The Role of Inflammation and Fibrosis in DMD: How Do We Fix It?

Parent Project Muscular Dystrophy
JOIN THE FIGHT. END DUCHENNE.

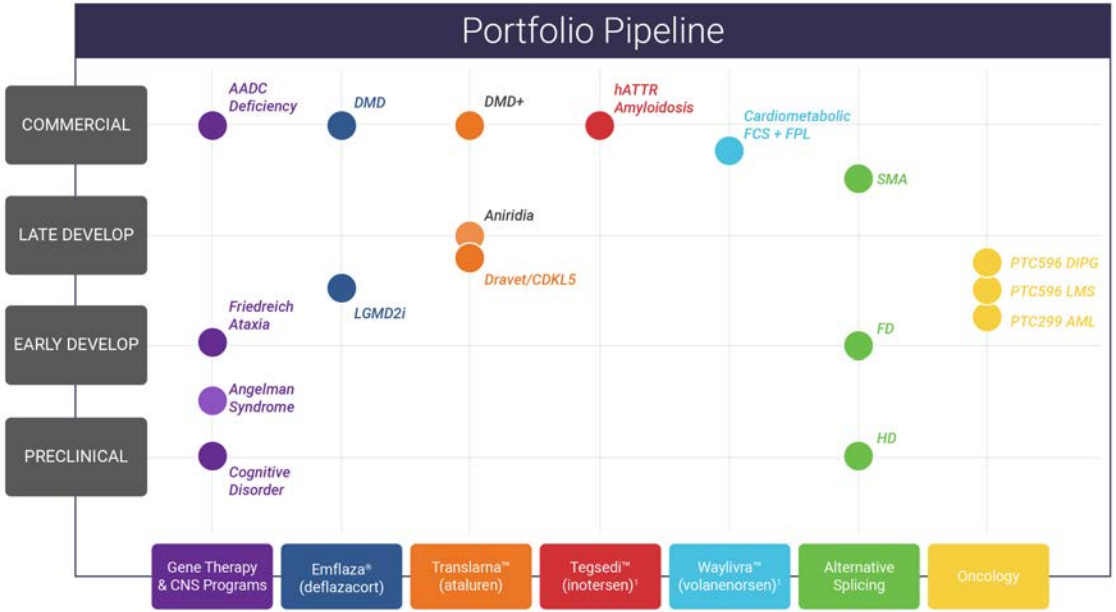
Brian Pfister PhD, MBA
Executive Director-PTC Therapeutics
06/28/2019

Thank you!

PTC Therapeutics is a small biotech company whose founder remains the current CEO

- 20+ year history in drug discovery, development and commercialization
- US HQ in South Plainfield, NJ
- Actively engaged in the discovery, development and commercialization of drugs for:
  - Genetic disorders
    - DMD, LG2I and SMA
    - Gene Therapy
      - AADC-D
  - Oncology
- ~ 600 employees worldwide
- Footprint in 47 countries, through local PTC teams and partnerships
- **Vision**: PTC is a fully integrated, innovative rare disorder company leveraging research capabilities and core technology platforms, building out world-class commercial capabilities, and being an ideal partner for late-stage, ultra-orphan disorders for which there is high unmet medical need

PTC Therapeutics:
Expanding the Pipeline Through Innovation[1]



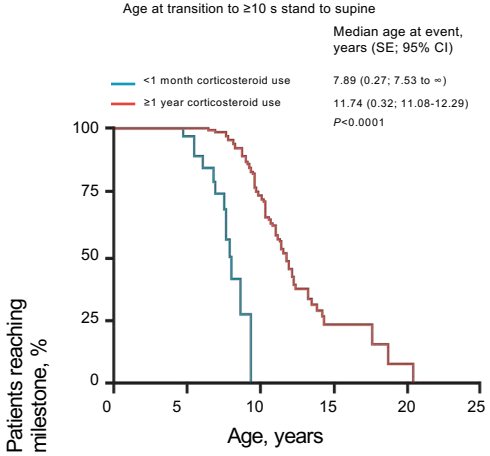
* Deflazacort is approved in the US.
† Ataluren is an investigational drug in the US.
‡ Marketing authorization has specific obligation to conduct additional nmDMD trial and requires annual renewal.
AADC = aromatic l-amino acid decarboxylase; CNS = central nervous system; DMD = Duchenne muscular dystrophy; CDKL5 = cyclin-dependent kinase-like 5; hATTR = hereditary amyloid transthyretin; FCS = familial chylomicronemia syndrome; SMA = spinal muscular atrophy; FD = familial dysautonomia; HD = huntington's disease; BMI1 = B cell-specific Moloney-murine leukemia virus integration site 1; DHODH = dihydroorotate dehydrogenase; US = United States; nmDMD = nonsense mutation Duchenne muscular dystrophy

1. PTC Therapeutics. Pipeline. https://www.ptcbio.com/en/pipeline. Accessed January 15, 2019.
2. Latin America and Caribbean commercialization rights unlicensed from Akcea Therapeutics.

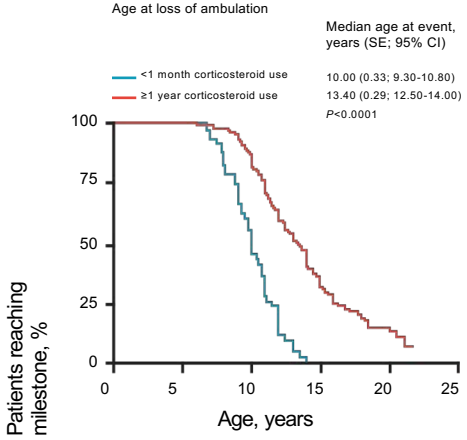
Corticosteroid Therapy as the Cornerstone of a Holistic Treatment Approach (SOC for Patients With DMD)

- DMD Care Considerations guidelines recommend daily dosing with corticosteroids in patients with DMD[1]
  - Corticosteroids should be integrated in multidisciplinary care interventions for added beneficial outcomes[2,3]

Corticosteroids delay functional declines



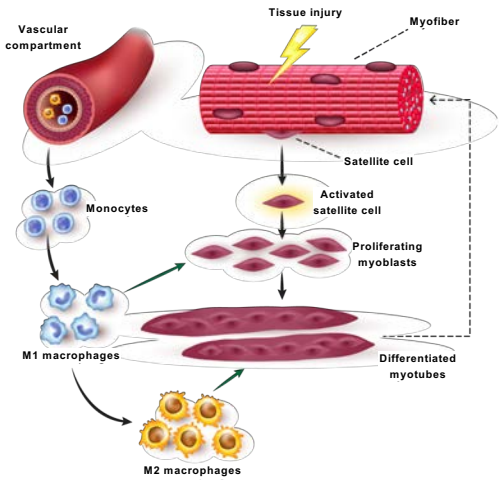
Corticosteroids delay age at loss of ambulation



CI=confidence interval; SE=standard error; SOC=standard of care.

