DESIGN THERAPEUTICS

DESIGNING A NOVEL CLASS OF GENOMIC MEDICINES

FOR GENETIC DISORDERS

3Q 2026

Disclaimers

This presentation contains forward-looking statements. All statements other than statements of historical facts contained in this presentation are "forward-looking statements" within the meaning of the Private Securities Litigation Reform Act of 1995. These statements include, but are not limited to projections from early-stage programs, preclinical data and early-stage clinical data; the therapeutic potential of DT-216P2, DT-168 and DT-818; the initiation and progression of studies and clinical trials for DT-216P2, DT-168, DT-818 and the timing thereof; the expected timing for data readouts; the potential benefits of restoring FXN in FA patients; clinical outcomes and potential benefits of DT-216P2 for Friedreich ataxia; historical placebo effect on mFARS and USS as a predictor of future placebo effect; the ability to advance 1 mg/kg intravenous (IV) weekly toward a potential registration path; the design, timing, duration, dose levels, enrollment, completion and expected results of ongoing and future studies of DT-216P2; potential regulatory pathways for FA; Design's plans to shift focus toward studies to support the potential future registration of DT-216P2, prioritize the IV route of administration, and obtain further clarity on development plans in the fourth quarter of 2026; Design's FECD GeneTAC® program and its potential therapeutic benefits and advantages; the impact of Design's FECD observational study on a clinical program for FECD; the potential utility of corneal endothelium biomarkers in clinical development; Design's DM1 GeneTAC® program and its potential therapeutic benefits and advantages; the benefit of a reduction in toxic foci in human myotubes as a predictor of restoring clinical splicing in DM1; DT-818's potential to be a best-in-disease treatment for DM1; Design's HD GeneTAC® candidates and their potential therapeutic benefits and advantages; the anticipated or implied market opportunities for Design's GeneTAC® programs; milestones, next steps, and Design's ability to deliver on its short- and long-term goals; the design and capabilities of Design's GeneTAC® platform; establishing clinical proof of concept for any product candidate, including through biomarker measurements; Design's estimated cash runway and the sufficiency of Design's resources to enable its programs and platform and support its planned operations; and the capabilities and potential advantages of Design's pipeline of GeneTAC® molecules. 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Challenging the status quo of genomic medicines with small molecules (GeneTAC® molecules) that dial up or dial down transcription…

…to treat significant monogenic disorders

BECAUSE WE BELIEVE YOUR FATE DOESN'T HAVE TO BE WRITTEN IN YOUR GENES

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Advancing four GeneTAC® molecule programs

		Gene	Monogenic disease	Differentiated profile	Status + Expected Milestone Timing	Market Overview
CLINICAL	**Friedreich Ataxia** **DT-216**	FRATAXIN (FXN)	GAA repeat expansion leads to reduced transcription	Restoration of endogenous frataxin with broad tissue distribution	RESTORE-FA positive 4-week data 12-week data 1Q 27 registrational update 4Q 26	**$7.3B** Biogen acquired Skyclarys® (REATA) in 2023
CLINICAL	**FECD** **DT-168**	TCF4	CTG repeat expansion causes corneal endothelial cell dysfunction	Allele-selective reduction of mutant transcript (TCF4) with an eye drop	Ph2 biomarker trial in pts ongoing data in 2027	**Over 1 million** TCF4 expansion pts in US (multi-billion $ opp)
CLINICAL	**DM1** **DT-818**	DMPK	CTG repeat expansion causes nuclear foci & cellular dysfunction	Allele-selective reduction of mutant DMPK leads to foci resolution & splicing correction	Ph1 patient dosing initiated data in 2027	**Est. >70K cases** in US (multi-billion $ opp)
PRECLINICAL	**Huntington's Disease**	HUNTINGTIN (HTT)	CAG repeat expansion leads to toxic mRNA & protein product	Allele-selective reduction of mutant HTT	Next step: Select DC	**~40,000 affected** by HD in US (multi-billion $ opp)

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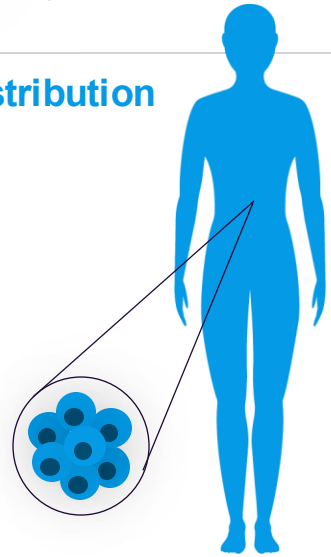
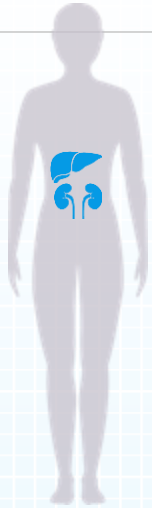
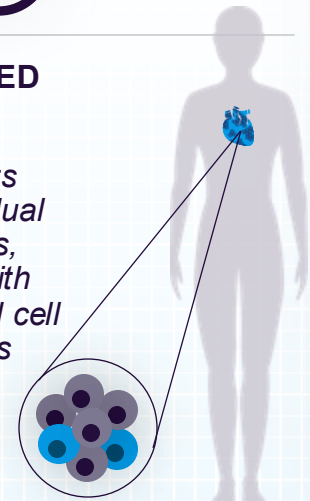
GeneTAC® molecules can distribute widely, overcoming a central challenge for traditional genomic medicines

	GeneTAC® Small Molecule	Oligonucleotide	Protein	Gene Therapy
MOLECULAR SIZE *(Dalton)*	1,000-3000	6,000-15,000	50,000-100,000	4,000,000-5,000,000
DISTRIBUTION	**Broad distribution** 	**LIMITED** *Distribution in most affected tissues often inadequate* 	**LIMITED** *Distributes widely, but with minimal cell access*	**LIMITED** *Targets individual organs, and with limited cell access* 
MOA	**Engage endogenous gene expression**		***RISK OF OVEREXPRESSION***	
DELIVERY COMPLEXITY				

- Successfully targeted cells
- Native cells

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DT-216P2 for Friedreich Ataxia

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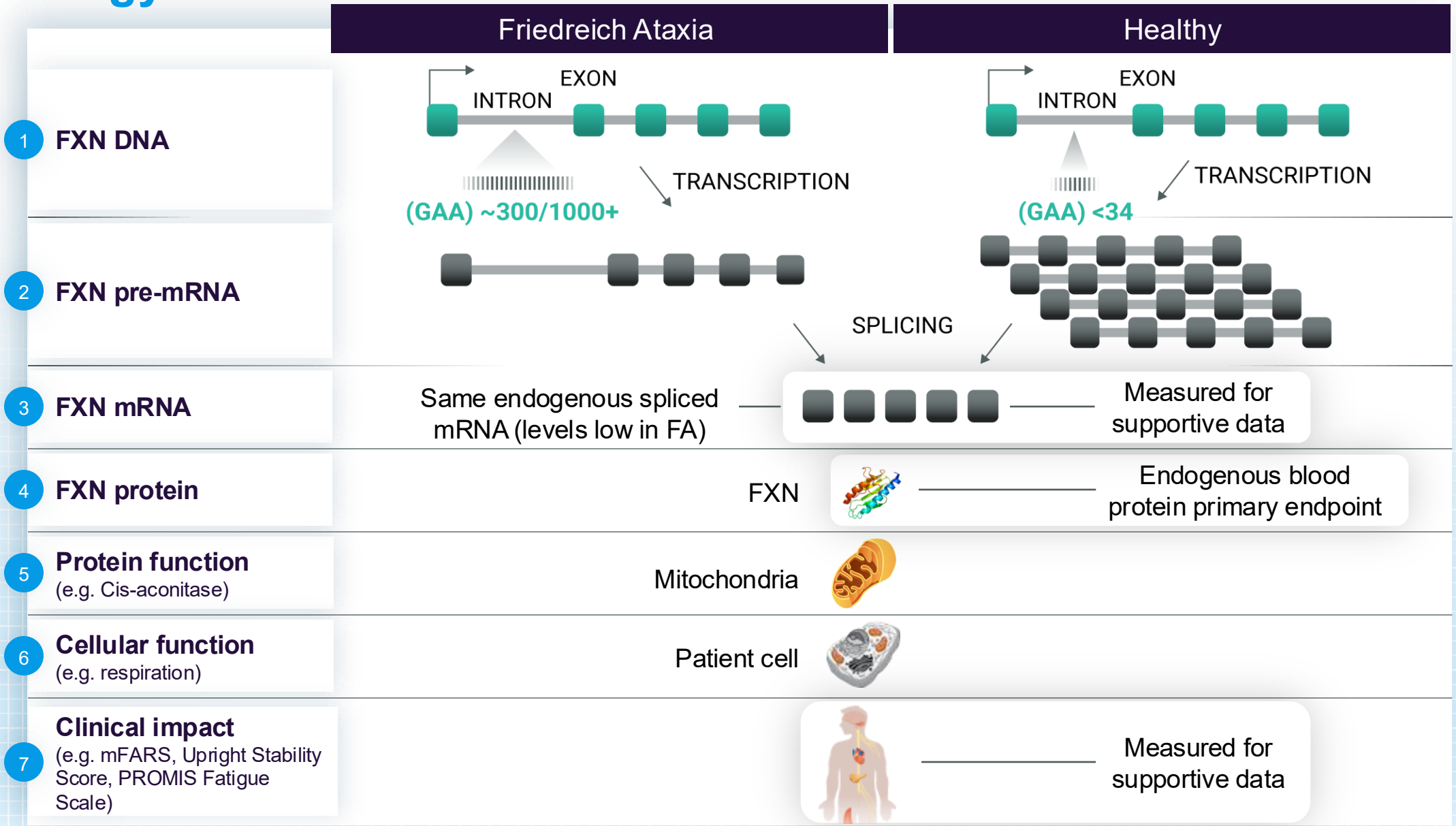
Pathogenic Cascade in Friedreich Ataxia and Clinical Biomarker Strategy



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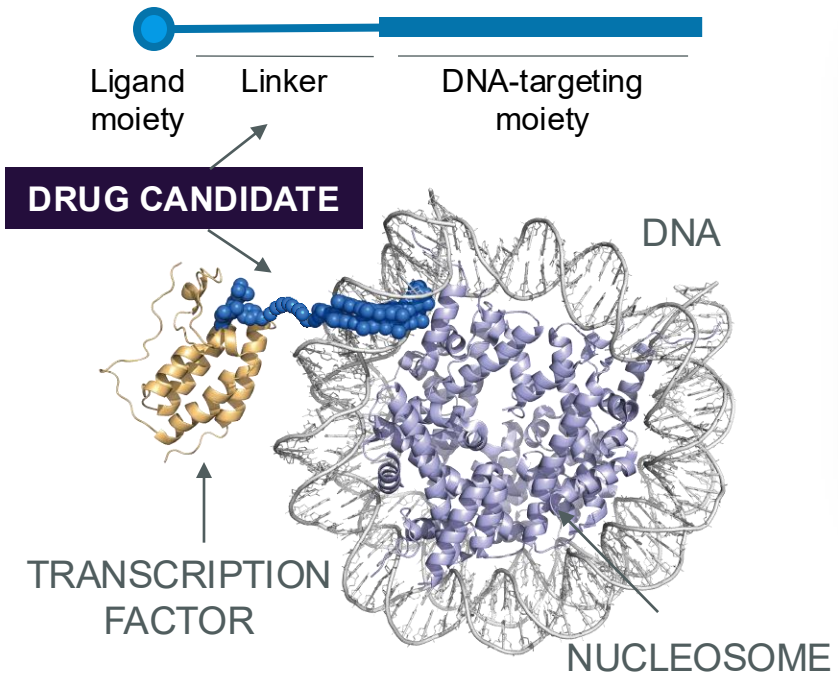
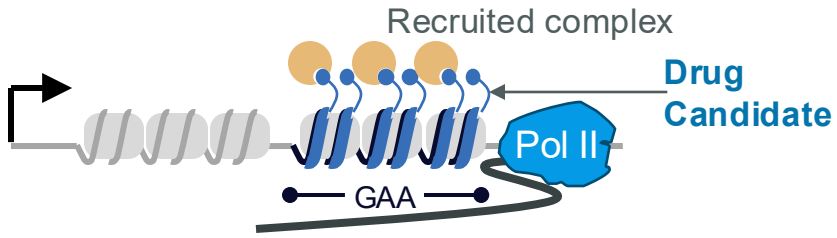
FA GeneTAC® molecules normalized FXN levels in FA patient cells but did not alter FXN levels in healthy cells



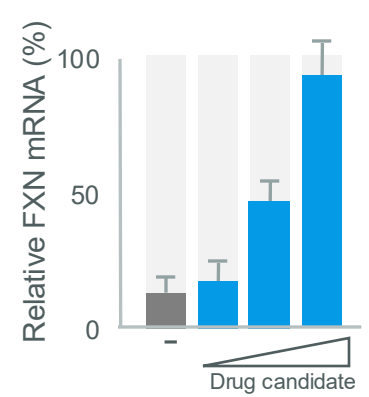
DIAL UP EXPRESSION



Designed to facilitate transcription through the locus

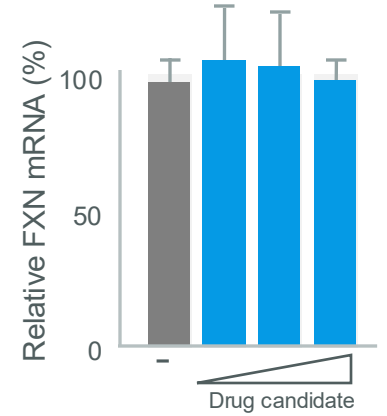
FA PATIENT (two expanded copies)

GeneTAC® molecules normalized levels



HEALTHY INDIVIDUAL (two normal copies)

FXN levels unaltered in healthy cells



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Endogenous blood FXN protein forms the foundation of the natural history studies in FA

Large scale natural history evaluation of endogenous blood frataxin protein:

