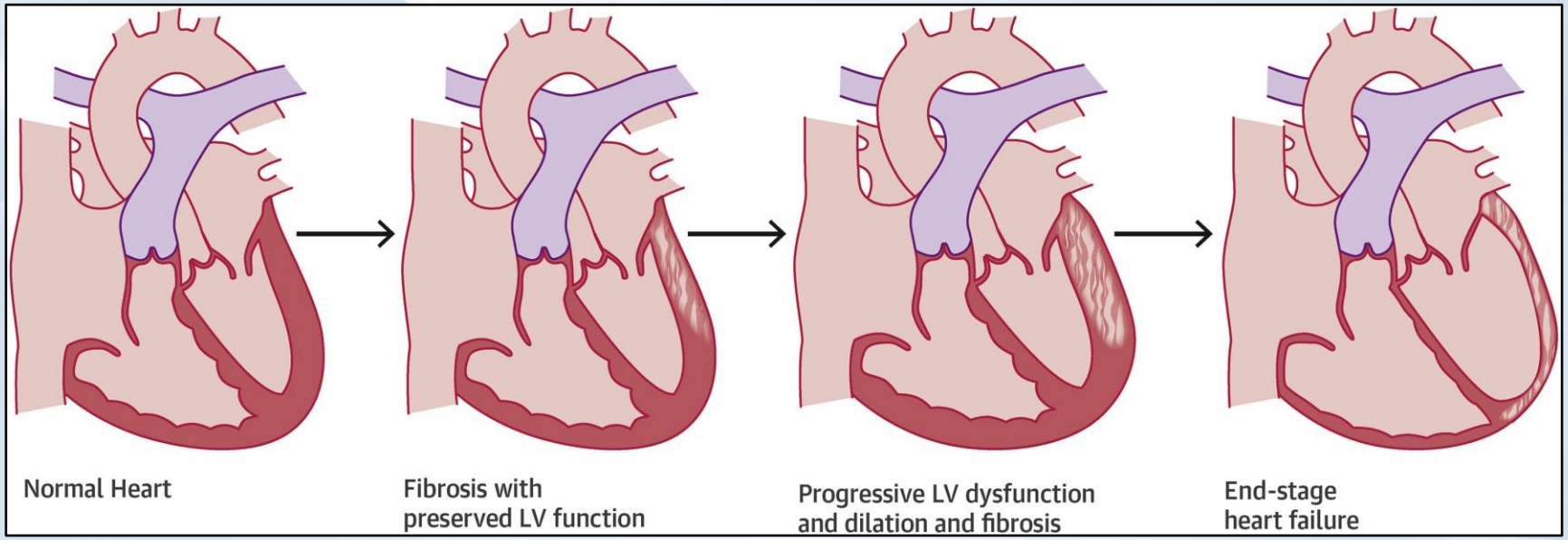
A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study with an Open-Label Extension to Determine the Safety, Pharmacokinetics and Efficacy of Oral Ifetroban in Subjects with Duchenne Muscular Dystrophy

John J. Parent, MD, MSCR
Associate Professor of Clinical Pediatrics
Riley Children's Hospital, Indiana University

MDA Conference
March 19, 2025

Duchenne MD-associated cardiomyopathy



Cardiomyopathy onset:

- 17% of patients <10 years
- 34% of those aged 10-15
- 59% of those aged >15-18 years
- >90% over age 18

Current Surveillance Strategies:

- ECHO
- MRI

Current Treatments Available:

