Results of the Fontan Udenafil Exercise Longitudinal (FUEL) Trial

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Presenting on behalf of the FUEL Writing Committee

and the Investigators of the Pediatric Heart Network

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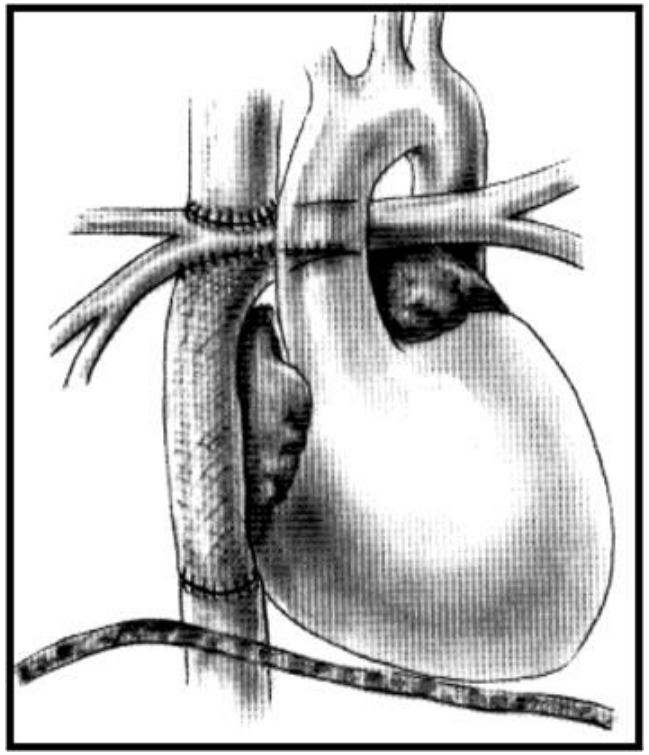
Disclosure

- This trial was conducted by the Pediatric Heart Network, funded by NIH / NHLBI, with financial support from the sponsor, Mezzion Pharma Co. Ltd.
- The contents of this work are solely the responsibility of the authors and do not necessarily represent the official views of NHLBI, NIH, DHHS, or Mezzion
- Dr. Goldberg and Dr. Paridon receive grant support from Mezzion and are co-inventors of patent US10137128B2

Background

- The Fontan operation is the final step in the staged palliation of the heterogeneous forms of congenital heart disease characterized by a functional single ventricle
  - Hypoplastic left heart syndrome, tricuspid atresia, double inlet left ventricle, pulmonary atresia with intact ventricular septum
- This procedure creates a total cavopulmonary connection, allowing for systemic venous return to bypass the heart and flow passively into the pulmonary arteries



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Background

- The circulation created by Fontan palliation is characterized by elevated central venous pressure and low cardiac output
- In this physiology, pulmonary vascular resistance plays a critical role in allowing for the efficient flow of blood through the lungs without the benefit of a ventricular pump
- While this circulation is typically stable through childhood, cardiovascular efficiency deteriorates over time, associated with a decline in exercise performance

Background

- Given the importance of pulmonary vascular resistance, modulators of PVR make sense as potential therapies
- Udenafil is a novel PDE5 inhibitor that has undergone Phase I/II testing in adolescents after Fontan (PHN / Mezzion)
- 87.5 mg twice daily was associated with the highest average serum concentration, with no dose-limiting adverse events
- In the FUEL Trial, we evaluate the effect of 87.5 mg of udenafil, given twice daily, on exercise performance in adolescents who have undergone Fontan palliation