- Blood samples taken from patients in the FACOMS and FACHILD natural history studies
- >600 patients with average ~10 years of clinical follow-up
- Two different assay platform technologies (lateral-flow antibody and LCMS)
- Measures of total frataxin, FXN-M and FXN-E

Conclusion

*"**FRATAXIN LEVELS** **directly correlate** with all major clinical outcomes in FA [patients] … such as age of onset and disease severity… loss of ambulation and long-term progression slopes of mFARS and USS…Peripheral frataxin quantification provides biologically grounded measure of the pathophysiology and disease progression."* [1]

Source: Rummey C, et al. Peripheral frataxin levels govern long-term clinical progression in Friedreich ataxia. BMJ Neurology Open. 2026

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RESTORE-FA MAD study in FA patients: 4-week cohorts completed

Dosing duration	Weekly IV infusion (target cohort size ≥ 4)	Biomarker endpoints Endogenous FXN biomarkers	Exploratory clinical endpoints
4 weeks	0.1 mpk (5-8 mg) 0.3 mpk (15-24 mg) 0.6 mpk (30-48 mg) 1 mpk (50-80 mg)	1. Whole blood mRNA and protein 2. Muscle biopsy mRNA and protein	1. mFARS[2] 2. Upright Stability Score (USS) 3. PROMIS Fatigue Scale 4. Various other exploratory endpoints

Note: Subcutaneous dosing still under exploration. 1. PK projections support multiple additional cohorts within nonclinical safety exposures. 2. modified Friedreich Ataxia Rating Scale

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Baseline characteristics

	Cohort 1 0.1 mg/kg IV (n = 4)	**Cohort 2** 0.3 mg/kg IV (n = 4)	**Cohort 3** 0.6 mg/kg IV (n = 4)	**Cohort 4** 1.0 mg/kg IV (n = 4)	**Total** (N = 16)
Age (years), Mean (SD)	43.5 (16.8)	39.5 (5.3)	26.75 (6.7)	34.75 (10.3)	36.125 (11.6)
Age at onset (years), Mean (SD)	26.5 (19.9)	18.75 (7.4)	14.75 (4.8)	18.5 (4.7)	19.625 (10.9)
Female, n (%)	4 (100%)	1 (25%)	3 (75%)	2 (50%)	10 (62.5%)
Functional Staging for Ataxia, Mean (SD)	3.9 (0.9)	4.4 (1.3)	4 (1.7)	3.9 (1.4)	4 (1.2)
GAA1 repeat length, Mean (SD)	368 (192)	377 (94)	696 (268)	303 (165)	436 (232)

10 of 16 patients on stable Omaveloxolone for an average of > 5 years

Note: Data analysis as of May 17 2026; GAA1 is the GAA repeat length of the shorter allele

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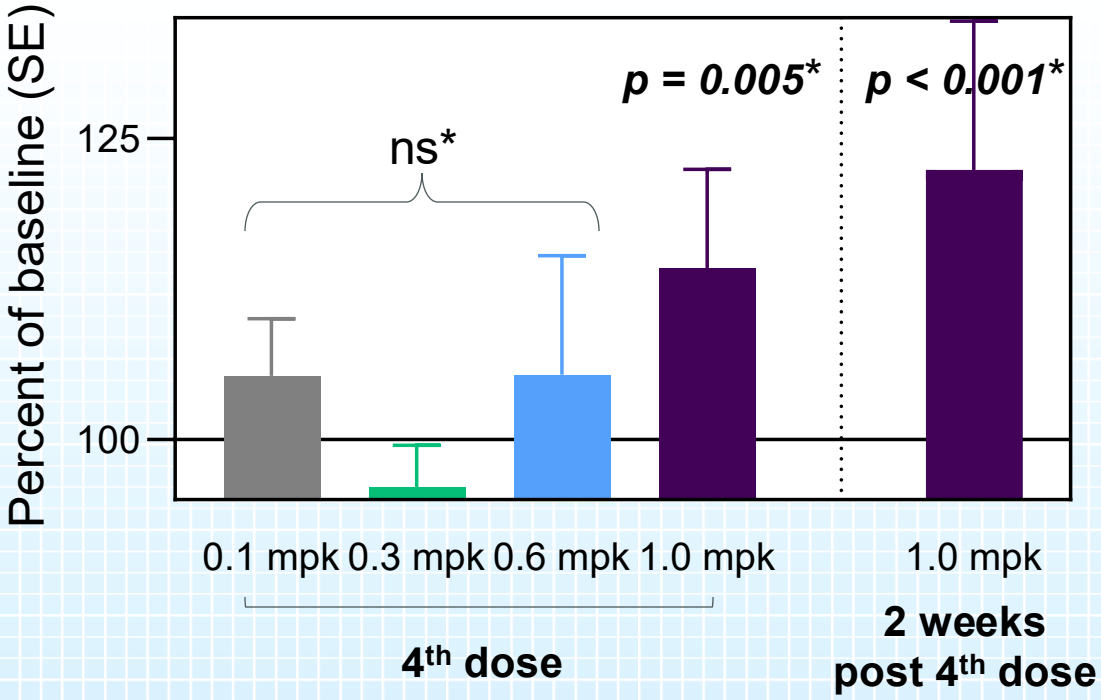
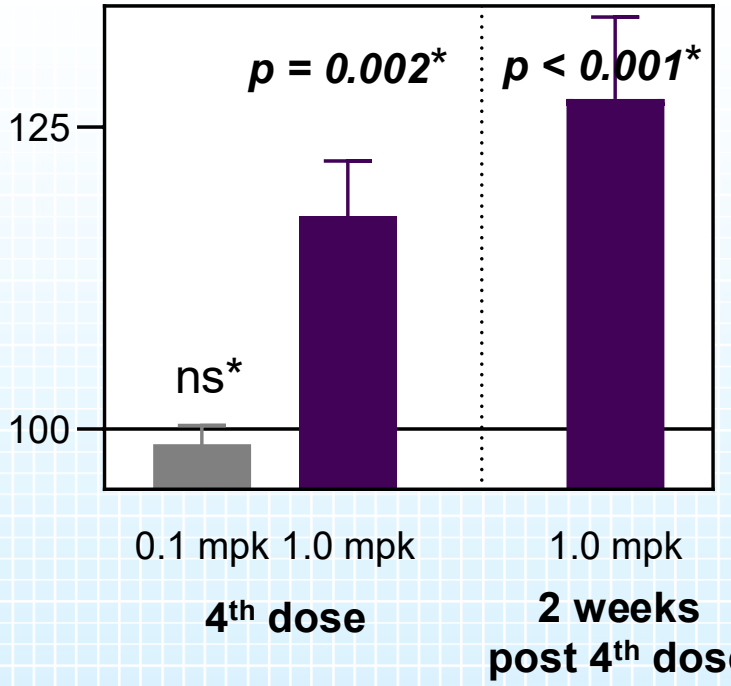
Endogenous FXN Protein: Increases in multiple isoforms of blood frataxin protein

Whole blood (FXN-M)



Whole blood (FXN-E)



Note: Data analysis as of May 17 2026; Data is shown as percent of baseline pre-dose FXN level; Exploratory statistical analysis (two-sided) compared to untreated individuals (data not shown), no formal hypothesis testing for any endpoint was prespecified. FXN-E was not measured for 0.3 and 0.6mpk cohorts

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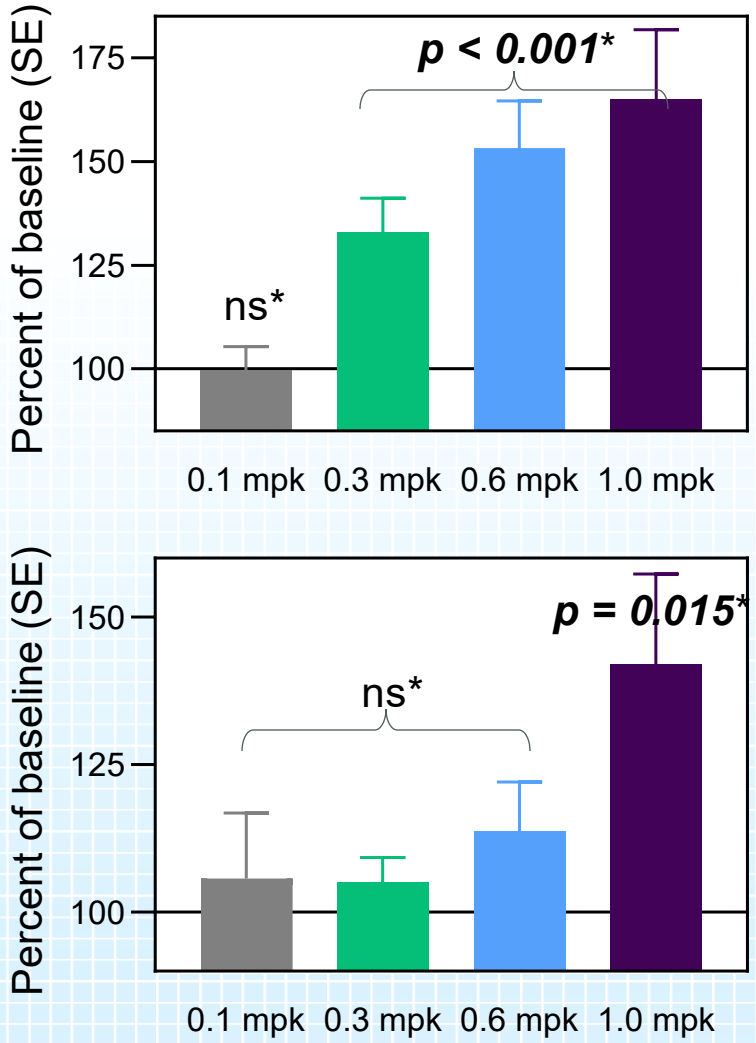
Endogenous FXN mRNA: Increases observed in multiple tissues

Whole blood

Sensitive assay with separation between patients and carriers

Muscle

Confirms activity multiple tissues



Note: Data analysis as of May 17 2026; Data is shown as percent of baseline pre-dose FXN level; Whole blood mRNA: in data from untreated individuals, the 90th percentile of FA patients is 24% above the FA patient average while the carrier range begins at 46% higher than FA patient average. * Exploratory statistical analysis (two-sided) compared to untreated individuals (data not shown), no formal hypothesis testing for any endpoint was prespecified.

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Historical placebo effect on mFARS and USS

Peak mean mFARS placebo cohort effects observed is 3 points

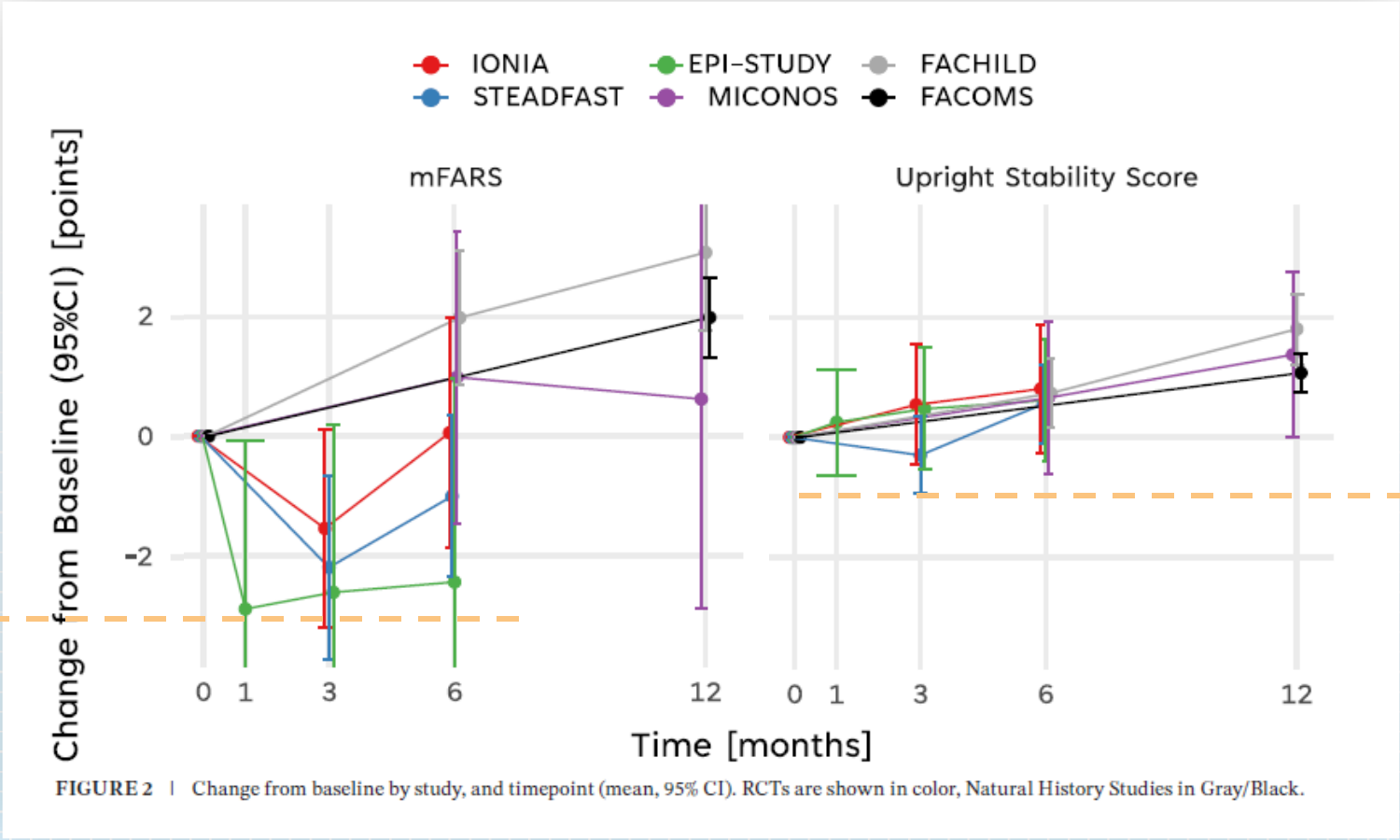

FIGURE 2 | Change from baseline by study, and timepoint (mean, 95% CI). RCTs are shown in color, Natural History Studies in Gray/Black.