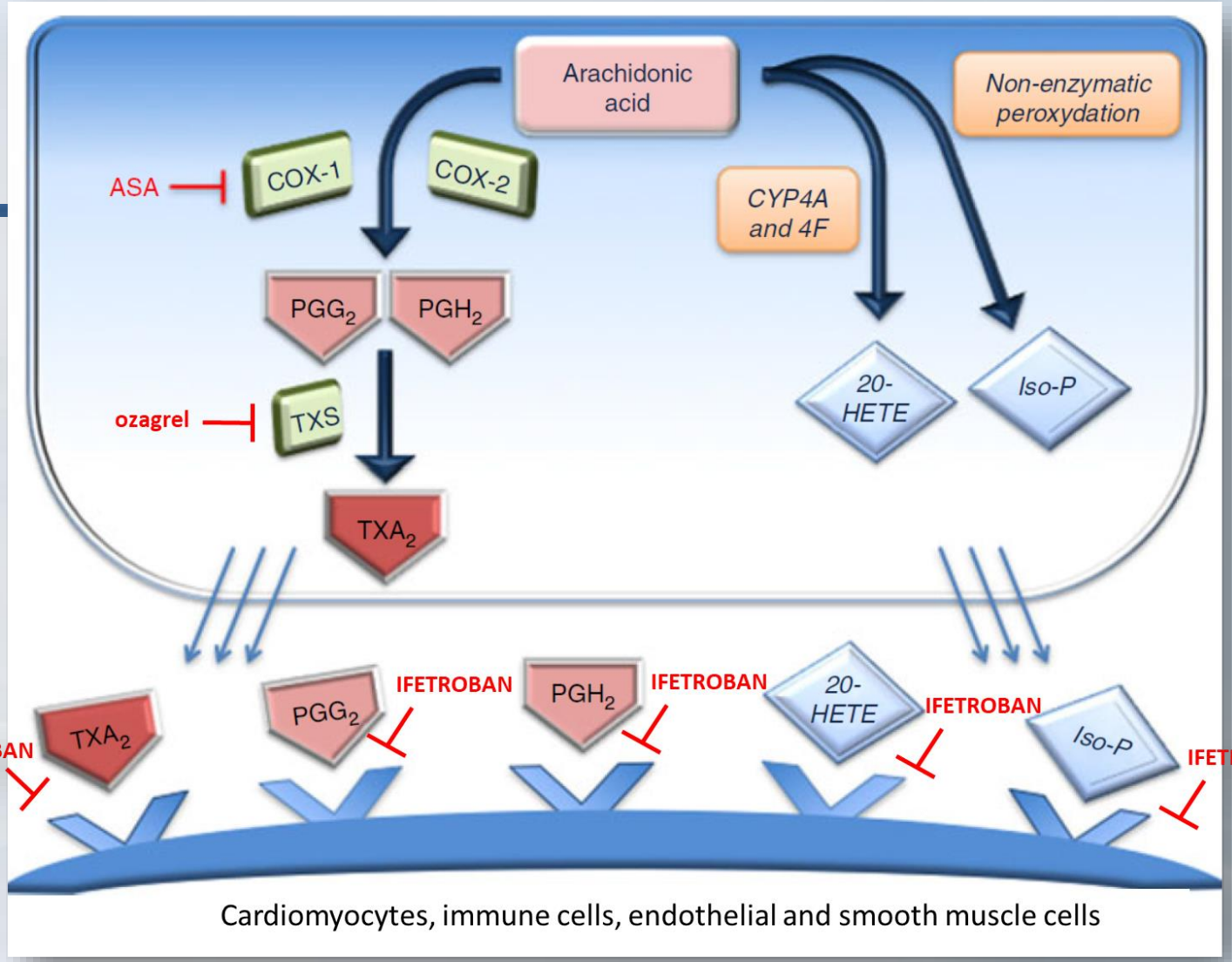
- ACEi
- ARB
- ARNi
- Beta-blockers
- Aldosterone inhibitors

Slows progression but no cure

Hor et al. *J Cardiovac Magn Reason.* 2013; Kamdar and Garry. *JACC*. 2016.