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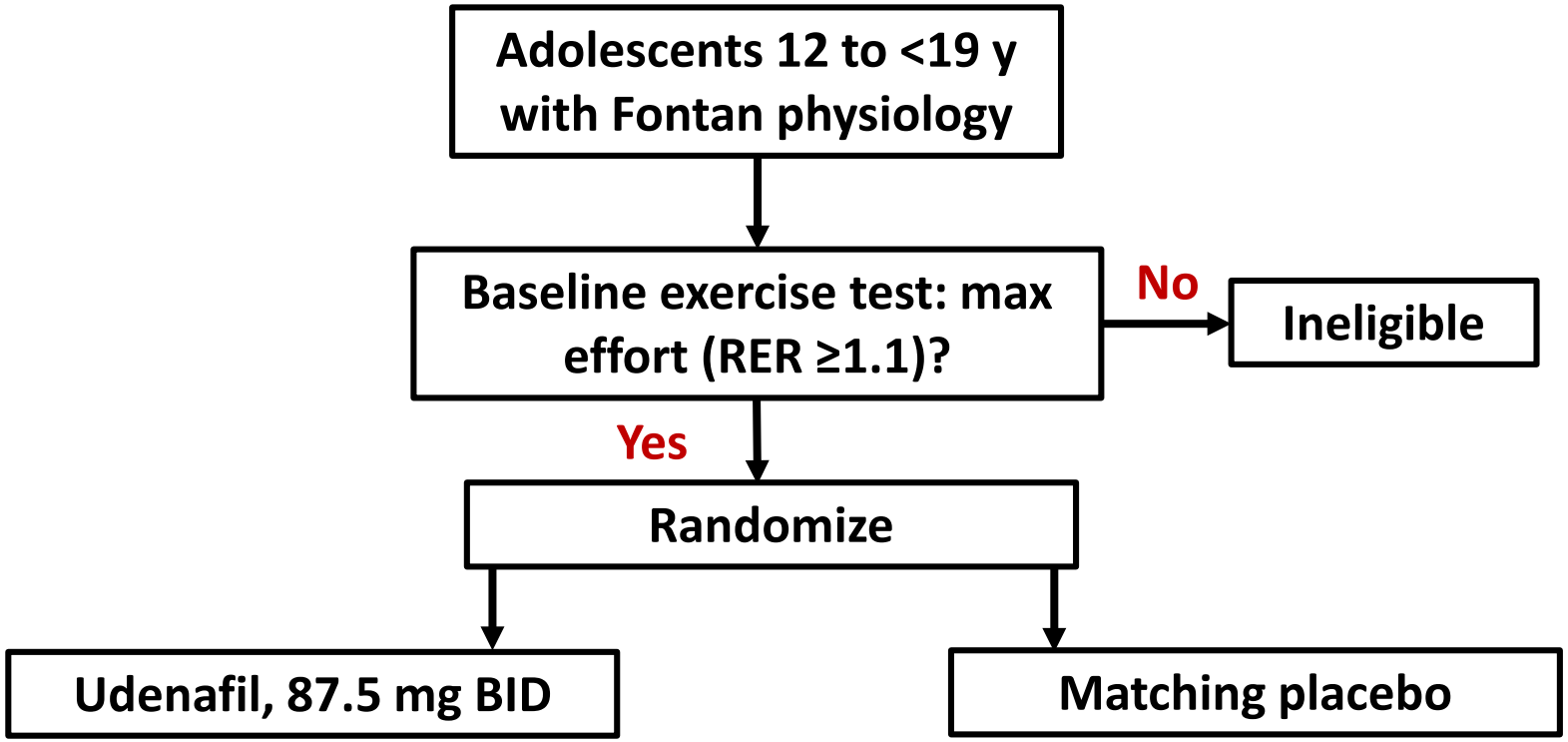
Inclusion:

1. Currently on anticoagulation
2. Fluent in English, Spanish, Korean

Exclusion:

1. Small body size
2. Significant co-morbidities
3. Current therapy with a pulmonary vasodilator
4. Peak VO_2 <50% predicted on a recent clinical exercise test

30 sites in North America and Republic of Korea



Primary Endpoint: Change in Peak VO_2 from baseline to 26 weeks

Key secondary endpoints:

1. Exercise measures at VAT
2. Myocardial performance index
3. Reactive hyperemia index
4. Brain natriuretic peptide

Statistical Analyses

- Primary efficacy endpoint: Between group difference in change in peak VO_2 from baseline to 26-weeks
- Sample size determined by number of participants needed to detect a 10% between-group difference with 90% power, assuming within-patient correlation of 0.33 and 15% dropout
- For primary outcome, missing data imputed as equal to baseline
- ANCOVA with fixed factors for ventricular morphology and continuous covariate of baseline peak VO_2