USS shows the least variability and is resistant to placebo effects

1 point improvement is beyond 95% confidence interval in previous placebo groups

Source: Rummey, Christian, et. al. 2026. "Domain Specific Placebo Response in the Modified Friedreich's Ataxia Rating Scale." *Annals of Clinical and Translational Neurology* 13 (2): 393–98.

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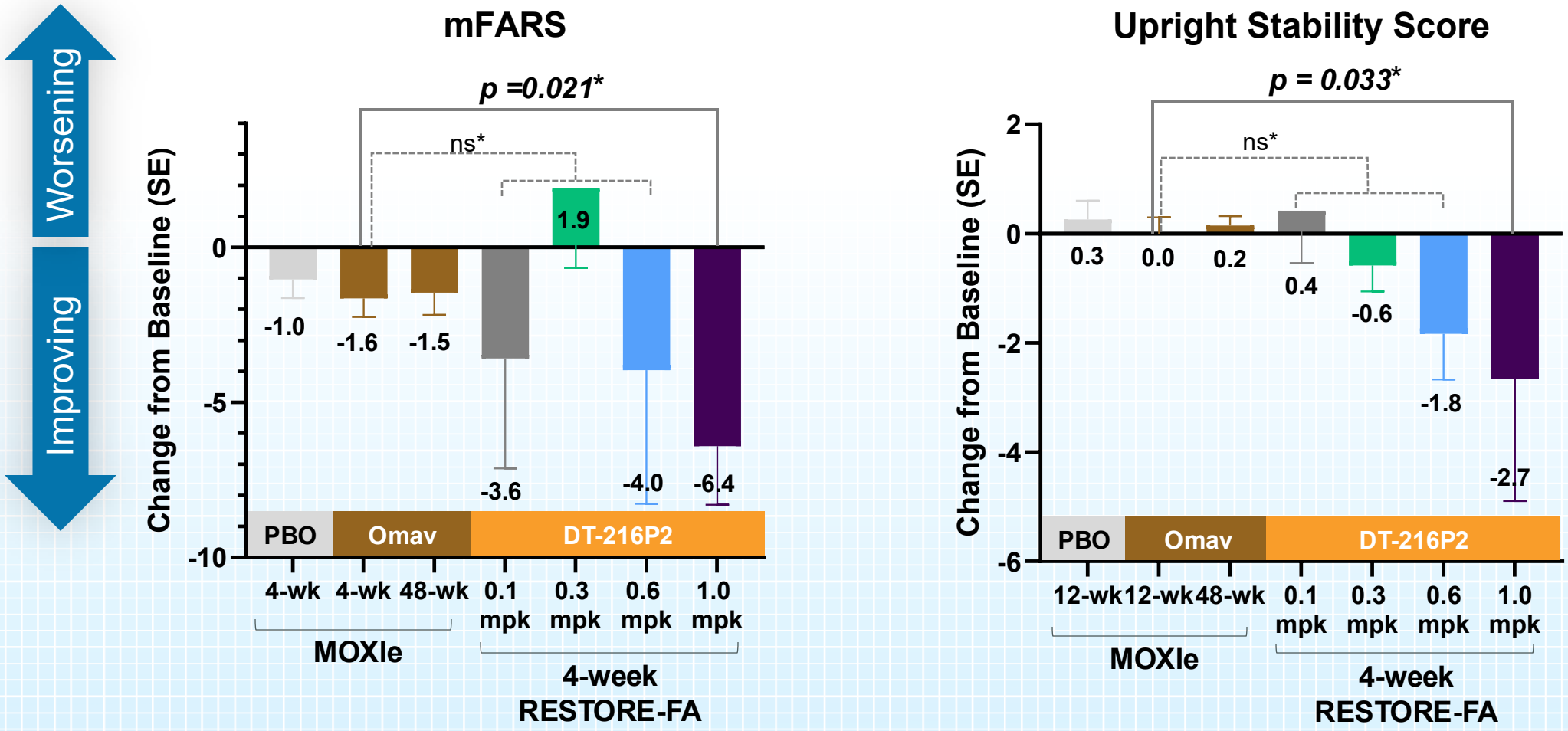
Ataxia measurement: mFARS and upright stability score improvement observed



Note: Data analysis as of May 17 2026; Bars are standard error. All DT-216P2 cohort data n=4,MOXIe placebo n= 42, MOXIe Omaveloxolone 4/12-week n=40, 48-week n=34. Placebo and Omaveloxolone data are from the MOXIe study; U.S. Food and Drug Administration (2022) *Clinical Reviews* (216718Orig1s000); Lynch, et. al., Annals of Neurology 2021; Mean baseline mFARS: RESTORE-FA DT-216P2 0.1 mpk 41.7, 0.3 mpk 48.7, 0.6 mpk 48.3, 1 mpk 42.7; MOXIe Omav 41.0; Placebo 38.8

*Exploratory statistical analysis (two-sided) compared to MOXIe study omaveloxolone arm 4-week mFARS and 12-week USS, no formal hypothesis testing for any endpoint was prespecified. Comparison between trials for illustrative purposes only; no head-to head trial has been conducted comparing DT-216P2 to omaveloxolone; differences exist between study designs, patient characteristics and other factors and caution should be exercised when comparing against unrelated studies.

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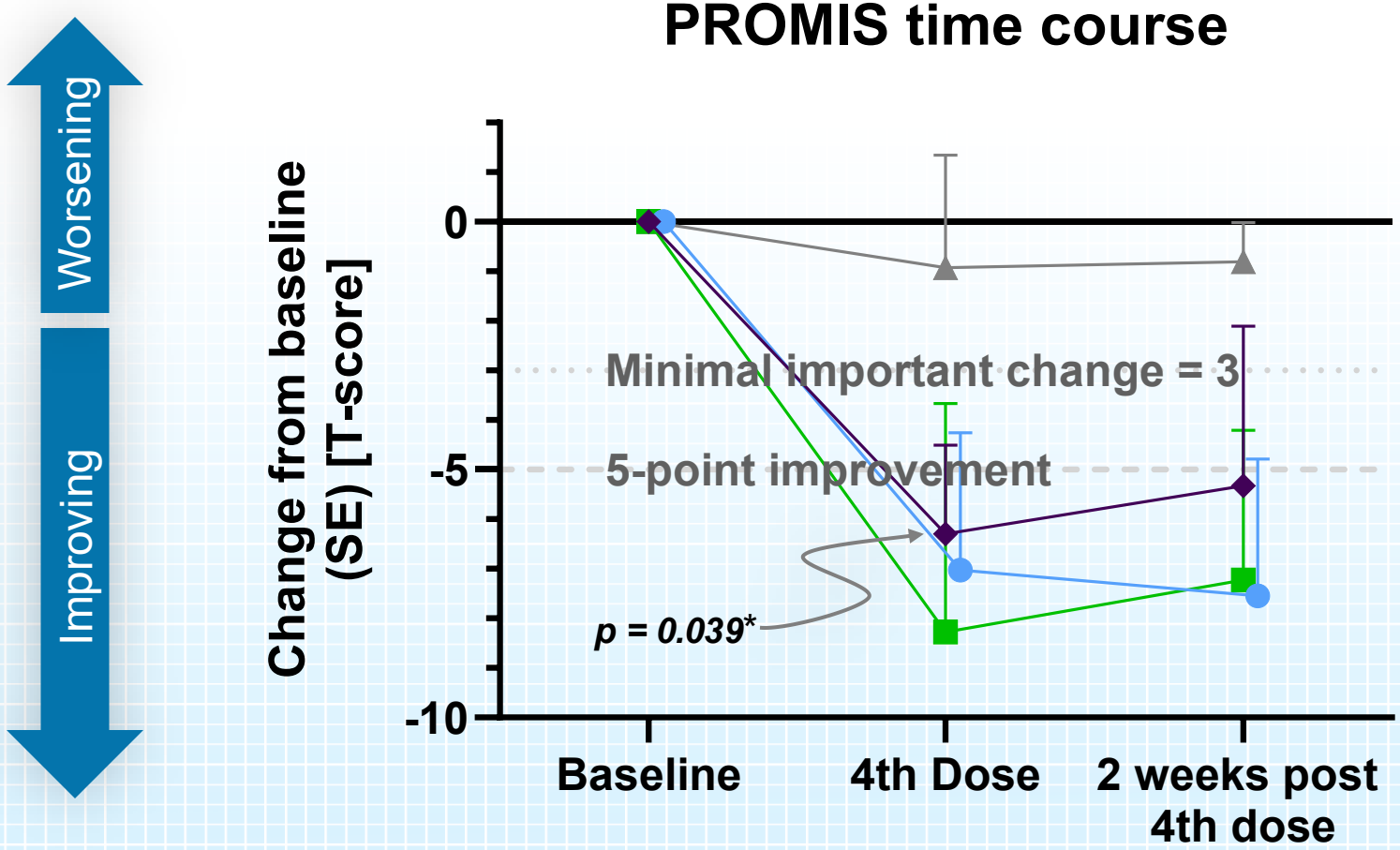
Fatigue: Change from baseline in PROMIS fatigue scale (T-score)



1.0 mpk
0.6 mpk
0.3 mpk
0.1 mpk

5-point improvement responders (post 4th dose)

1.0 mpk	3/4
0.6 mpk	2/4
0.3 mpk	1/4
0.1 mpk	0/4

Note: Data analysis as of May 17 2026; Bars are standard error; All DT-216P2 cohort data n=4; Minimal important mean change; Terwee et. al. Minimal important change (MIC): a conceptual clarification and systematic review of MIC estimates of PROMIS measures. Qual Life Res. 2021; * Exploratory statistical analysis (two-sided) compared to baseline, no formal hypothesis testing for any endpoint was prespecified.

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Safety data

- DT-216P2 was generally well-tolerated
  - No serious adverse events
  - No study discontinuations
  - All adverse events were mild to moderate

- Adverse events possibly or probably considered related to DT-216P2 occurring in more than one patient:
  - Three patients experienced transient asymptomatic ALT elevations (mild to moderate, <5x ULN) with no bilirubin increases – all three were on background omaveloxolone

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Leerink research report[1]: *"One KOL noted that LFT increases with Skyclarys appeared to correlate with response in the clinical trial and may reflect an on-target metabolic effect rather than liver toxicity… …The broader implication is that AST/ALT elevations could potentially appear with other agents that restore frataxin in the liver, though the clinical meaning and relationship to efficacy would still need to be assessed drug by drug."*

Note: Data analysis as of May 17 2026; [1]Leerink Partners, *Neuro in Focus: Takeaways from Our Friedreich's Ataxia MEDACorp Pulse Call,* 2026.

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Possible registration paths – update on registrational plans in 4Q

Potential approval frameworks based on	
Accelerated	**Traditional**
Initial approval based on surrogate marker reasonably likely to predict clinical benefit Followed by clinical confirmatory study	**Approval based on clinical efficacy**
FXN endpoint is primary	**Clinical endpoint is primary**
Clinical endpoint(s) supportive	**FXN endpoint(s) supportive**

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RESTORE-FA Patient Study: 12-week cohorts
Data following 12 weeks of dosing expected 1Q 2027

- Continuing evaluation of **1 mpk as the planned go-forward dose** in **10 patients**
- **Specifying change from baseline in endogenous blood FXN protein** as the primary efficacy endpoint
- Exploring a **dose level above 1 mpk**

Weekly IV infusion

1 mpk (50-80 mg)
10 patients

Above 1 mpk[1]

Primary efficacy endpoint

Percent change from baseline of **endogenous blood FXN protein**

Supportive efficacy measures

Other biomarker and clinical endpoints included for supportive trends

Dosing duration

12 weeks plus planned extension

Note:1. PK projections support multiple additional cohorts within nonclinical safety exposures.

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Observations in mFARS across FA landscape
(modified Friedreich Ataxia Rating Scale)

- The mFARS is a clinician-administered tool to measure neurologic dysfunction and disease progression in FA
- Omaveloxolone (SKYCLARYS™) pivotal trial (MOXIE study) used mFARS as the primary endpoint
- Omaveloxolone is now using Upright Stability Score (USS), a component of mFARS, in the ongoing pediatric study (BRAVE study); USS is considered the most objective, least variable component of mFARS

Biogen
Omaveloxolone
NRF2 activator

1.56 improvement over baseline (N=34) at 48 weeks

LEXEO therapeutics
AAV gene therapy targeting cardiac tissue

Approx. 0.8 at 1 year and modeled 2-point improvement over baseline (n=16) at 2 years

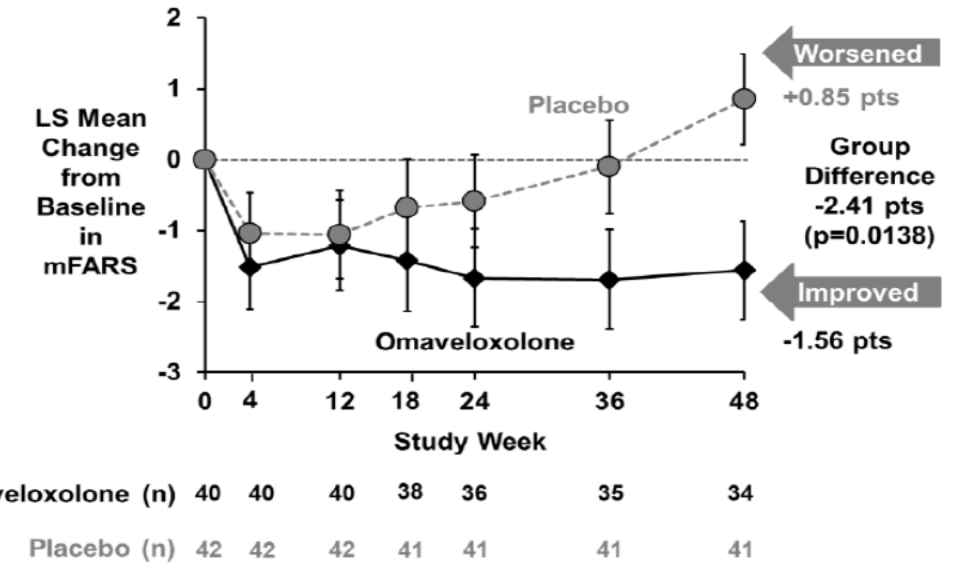
Larimar Therapeutics
Nomlabafusp
HIV-TAT-FXN protein