Ifetroban

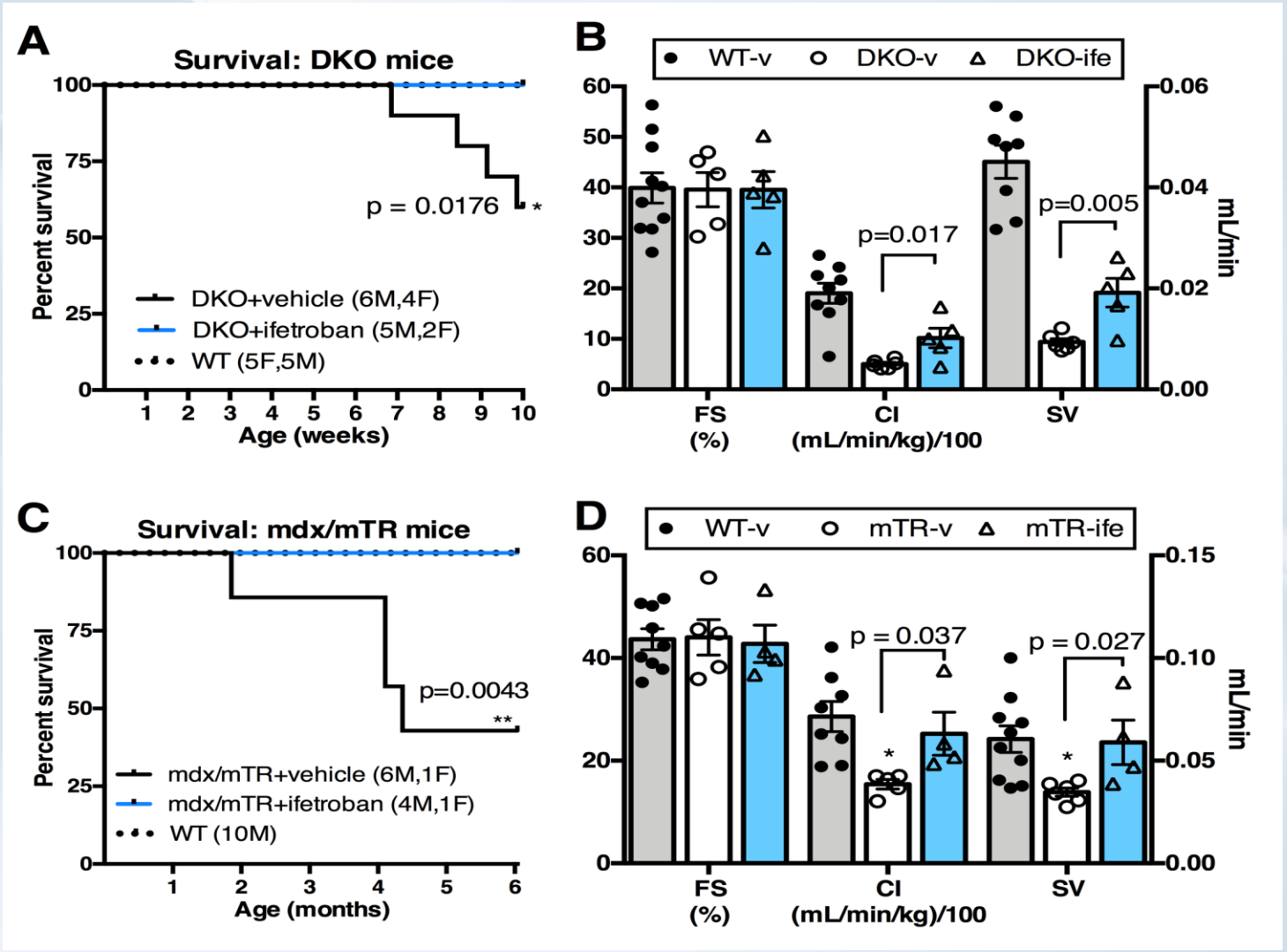
- A once daily, oral medication taken in a fasted state that selectively blocks the thromboxane receptor (TPr) expressed on many cell types including platelets, immune cells, smooth muscle and cardiomyocytes
- Safety is well established with over 1,400 subjects dosed in 27 clinical trials
- Isoprostanes are elevated in Becker MD and Duchenne MD plus class IV heart failure from other causes*
- TPr activation causes increased intracellular calcium, arrhythmia and cell death in ventricular cardiomyocytes**



Adapted from Capra *J Thromb Haemost* 2014

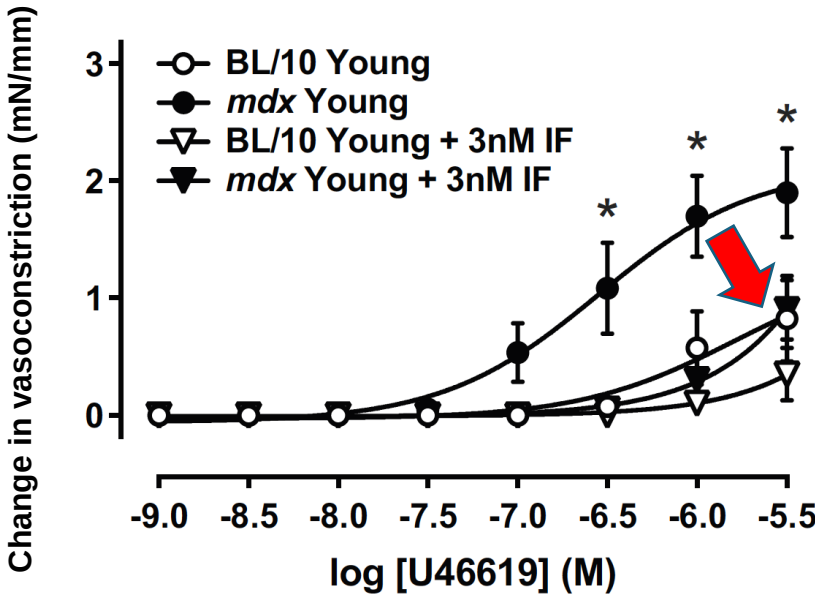
*Grosso et al. *Brain & Development*. 2008; **Mallat et al. *Circulation*. 1998; Nonaka-Sarukawa et al. *Heart*. 2003; Polidori et al. *J Card Fail*. 2004

