DESIGN THERAPEUTICS

DESIGNING A NOVEL CLASS OF GENOMIC MEDICINES

FOR GENETIC DISORDERS

1Q2026

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; DT-216P2's potential to be a promising candidate for the treatment of FA patients; 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 expected 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 the potential to have multiple programs with clinical proof-of-concept with Design's current cash runway; 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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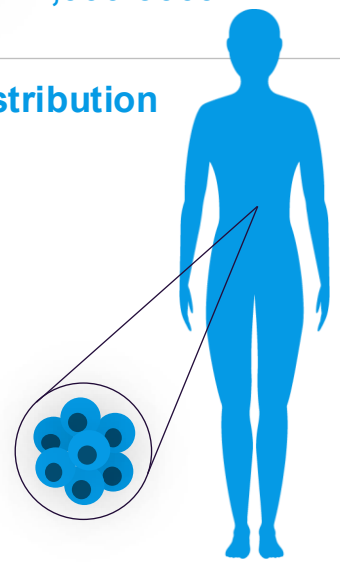
Advancing four GeneTAC® molecule programs

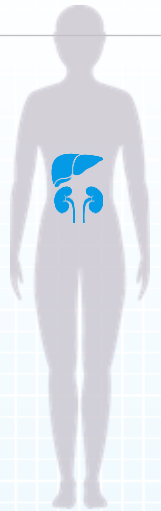
		Gene	Monogenic disease	Differentiated profile	Status	Market Overview
CLINICAL	**Friedreich Ataxia**	FRATAXIN (FXN)	GAA repeat expansion leads to reduced transcription	Restoration of endogenous frataxin with broad tissue distribution	RESTORE-FA MAD trial ongoing; 12-wk pt data expected 2H 2026	**$7.3B** Biogen acquired Skyclarys® (REATA)
CLINICAL	**FECD**	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 expected 2H 2026	**Over 1 million** TCF4 expansion pts in US (multi-billion $ opp)
CLINICAL	**DM1**	DMPK	CTG repeat expansion causes nuclear foci & cellular dysfunction	Allele-selective reduction of mutant DMPK leads to foci resolution & splicing correction	DT-818 pt dosing expected 1H 26	**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)

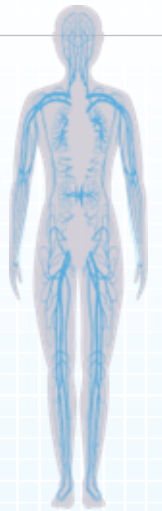
GeneTAC® molecules can distribute widely overcoming a central challenge for traditional genomic medicines

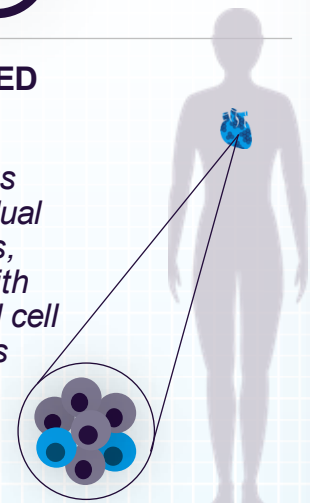
	GeneTAC® Small Molecule	Oligonucleotide	Protein	Gene Therapy
MOLECULAR SIZE *(Dalton)*	1,000-3000	6,000-15,000	50,000-100,000	4,000,000-5,000,000
DISTRIBUTION	**Broad distribution**	**LIMITED** *Distribution in most affected tissues often inadequate*	**LIMITED** *Distributes widely, but with minimal 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*









DT-216P2 for Friedreich Ataxia

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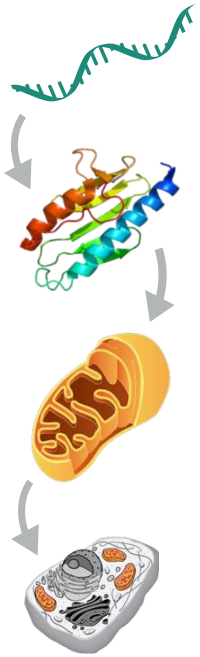
FA: Debilitating disease with limited treatment options today

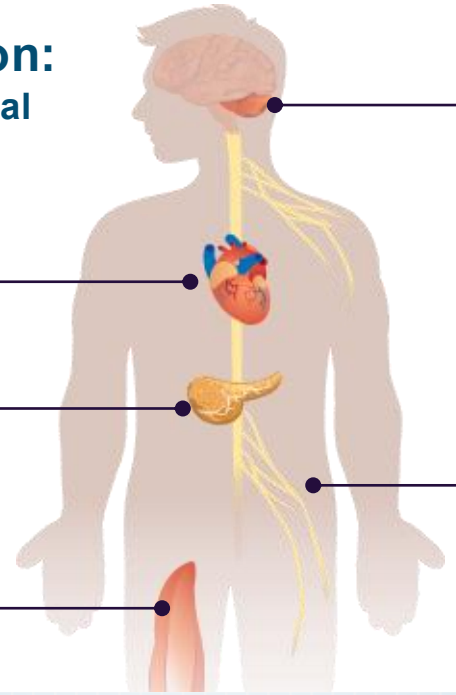
Monogenic disease caused by GAA-repeat expansion in 1st intron of frataxin (FXN) gene

Mutation leads to reduced FXN transcription, which is necessary for mitochondrial and cellular function



Multi-organ dysfunction:

muscle, central and peripheral nervous systems, heart, and pancreas



CENTRAL NERVOUS SYSTEM
ataxia, loss of coordination, slurred speech

HEART
cardiomyopathy, arrhythmias

PANCREAS
diabetes

PERIPHERAL NERVOUS SYSTEM
neuropathy

SKELETAL MUSCLE
stiffness, weakness

Unmet need in FA remains significant

Biogen

REATA PHARMACEUTICALS

- Skyclarys® does not address the genetic root cause of FA or change FXN level
- Skyclarys® slows disease progression on neurological end point (mFARS) but only during the 1st year
- Estimated peak sales of $1.6B/yr

Larimar Therapeutics

HIV-TAT-FXN protein

LEXEO therapeutics

AAV gene therapy targeting cardiac tissue

- Other drug candidates in clinical development that aim to address the root cause of FA involve complex modalities
- None of these change endogenous FXN

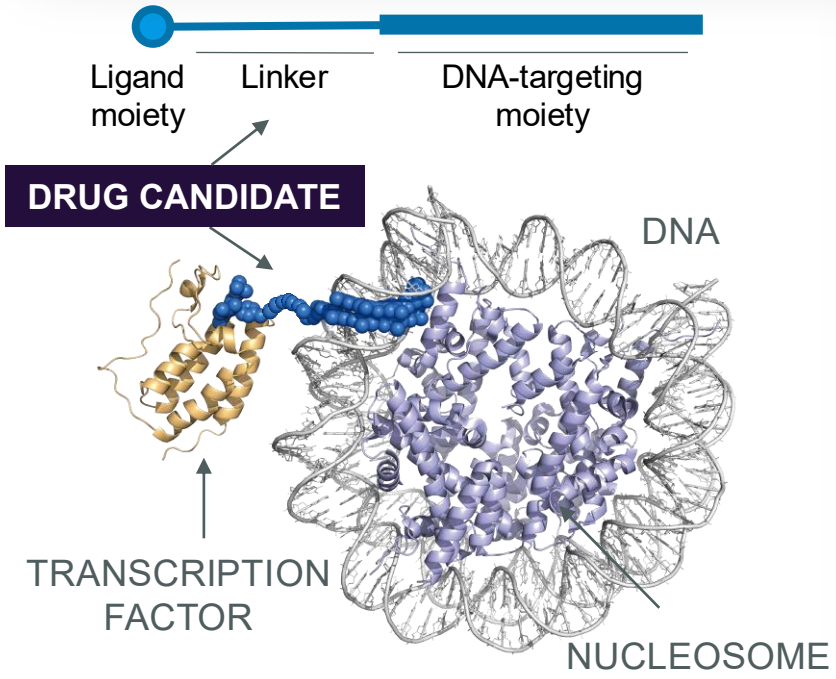
FA GeneTAC® molecules normalized FXN levels in FA patient cells but did not alter FXN levels in healthy cells

Therapeutic goal: increase FXN

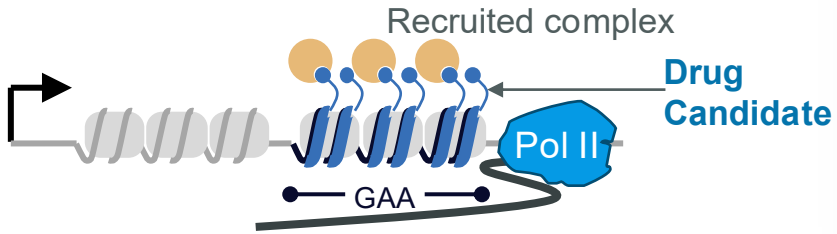
FA patients, carriers and controls have different average FXN levels

Carriers are free of FA symptoms

~2X increase of FXN levels could potentially bring patients' levels into asymptomatic carrier range



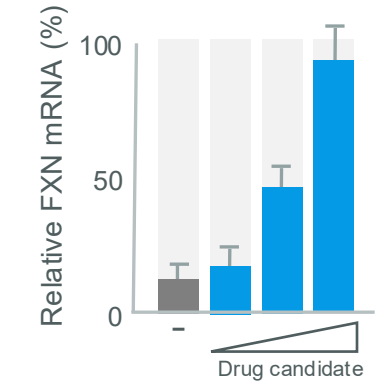
DIAL UP EXPRESSION



Designed to facilitate transcription through the locus

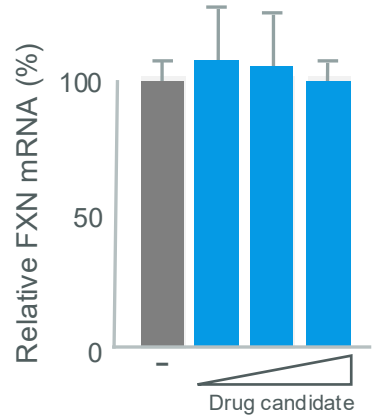
FA PATIENT (two expanded copies)

GeneTAC® molecules normalized levels[1]



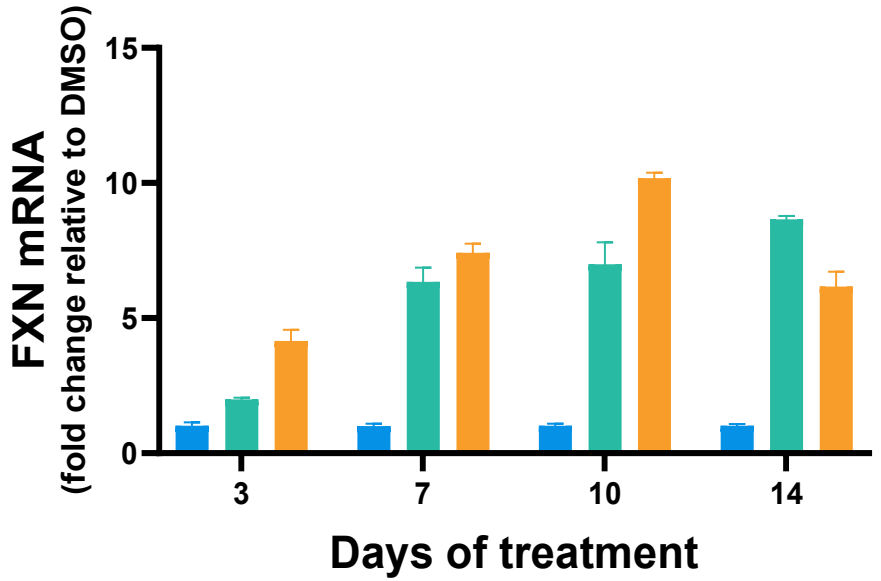
HEALTHY INDIVIDUAL (two normal copies)