1.0-point improvement over baseline (n=13) at 1 year

Rolling BLA filing initiated

Omaveloxolone pivotal trial results (MOXIE study)

Figure 6 mFARS Change from Baseline by Visit (FAS Population)



Source: Omaveloxolone summary basis of approval; Lexeo and Larimar corporate communications; Lexeo data at 1-2 years, Larimar data at 12 months

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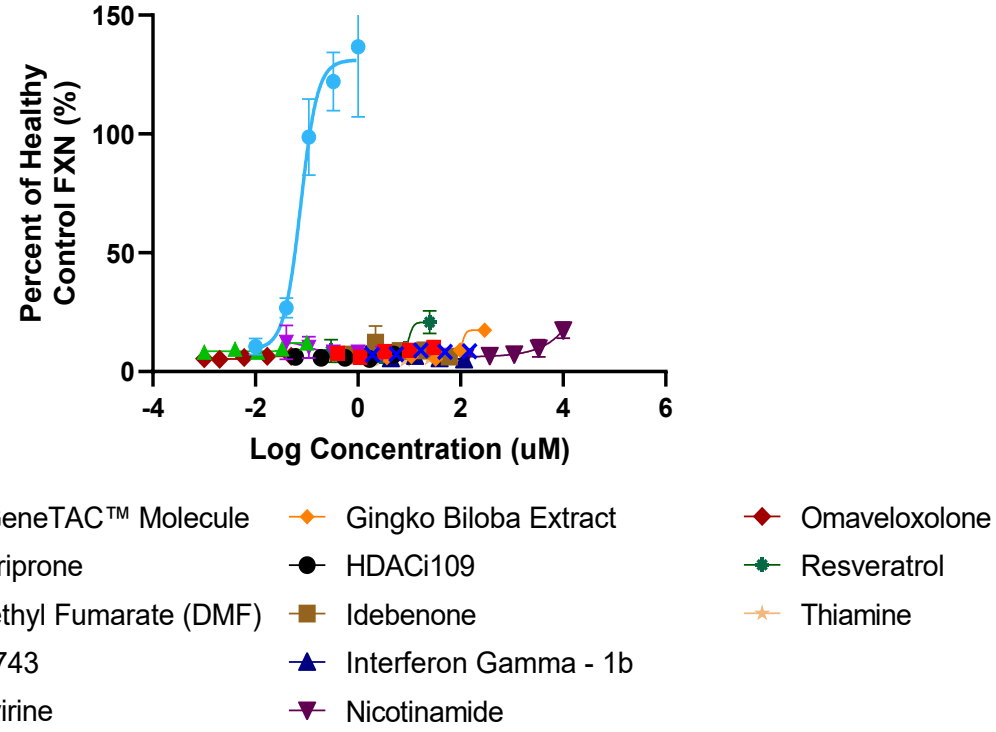
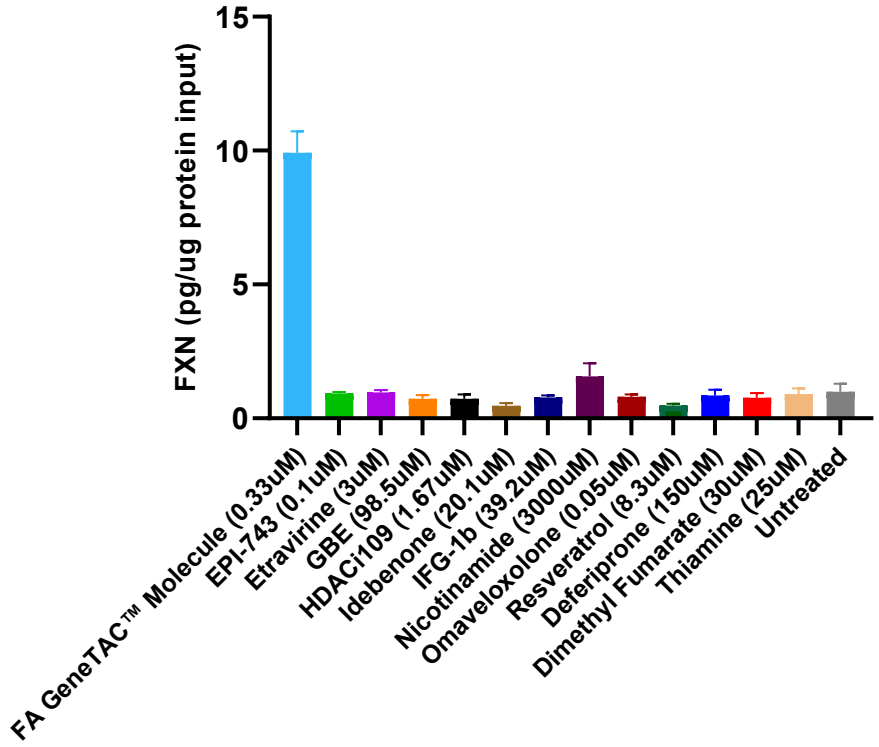
Activity of FA GeneTAC™ molecules compared with other compounds that have purportedly increased frataxin

FXN mRNA (1 day)



FXN Protein (3 days)



Note: Molecules tested in FA patient lymphoblastoid cells. Bars represent standard error of the mean. Cells treated with DT-003 FA GeneTAC™ molecule. Concentrations selected based on published active ranges. Omaveloxolone is a NRF2 activator that was not purported to increase FXN.

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DT-168 for Fuchs Endothelial Corneal Dystrophy

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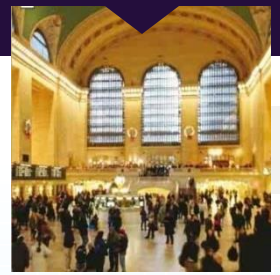
FECD is a progressive corneal disease caused by a single gene mutation in a majority of cases

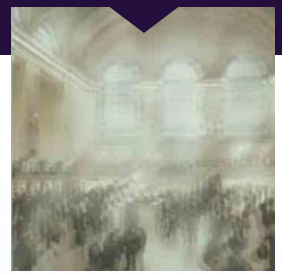
Increasing Endothelial Cell Dysfunction — Loss of cells, pump function, corneal edema

Diagnosed by community optometrist

~2M diagnosed patients (U.S.)[1]



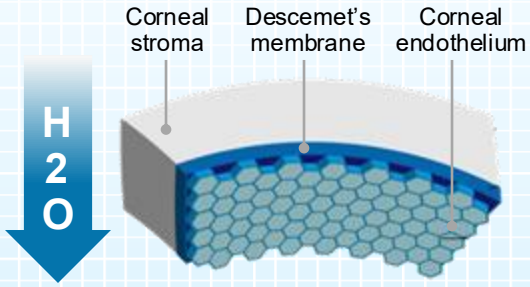
Loss of visual quality



Patient can't stand symptoms

Corneal transplant surgery

Surgical Descemet membrane stripping or corneal transplant limited to 18–30k[2] per year (US)

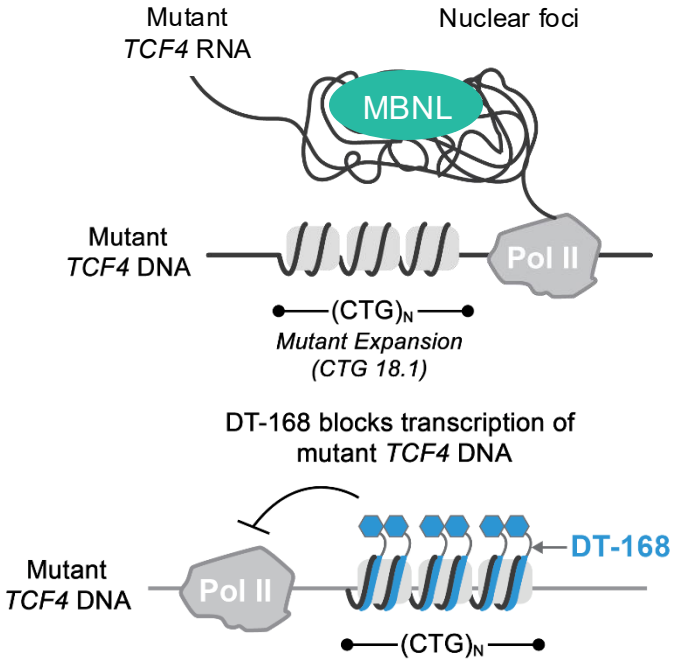


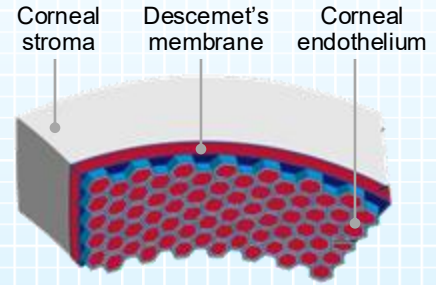
Corneal endothelial cells (CECs) **pump water out of the stroma** to prevent edema and maintain corneal transparency

Most cases are **caused by a CTG repeat expansion in the TCF4 gene** (CTG 18.1)

Expression of mutant *TCF4* RNA leads to spliceopathy, **CEC dysfunction and loss**

DT-168 eye drops designed to block the expression of mutant *TCF4* RNA





Tissues **removed during surgery**

Source: (1) IRIS registry prevalence by age, (2) Vianna et al. JAMA Ophthamol (2015)

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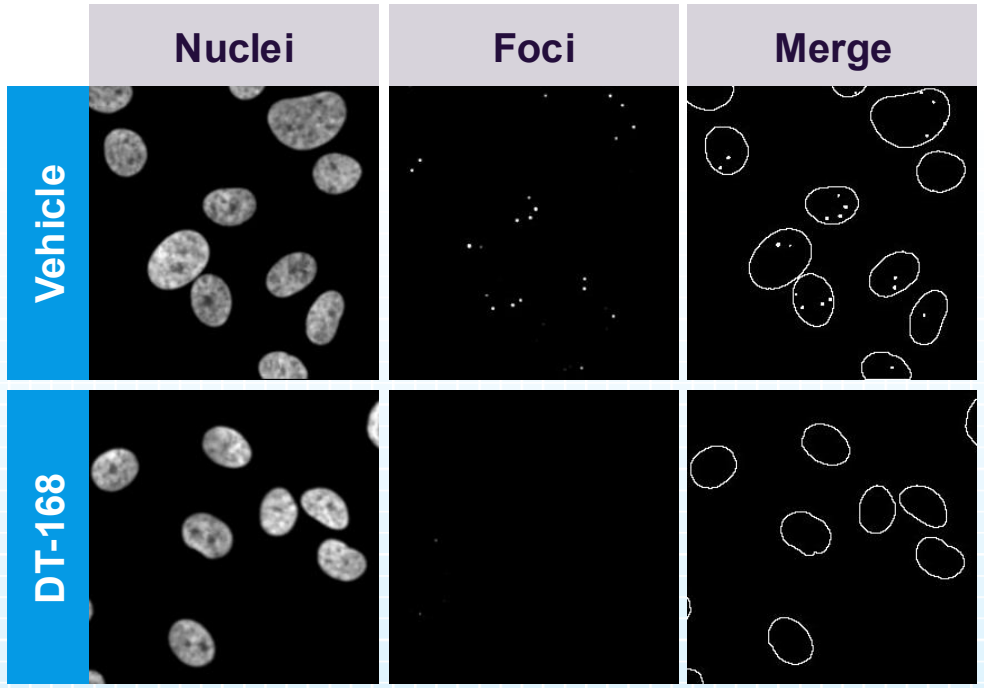
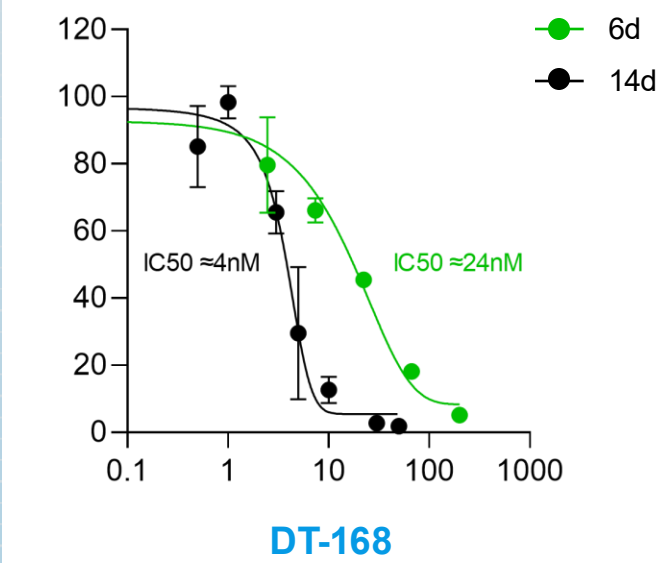
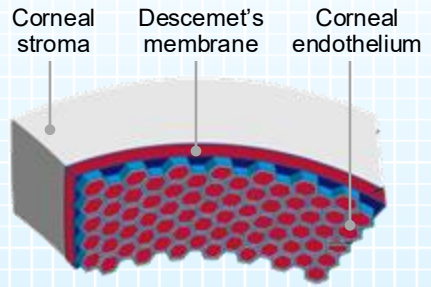
DT-168 reduction of nuclear foci observed in primary CECs isolated from patients with FECD with high potency (<5nM foci IC50)



CECs treated daily for 6 or 14 days with DT-168



Cells taken from discarded FECD corneal endothelium used to **evaluate efficacy across patients**