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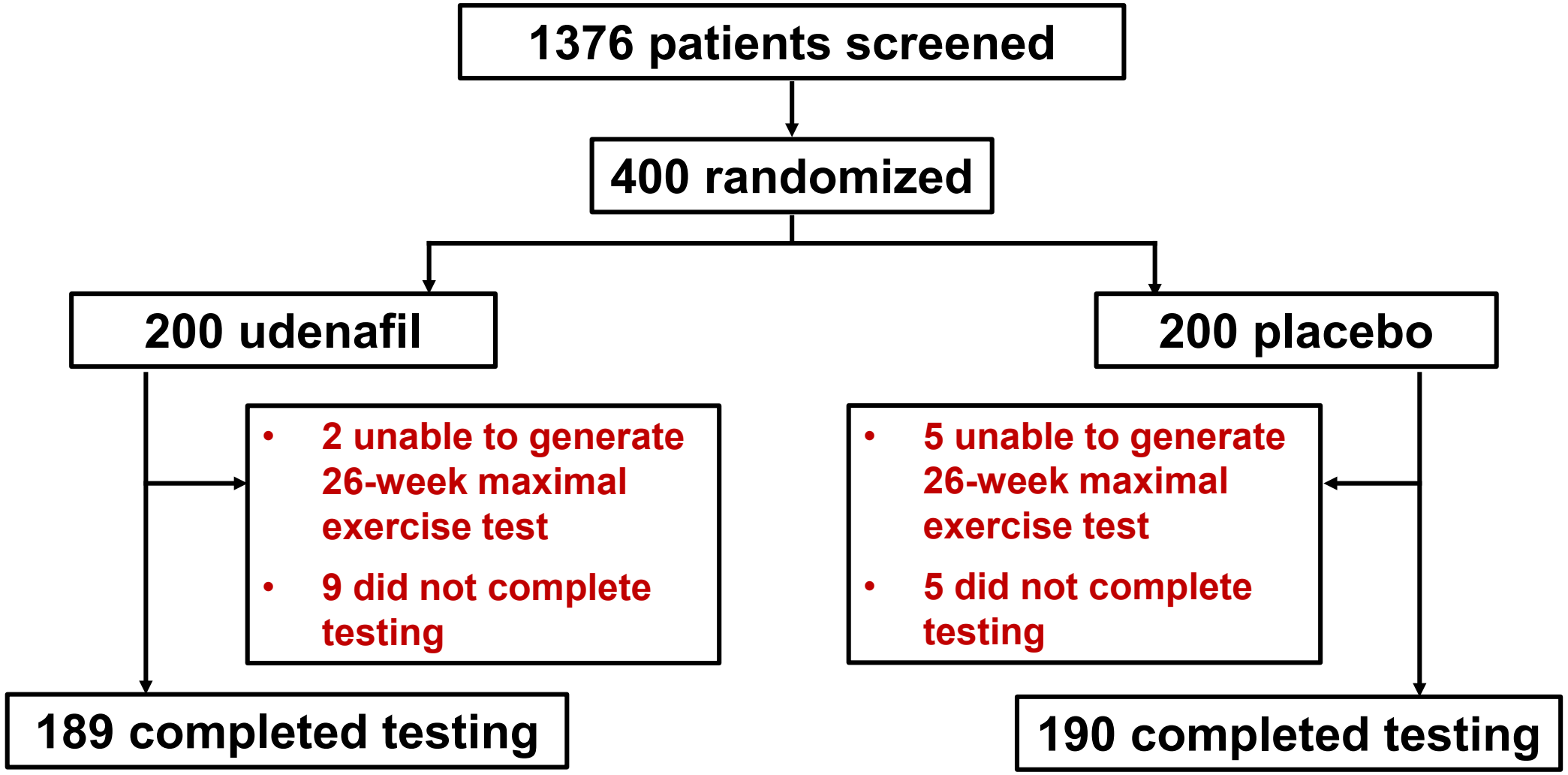
Results


1376 patients screened
400 randomized
200 udenafil
200 placebo
• 2 unable to generate 26-week maximal exercise test
• 9 did not complete testing
• 5 unable to generate 26-week maximal exercise test
• 5 did not complete testing
189 completed testing
190 completed testing

Baseline Characteristics, Mean ± SD / n (%)

