 26-week                |                                       |              |
| Heart rate (bpm)                | 87.5 $\pm$ 15.3 (200)  | 86.6 $\pm$ 15.4 (191)  | 88.1 $\pm$ 14.1 (200)  | 87.4 $\pm$ 16.1 (195)  | <b>-0.6<math>\pm</math>12.7 (195)</b> | <b>0.78</b>  |
| Systolic blood pressure (mmHg)  | 112.3 $\pm$ 12.1 (200) | 110.5 $\pm$ 12.0 (191) | 113.2 $\pm$ 12.9 (200) | 112.8 $\pm$ 11.6 (195) | <b>-0.2<math>\pm</math>12.2 (195)</b> | <b>0.18</b>  |
| Diastolic blood pressure (mmHg) | 68.4 $\pm$ 9.5 (200)   | 65.3 $\pm$ 9.9 (191)   | 69.3 $\pm$ 10.1 (200)  | 69.4 $\pm$ 9.1 (195)   | <b>0.2<math>\pm</math>10.7 (195)</b>  | <b>0.003</b> |
| Oxygen saturation (%)           | 92.8 $\pm$ 3.9 (200)   | 93.3 $\pm$ 3.5 (191)   | 93.2 $\pm$ 3.8 (200)   | 92.9 $\pm$ 3.7 (195)   | <b>-0.3<math>\pm</math>2.8 (195)</b>  | <b>0.002</b> |
| <i>Peak exercise</i>            |                        |                        |                        |                        |                                       |              |
| Oxygen consumption (mL/min)*    | 1562 $\pm$ 437 (200)   | 1606 $\pm$ 452 (200)   | 1627 $\pm$ 414 (200)   | 1623 $\pm$ 432 (200)   | <b>-3.7<math>\pm</math>228 (200)</b>  | <b>0.071</b> |
| Work rate (W)                   | 120 $\pm$ 32 (198)     | 124 $\pm$ 32 (187)     | 123 $\pm$ 32 (199)     | 127 $\pm$ 32 (189)     | <b>2.6<math>\pm</math>14 (188)</b>    | <b>0.85</b>  |
| Heart rate (bpm)                | 165 $\pm$ 20 (200)     | 165 $\pm$ 20 (189)     | 168 $\pm$ 22 (199)     | 166 $\pm$ 21 (190)     | <b>-2.5<math>\pm</math>13 (189)</b>   | <b>0.56</b>  |
| Respiratory rate (breaths/min)  | 51 $\pm$ 11 (199)      | 50 $\pm$ 12 (188)      | 51 $\pm$ 13 (200)      | 50 $\pm$ 12 (189)      | <b>-1.5<math>\pm</math>10 (189)</b>   | <b>0.72</b>  |
| Minute ventilation (L/min)      | 71 $\pm$ 21 (199)      | 73 $\pm$ 22 (189)      | 76 $\pm$ 22 (200)      | 76 $\pm$ 21 (190)      | <b>-0.1<math>\pm</math>14 (190)</b>   | <b>0.84</b>  |
| Oxygen saturation (%)           | 89.2 $\pm$ 5.3 (195)   | 89.6 $\pm$ 4.9 (190)   | 89.8 $\pm$ 5.0 (197)   | 89.7 $\pm$ 5.0 (192)   | <b>-0.1<math>\pm</math>3.4 (190)</b>  | <b>0.21</b>  |
| <i>Anaerobic Threshold</i>      |                        |                        |                        |                        |                                       |              |
| Oxygen consumption (mL/min)     | 1039 $\pm$ 301 (170)   | 1073 $\pm$ 297 (170)   | 1021 $\pm$ 280 (181)   | 1009 $\pm$ 276 (172)   | <b>-9.0<math>\pm</math>193 (162)</b>  | <b>0.012</b> |
| Work (W)                        | 66.2 $\pm$ 26 (167)    | 70.3 $\pm$ 27 (166)    | 66.1 $\pm$ 23 (177)    | 66.7 $\pm$ 22 (166)    | <b>0.34<math>\pm</math>14 (157)</b>   | <b>0.021</b> |
| VE/VCO2                         | 34.3 $\pm$ 4.9 (170)   | 33.5 $\pm$ 4.7 (170)   | 34.8 $\pm$ 5.2 (181)   | 34.5 $\pm$ 4.7 (172)   | <b>-0.06<math>\pm</math>3.1 (162)</b> | <b>0.014</b> |