Tissues **removed during surgery**

CECs = Corneal endothelial cells
Note: Bars represent standard deviation

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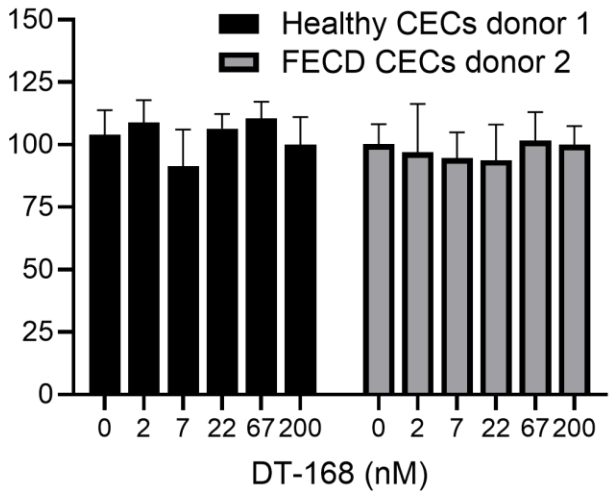
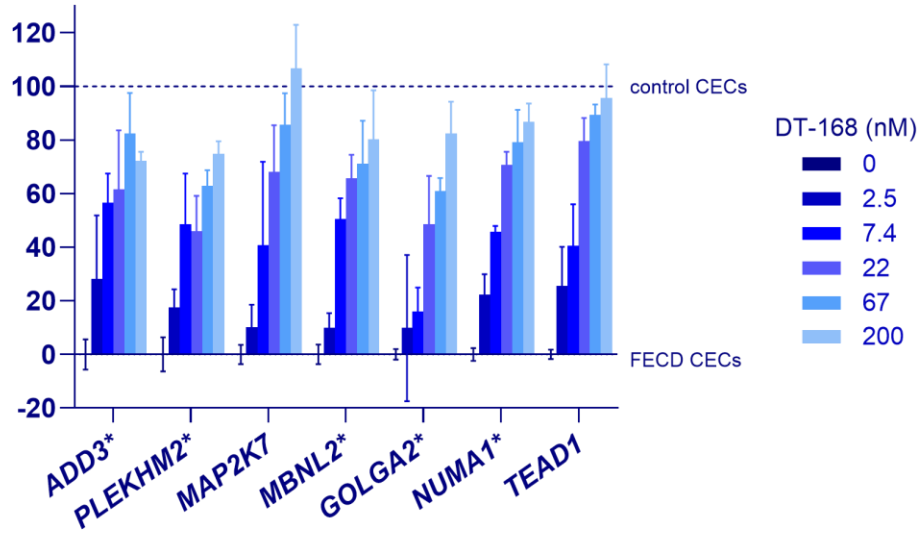
Treatment with DT-168 left wild-type TCF4 transcripts unaffected in primary control and FECD CECs while improving spliceopathy

TCF4 mRNA
Percent of untreated



Patient-derived FECD CECs + DT-168
6d treatment; percent spliced



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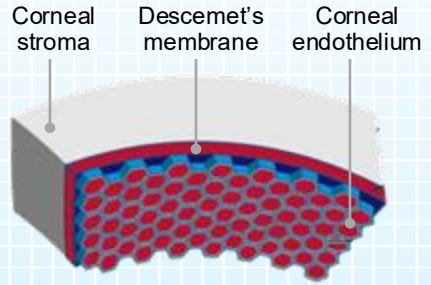

Tissues **removed during surgery**

Notes: (LEFT FIGURE) Control CECs (Corneal endothelial cells) from donor 1 and patient-derived FECD CECs from donor 2 were incubated with DT-168 for 6 days, after which mRNA was purified and used to quantify wild-type TCF4 transcripts using a primer-probe set targeting exons 18/19. Data represent averages of N=3 replicates, and error bars represent standard deviation. Data source: DSGN-2023-DT168-1006.

* (RIGHT FIGURE) Previously reported as mis-spliced genes in primary FECD CECs (Fautsch et al., 2021) Bars represent standard deviation.

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DT-168 Phase 1 SAD/MAD study in healthy participants assessed safety, tolerability, and systemic PK

- DT-168 eye drops were **well-tolerated in all subjects**
- There were **no serious adverse events**, no ocular adverse events, or participant discontinuations due to adverse events[1]
- All observed adverse events were **non-ocular** and were considered **not related to drug product** by the investigator
- There were **no clinically significant findings observed in any safety assessments**
- **Pharmacokinetic analysis** demonstrated **systemic exposure below the limit of quantitation** following administration of DT-168 across all timepoints and all dose groups

1) One placebo participant discontinued from study treatment early on day 4 due to personal reasons; that participant completed all early termination events, follow-up events, and completed the study.

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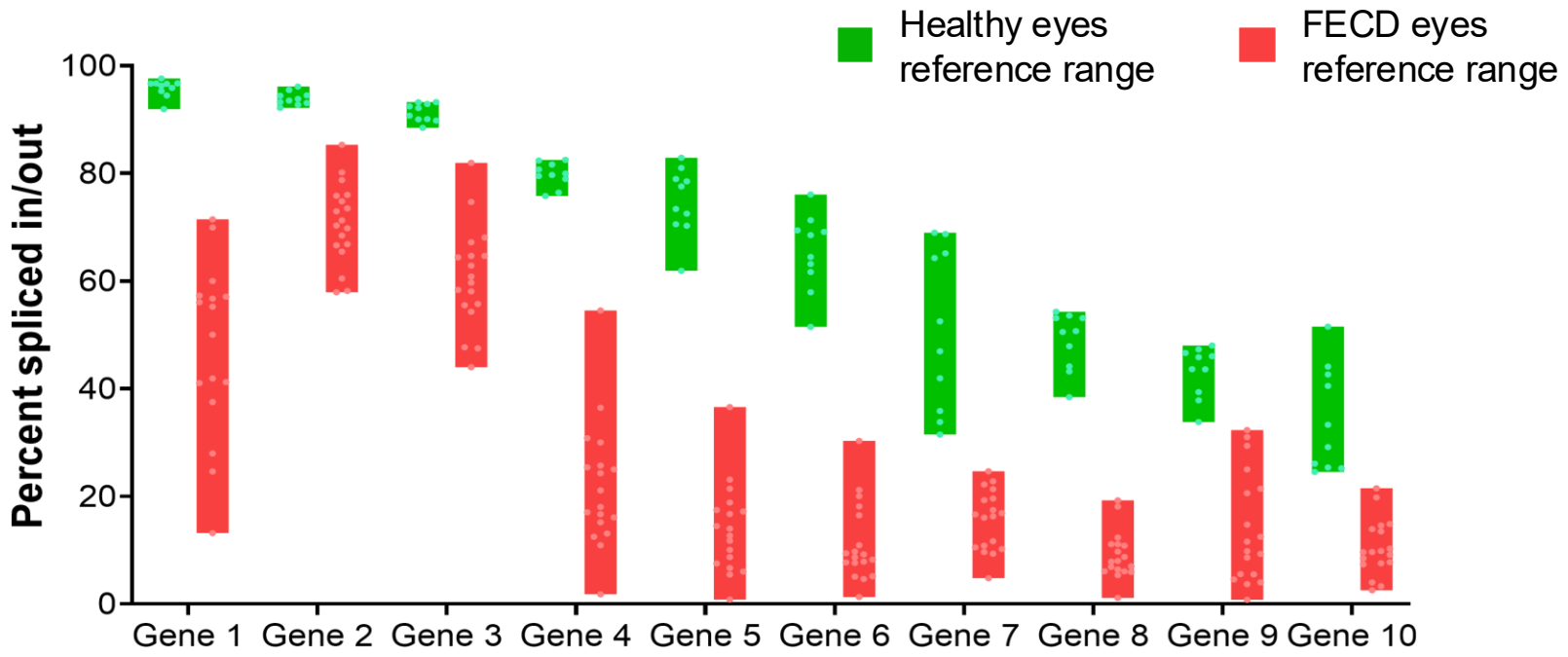
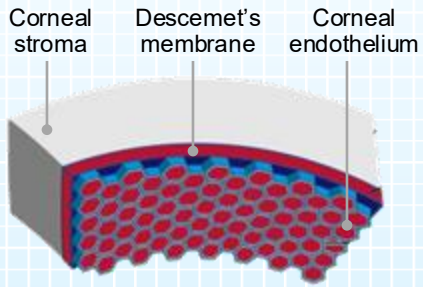
Splicing biomarker is measurable in surgically removed corneal endothelial cells

- Design conducted reference range studies showing **consistently different splicing** between unaffected eyes and mutant TCF4 FECD surgical samples
- Design has developed RNA biomarker measurements **potentially suitable for use as a clinical proof-of-concept measure of drug activity**

Splicing differences between TCF4 mutant FECD and unaffected eyes



Cells taken from discarded FECD corneal endothelium used to **evaluate efficacy across patients**



Tissues **removed during surgery**

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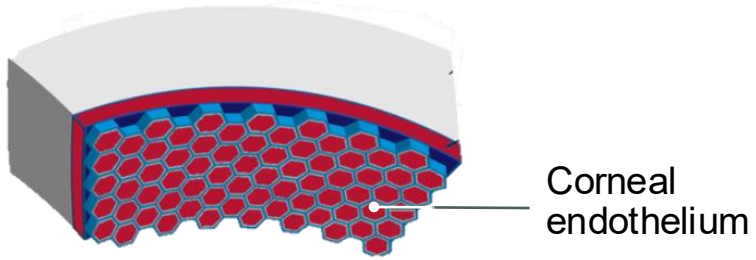
DT-168 Phase 2 biomarker study with data in 2027

Objectives: *Safety and tolerability; corneal endothelial biomarkers*

FECD corneal endothelium | *TCF4+ FECD patients scheduled for surgery*

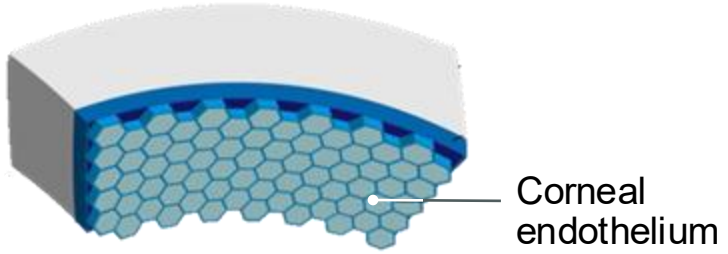


Tissues removed during **corneal transplant surgery**

FECD UNTREATED REFERENCE → **FECD eye reference range biomarker result**

FECD TREATED
0.5% DT-168 BID for ~4 weeks or longer
→ **Treated FECD eye biomarker result**

Unaffected corneal endothelium



Tissue from unaffected **eye donors**

HEALTHY UNTREATED REFERENCE → **Unaffected eye reference range biomarker result**

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Myotonic Dystrophy Type 1 (DM1)

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DT-818 summary

Summary

- DT-818 nominated as development candidate for the treatment of DM1 with potential best-in-disease profile; designed to selectively target mutant DMPK
- In preclinical studies, DT-818 has demonstrated a greater than 90% reduction in toxic RNA foci in DM1 patient cells, corresponding splicing correction and selective targeting of mutant DMPK

Phase 1

- Initiated dosing DM1 patients in Phase 1 MAD trial of DT-818
  - Injectable (initially once weekly IV, exploring subcutaneous route)
- Endpoints:
  - Safety
  - Correction of mis-splicing
- Results anticipated in 2027

MAD = multiple-ascending dose

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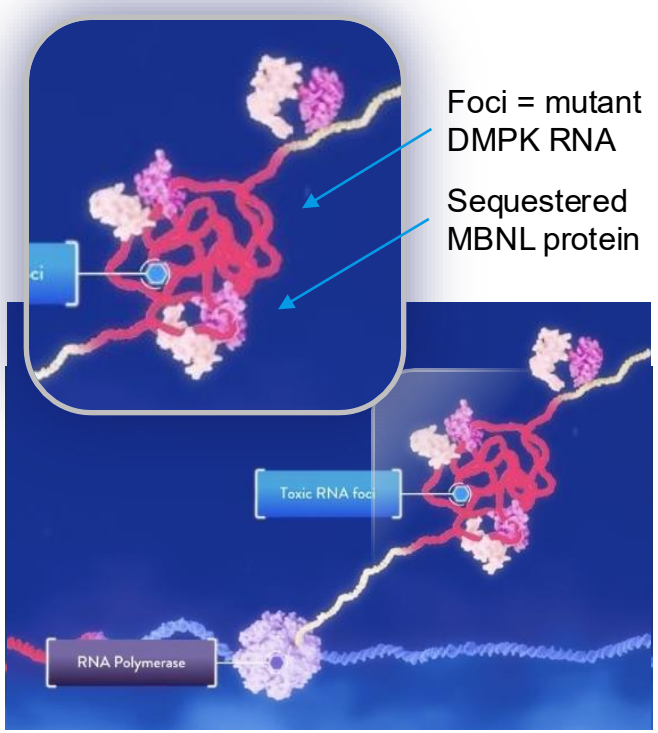
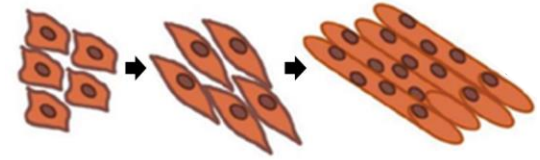
DM1 (Myotonic dystrophy type 1)

1 Mechanism of disease

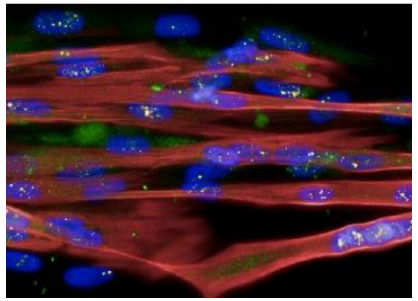


2 Preclinical human cells



- Similar spliceopathy and repeat length as affected muscle
- Derived from primary myoblasts or iPSCs