1. McDonald CM, et al. *Lancet*. 2018;392:451-461. 2. Bushby K, et al. *Lancet Neurol*. 2010;9:177-189. 3. Birnkrant D, et al. *Lancet Neurol*. 2018;17:347-361.

What is Happening to My Muscles?



Inflammation and macrophage polarization in skeletal muscle injury and repair

- DMD disease pathophysiology
  - Inflammatory disease
  - Neuromuscular disease
- What impact does the immune system have on disease pathophysiology?
  - Innate vs adaptive immunity
  - Macrophage polarization (M1 and M2 macrophage modulation)
  - Th1 and Th2 cell modulation
- Resident macrophages and monocyte-derived cells during inflammation
- Immunosuppression vs immunomodulation

Th=T helper.

Kharraz Y, et al. Mediators Inflamm. 2013;2013: 491497

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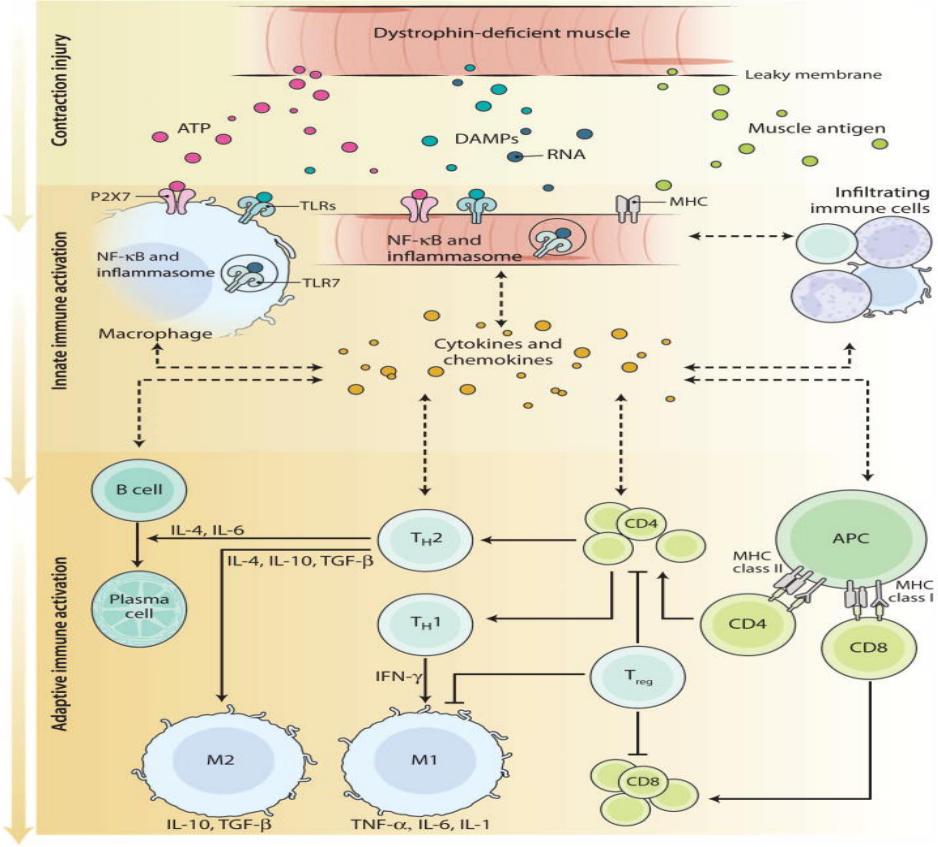
Why Don't My Muscles Just Get Better with an Anti-inflammatory Medicine?

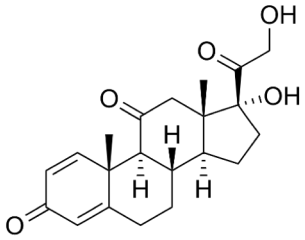


Rosenberg et al. Sci Transl Med. 2015 Aug 5;7(299):299rv4.

Aren’t All DMD Drugs the Same?

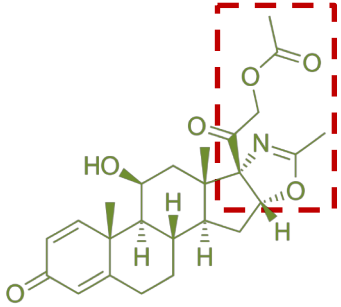
Emflaza® and Prednisone Aren't the Same

Prednisone is off-label usage in Duchenne



Prednisone

Emflaza is FDA approved for the treatment of Duchenne in patients 2 years of age and older

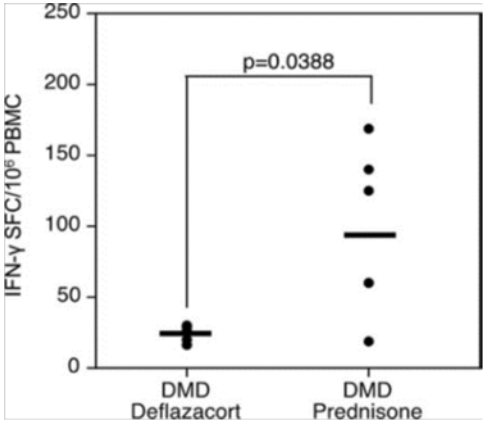


deflazacort

Deflazacort is a synthetic corticosteroid created by the insertion of a methyl-oxazoline ring in the chemical structure of prednisolone 21-acetate