FXN levels unaltered in healthy cells[1]

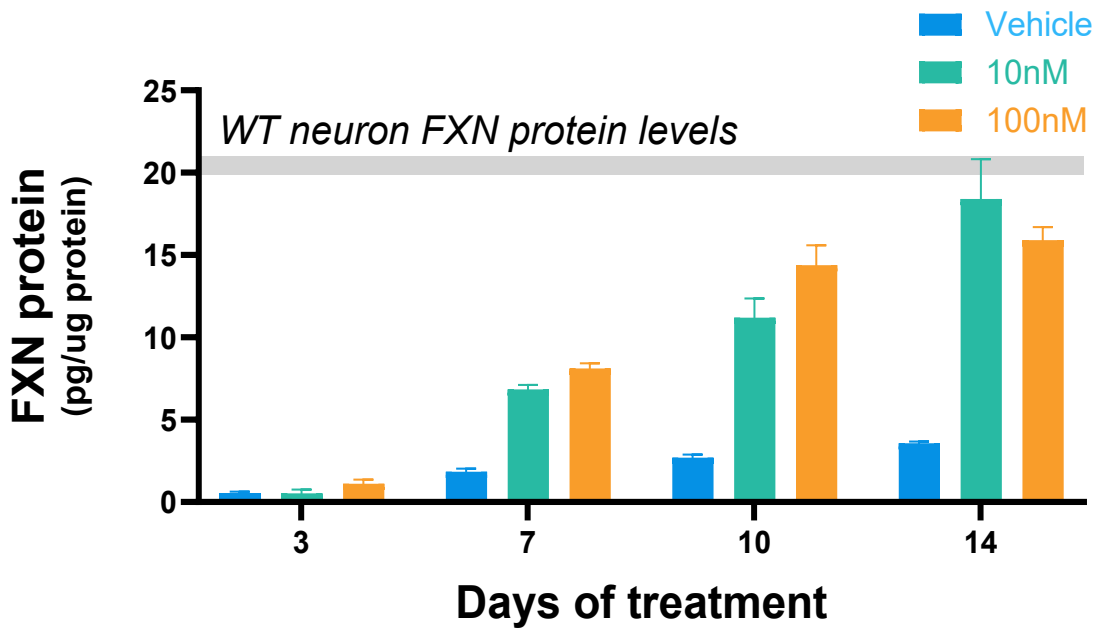


Low concentrations of DT-216 molecule restored endogenous FXN levels in FA patient iPS-neurons

FXN mRNA



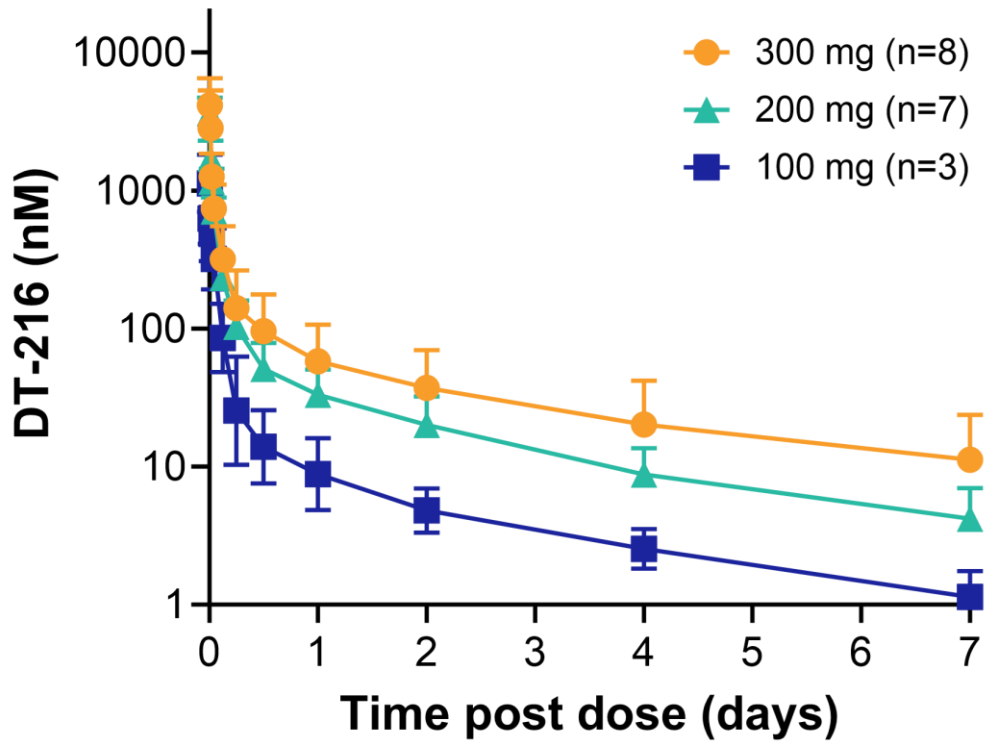
FXN Protein



Note: Bars represent standard error of the mean. Cells treated with DT-216 FA GeneTAC® molecule.

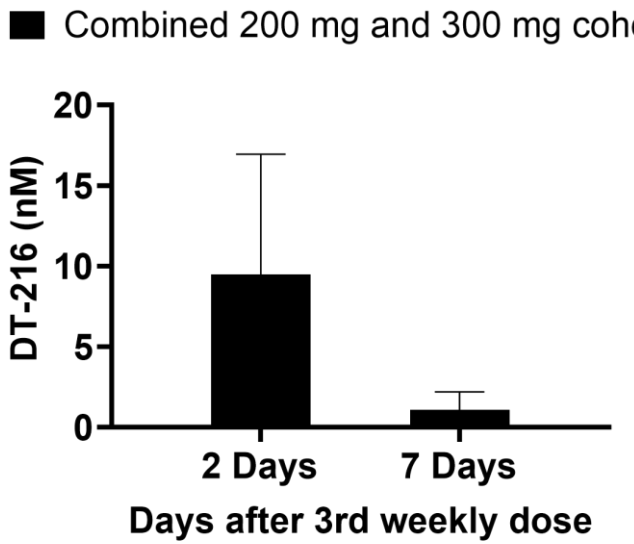
Prior DT-216 drug product Phase 1 MAD study revealed plasma PK and tissue distribution were both transient with QW IV dosing

Plasma DT-216 PK after 3rd Dose



Muscle DT-216 PK after 3rd Dose

- Average DT-216 levels in skeletal muscle at both 200mg and 300mg cohorts were ~8-10nM two days after 3rd weekly dose & ~1nM seven days after 3rd weekly dose



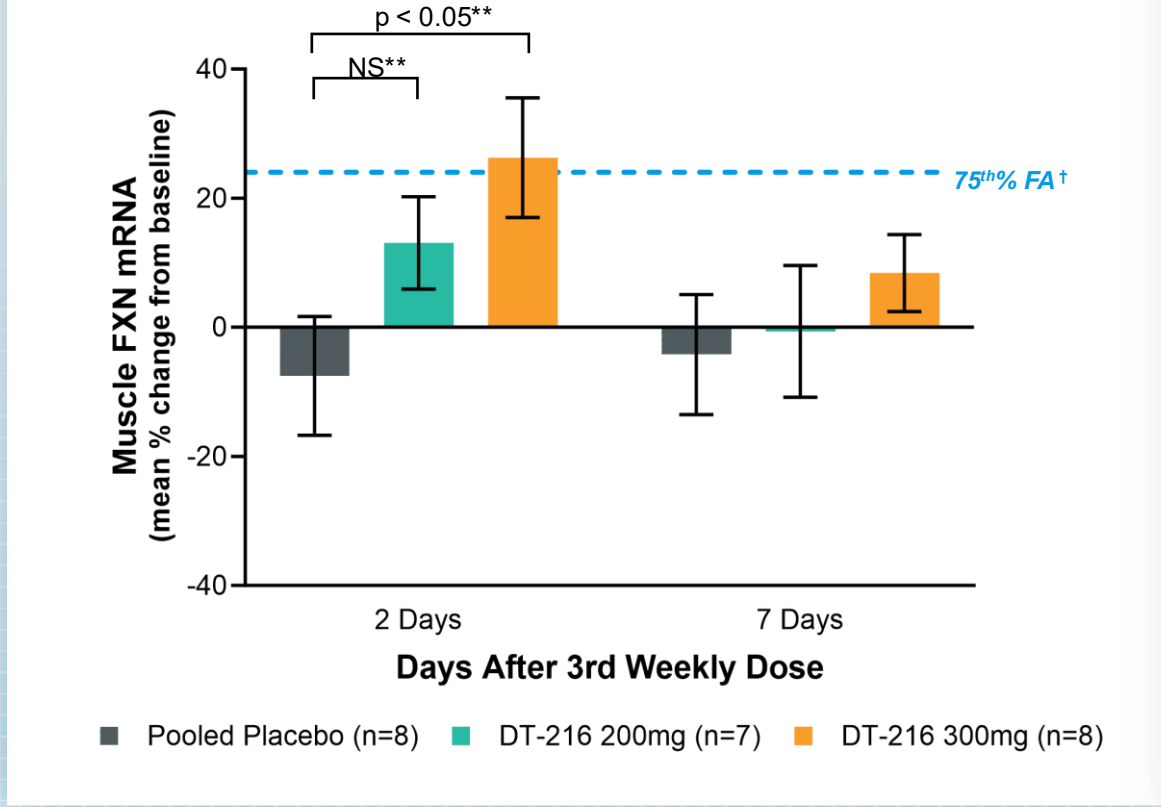
- DT-216 concentrations in muscle were lower than projected based on nonclinical studies

Note: Bars represent standard deviation.