DM1 patient myotube model



Foci Nuclei MBNL1 Troponin T

3 Preclinical animal models

HSA^{LR} mouse model

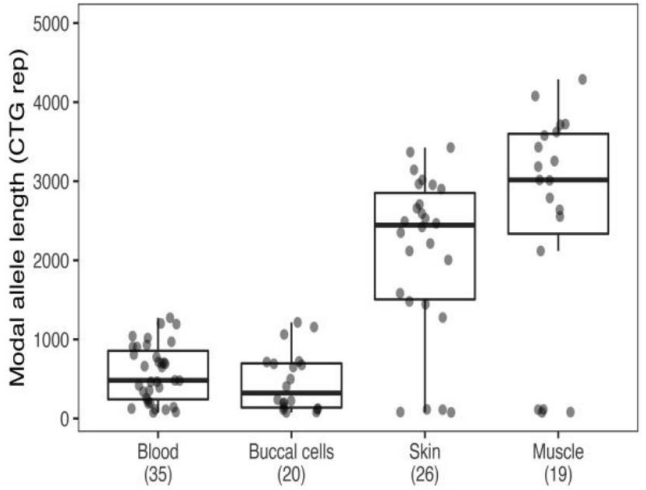
Actin transgene with CTG repeats
Used because DMPK expanded CTG repeat model has limited myotonia

Wild type NHP

Contain no CTG expansions
Suitable for testing oligonucleotides that target non-CTG DMPK sequences

4 Longer DMPK CTG repeats in affected tissues cause disease

CTG repeat number



Reported repeat length in clinical trials

Repeat length in affected tissue

5 Symptoms

intellectual impairment and excessive daytime sleepiness

cataracts

heart problems

digestive problems causing stomach pain

skeletal muscle weakness

muscle atrophy

myotonia

70,000+ individuals affected in the **U.S.**

90,000+ individuals affected in **Europe**

Source: Morales et. al. Individual-specific levels of CTG•CAG somatic instability are shared across multiple tissues in myotonic dystrophy type 1. Hum Mol Genet. 2023

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DM1 clinical stage programs

	AVIDITY BIOSCIENCES / NOVARTIS	Dyne THERAPEUTICS	PepGen	entrada THERAPEUTICS / VERTEX	arrowhead pharmaceuticals / SAREPTA THERAPEUTICS
Approach[1]	>100kDa siRNA linked to transferrin receptor mAb	>50kDa Degrading ASO linked to transferrin receptor Fab	>10kDa Blocking ASO linked to peptide	>10kDa Blocking ASO linked to cyclic peptide	>10kDa RNAi linked to targeting ligand
Stage of development	Registrational trials (vHOT primary)	Registrational trials (vHOT primary)	Phase 2	Phase 1/2	Phase 1/2
Distribution	Muscle, small intestine	Muscle	Muscle	Muscle	Muscle
Allele selectivity	Preferentially degrades cytoplasmic (wild type) DMPK	Non-selective	Selective	Selective	Non-selective
Clinical CASI-22 splicing	16%[2]	25%[5]	53.7%[7]	Data not available	Data not available
Preclinical human myotube foci	~55%[3] reduction	~30%[6] reduction	54%[7] reduction	~55%[8] reduction	Data not available
Preclinical animal model	Nonhuman primate: >75% DMPK reduction (wild type)[4]	HSA^{LR} mouse: ~80 to >90% splicing improvement, near complete myotonia elimination[6]	HSA^{LR} mouse: near complete restoration of splicing and myotonia elimination[7]	HSA^{LR} mouse: ~67% foci reduction, near 100% restoration of splicing[8]	TREDT960i/HSA-rTA mouse: >50% DMPK reduction, >50% restoration of splicing[9]

Note: Patient cell data refers a DM1 patient cell line containing ~2600 repeats; Source: 1. Company materials, INN structures where available, Anand P, et, al, Metabolic Stability and Targeted Delivery of Oligonucleotides. J Med Chem. 2025; 2. Avidity Biosciences, Corporate Presentation, May 2023; 3. WMS 2023 Poster; 4. AAN 2021 Presentation; 5. Dyne Therapeutics, ACHIEVE Clinical Update, Jan 2025; 6. ASGCT 2021 Presentations; 7. PepGen, Corporate Presentation, Oct 2025; 8. Entrada Therapeutics, Myology Congress Poster, Sept 2022; 9. Arrowhead Pharmaceuticals, MDA 2024 Poster Mar 2024,

1-3kDa GeneTAC® small molecule

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Designing a better DM1 approach

Design hypothesis

We believe reduction of toxic foci in human myotubes is a better predictor of clinical splicing biomarker observations

- Animal preclinical models (e.g. HSA-LR or wild-type NHPs) are supportive but have not been predictive of clinical splicing results

We believe that the limited clinical benefit for therapeutics in clinic are driven by

- Targeting muscle leaves many target organs untreated
- Reduced efficacy in cells with somatically expanded (longer) repeats
- Incomplete splicing improvement; toxic RNA tangles are refractory to degradation mechanisms
- Safety concerns about dosing higher

Features designed into DT-818

Greater than 90% reduction of toxic foci and restoration of splicing in human myotubes

- Human genetic models seem to better correlate to what has been observed in the clinic so far

- Broad distribution to key affected tissues
- Efficacy in cells with somatically expanded repeats
- DT-818 mechanism works upstream of oligos resulting in greater than 90% restoration of splicing in human myotubes
- Maintain expression of wild-type DMPK

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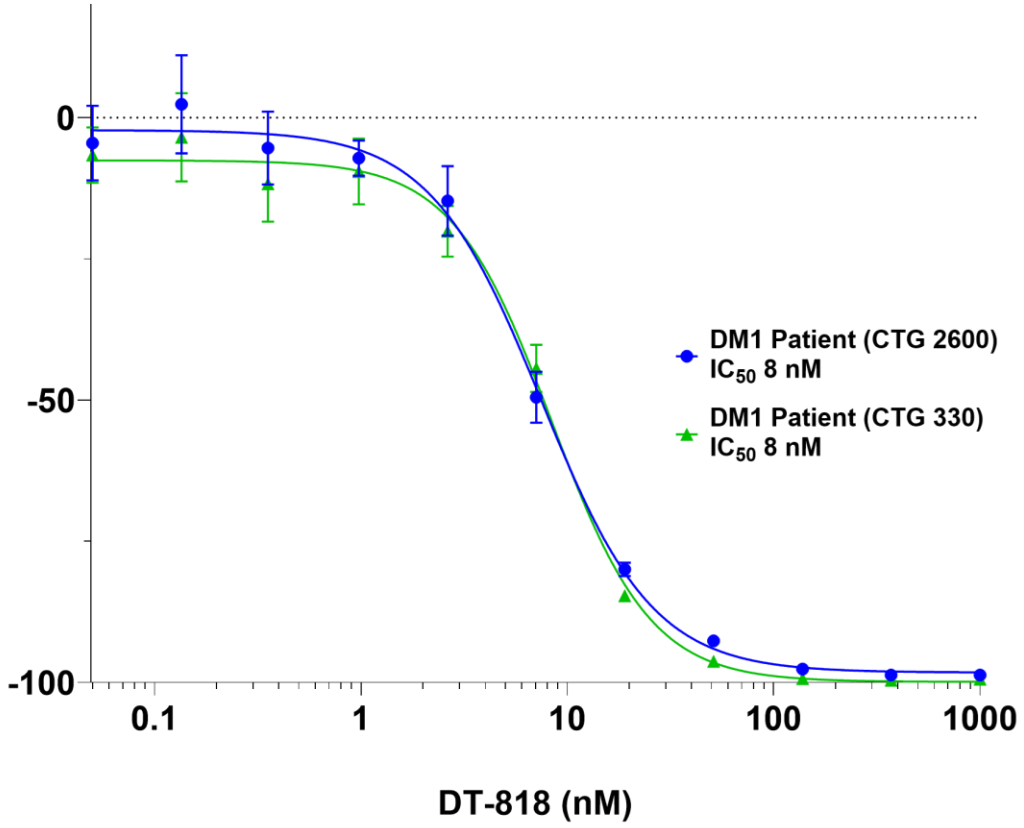
DT-818 treatment results in foci reduction, leads to improvement in splicing, regardless of repeat length or patient genetics

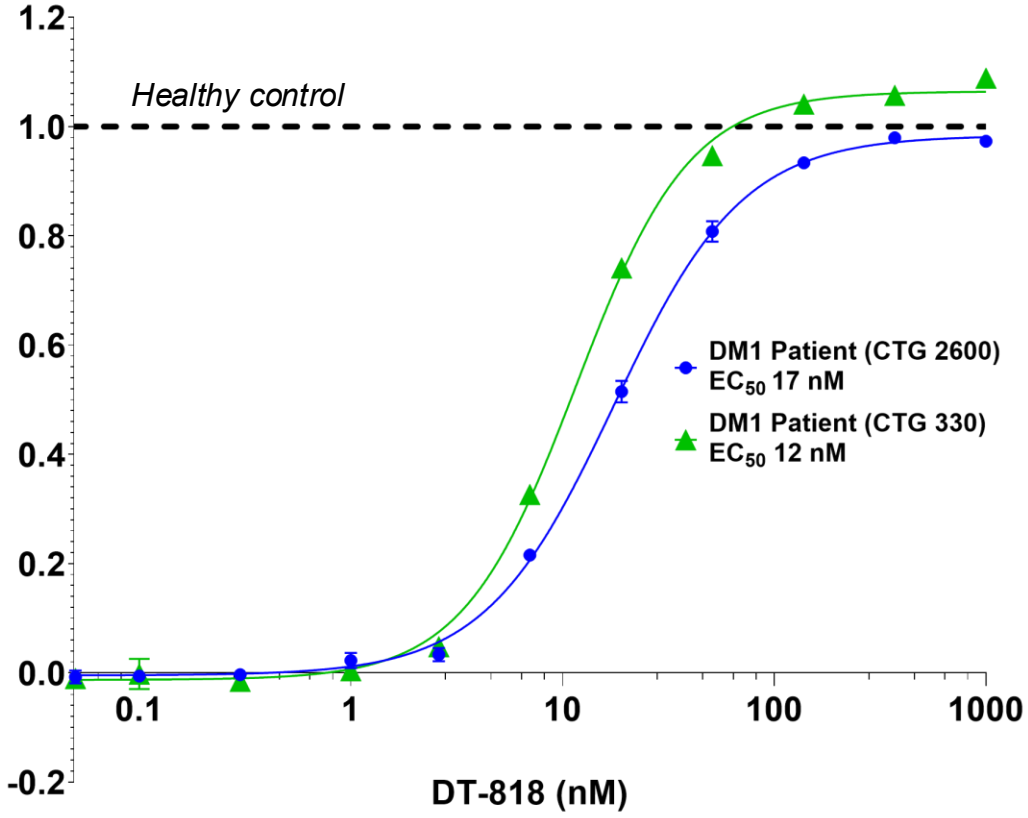
DT-818 reduces toxic RNA nuclear foci in DM1 myotubes

Foci per nucleus
Percent change relative to untreated (FISH)



DT-818 corrects splicing in DM1 myotubes

Splice index
Index relative to healthy control myotubes



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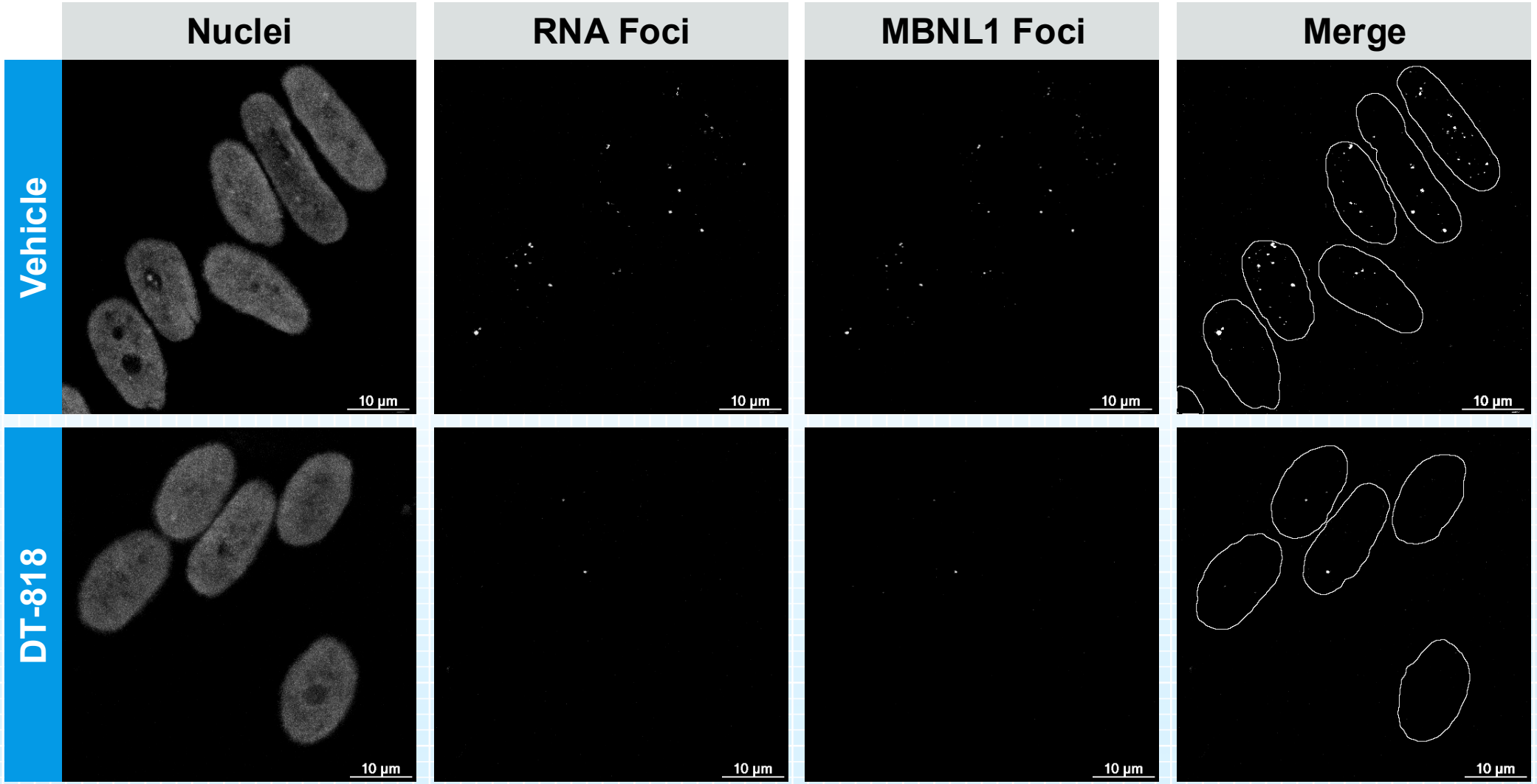
DT-818 treatment reduces toxic RNA foci and liberates MBNL1 protein in DM1 patient myotubes