Emflaza® and Prednisone Affect The Immune System Differently

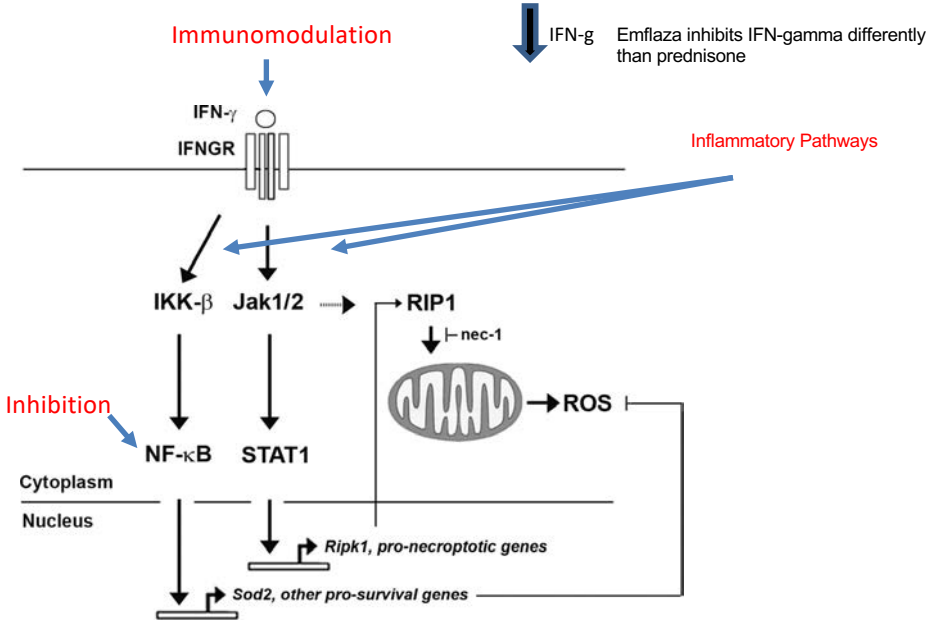
- There are distinct differences in the T-cell expression, as measured by IFN-gamma, between prednisone and deflazacort
- The difference in the mean number of spotforming colonies (SFC) per 10 PBMCs between the two groups is both marked and statistically significant, raising the possibility that deflazacort is more efficacious in modulating T-cell pathways



Flanigan KM, et al. Hum Gene Ther. 2013;24(9):797-806.

Aren't All Steroids the Same?

- Emflaza® works differently than prednisone on the components of inflammation



https://mcb.asm.org/content/31/14/2934/F11

Are You Sure?

How Do You Know?

What Side Effects Can I Expect?

Show Me……..

Study Design: Post Hoc Analysis of ACT DMD, a 48-week Trial of Ataluren For nmDMD

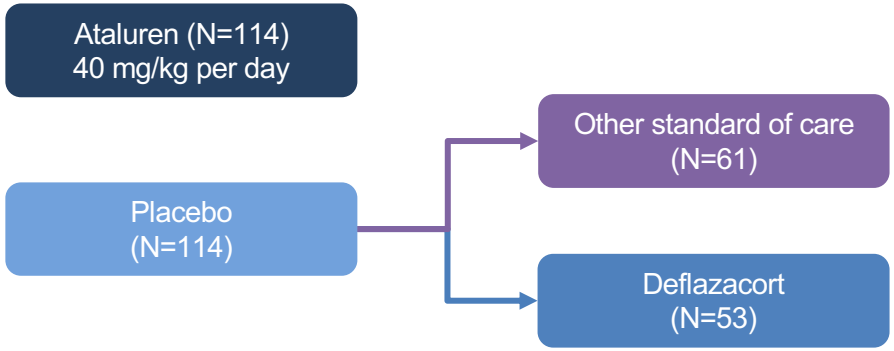
Key Inclusion Criteria

- Male; 5-15 years of age with nmDMD
- Ambulatory
- Corticosteroid therapy ≥6 months at study entry

Key Data Points

- Change from baseline in 6-minute walk distance at week 48
- Timed function tests:
  - 10-meter run/walk
  - 4-stair climb
  - 4-stair descent
- Exploratory endpoint
- Safety monitoring

Multi-center, randomized, double-blind (N=228)