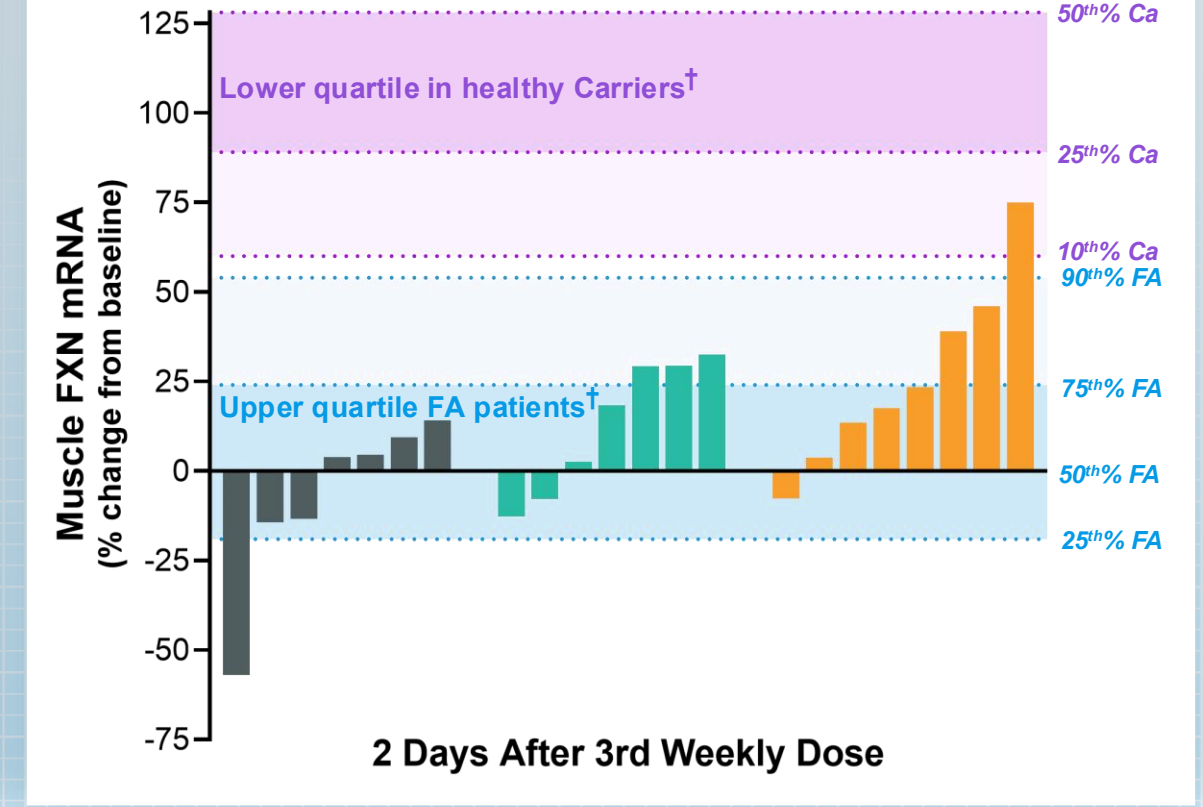
Prior DT-216 drug product Phase 1 MAD study showed FXN expression dialed up in response to drug exposure in FA Patients

Muscle FXN mRNA response correlated with dose and muscle DT-216 exposure, p < 0.05*

Cohorts: 200mg and 300mg



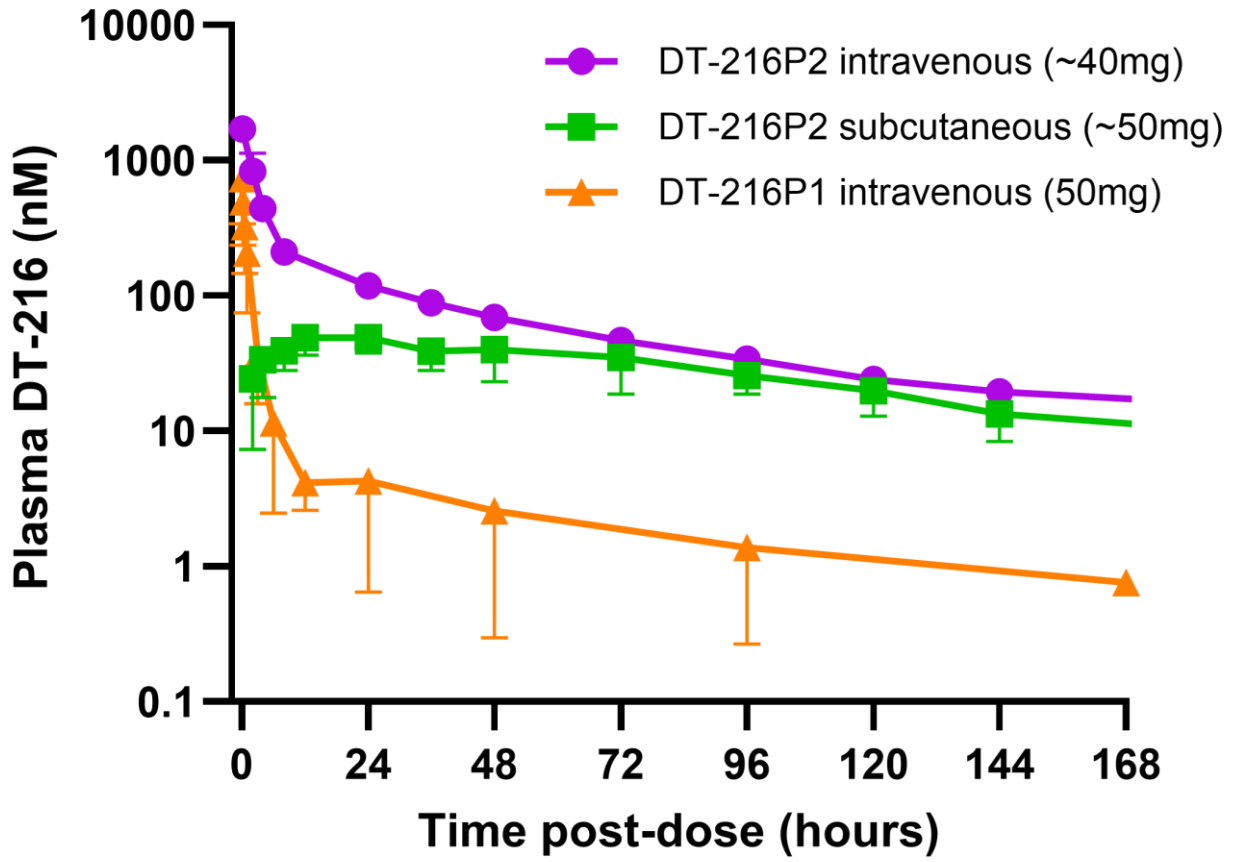
Individual FA Patients



* Exploratory analyses for dose-response and exposure-response were conducted using a non-parametric trend test and non-parametric correlation test, respectively.
** Exploratory analyses were conducted using a non-parametric Wilcoxon Rank-Sum model. A parametric ANCOVA model gave similar results. Error bars represent standard error of the mean. NS, not significant.
† Percentiles and quartiles assume individual FA patient baselines in the MAD study are the median FA patient FXN mRNA value from the observational muscle biopsy study.

DT216P2 generally well-tolerated and has exhibited improved exposure over the prior formulation (DT-216P1) at comparable doses

Human PK

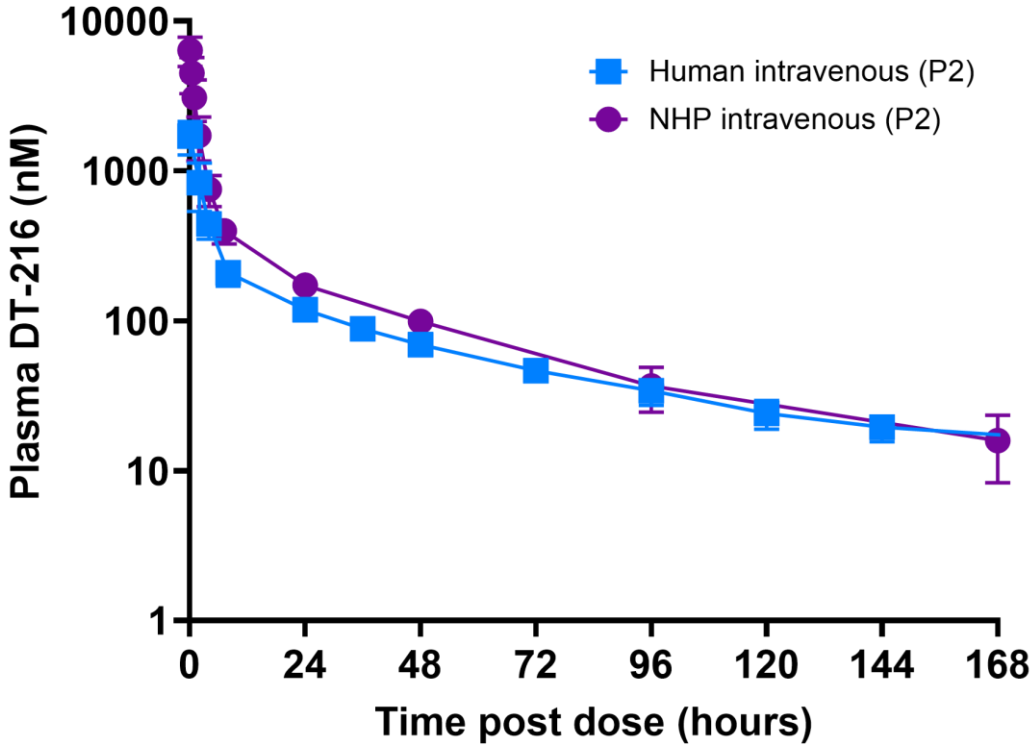


Note: Data from SAD study; Error bars represent standard deviation; when error bars not visible, they are within the size of the symbol; dose quantities of DT-216P2 are blinded cohort averages

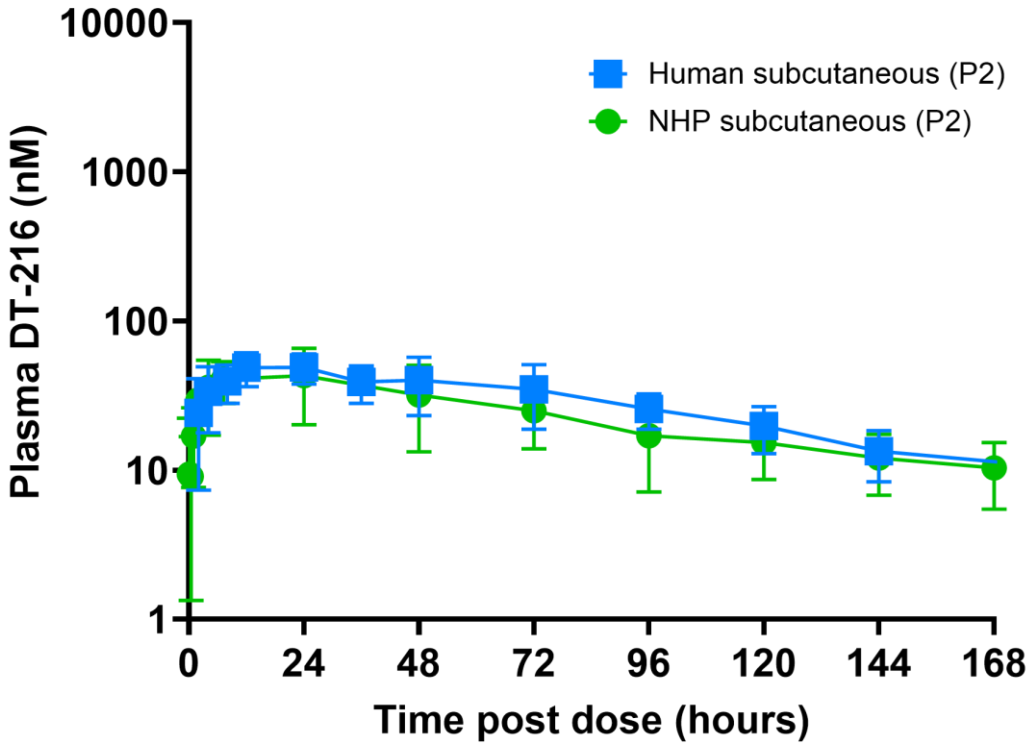
Observed human plasma PK profile of DT-216P2 consistent with NHPs