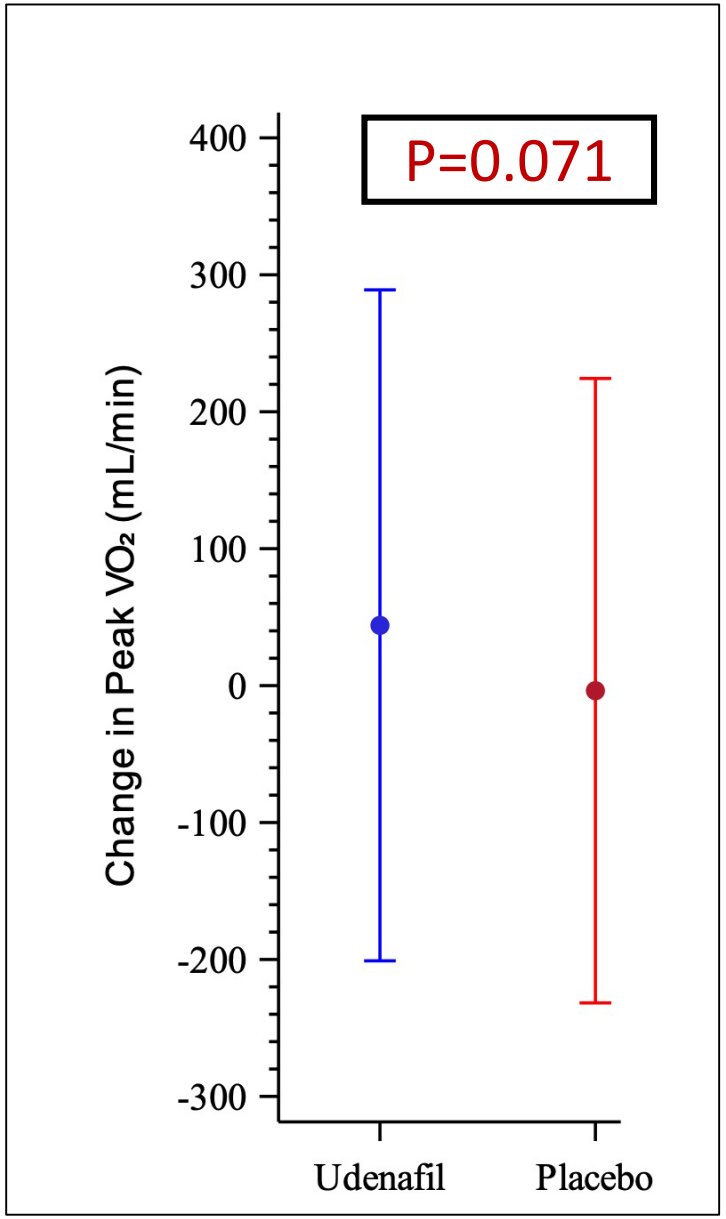
	Udenafil (n=200)	Placebo (n=200)
Age, years	15.4 ± 2.0	15.6 ± 2.0
Female	89 (44%)	72 (36%)
White	169 (84%)	155 (78%)
Left ventricle	94 (47%)	95 (48%)
Fenestration	73 (36%)	58 (29%)
Height, cm	162 ± 10	165 ± 9
Weight, kg	57 ± 14	59 ± 13
BMI	22 ± 4	22 ± 4