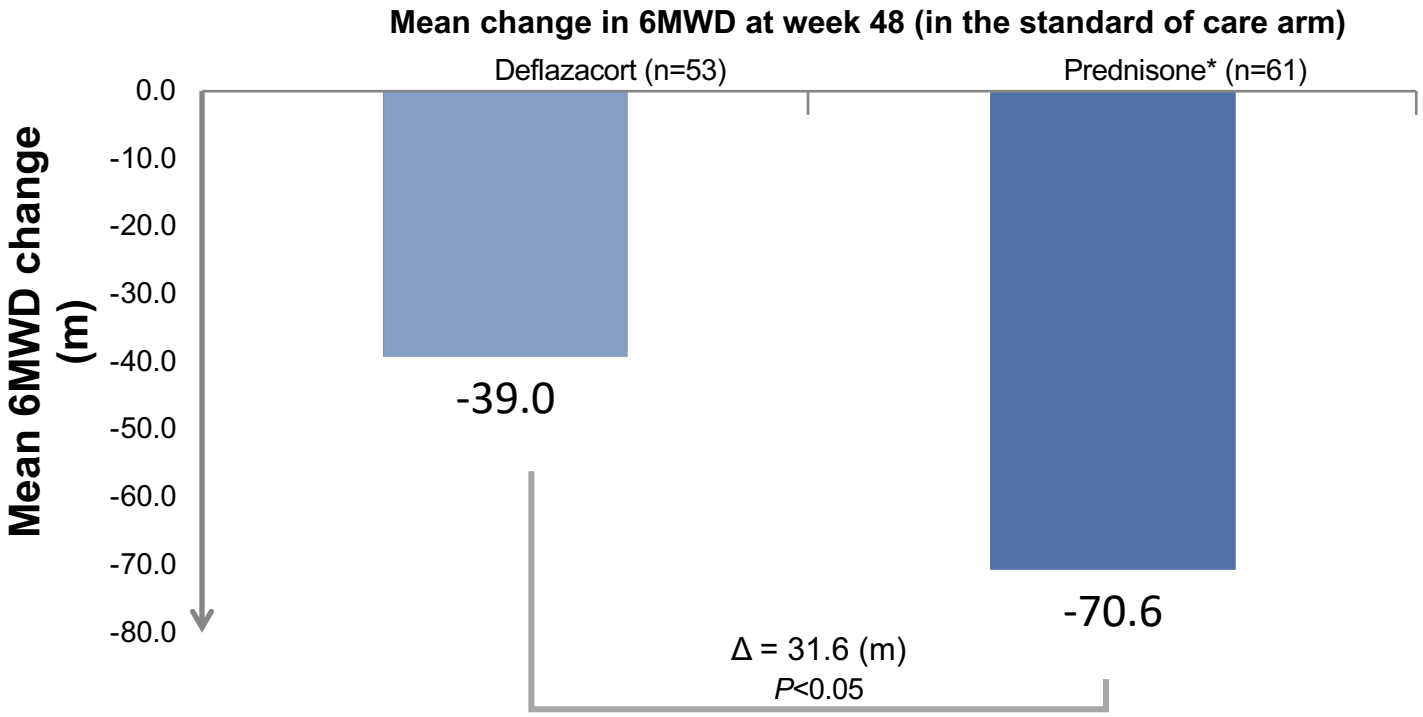


This post hoc analysis compares efficacy and safety for deflazacort and the other standard of care in the placebo arm

nmDMD=nonsense mutation Duchenne muscular dystrophy

Shieh PB, et al. *Muscle Nerve*. 2018;58:639-645; McDonald CM, et al. *Lancet*. 2017;390:1489-1498

Kids on Deflazacort Showed Significantly Less Decline in 6MWD at Week 48 vs Prednisone[1]

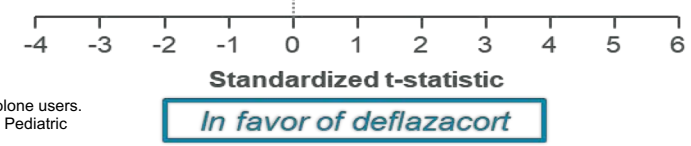


* Prednisone cohort comprised of prednisone/prednisolone users.
6MWD = 6-minute walk distance.

1. Shieh PB, et al. *Muscle Nerve*. 2018 Jul 20 [Epub ahead of print]. **2.** Narayanan S, et al. Disease burden and treatment landscape in Duchenne muscular dystrophy in the United States. Poster presented at: ISPOR 22nd Annual International Conference; May 23, 2017; Boston, MA.

Results from Other Measurements in the Study

Secondary Efficacy Endpoints*	In Favor of Deflazacort	LS Mean Difference (95% confidence interval)
6MWD (m)		31.6 (0.2, 62.9)
10-m Run/Walk (s)		0.1 (-1.9, 2.1)
4-Stair Climb (s)		2.9 (0.5, 5.23)
4-Stair Descend (s)		1.8 (-1.0, 4.5)
Rise from Supine (s)		2.6 (-0.0, 5.2)
NSAA (Total)		1.1 (-0.4, 2.6)
PODCI (Mobility)		1.7 (-3.9, 7.2)
PODCI (Sports)		6.0 (0.7, 11.3)
LOA (y)		3.84 (-2.43, 10.11)



* Prednisone cohort comprised of prednisone/prednisolone users.
NSAA = North Star Ambulatory Assessment; PODCI = Pediatric Outcomes Data Collection Instrument.

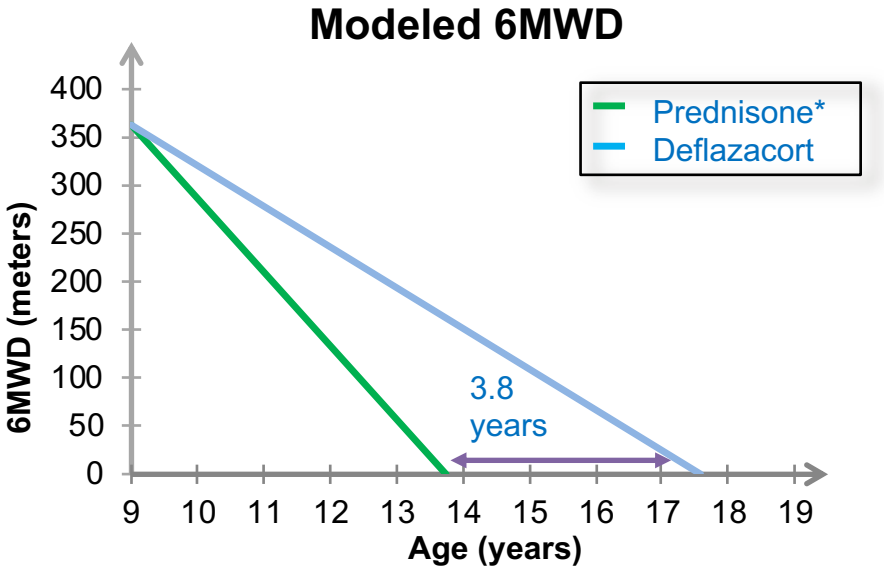
1. Shieh PB, et al. *Muscle Nerve*. 2018;58(5):639-645

An incremental delay in loss of ambulation of 3.8 years was predicted with Emflaza® vs prednisone based on 6MWD results in ACT DMD[1]

Extrapolation of Impact of 6MWD on Loss of Ambulation[1]

Methods:

- The 48-week decline in 6MWD observed in ACT DMD patients taking deflazacort and prednisone* was annualized and then extrapolated to estimate the number of years it would take to reach a 6MWD of 0 meters, if the initial annual rate of decline in 6MWD continued over the years
- Point of reaching a 6MWD of 0 meters was defined as loss of ambulation



* Prednisone cohort comprised of prednisone/prednisolone users.
6MWD = 6-minute walk distance.