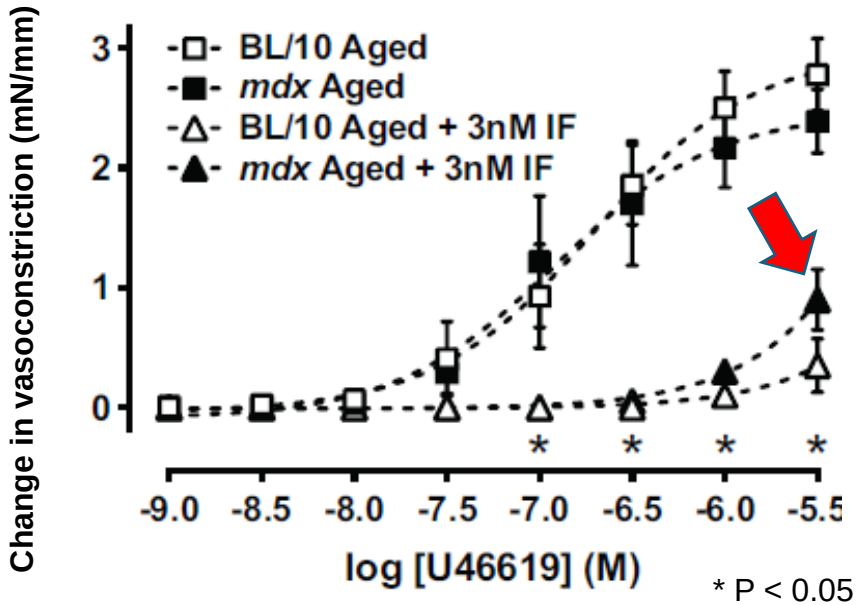
Ifetroban increased survival & cardiac output in two severe DMD models



West et al. *JAHA* 2019

Ifetroban reduces the coronary artery dysfunction caused by DMD, improving blood supply to the heart