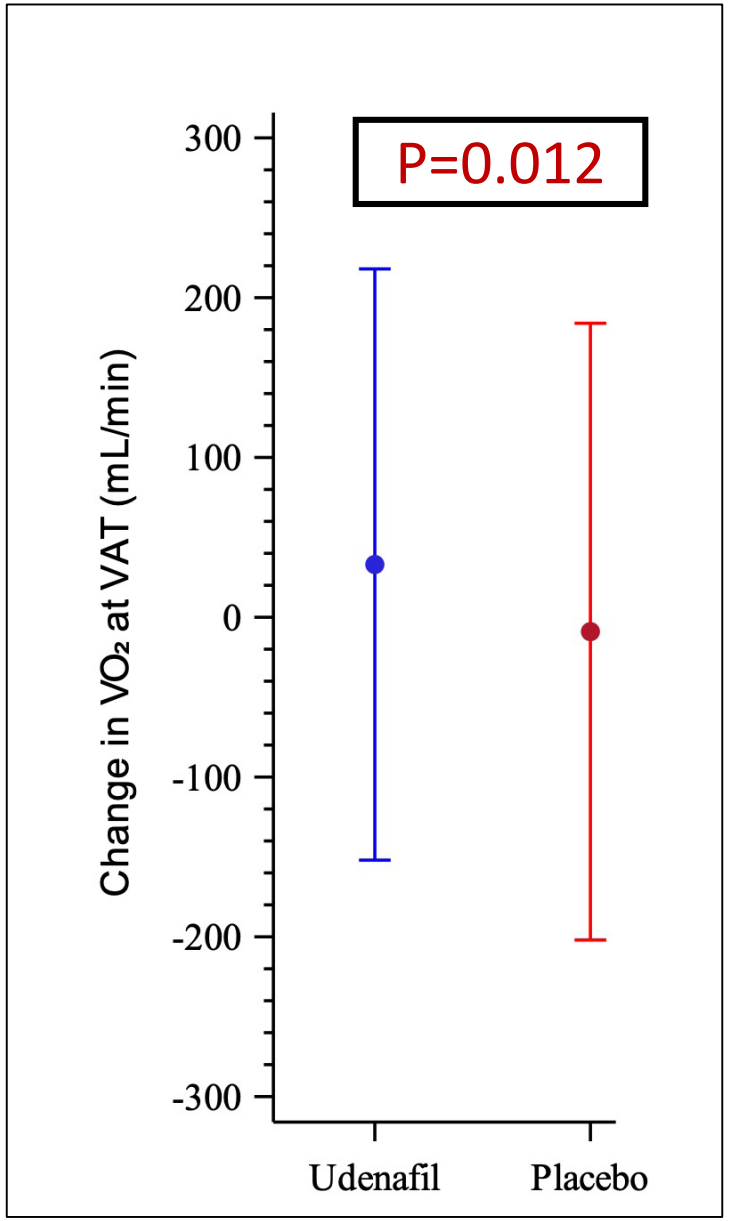
Exercise Data, Mean ± SD (n)

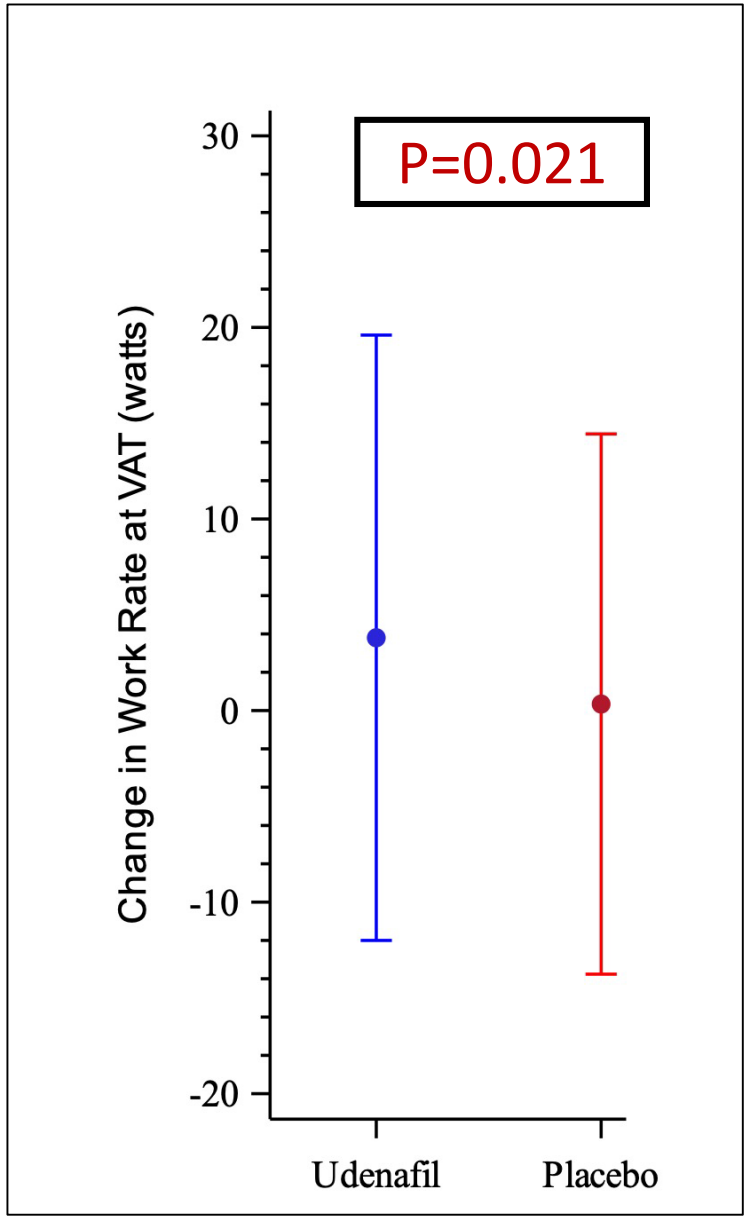
	Udenafil		Placebo		p
	Baseline	Change	Baseline	Change	
Peak VO_2 (ml/kg/min)	27.8±6.9 (200)	-0.23±4.1 (200)	28.0±6.6 (200)	-0.89±3.7 (200)	0.092
Peak VO_2 (ml/min)	1562±437 (200)	44±245 (200)	1627±414 (200)	-3.7±228 (200)	0.071
Peak heart rate (bpm)	165±20 (200)	-1.4±11 (189)	168±22 (199)	-2.5±13 (189)	0.56
O_2 sat at peak (%)	89.2±5.3 (195)	0.4±3.4 (186)	89.8±5.0 (197)	-0.1±3.4 (190)	0.21
VO_2 at VAT (ml/min)	1039±301 (170)	33±185 (155)	1021±280 (181)	-9.0±193 (162)	0.012
Work rate at VAT (W)	66.2±26 (167)	3.8±16 (152)	66.1±23 (177)	0.34±14 (157)	0.021
VE/VCO_2 at VAT	34.3±4.9 (170)	-0.8±3.7 (155)	34.8±5.2 (181)	-0.06±3.1 (162)	0.014