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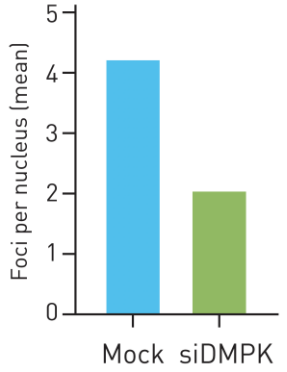
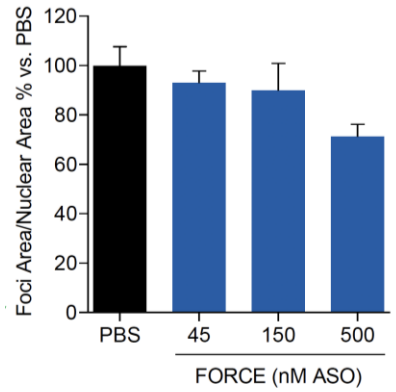
DT-818 treatment shows best-in-disease potential for foci reduction in patient cell line with 2,600 repeats

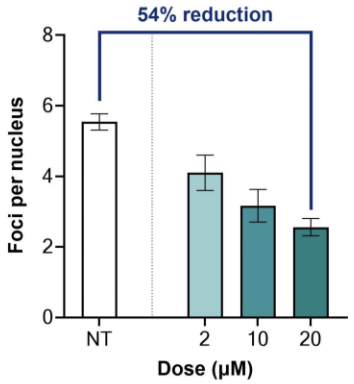
AVIDITY BIOSCIENCES Estimated*1 ~55%



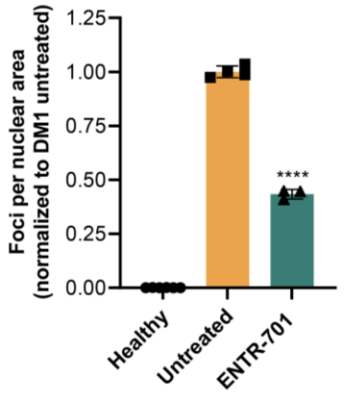
Dyne THERAPEUTICS Estimated*2 ~30%



PepGen™ 54% foci reduction[3]

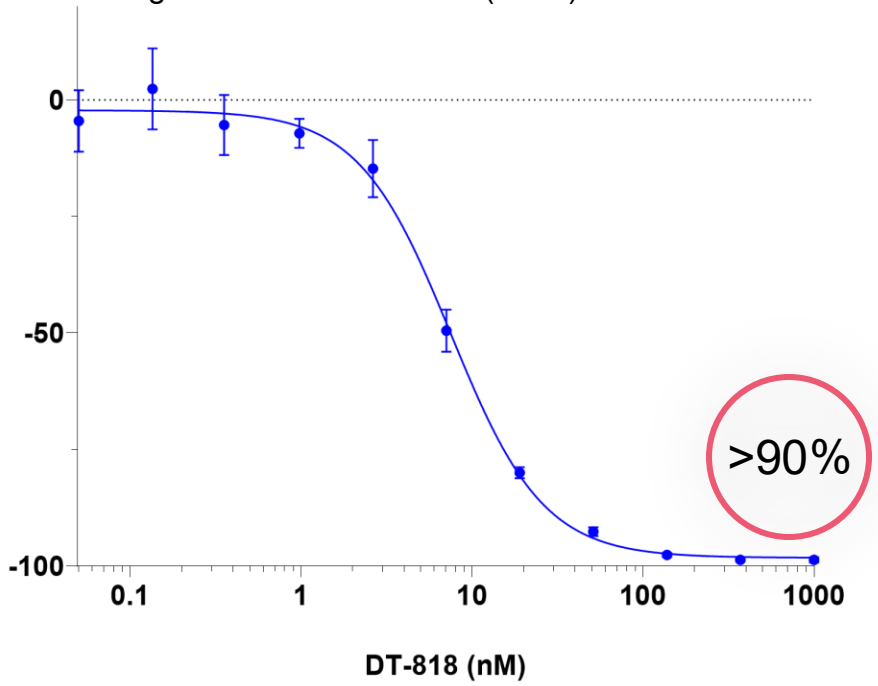


entrada THERAPEUTICS Estimated*4 ~55%



DESIGN THERAPEUTICS

Foci per nucleus
Percent change relative to untreated (FISH)



Note: Foci reduction evaluated in DM1 patient myotubes containing ~2600 repeats in all cases except Avidity where repeat length not noted. *.Estimates are based on the graphs provided since the company has not provided quantitative values from graphs; References: 1. Avidity Biosciences, WMS 2023 Poster; 2. Dyne Therapeutics, ASGCT 2021 Presentations; 3. PepGen, Corporate Presentation, Jan 2024; 4. Entrada Therapeutics, WMS 2022 Presentation

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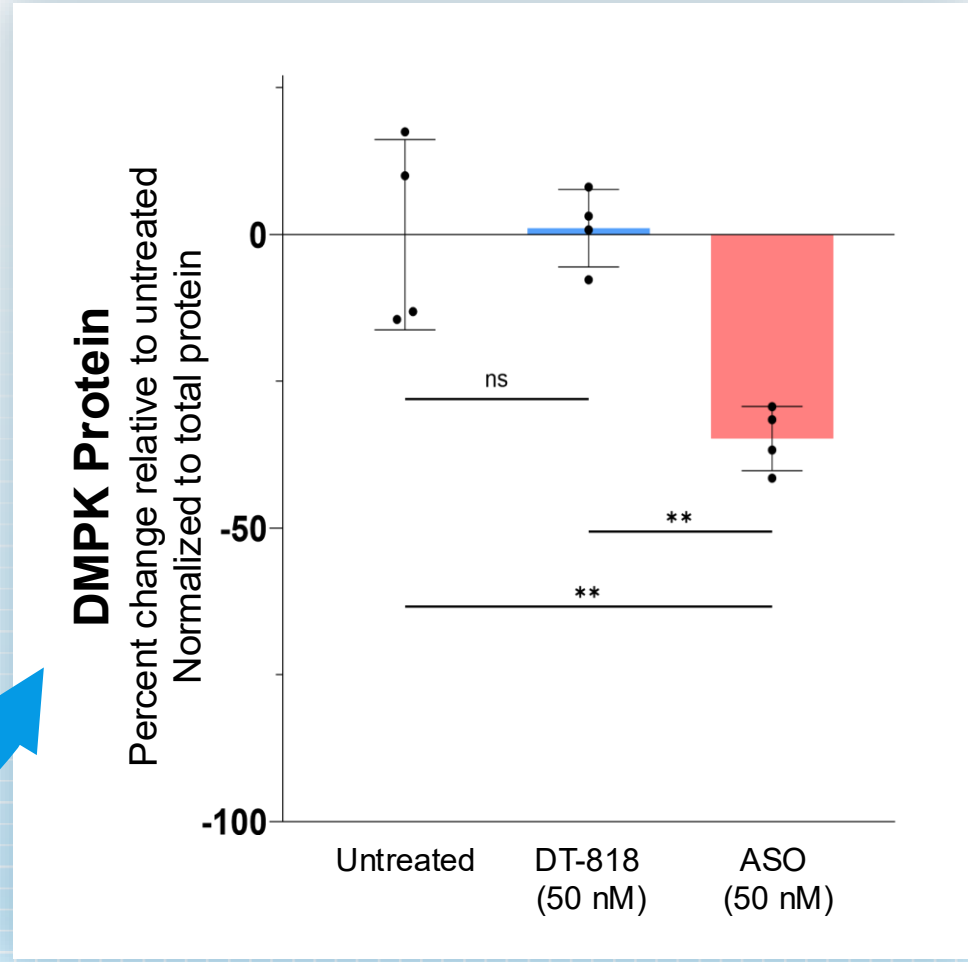
DT-818 selectively targets mutant DMPK

Allele-specific mechanism spares DMPK protein

DM1 patients have two DMPK alleles

Mutant allele	Healthy allele
CTG expansion	No CTG expansion
RNA retained in nucleus, forms foci	RNA exported to cytoplasm
No protein (RNA trapped in nucleus)	RNA translated into protein



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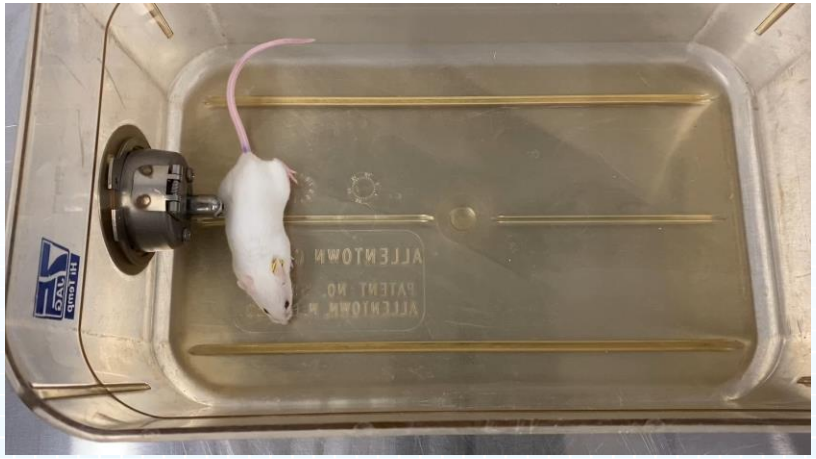
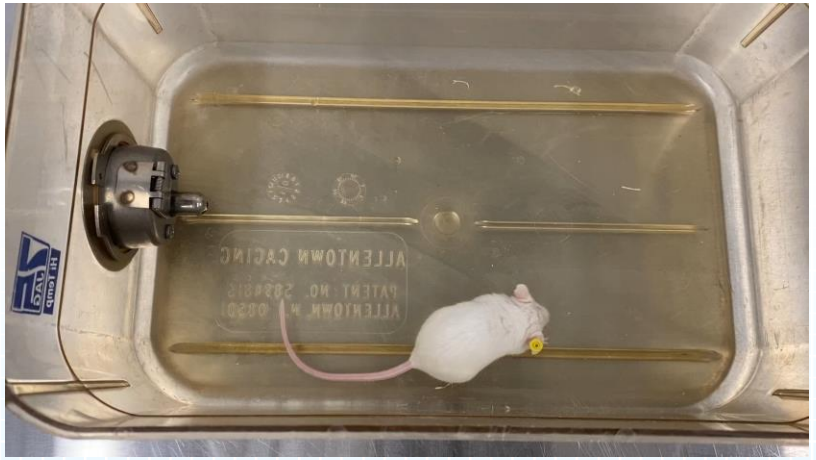
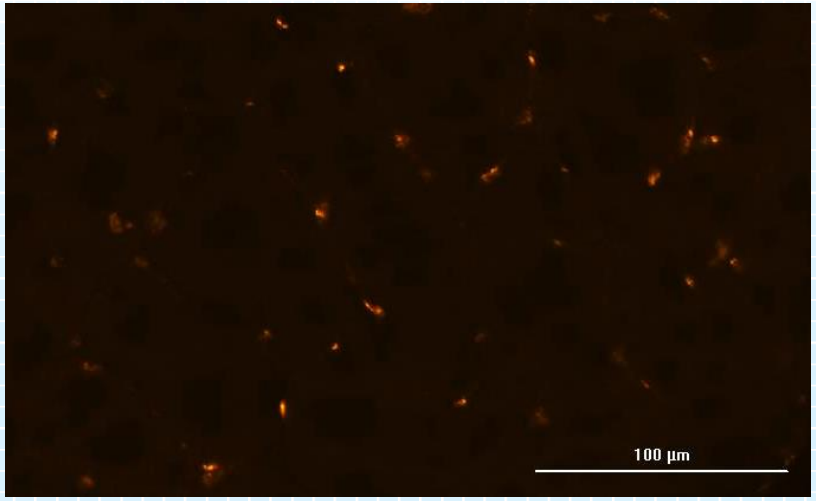
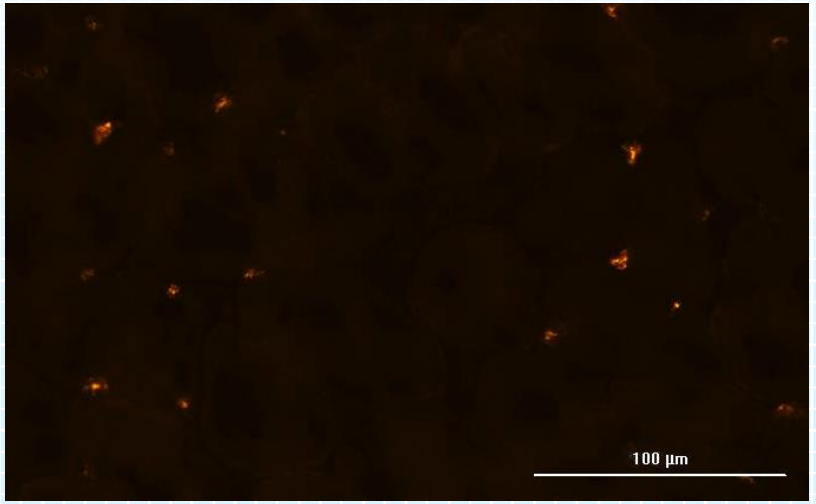
Splicing and myotonia improved in actin repeat (HSA^{LR}) mice treated with DT-818