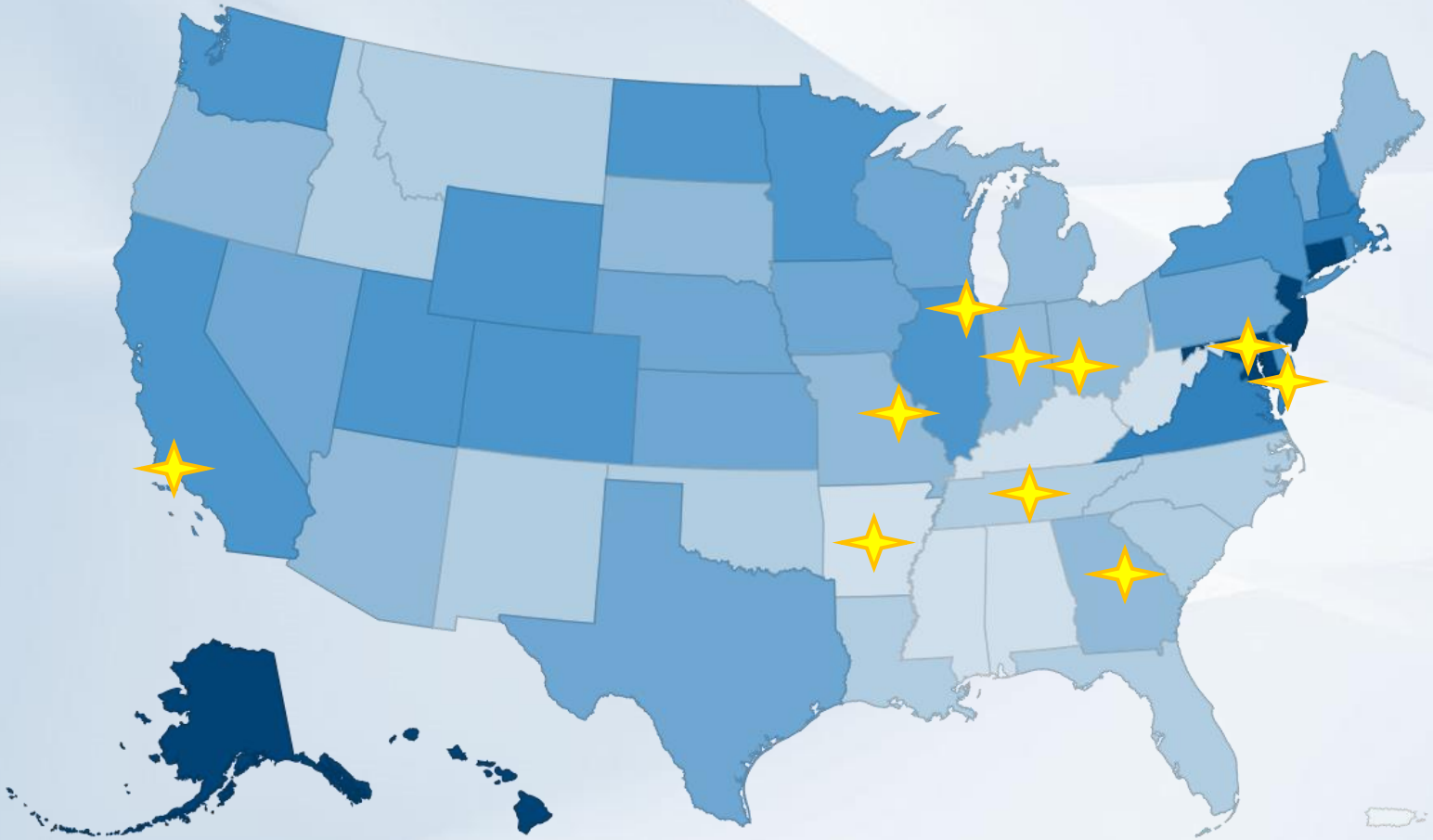


* P < 0.05 vs untreated BL/10

- Thromboxane receptor signaling is enhanced in young mdx/DMD mice
- Coronary vasoconstriction was measured without/with ifetroban
- Ifetroban reduced the abnormal coronary vasoconstriction in young mdx/DMD & both aged mdx/DMD & control mice

Mitchell et al. *Am J Physiol Heart Circ Physiol* 2021

The FIGHT DMD Trial



U.S. Locations:

- Riley Children's (IN)
- Children's National (DC)
- Emory/CHOA (GA)
- UCLA (CA)
- Vanderbilt (TN)
- Lurie Children's Hospital (IL)
- Arkansas Children's (AR)
- Washington University (MO)
- Cincinnati Children's (OH)
- Krieger Research Institute (MD)

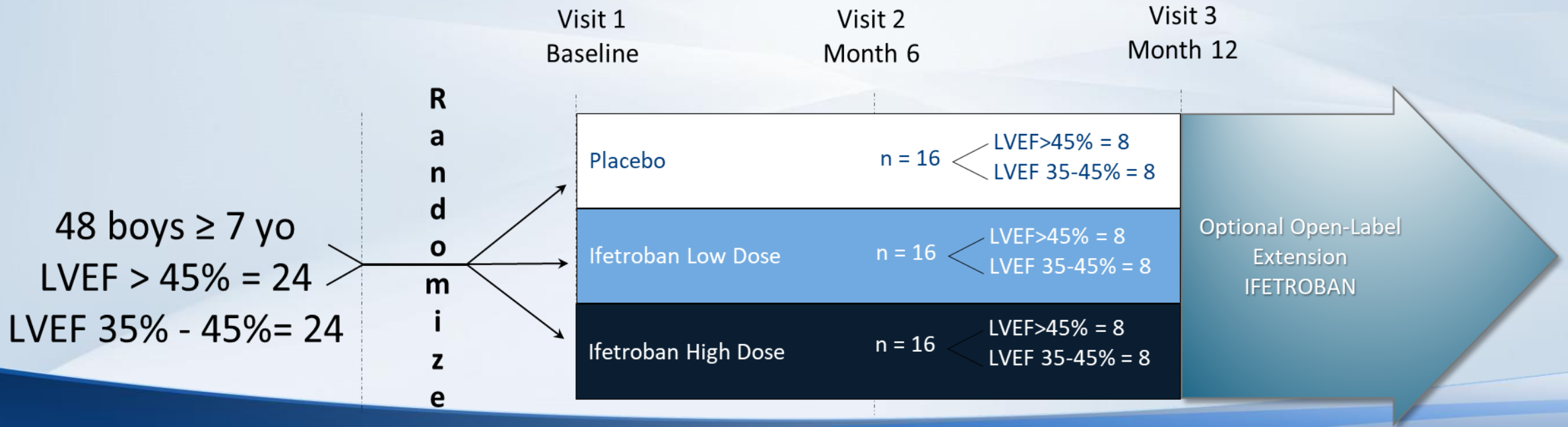
ClinicalTrials.gov Identifier: NCT03340675