P value represents between group difference in change in variable from baseline to 26-weeks

Relative Improvement in Exercise Measures







Secondary Outcomes, Mean ± SD (n)

	Udenafil		Placebo		p
	Baseline	Change	Baseline	Change	
MPI	0.44±0.21 (150)	-0.02±0.11 (122)	0.45±0.16 (155)	-0.01±0.19 (128)	0.34
lnRHI	0.46±0.24 (184)	0.07±0.30 (163)	0.47±0.33 (186)	0.05±0.37 (165)	0.59
Log BNP	2.46±1.00 (200)	0.08±0.90 (187)	2.27±1.14 (199)	0.03±1.13 (191)	0.18

P value represents between group difference in change in variable from baseline to 26-weeks

Safety

	Udenafil	Placebo	p
Headache / migraine	69 (35%)	50 (25%)	0.049
Facial flushing	32 (16%)	12 (6%)	0.002
Increased erection (*males only*)	13 (12%)	2 (2%)	0.002
Abdominal pain / discomfort	13 (7%)	13 (7%)	1.0
Epistaxis	11 (6%)	3 (2%)	0.053
Dizziness	9 (5%)	15 (8%)	0.29
Nausea / vomiting	10 (5%)	11 (6%)	1.0

P value represents between group difference in listed adverse event

Limitations

- This study did not include detailed hemodynamics (e.g., cardiac catheterization or cardiac MRI)
- Based on exclusion criteria, these results may not apply to patients with significant co-morbidities or very low peak VO_2
- The duration of the trial precluded long-term assessment of safety, addressed in the FUEL Open-Label Extension Trial

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Conclusion

- Treatment with udenafil (87.5 mg bid) was:
  - Not associated with a statistically significant improvement in oxygen consumption at peak exercise
  - Associated with statistically significant improvements in sub-maximal exercise performance measured at the ventilatory anaerobic threshold
  - Not associated with changes in myocardial performance index, reactive hyperemia index, or log BNP
  - Well-tolerated and safe, with adverse events limited to those known to be associated with PDE5 inhibitors

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Clinical Implications

- Our study extends recent findings highlighting the importance of sub-maximal exercise in the understanding of Fontan physiology
- Unlike peak VO_2, sub-maximal exercise is not constrained by the physiologic ceiling of central venous pressure inherent in exercise physiology after Fontan palliation
- An improvement in sub-maximal exercise has real implications for the day-to-day activities of adolescents with Fontan physiology
- This is first large clinical trial to show improvements in measures of clinically relevant exercise performance in those with single ventricle heart disease after Fontan palliation

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Acknowledgements

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- Thank you to the advocacy groups that supported this effort
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