Human/NHP PK

Intravenous



Subcutaneous



Note: Data from SAD study and nonclinical studies; Error bars represent standard deviation; when error bars not visible, they are within the size of the symbol;

DT-216P2 clinical plan

Single Ascending Dose study in healthy volunteers

Additional IV cohorts

Additional SC cohorts

- Escalate single doses
- Evaluate route of administration

Cohort 1 - IV

Cohort 1 - SC

- Evaluate PK, tolerability in healthy volunteers after a single dose
- Evaluate both IV (infusion) and SC (injection and infusion) administration

Dosing paradigm for the MAD study in FA patients to be determined

RESTORE-FA Multiple Ascending Dose study in FA patients

Additional FA MAD cohorts

- Escalate multiple doses

FA MAD cohorts

- Evaluate safety, tolerability, PK and PD in FA patients after multiple doses
- 12-week frataxin data anticipated in 2H 2026

RESTORE-FA: Reactivating Expression Suppressed Through Overcoming Repeat Expansion for FA

DT-168 for Fuchs Endothelial Corneal Dystrophy

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

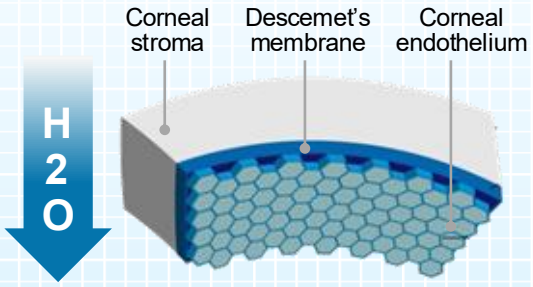
~2M diagnosed patients (U.S.)[1]

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)

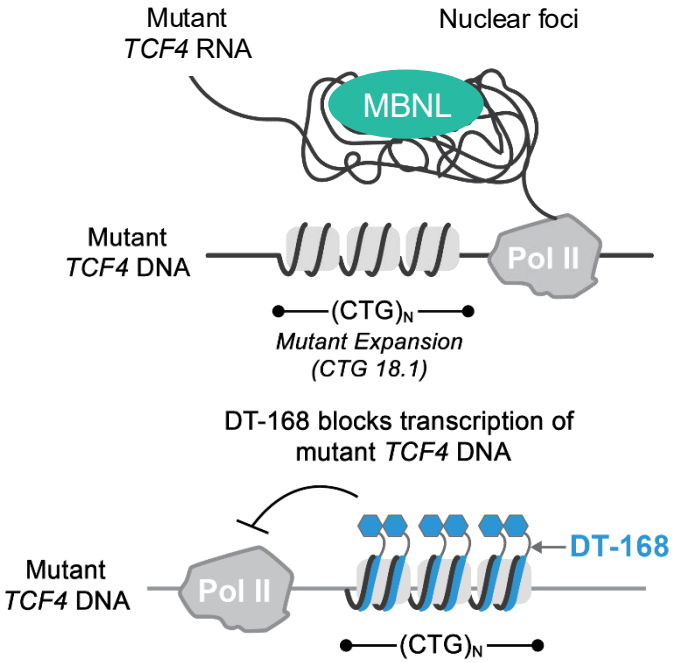


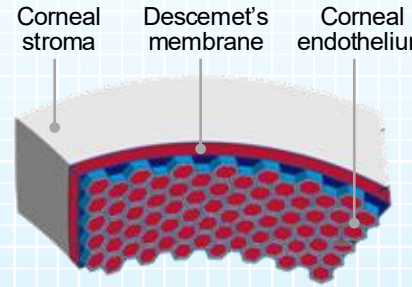
Corneal endothelial cells (CECs) **pump water out of the stroma** to prevent edema and maintain corneal transparency

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

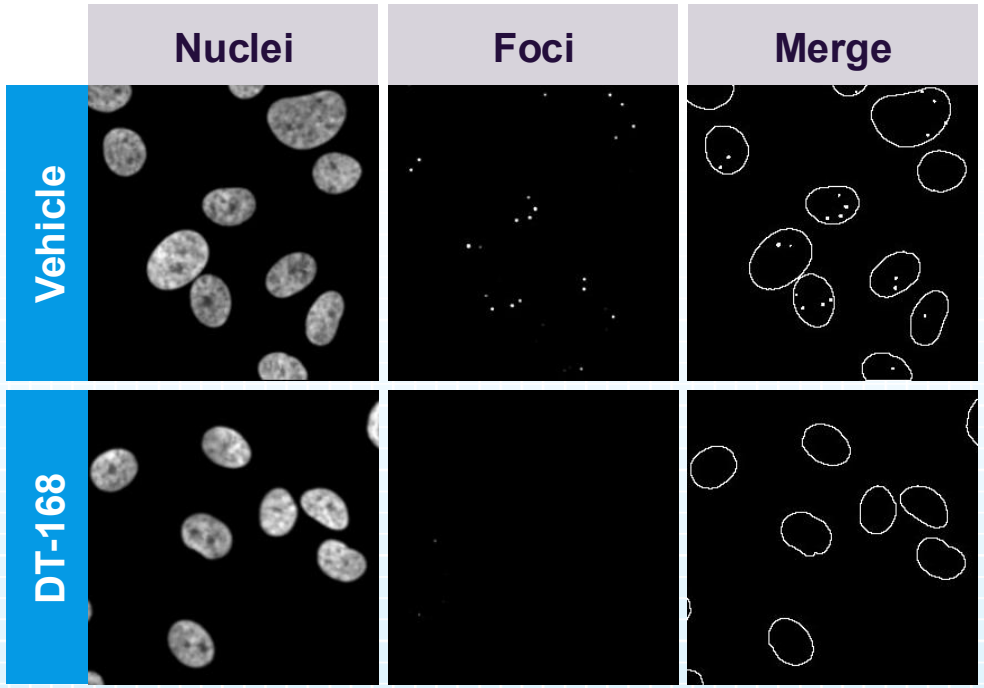




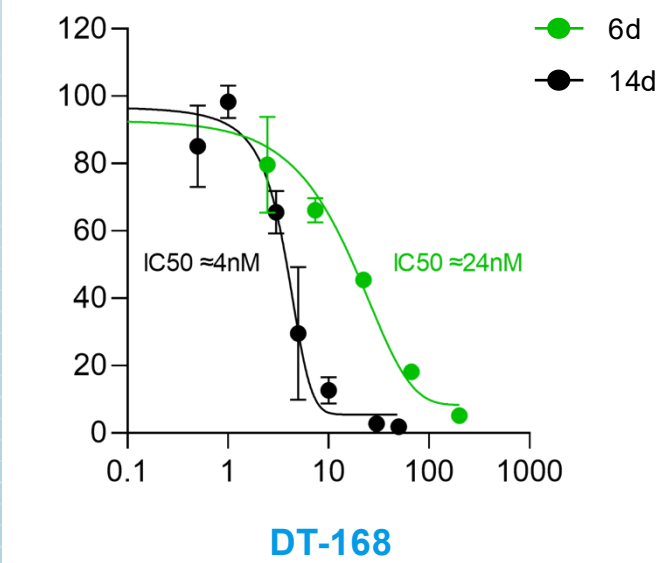
Tissues **removed during surgery**

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

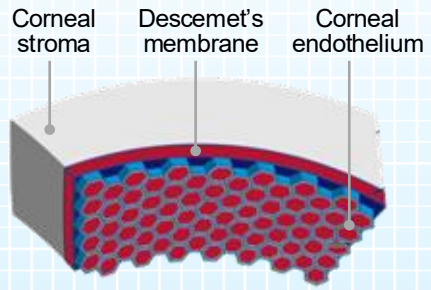
DT-168 reduction of nuclear foci observed in primary CECs isolated from patients with FECD with high potency (<5nM foci IC50)



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



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

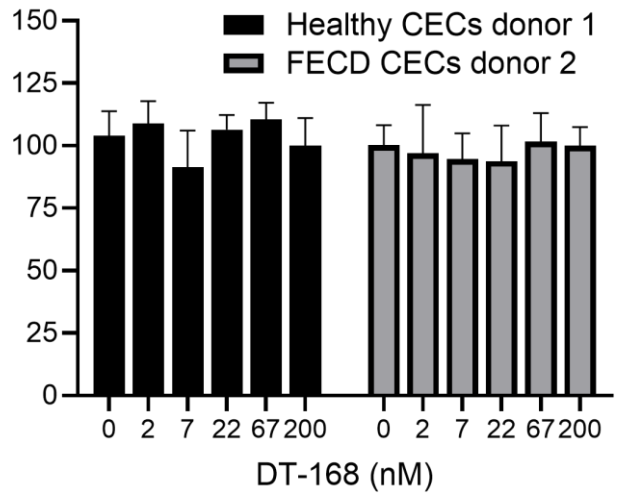


Tissues **removed during surgery**

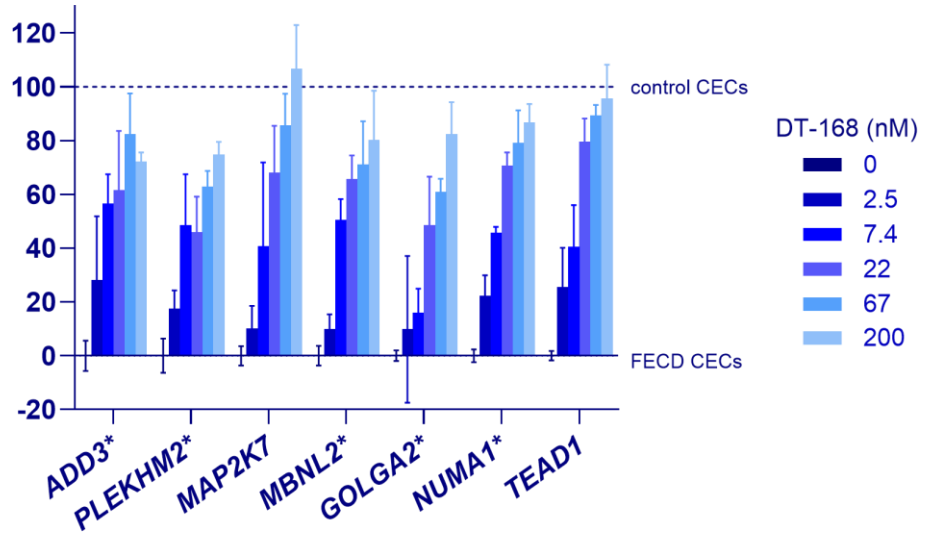
CECs = Corneal endothelial cells
Note: Bars represent standard deviation

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

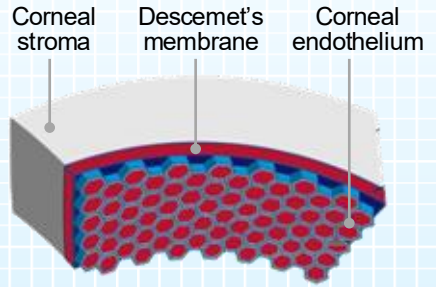
TCF4 mRNA
Percent of untreated



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



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



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 errorbars 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.