	Vehicle	DT-818
Myotonia		
Foci		

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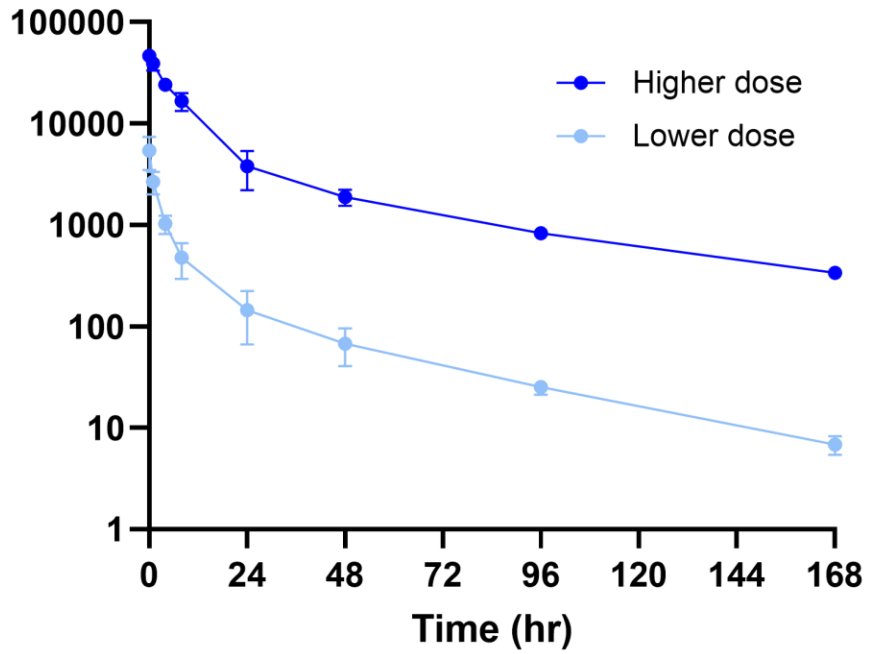
DT-818 shows good exposure and long half-life

NHP PK

Single IV dose
nM DT-818 in plasma



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DT-818 summary

Summary

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  - Injectable (initially once weekly IV, exploring subcutaneous route)
- Endpoints:
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  - Correction of mis-splicing
- Results anticipated in 2027

MAD = multiple-ascending dose

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Huntington’s Disease (HD)

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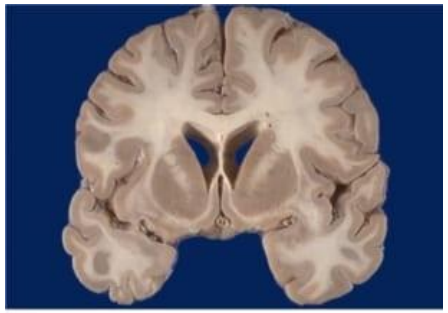
Huntington's Disease (HD)

GeneTAC® molecules selectively reduce mutant Huntingtin and spare the normal Huntingtin allele

- Causes brain atrophy due to death of neurons
- Symptoms range from motor function to neurological
- Universally fatal
- HD Prevalence: >40,000 in the U.S.

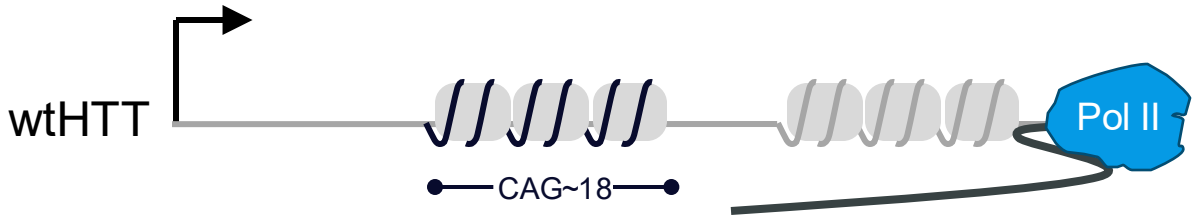


Control – no atrophy

HD

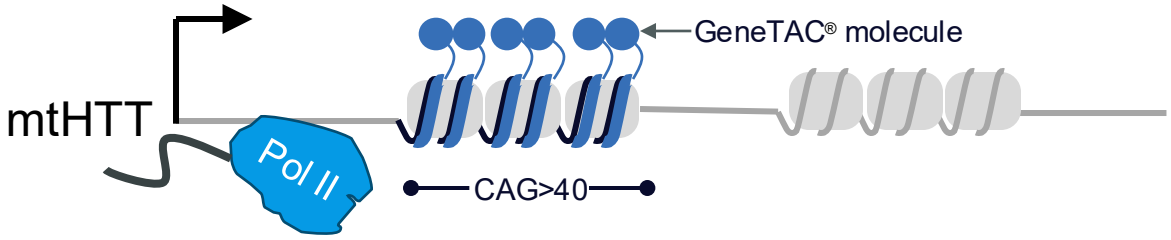
Normal HTT gene — *thought to be important to normal state*

GeneTAC® molecules ***preserve transcription*** at the ***wild type locus***



HTT gene with expansion

GeneTAC® molecules ***block transcription*** specifically at the ***mutant locus***



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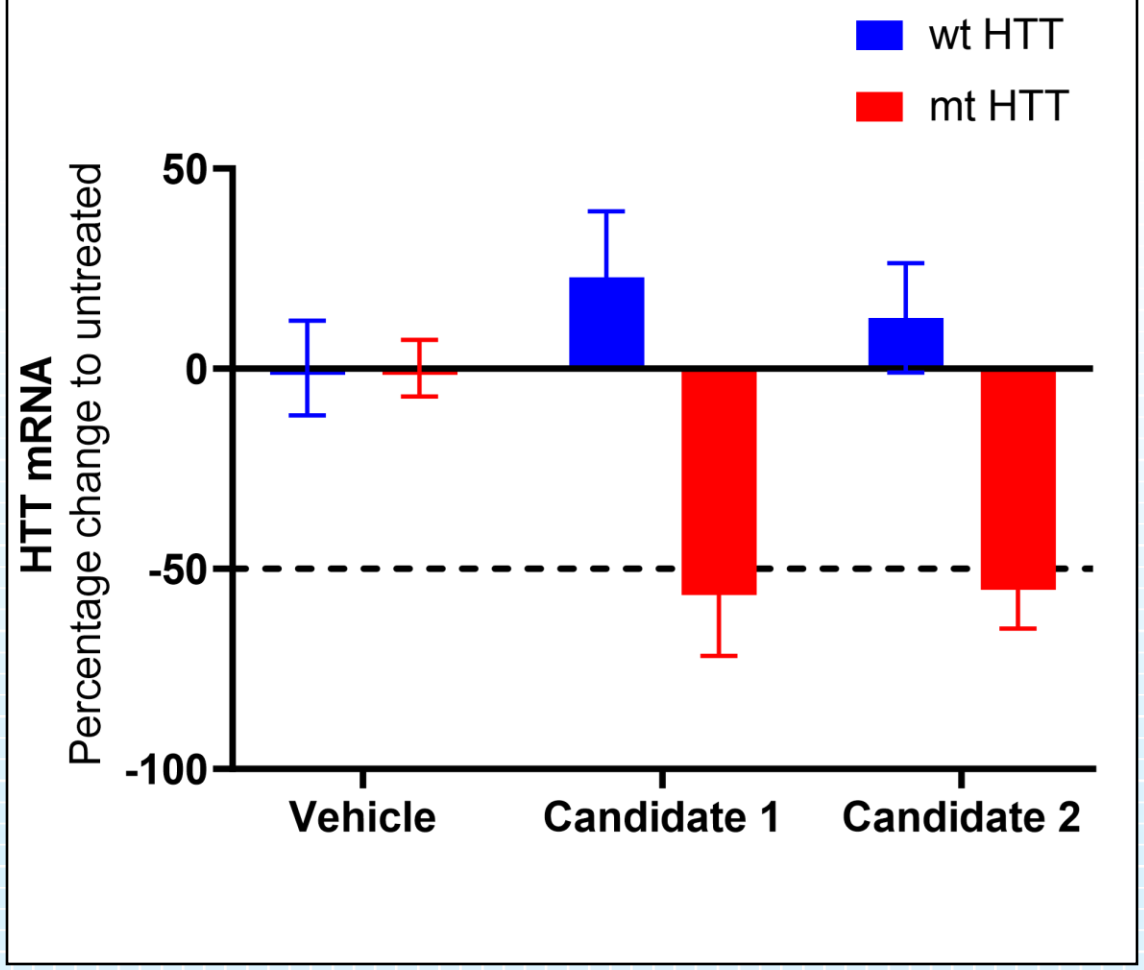
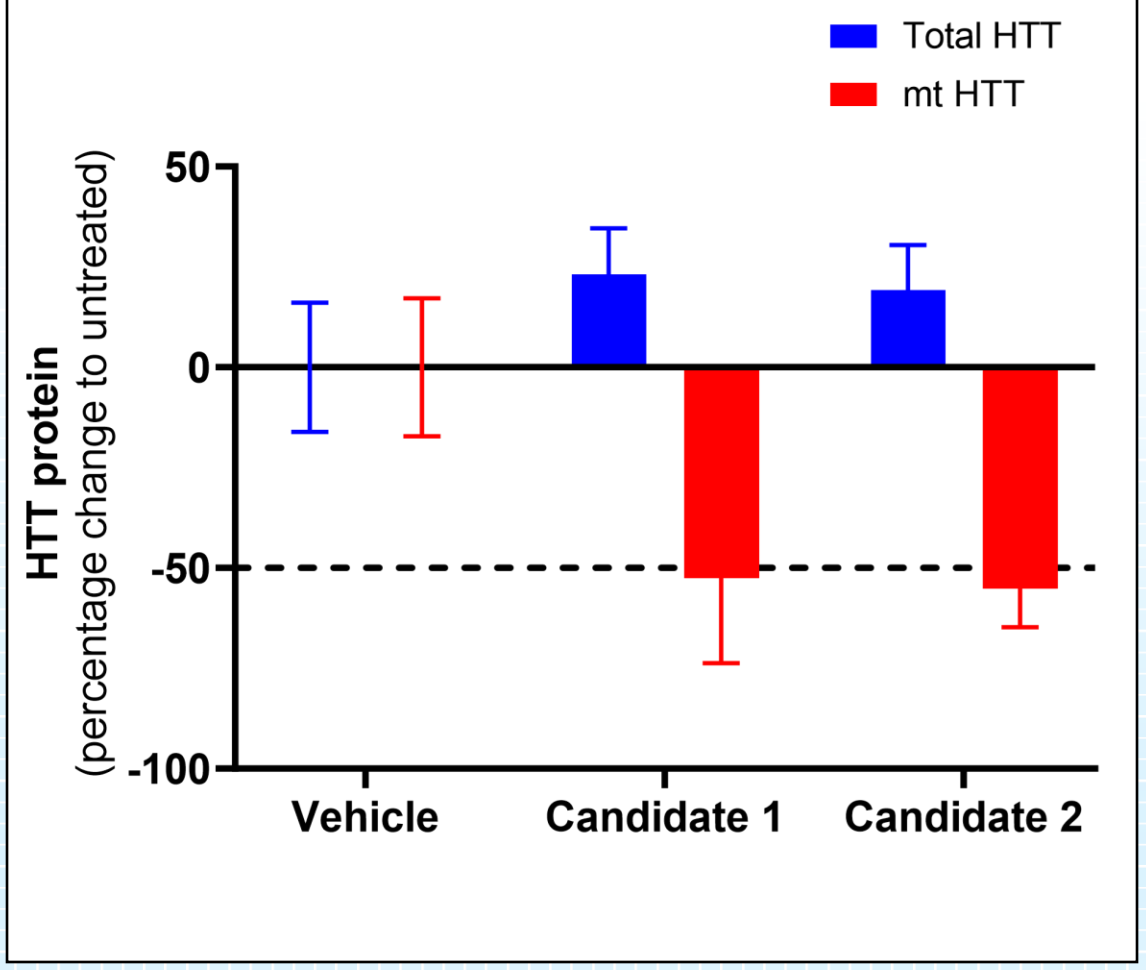
Allele-specific reductions of RNA and protein observed in the brain in zQ175DN HD mouse model after 8 weeks of systemic administration

HTT RNA level in striatum



HTT protein level in striatum



Note: mice were treated with Candidate 1 or Candidate 2 for 8 weeks, vehicle group treated for 4 weeks. Percent change calculated based on treated compared to untreated. RNA level determined with RT-PCR. Protein level determined with TR-FRET. Data presented as Mean ± SD.

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GeneTAC® HD candidates have significant advantages over other HTT lowering therapeutic approaches

Allele-selective
Reduce mutant Huntingtin and spare the normal Huntingtin

Non-selective
Reduce both normal and mutant Huntingtin

	GeneTAC® HD candidates	WVE-003	uniQure AMT-130	Roche IONIS Tominersen	PTC THERAPEUTICS PTC-518
Modality	**Small molecule** Facilitate drug biodistribution to the whole brain	**ASO**			
Delivery	**Parenteral administration**	**Intrathecal administration**			
Target somatic expansion	**Yes** Target repeats, increased efficacy as repeats expand during disease progression	**No** Target SNP3			
Patient population	**All HD patients**	**~40% of patients with SNP3**			
Status	• **Selective reduction of mtHTT in patient cells (IC50=~1nM)** • **Characterizing several candidates prior to DC selection**	**Phase 1/2** • **Reduced mtHTT** • **Increased NfL observed**			

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Strong financial position to enable programs and platform

PLATFORM

- **Proprietary GeneTAC® platform** designed to generate blockbuster products with first/best-in-class profiles for severe monogenic disorders

PROGRAMS

- **Three clinical-stage programs** (FA, FECD, and DM1) in 2026
  - DT-216 restores endogenous frataxin with broad tissue distribution
  - DT-168 eye drop targeting the genetic mutation in FECD
  - DT-818 potential for best-in-disease profile in DM1
- Active research pipeline with HD GeneTAC® program

CASH POSITION

- Balance sheet of **$207.4 million** as of *June 30, 2026*

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