FightDMDtrial.com ▪ fightdmd@cumberlandpharma.com

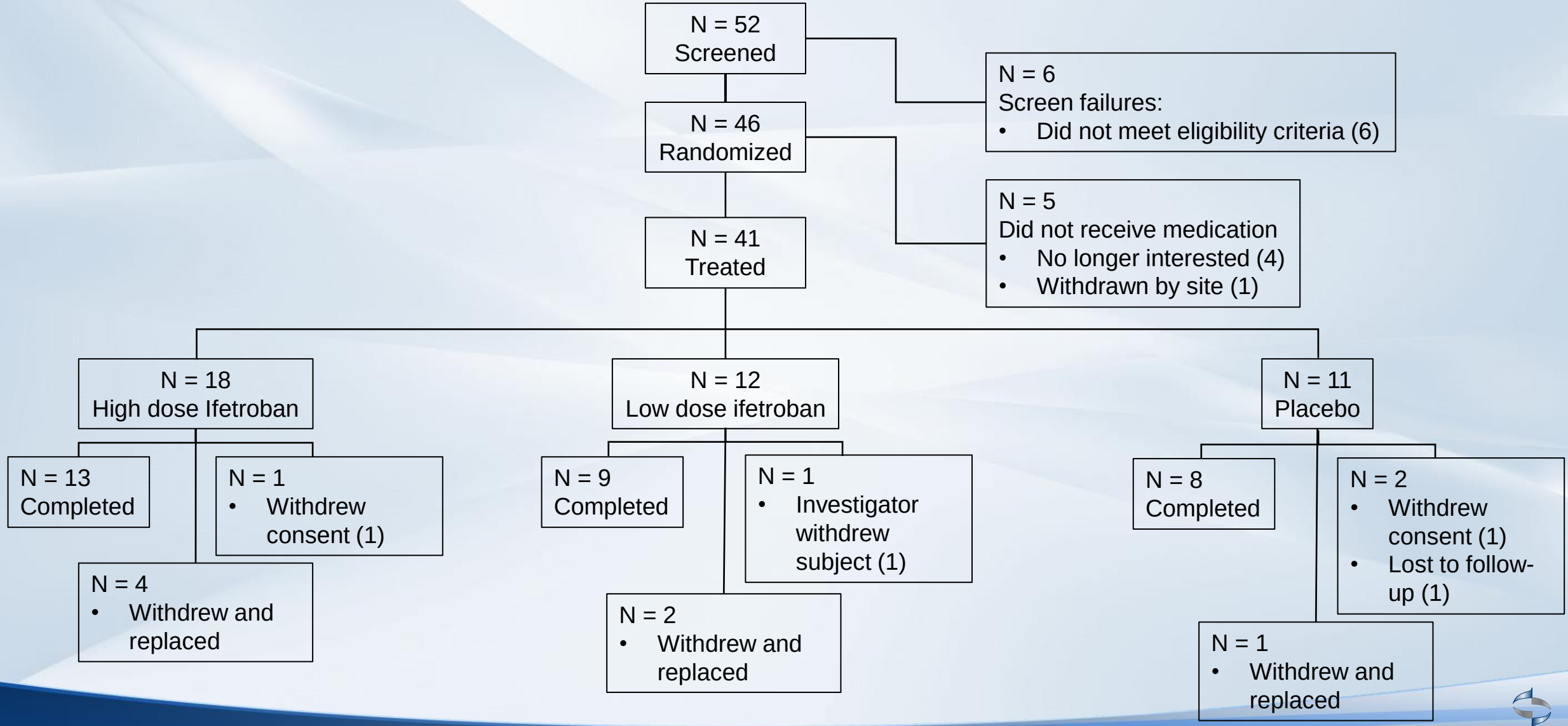
The FIGHT DMD Trial Design

- Key assessments at baseline, Month 6 & Month 12 visits
  - Cardiac MRI, PFT, Muscle Strength, Qualify-of-life surveys, 7-day activity monitoring
  - Day 0 PK completed within 4 hours at site using finger stick; 8-hr and 24-hr post-dose at home
  - Day 7 PK completed at home: pre-dose and 30 minutes post-dose
  - No biopsy or 6-minute walk test