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

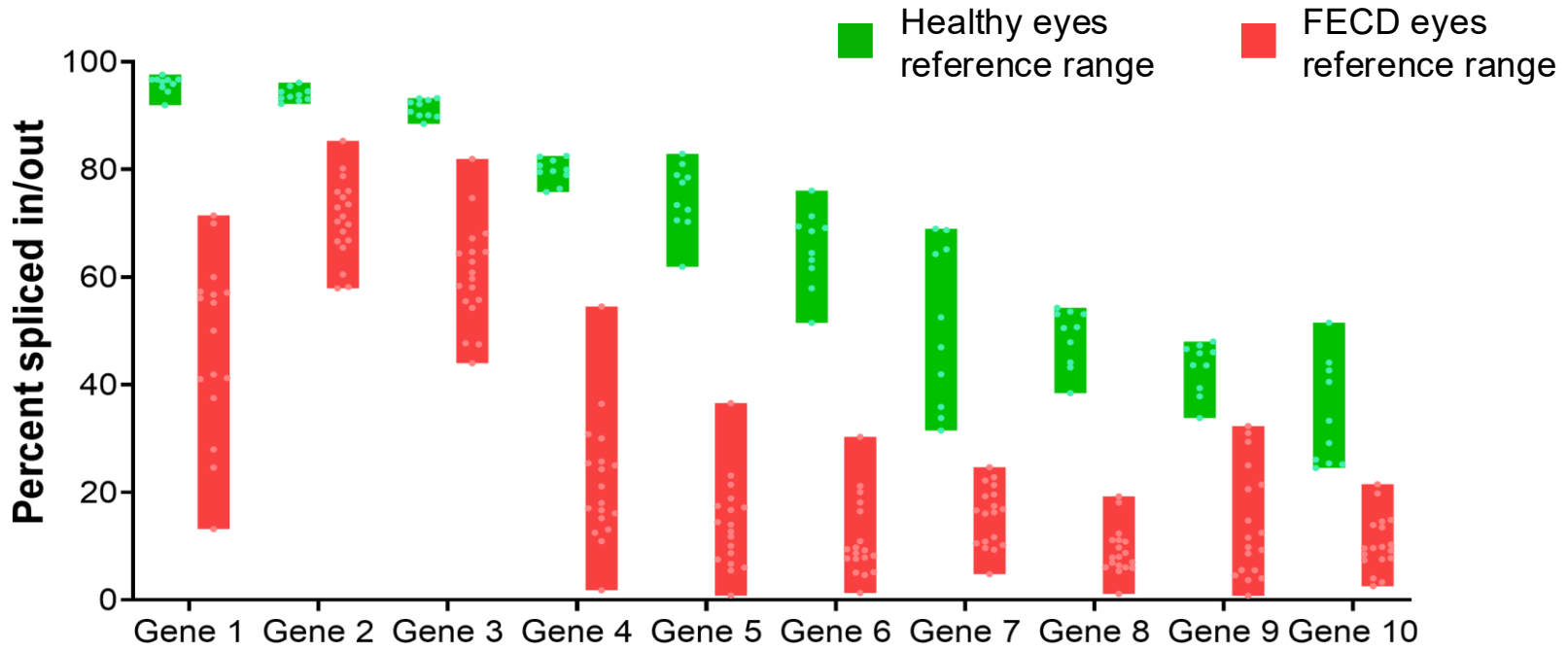
- DT-168 eye drops were **well-tolerated in all subjects**
- There were **no serious adverse events**, no ocular adverse events, or participant discontinuations due to adverse events[1]
- All observed adverse events were **non-ocular** and were considered **not related to drug product** by the investigator
- 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.

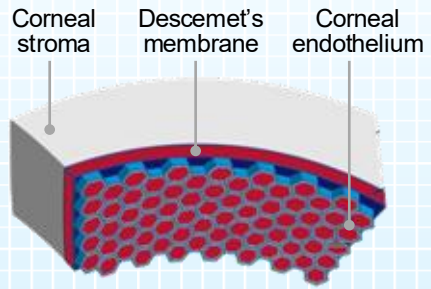
Splicing biomarker is measurable in surgically removed corneal endothelial cells

- 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**

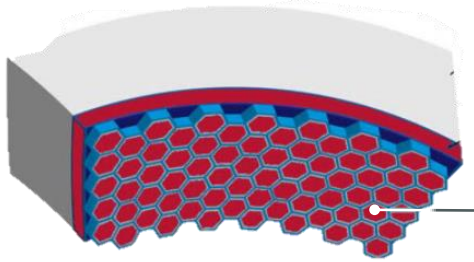


Tissues **removed during surgery**

DT-168 Phase 2 biomarker study with data in 2H 2026

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

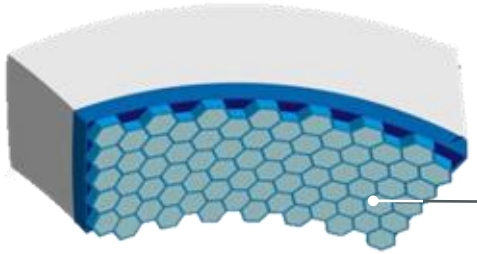
FECD eye reference range biomarker result

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

Myotonic Dystrophy Type 1 (DM1)

DESIGN THERAPEUTICS

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
- Ex-US regulatory clearance obtained to initiate Phase 1 development

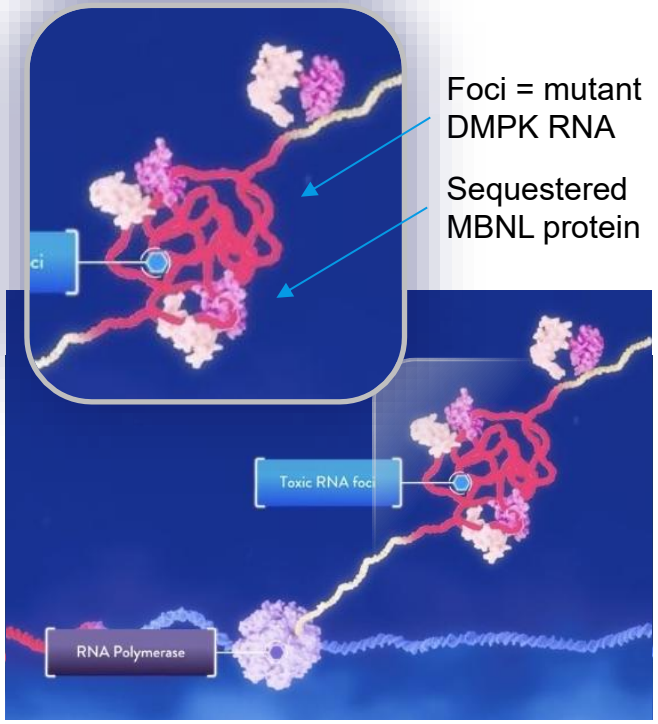
Phase 1

- Begin dosing DM1 patients in a Phase 1 MAD trial of DT-818 in Australia in 1H 2026
  - Injectable (initially once weekly IV, exploring subcutaneous route)
- Endpoints:
  - Safety
  - Correction of mis-splicing
- Results anticipated in 2027

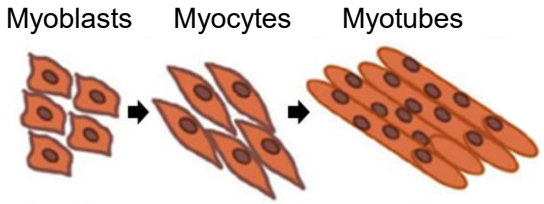
MAD = multiple-ascending dose

DM1 (Myotonic dystrophy type 1)

1 Mechanism of disease

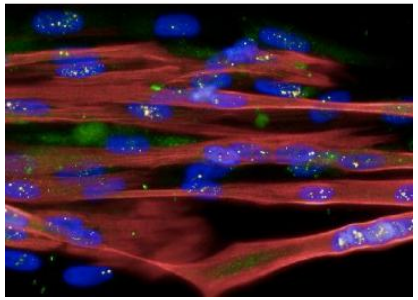


2 Preclinical human cells



- 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

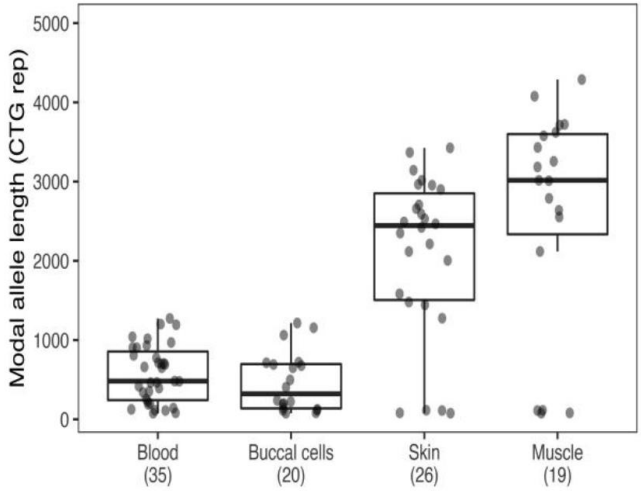
Actin transgene with CTG repeats
Used because DMPK expanded CTG repeat model has limited myotonia

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 multipletissues in myotonic dystrophy type 1. Hum Mol Genet. 2023

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

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

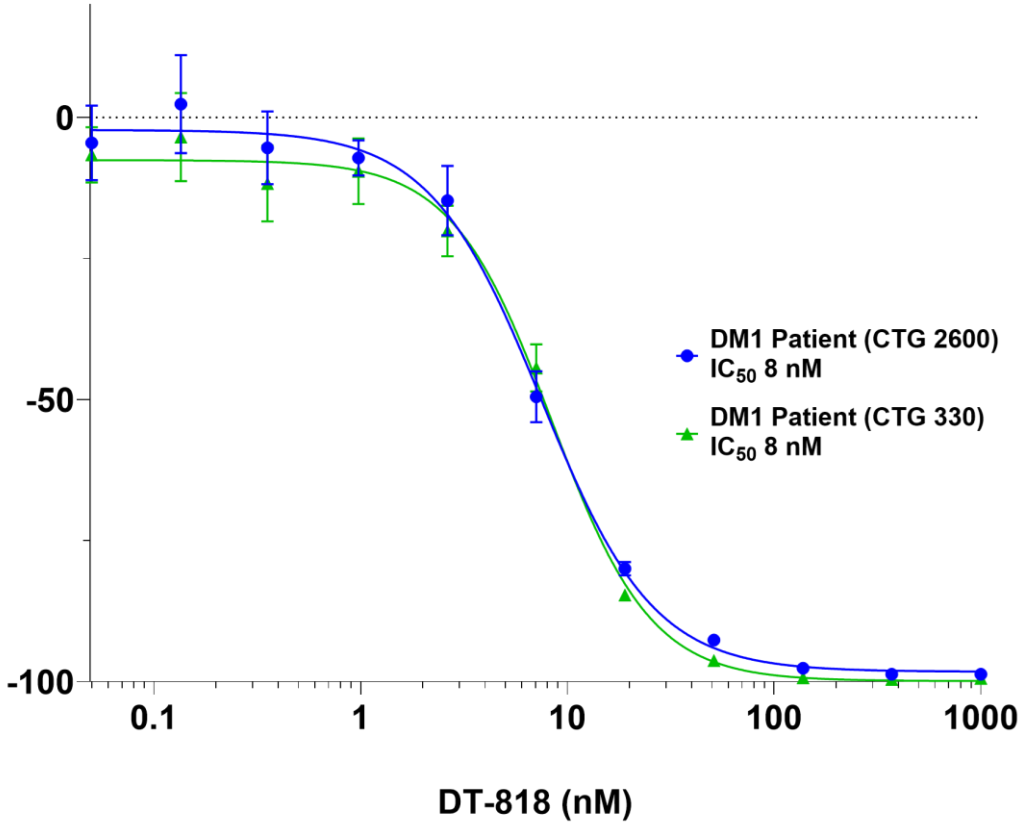
- Human genetic models seem to better correlate to what has been observed in the clinic so far