1. Shieh PB, et al. *Muscle Nerve*. 2018 Jul 20 [Epub ahead of print].

ACT DMD

Most Common (Incidence of ≥5%) Side Effects of Corticosteroid Use in Duchenne

Side effects occurring in ≥5% of patients in either subgroup	Deflazacort (N=53) n (%)	Other standard of care (N=62) n (%)
Pain in abdomen (including upper abdomen)	0 (0)	18 (29)
Nasopharyngitis	6 (11)	17 (27)
Headache	10 (19)	11 (18)
Vomiting	10 (19)	11 (18)
Fall	8 (15)	12 (19)
Pain in extremity	6 (11)	8 (13)
Cough	5 (9)	8 (13)
Pyrexia	4 (8)	8 (13)
Constipation	4 (8)	6 (10)
Back pain	2 (4)	6 (10)
Upper respiratory tract infection	0 (0)	6 (10)
Diarrhea	5 (9)	5 (8)
Ligament sprain	3 (6)	4 (6)
Nausea	3 (6)	4 (6)
Oropharyngeal pain	2 (4)	4 (6)

Shieh PB, et al. *Muscle Nerve*. 2018 [Epub ahead of print]

Study Design: Prednisone and Deflazacort Regimens in the CINRG Study

Key Inclusion Criteria

- Patients from CINRG Duchenne Natural History Study + additional patients aged 4-8 years

Key Exclusion Criteria

- Naive to corticosteroid treatment and ambulated without assistance past their 13th birthday
- Use of corticosteroid therapy and ambulated without assistance past their 16th birthday

Study Duration

- Patients were followed up for 10 years

Deflazacort (N=107)

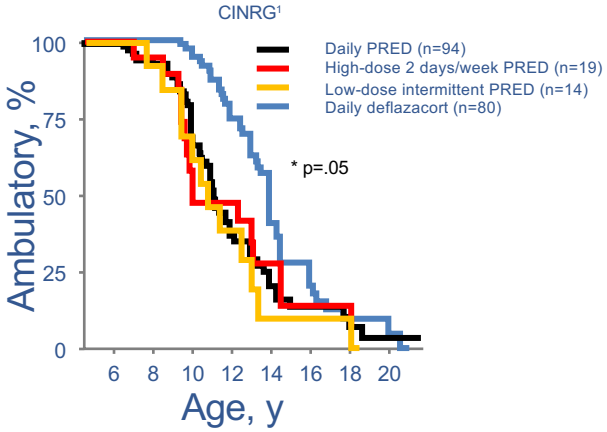
Prednisone (N=103)

Disease progression milestones including ***age at loss of ability to stand from supine, loss of ambulation, and loss of hand-to-mouth function*** *were studied*

CINRG=Cooperative International Neuromuscular Research Group
McDonald CM, et al. *Lancet*. 2017;391:451-461

What Happens Long-term with the treatment of Different DMD Dystrophin Sparing Therapies?

Probability of ambulation by treatment regimen



PRED=prednisone or prednisolone.

1. Bello L et al. *Neurology*. 2015;85(12):1048-1055. 2. Wang RT et al. *PLoS Curr*. 2014;6.

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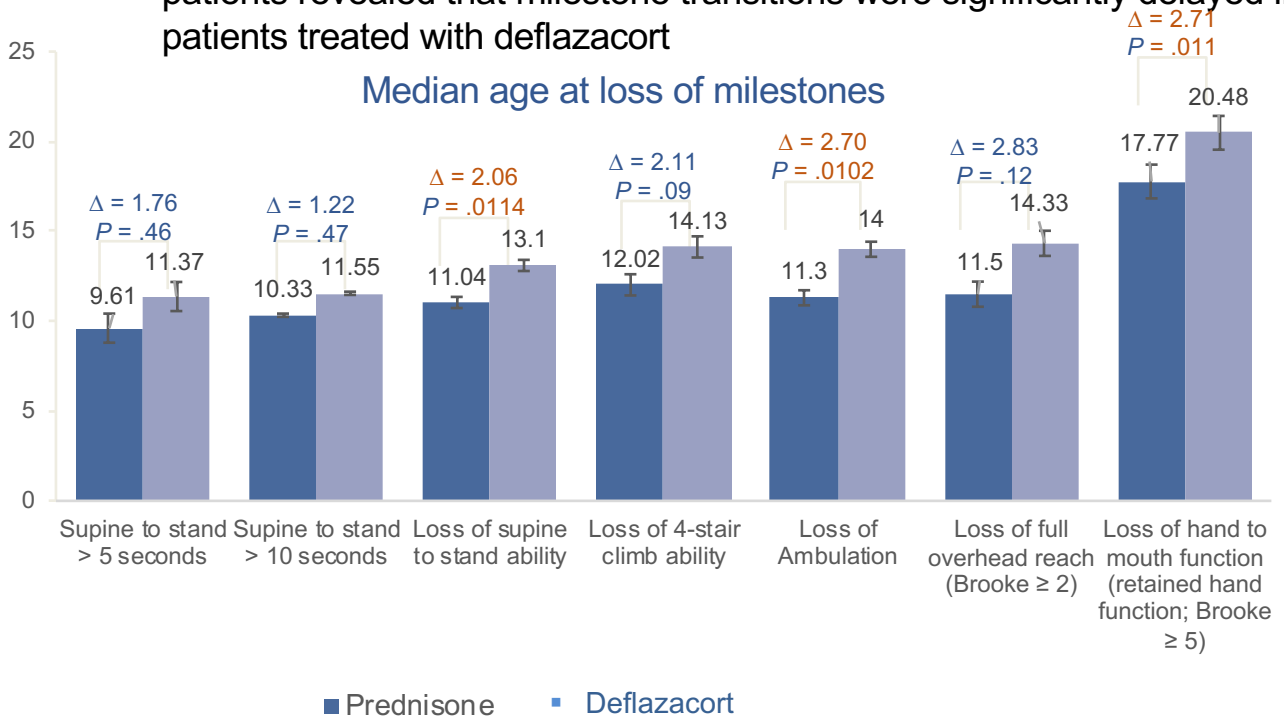
"Real Life" Emflaza® vs. Prednisone Long-term Outcomes

- Results from analysis of effect of treatment with corticosteroids in 440 patients revealed that milestone transitions were significantly delayed in patients treated with deflazacort



McDonald CM, et al. *Lancet*. 2018;391:451-461.