- Key eligibility and study features
  - All DMD boys ≥ 7 yo regardless of mutation type, ambulation status & steroid use eligible
  - Standard of care meds allowed including: deflazacort, eteplirsen, golodirsen, viltolarsen and casimersen
  - Pre-specified supplement of placebo group with natural history study subjects matched on age, baseline LVEF, and background therapies using identical CMR protocols and visit schedules



Subject Disposition



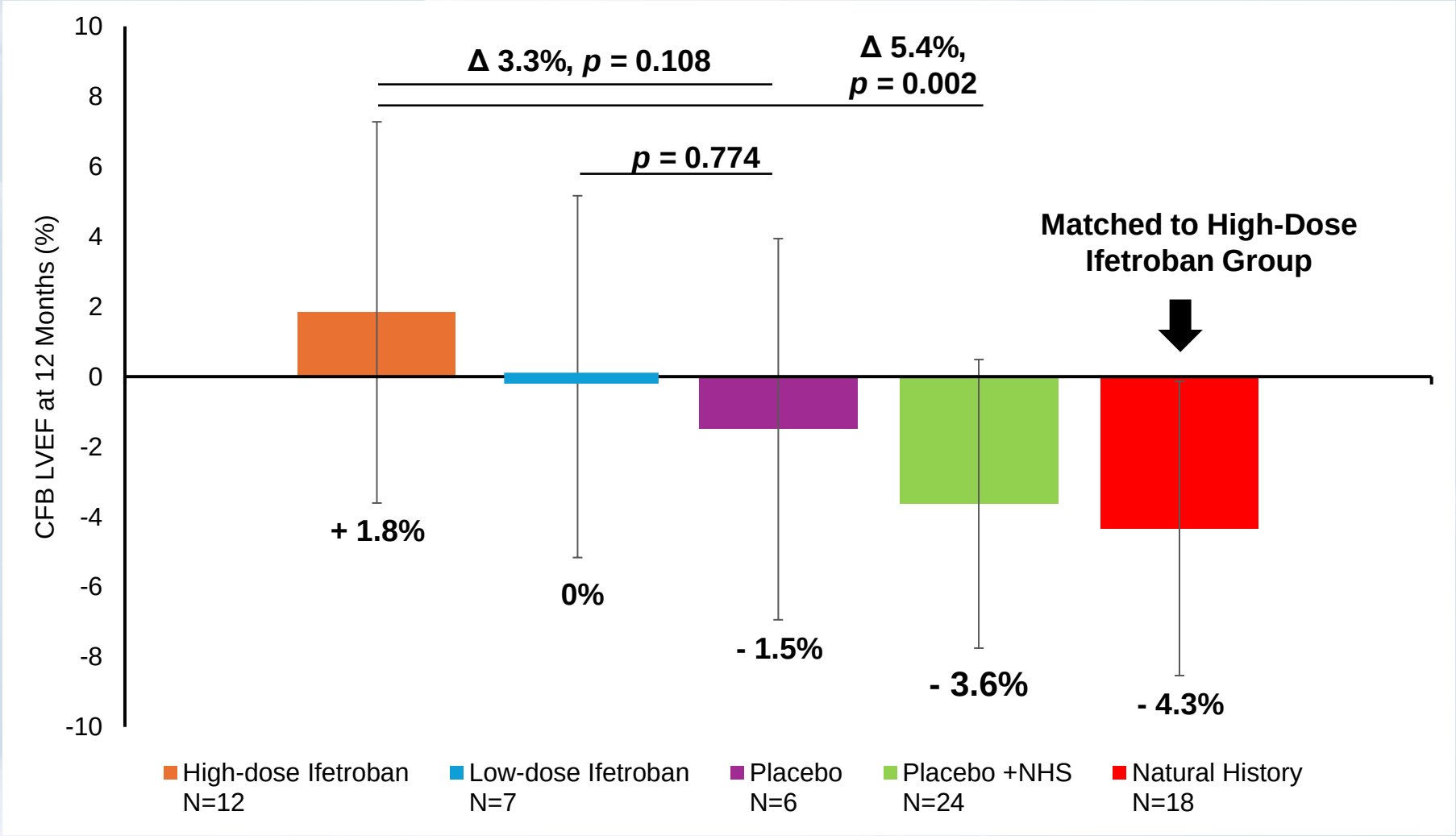
Safety: Adverse Event Summary

- No unexpected, drug-related AEs
- Most reported adverse events related to underlying disease
- No SAEs deemed related to study medication
- AEs possibly related to ifetroban: Contusion (2 high-dose, 1 low-dose), and petechiae (1 high-dose).