- 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

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

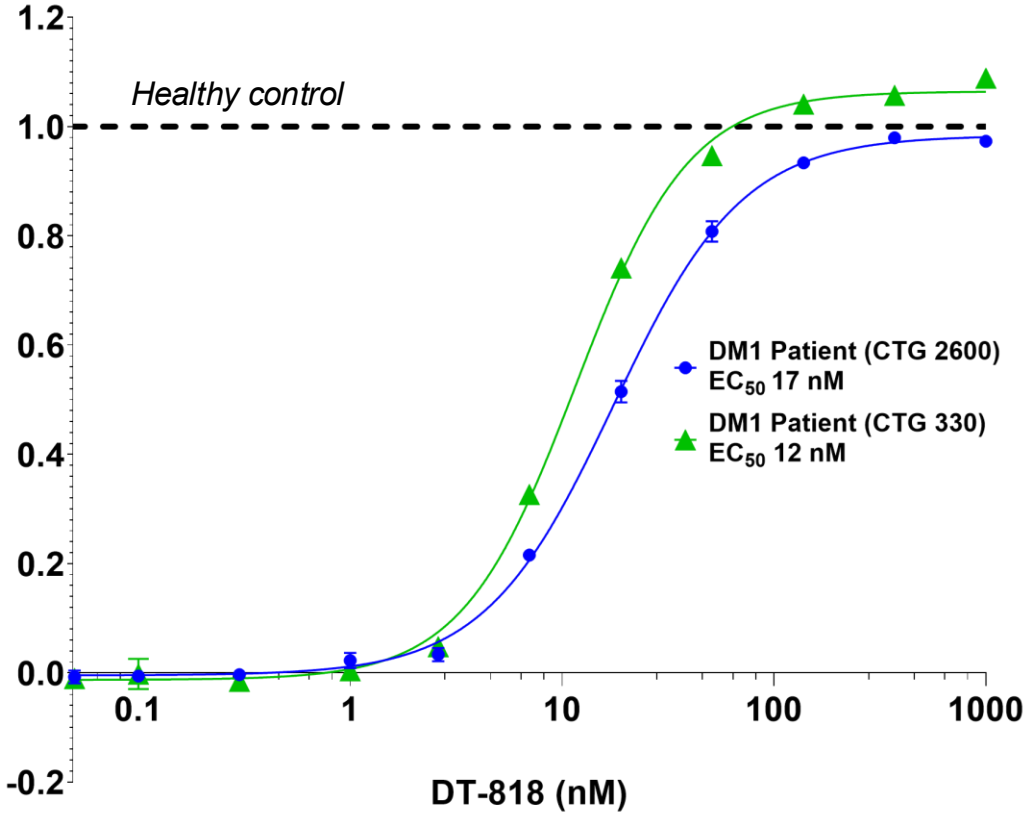
DT-818 reduces toxic RNA nuclear foci in DM1 myotubes

Foci per nucleus
Percent change relative to untreated (FISH)

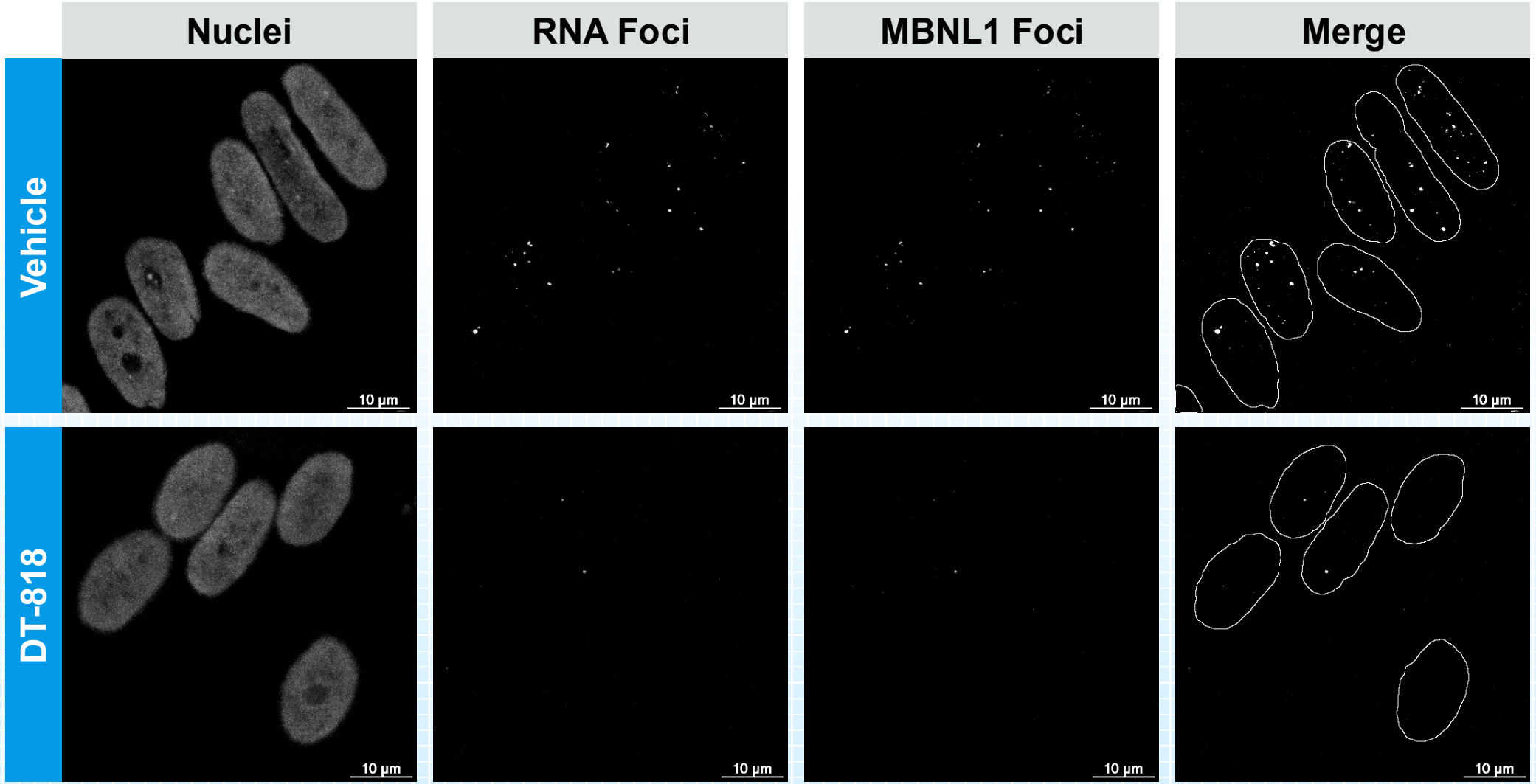


DT-818 corrects splicing in DM1 myotubes

Splice index
Index relative to healthy control myotubes

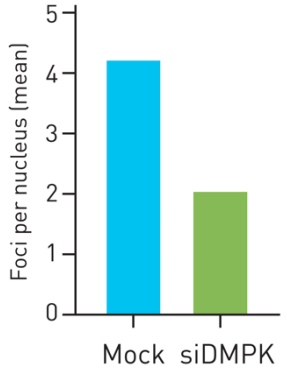


DT-818 treatment reduces toxic RNA foci and liberates MBNL1 protein in DM1 patient myotubes

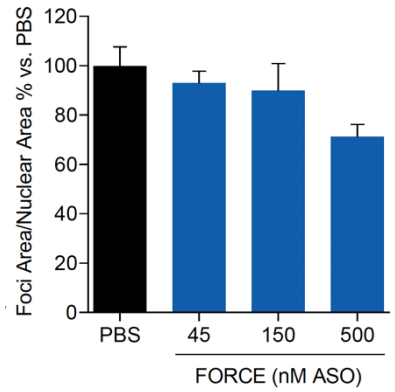


DT-818 treatment shows best-in-disease potential for foci reduction in patient cell line with 2,600 repeats

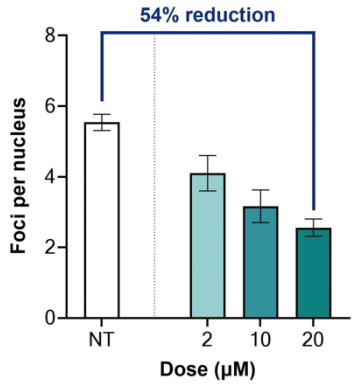
AVIDITY BIOSCIENCES Estimated*1 ~55%



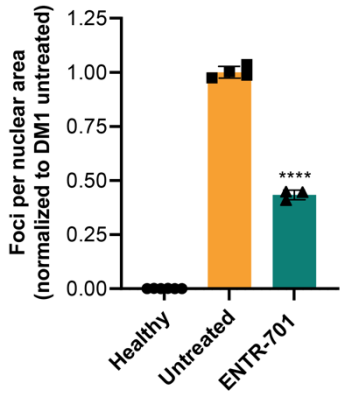
Dyne THERAPEUTICS Estimated*2 ~30%



PepGen™ 54% foci reduction[3]