Partial List of Side Effects of Corticosteroid Use in Duchenne (only adverse events occurring in >1% total person-years exposure shown)

	Deflazacort n (%)		Other Standard of Care n (%)		Total
Total person-years exposure	Daily 877	Intermittent* 82	Daily 191	Intermittent* 698	1848
Weight gain	48 (5)	6 (7)	26 (14)	62 (9)	142
Cushingoid	57 (6)	4 (5)	17 (9)	41 (6)	119
Behavioral changes	26 (3)	4(5)	11 (6)	33 (5)	74
Growth delays	45 (5)	4 (5)	8 (4)	20 (3)	77
Cataracts	26 (3)	1 (1)	1 (<1)	7 (1)	35

*Intermittent includes participants who consistently used a non-daily regimen or those who switched between daily and non-daily regimens throughout the study; **% of total calculated as the number of side effects/total person-years exposure for that type of drug, regimen

Supplemental appendix to McDonald CM, et al. *Lancet*. 2017;391:451–461

Study Design – Phase 3 Multicenter, Randomized, Double-Blind, Placebo-Controlled: Safety and Efficacy of Deflazacort

Key Inclusion Criteria

- Male; 5-15 years of age with Duchenne*

Key Exclusion Criteria

- Prior long-term use (>1 year) of oral corticosteroids
- Use of oral steroids for ≥1 month within 6 months and any use of oral steroids for <1 month within 2 months of study entry

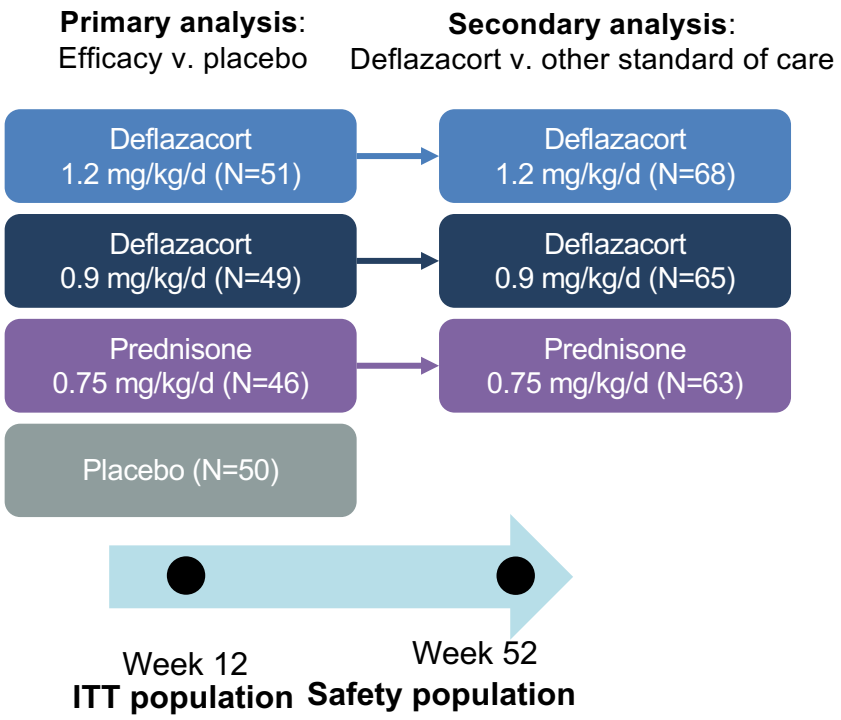
Key Data Points

Efficacy

- Primary - Change in average muscle strength from baseline to week 12 (modified MRC score)
- Secondary - Change in average muscle strength from week 12 to week 52, pulmonary function testing
- Additional – TFTs, physician assessment

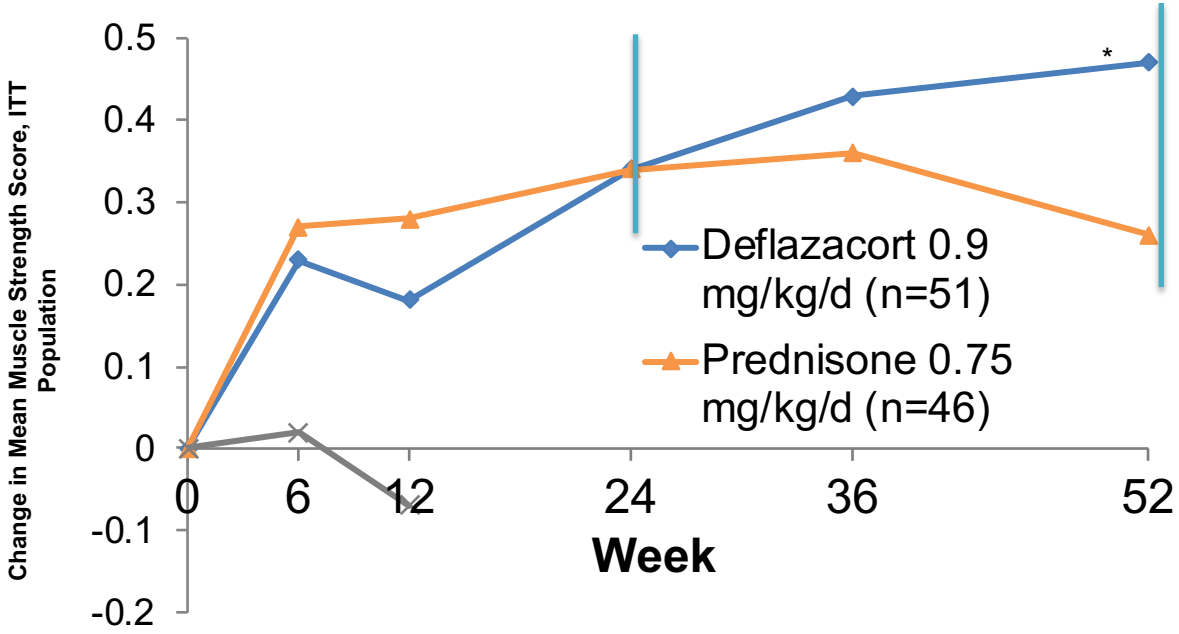
Safety

- Adverse events, clinical lab assessments, and vital signs



*7 out of 196 patients presented with neck flexor grades ≥4 at the screening visit suggesting Becker muscular dystrophy
MRC=Medical Research Council; TFT=Timed Functional Testing; ITT=Intent-To-Treat
Griggs RC, et al. *Neurology*. 2016;87:2123-2131

Long-term Benefit Should be Considered



ITT=intent-to-treat.