Demographics, Baseline Characteristics, and Safety

Category	Statistic or Parameter	High-Dose Ifetroban N=18	Low-Dose Ifetroban N=12	Placebo N=11
Age (years)	Mean (SD)	18.2 (5.9)	17.3 (5.8)	**14.7 (4.9)**
Weight (kg)	Mean (SD)	54.3 (17.9)	53.2 (20.7)	**42.4 (16.9)**
Ambulatory	Yes	8 (44)	4 (33)	4 (36)
	No	10 (56)	8 (67)	7 (64)
Ventilatory Support	Yes	2 (11)	2 (17)	0 (0)
	No	16 (89)	10 (83)	11 (100)
Stage of DMD Cardiomyopathy	Early (LVEF >45%)	14 (78)	11 (92)	**11 (100)**
	Late (LVEF 35-45%)	4 (22)	1 (8)	**0 (0)**
Background DMD Therapy	None	2 (11)	1 (8)	1 (9)
	Steroids	11 (61)	6 (50)	6 (55)
	Steroids + ASO	5 (28)	5 (42)	4 (36)
Background Cardiac Therapy	Carvedilol	4 (22.2)	3 (25)	4 (36.4)
	Enalapril	1 (5.6)	1 (8.3)	1 (9.1)
	Entresto	3 (16.7)	0 (0)	0 (0)
	Eplerenone	10 (55.6)	3 (25)	4 (36.4)
	Irbesartan	0 (0)	0 (0)	1 (9.1)
	Lasix	0 (0)	1 (8.3)	0 (0)
	Lisinopril	10 (55.6)	9 (75)	7 (63.6)
	Losartan	4 (22.2)	1 (8.3)	0 (0)
	Metoprolol	2 (11.1)	1 (8.3)	1 (9.1)
	Metoprolol succinate	3 (16.7)	1 (8.3)	0 (0)
	Spironolactone	5 (27.8)	6 (50)	3 (27.3)

Dose-dependent Preservation of Cardiac Function with Ifetroban Treatment



Clinical Implications

- Novel therapeutic mechanism:
  First evidence that thromboxane receptor antagonism protects cardiac function in DMD
- Clinically meaningful effect:
  5.4% LVEF difference counteracts the typical 2% annual LVEF decline in DMD
- Compatible with current therapies:
  Can be used alongside steroids and other standard DMD treatments
- Broad applicability:
  Potentially beneficial for all DMD patients regardless of mutation type

Key Takeaway

Ifetroban represents a potentially transformative approach to DMD cardiac care, targeting a novel pathway to address cardiomyopathy – a leading cause of mortality

Summary

- Ifetroban was well-tolerated in DMD subjects at doses up to 300 mg per day for 12 months
- A dose-dependent effect on LVEF was observed over 1 year:
  - High-dose ifetroban: 1.8% increase in LVEF
  - Low-dose ifetroban: no change in LVEF
  - Placebo: 1.5% decline in LVEF
  - Placebo + natural history: 3.6% decline in LVEF
  - Between group difference in LVEF for high-dose vs placebo was 3.3% or 5.4% with the natural history supplement

Ifetroban was effective at protecting the heart over 1 year of treatment

Acknowledgements

FIGHT DMD Families and Study Participants

Larry Markham, MD – Study PI

Jonathan Soslow, MD (Co-PI and CMR centralized reviewers)

Study investigators and staff

Kristen George-Durrett, BS, RT(R)(MR)

Erica Carrier, PhD (preclinical/translational collaborator)

James West, PhD (preclinical/translational collaborator)

Lausanne Foundation

Fight DMD Foundation

FDA OOPD - 1R01FD006371-01A1

MDA Muscular Dystrophy Association

Parent Project Muscular Dystrophy

FIGHT DMD.com

CUMBERLAND PHARMACEUTICALS

ClinicalTrials.gov Identifier: NCT03340675

FightDMDtrial.com ▪ fightdmd@cumberlandpharma.com