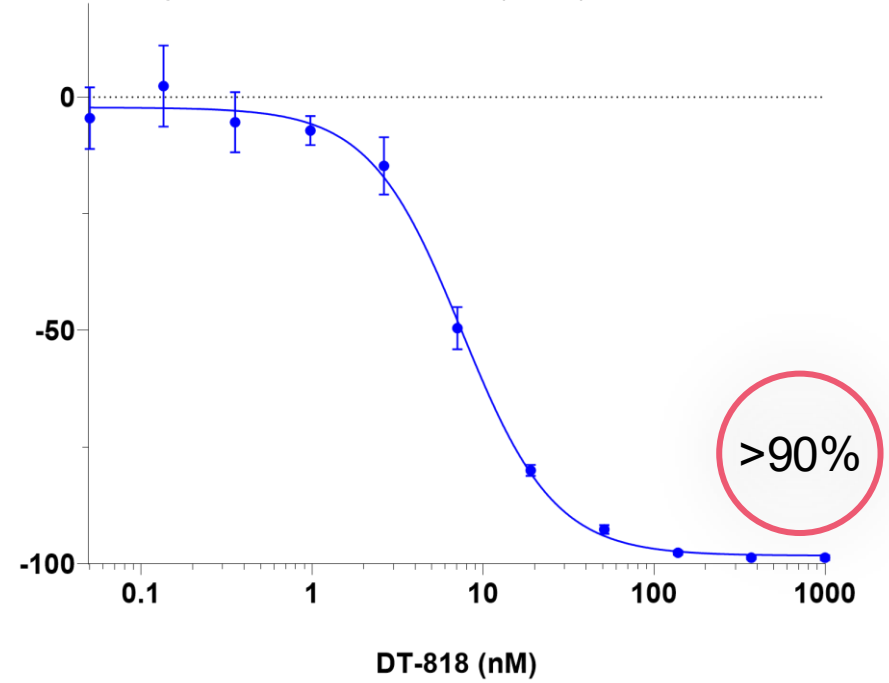


entrada THERAPEUTICS Estimated*4 ~55%



DESIGN THERAPEUTICS

Foci per nucleus
Percent change relative to untreated (FISH)



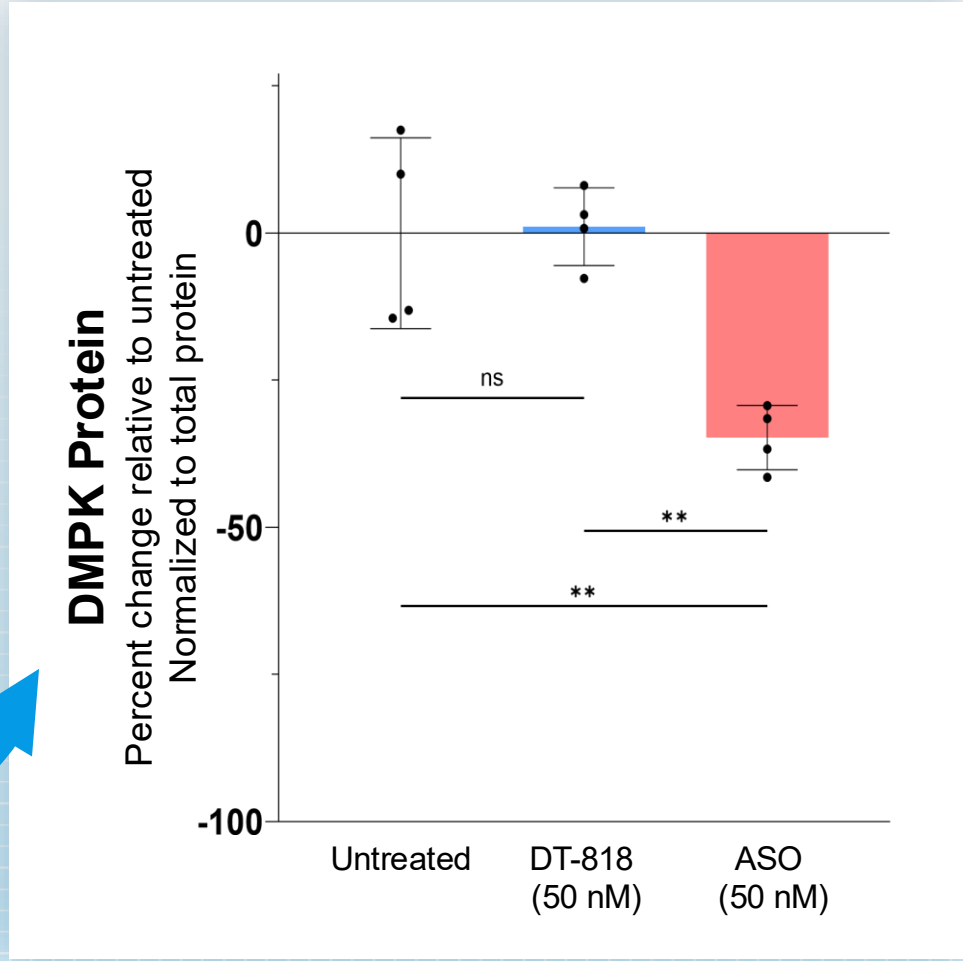
Note: Foci reduction evaluated in DM1 patient myotubes containing ~2600 repeats in all cases except Avidity where repeat length not noted. *.Estimates are based on the graphs provided since the company has not provided quantitative values from graphs; References: 1. Avidity Biosciences, WMS 2023 Poster;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

DT-818 selectively targets mutant DMPK

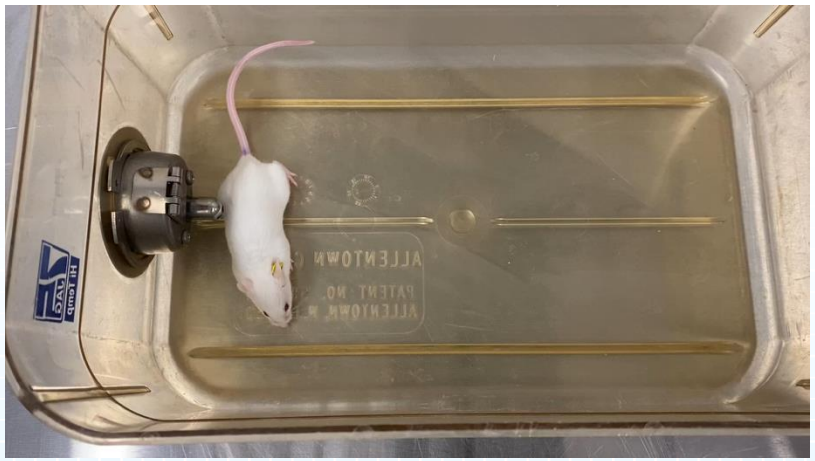
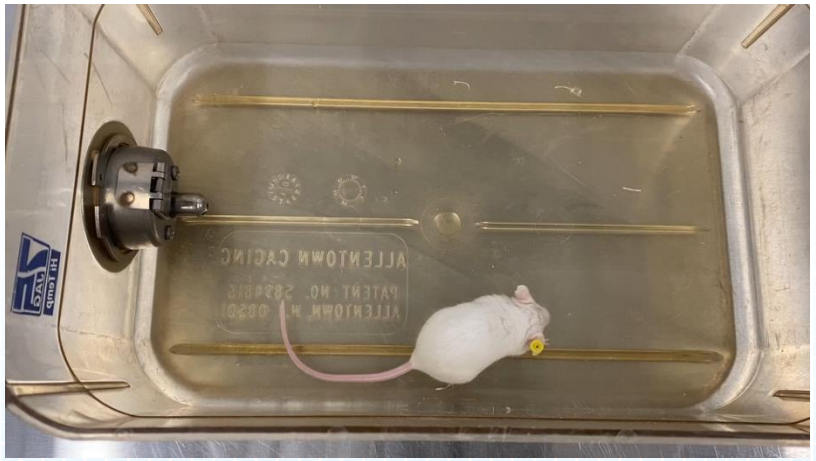
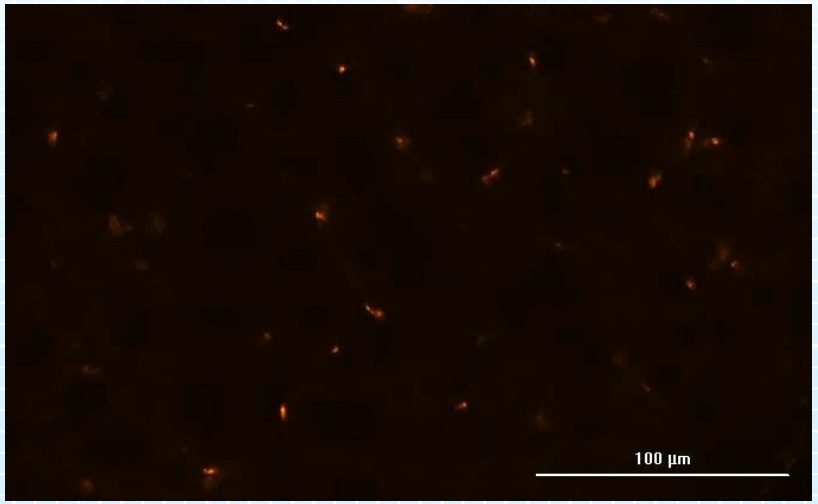
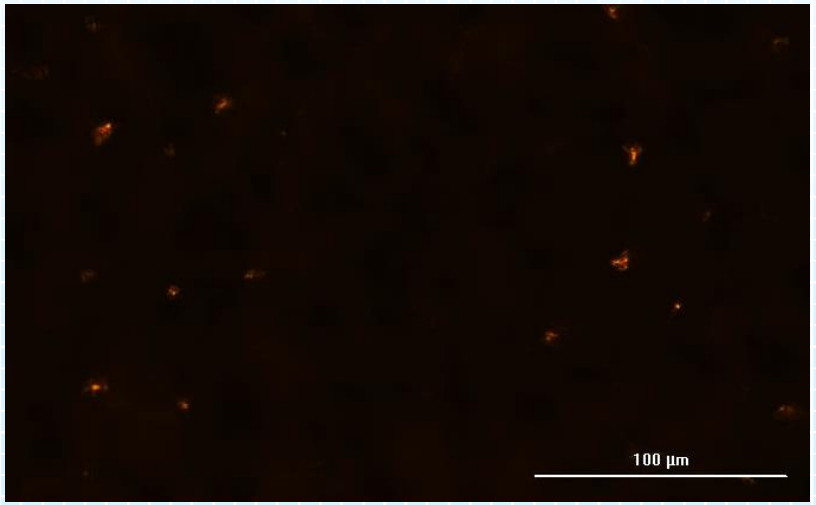
Allele-specific mechanism spares DMPK protein

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



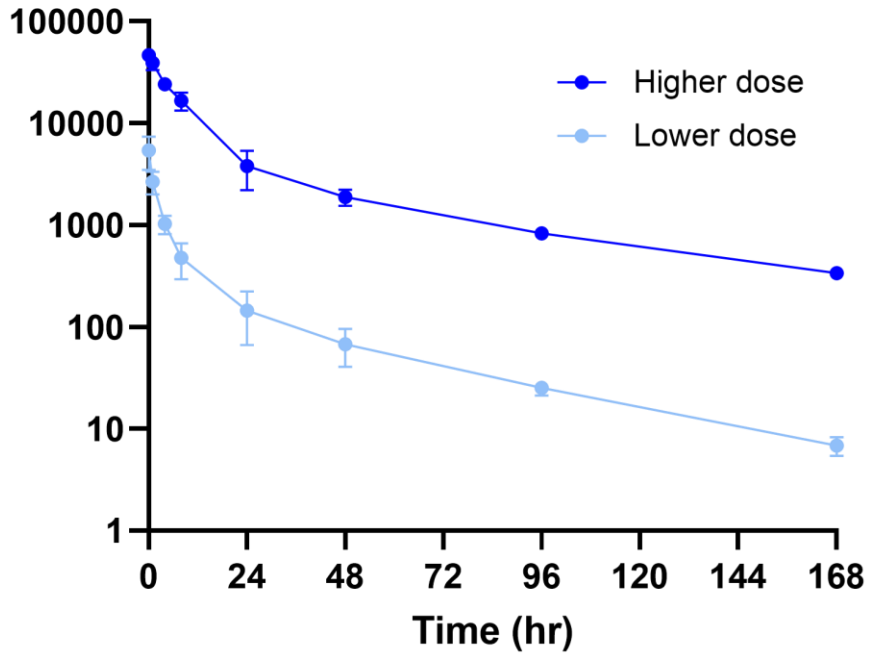
Splicing and myotonia improved in actin repeat (HSA^{LR}) mice treated with DT-818