Griggs RC, et al. Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy. Neurology. 2016;87.

Side Effects of Emflaza® vs. Prednisone

	TEAEs occurring in ≥10% of patients in any treatment group (safety population)	Deflazacort 0.9 mg/kg/d (N=68) n (%)	Prednisone 0.75 mg/kg/d (N=63) n (%)	Placebo (N=50) n (%)
	Number of patients with ≥1 TEAE	58 (85.3)	58 (92.1)	38 (76.0)
P<0.05	**Cushingoid** (*puffy face, among other symptoms*)	41 (60.3)	49 (77.8)	6 (12.0)
	Hirsutism (*abnormal hair growth*)	24 (35.3)	28 (44.4)	1 (2.0)
	Erythema (*skin redness*)	19 (27.9)	33 (52.4)	3 (6.0)
	Weight gain	19 (27.9)	22 (34.9)	3 (6.0)
P<0.01	**Central obesity**	17 (25.0)	27 (42.9)	2 (4.0)
	Nasopharyngitis (*e.g. common cold*)	16 (23.5)	10 (15.9)	3 (6.0)
	Headache	15 (22.1)	17 (27.0)	11 (22.0)
	Upper respiratory tract infection	10 (14.7)	7 (11.1)	5 (10.0)
	Pollakiuria (*frequent daytime urination*)	10 (14.7)	3 (4.8)	1 (2.0)
	Increased appetite	8 (11.8)	12 (19.0)	1 (2.0)
	Cough	7 (10.3)	8 (12.7)	3 (6.0)
	Constipation	7 (10.3)	4 (6.3)	3 (6.0)
	Abdominal pain upper	6 (8.8)	10 (15.9)	4 (8.0)
	Abnormal behavior	6 (8.8)	9 (14.3)	3 (6.0)
	Pyrexia (*raised body temperature, e.g. fever*)	6 (8.8)	6 (9.5)	4 (8.0)
	Influenza	4 (5.9)	10 (15.9)	2 (4.0)

TEAE = treatment-emergent adverse event

Griggs RC, et al. *Neurology*. 2016;87:2123-2131

Takeaways

So What?

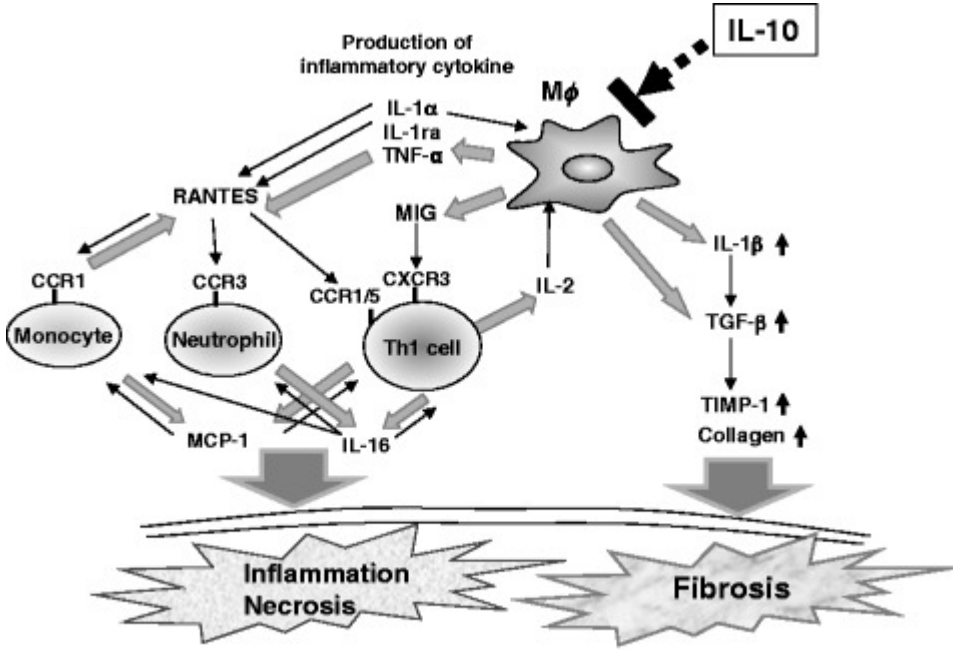
- Controlling inflammation and the immune system are important targets to in treating DMD
- Emflaza® and Prednisone are not the same structurally or functionally.
- Emflaza® has shown repeatedly to slow the functional decline in DMD boys
  - CINRG (Prospective Study)
  - ACT DMD Standard of Care Comparison (RCT)
  - Griggs Pivotal Trial (RCT)
- When long-term comparisons are available, Emflaza® consistently shows different effectiveness than prednisone in clinical outcomes in DMD
- These differences in molecular may result in better outcomes for DMD boys
- Emflaza® consistently resulted in different outcomes as compared to prednisone in treating DMD

Questions?

Thank you!

Backup Slides

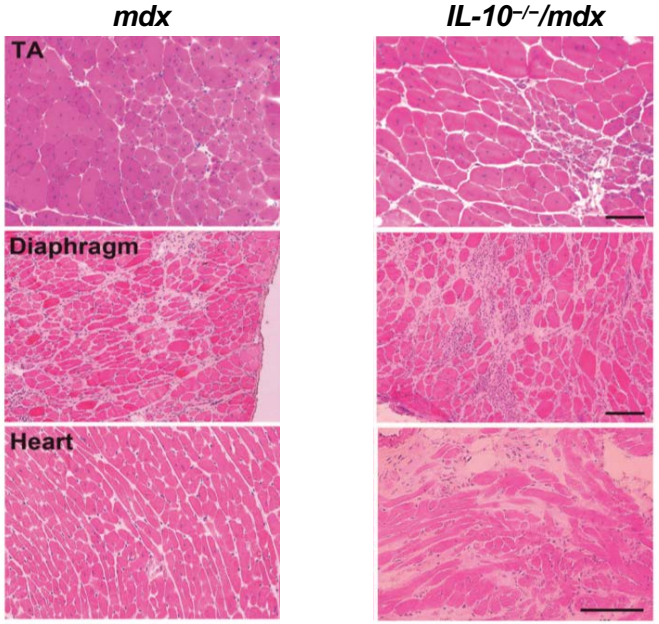
Role of IL-10 and Fibrosis



Nitahara-Kasahara, Y. et al (2016). *Inflammation and regeneration*, *36*, 14.