\* For analysis of the primary outcome, missing data at the 26-week visit was imputed as equal to the baseline value (no change). *p* value determined for difference in change, comparing udenafil to placebo, using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and a continuous covariate of baseline peak VO<sub>2</sub>.

Secondary non-exercise outcomes with comparison based on treatment arm. Summaries presented as mean  $\pm$  standard deviation (n).

**Table 3:**

|   | <i>Udenafil</i>       |                       | <i>Placebo</i>         |                       | <i>p</i> value        |                                    |
|---|-----------------------|-----------------------|------------------------|-----------------------|-----------------------|------------------------------------|
|   | Baseline              | 26-week               | Change                 | Baseline              |                       | 26-week                            |
| <b><i>Echocardiography</i></b>            |                       |                       |                        |                       |                       |                                    |
| Myocardial performance index              | 0.44 $\pm$ 0.21 (150) | 0.42 $\pm$ 0.15 (146) | -0.02 $\pm$ 0.11 (122) | 0.45 $\pm$ 0.16 (155) | 0.45 $\pm$ 0.21 (148) | -0.01 $\pm$ 0.19 (128) <b>0.34</b> |
| <b><i>EndoPAT</i></b>                     |                       |                       |                        |                       |                       |                                    |
| Natural log reactive hyperemia index      | 0.46 $\pm$ 0.24 (184) | 0.52 $\pm$ 0.30 (174) | 0.07 $\pm$ 0.30 (163)  | 0.47 $\pm$ 0.33 (186) | 0.51 $\pm$ 0.30 (170) | 0.05 $\pm$ 0.37 (165) <b>0.59</b>  |
| <b><i>Biomarker</i></b>                   |                       |                       |                        |                       |                       |                                    |
| Log serum brain type natriuretic peptide* | 2.46 $\pm$ 1.00 (200) | 2.53 $\pm$ 1.01 (187) | 0.08 $\pm$ 0.90 (187)  | 2.27 $\pm$ 1.14 (199) | 2.30 $\pm$ 1.19 (192) | 0.03 $\pm$ 1.13 (191) <b>0.18</b>  |

\* BNP measurements reported by the lab as  $<2.0$  were imputed as 1.0. *p* value determined for difference in change using ANCOVA with fixed factors for ventricular morphology (single left versus single right or mixed) and a continuous covariate of baseline peak VO<sub>2</sub>.

Adverse events possibly, probably, or definitively related to study drug that occurred in at least 5% of participants in either treatment group. Number of participants that experienced an adverse event presented as n (%).

**Table 4:**

|                                 | All Participants | Udenafil  | Placebo   | p value* |
|---------------------------------|------------------|-----------|-----------|----------|
| Headache / migraine             | 119 (29.8)       | 69 (34.5) | 50 (25.0) | 0.049    |
| Flushing                        | 44 (11.0)        | 32 (16.0) | 12 (6.0)  | 0.002    |
| Abdominal pain / discomfort     | 26 (6.5)         | 13 (6.5)  | 13 (6.5)  | 1.0      |
| Dizziness                       | 24 (6.0)         | 9 (4.5)   | 15 (7.5)  | 0.29     |
| Nausea / vomiting               | 21 (5.3)         | 10 (5.0)  | 11 (5.5)  | 1.0      |
| Increased erection <sup>†</sup> | 15 (6.3)         | 13 (11.7) | 2 (1.6)   | 0.002    |
| Epistaxis                       | 14 (3.5)         | 11 (5.5)  | 3 (1.5)   | 0.053    |

<sup>†</sup>Percentage of male participants.

\*Fisher's exact test.