	Vehicle	DT-818
Myotonia		
Foci		

DT-818 shows good exposure and long half-life

NHP PK

Single IV dose
nM DT-818 in plasma



DT-818 summary and next steps

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MAD = multiple-ascending dose

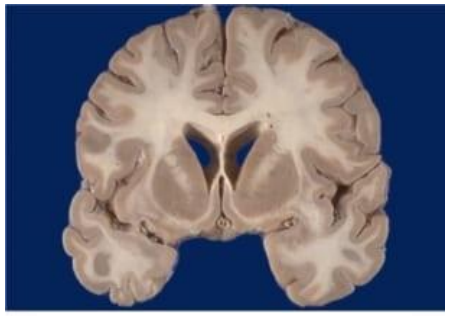
Huntington’s Disease (HD)

DESIGN THERAPEUTICS

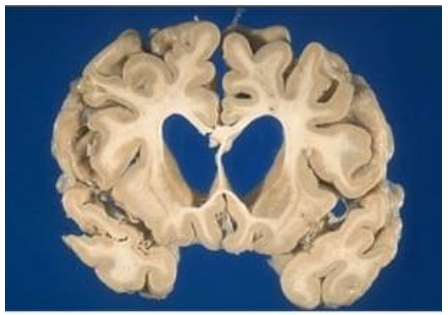
Huntington's Disease (HD)

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.



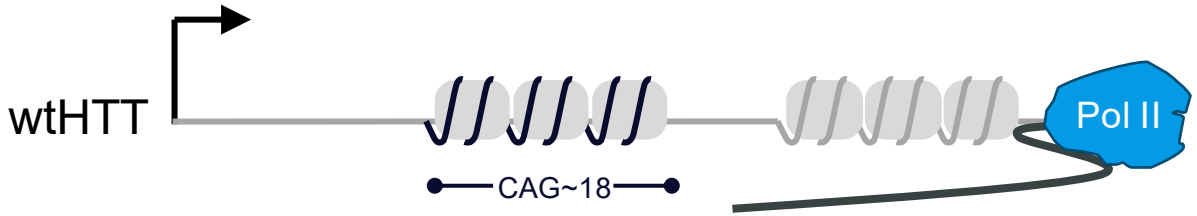
Control – no atrophy



HD

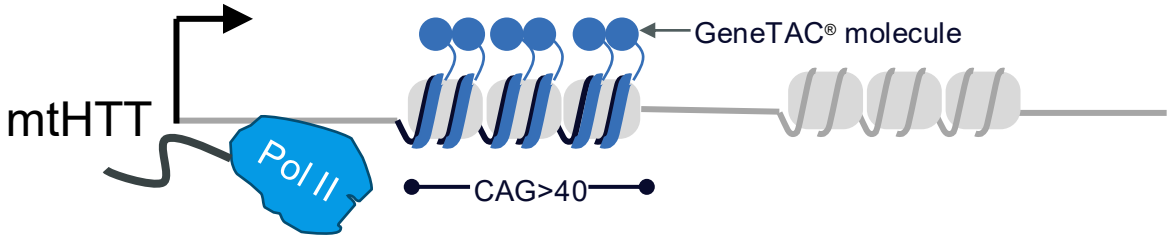
Normal HTT gene — *thought to be important to normal state*

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



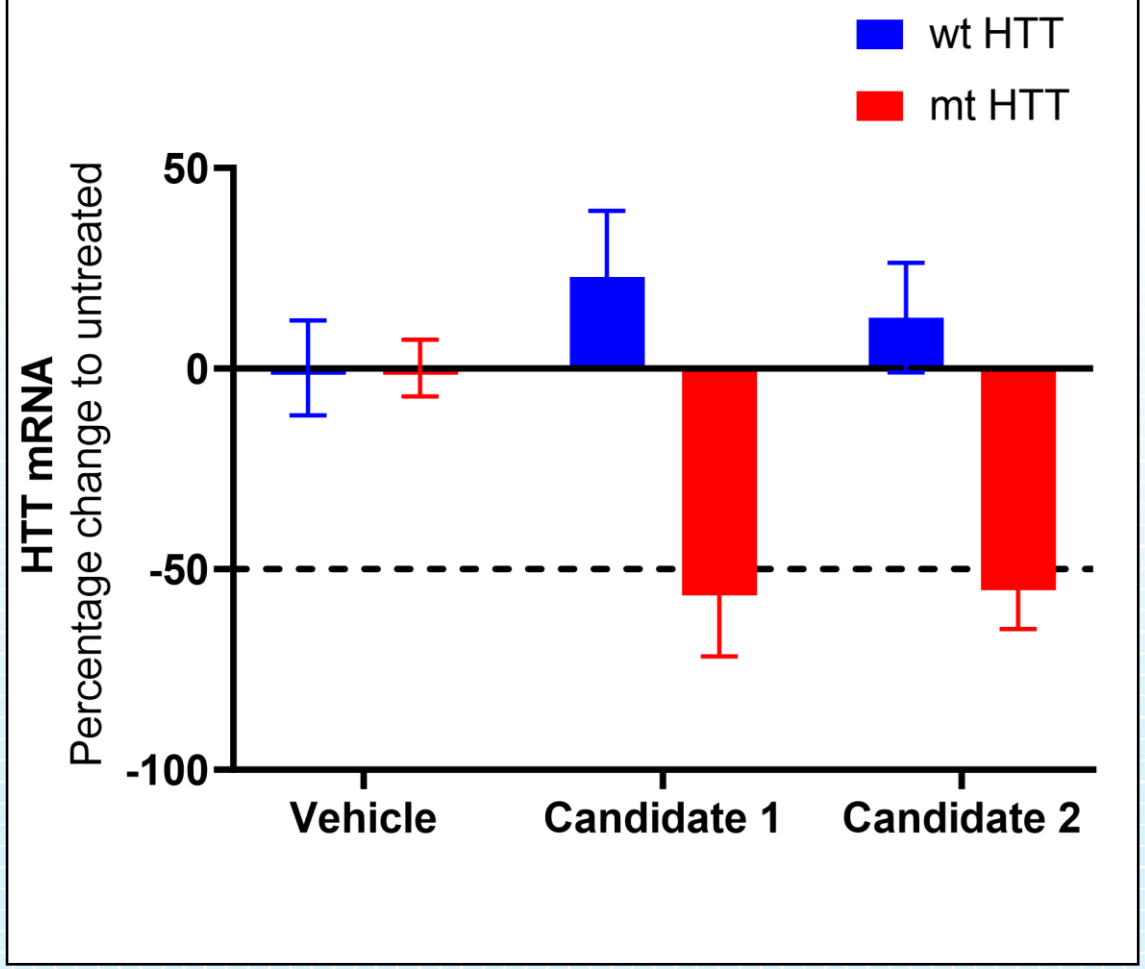
HTT gene with expansion

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

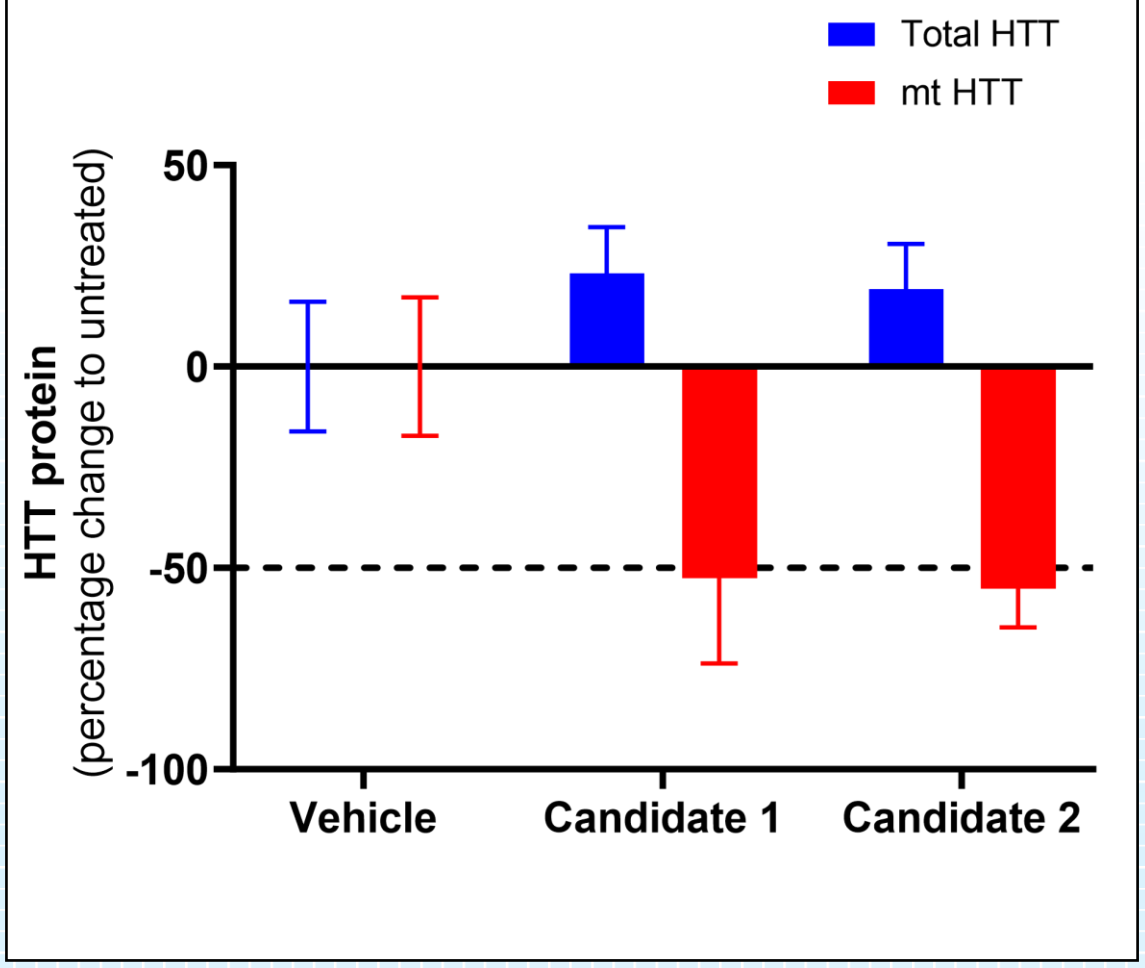


Allele-specific reductions of RNA and protein observed in the brain in zQ175DN HD mouse model after 8 weeks of systemic administration

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.

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 LIFE SCIENCES 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**	

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 **$219.8 million** as of *December 31, 2025,* expected to fund planned operations into 2029