Immune-Mediated Pathology in DMD: IL-10 as an Important Immunomodulator in DMD

H&E staining of TA muscle, diaphragm and heart sections from 8-month-old mdx and *IL-10*$^{-/-}$*/mdx* mice (Bar = 100 µm)



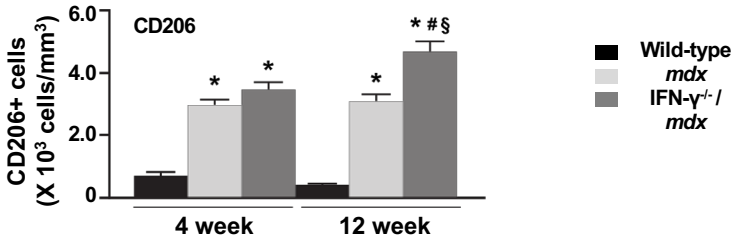
- Effects of IL-10 on inflammation and severity of DMD were studied in mice lacking both dystrophin and IL-10 (*IL-10*$^{-/-}$*/mdx* mice)[1]
  - IL-10 is an anti-inflammatory cytokine
- IL-10 might be an important immune modulator in human dystrophic muscles, because IL-10 ablation in *mdx* mice causes an increase in inflammation, muscle necrosis, and fibrosis[2]

H&E=hematoxylin and eosin; IL=interleukin; TA=tibialis anterior.

1. Nitahara-Kasahara Y, et al. *Hum Mol Genet*. 2014;23:3990-4000. 2. Nitahara-Kasahara Y, et al. *Inflamm Regen*. 2016;36:14.

Immune-Mediated Pathology in DMD: Role of IFN-γ

IFN-γ represses the M2a macrophage activation during regeneration



- Number of M2a macrophages is elevated in dystrophic muscles
- Ablation of IFN-γ in *mdx* muscles further elevates M2a cells
- Suppression of IFN-γ signaling in muscular dystrophy **reduces muscle damage and improves motor performance by promoting M2 polarization over M1**

IFN=interferon.

Villalta SA, et al. J Immunol. 2011;187:5419-5428

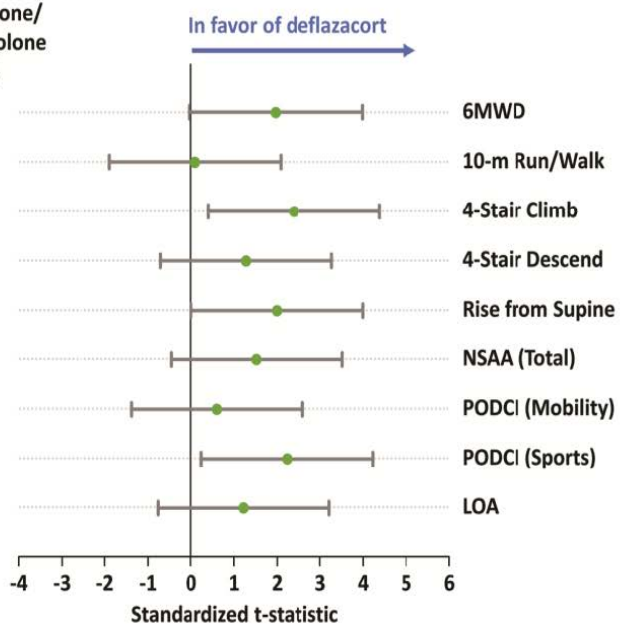
T-Cells and IFN-gamma-So What?

- T-cells carryout a various number of functions and signal specific activities
- IFN-γ is a strong inducer of the M1 phenotype and is elevated in mdx dystrophy
  - M1 phenotype is associated with muscle damage
- Ablation of IFN-γ reduced muscle damage in vivo during the regenerative stage of the disease and increased activation of the M2 phenotype and improved motor function of mdx mice at that later stage of the disease
- IFN-γ also inhibited muscle cell proliferation and differentiation in vitro
  - IFN-γ can have direct effects on muscle cells that could impair repair
- The findings show that suppression of **IFN-γ signaling in muscular dystrophy reduces muscle damage and improves motor performance by promoting the M2 macrophage phenotype and by direct actions on muscle cells**

https://www.ncbi.nlm.nih.gov/pubmed/22013114
Villalta SA, Deng B, Rinaldi C, et al. J Immunol. 2011 Nov 15;187(10):5419-28. doi: 10.4049/jimmunol.1101267. Epub 2011 Oct 17.

EMFLAZA Resulted in Improvements vs Prednisone Across All Clinical Outcomes and Quality of Life Measures in the ACT DMD Trial[1]

	Deflazacort (n)	Prednisone/ Prednisolone (n)	LS Mean Difference (95% CI)
6MWD	53	61	31.6 (0.2, 62.9) (meters)
10-m Run/Walk	53	61	0.1 (-1,9, 2.1) (sec)
4-Stair Climb	53	61	2.9 (0.5, 5.23) (sec)
4-Stair Descend	53	61	1.8 (-1.0, 4.5) (sec)
Rise from Supine	53	61	2.6 0 (-0.0, 5.2) (sec)
NSAA (Total)	53	61	1.1 (-0.4, 2.6)
PODCI (Mobility)	53	61	1.7 (-3.9, 7.2)
PODCI (Sports)	53	61	6.0 (0.7, 11.3)
LOA	53	61	3.84 (-2.43, 10.11) (years)



ACT DMD

- * Prednisone cohort comprised of prednisone/prednisolone users.
- NSAA = North Star Ambulatory Assessment; PODCI = Pediatric Outcomes Data Collection Instrument.
- **1.** Shieh PB, et al. *Muscle Nerve*. 2018;58(5):639-645.

Prednisone*