UNITED STATES
SECURITIES AND EXCHANGE COMMISSION
WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): January 13, 2025

Design Therapeutics, Inc.

(Exact name of Registrant as Specified in Its Charter)

Delaware	**001-40288**	**82-3929248**
(State or Other Jurisdiction of Incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

6005 Hidden Valley Road Suite 110 Carlsbad, California	**92011**
(Address of Principal Executive Offices)	**(Zip Code)**

Registrant's Telephone Number, Including Area Code: (858) 293-4900

N/A
(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions:

☐ Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

☐ Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

☐ Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

☐ Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Securities registered pursuant to Section 12(b) of the Act:

Title of each class	**Trading Symbol(s)**	**Name of each exchange on which registered**
Common Stock, $0.0001 par value per share	DSGN	Nasdaq Global Select Market

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§ 230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§ 240.12b-2 of this chapter).

Emerging growth company ☒

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. ☒

Item 7.01 Regulation FD Disclosure.

On January 13, 2025, Design Therapeutics, Inc. (the "Company") updated its corporate presentation for use in meetings with investors, analysts and others. A copy of the updated presentation is attached as Exhibit 99.1 to this Current Report on Form 8-K.

The information under this Item 7.01 of this Current Report on 8-K, including Exhibit 99.1, is furnished and shall not be deemed "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that Section, nor shall it be deemed incorporated by reference into any filing under the Exchange Act or the Securities Act of 1933, as amended, whether filed before or after the date hereof and regardless of any general incorporation language in such filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	**Description**
99.1	Company Presentation
104	Cover Page Interactive Data File (embedded within the Inline XBRL document)

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned thereunto duly authorized.

Design Therapeutics, Inc.

Date: January 13, 2025

By: /s/ Pratik Shah, Ph.D.
Pratik Shah, Ph.D.
President, Chief Executive Officer and Chairperson

Exhibit 99.1


DESIGN
THERAPEUTICS
DESIGNING A NOVEL CLASS
OF GENOMIC MEDICINES
FOR GENETIC DISORDERS
1Q2025
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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; expectations for initiating clinical trials for DT-216P2; the potential benefits of restoring FXN in FA patients; DT-216P2's potential to be a promising candidate for future treatment of FA patients; Design's FECD GeneTAC® program and its potential therapeutic benefits and advantages; expectations for reporting data for the FECD Phase 1 clinical trial and the timing thereof; the impact of Design's FECD observational study on a clinical program for FECD; Design's DM1 and HD GeneTAC® programs and their potential therapeutic benefits and advantages; the expectations for selecting a development candidate for Design's DM1 program; Design's ability to deliver on its short- and long-term goals; Design's ability to design and tailor GeneTAC® molecules from our novel platform to address diverse monogenic diseases; projected R&D spend; Design's estimated financial runway and the sufficiency of its resources to support its planned operations; Design's ability to execute multiple programs through human proof of concept; and the capabilities and potential advantages of Design's pipeline of GeneTAC® molecules. Because such statements are subject to risks and uncertainties, actual results may differ materially from those expressed or implied by such forward-looking statements. Words such as "believes," "designed to," "anticipates," "planned," "expects," "estimate," "intends," "will," "potential" and similar expressions are intended to identify forward-looking statements. These forward-looking statements are based upon Design's current expectations and involve assumptions that may never materialize or may prove to be incorrect. Actual results and the timing of events could differ materially from those anticipated in such forward-looking statements as a result of various risks and uncertainties, which include, without limitation, risks associated with conducting a clinical trial and patient enrollment, which is affected by many factors, and any difficulties or delays encountered with such clinical trial or patient enrollment that may delay or otherwise adversely affect such clinical trial; the process of discovering and developing therapies that are safe and effective for use as human therapeutics and operating as a development stage company; expenses may be higher than projected; Design's ability to develop, initiate or complete preclinical studies and clinical trials for its product candidates; the risk that promising early research or clinical trials do not demonstrate safety and/or efficacy in later preclinical studies or clinical trials; changes in Design's plans to develop its product candidates; uncertainties associated with performing clinical trials, regulatory filings and applications; risks associated with reliance on third parties to successfully conduct clinical trials and preclinical studies; Design's ability to raise any additional funding it will need to continue to pursue its business and product development plans; regulatory developments in the United States and foreign countries; Design's reliance on key third parties, including contract manufacturers and contract research organizations; Design's ability to obtain and maintain intellectual property protection for its product candidates; Design's ability to recruit and retain key scientific or management personnel; competition in the industry in which Design operates, which may result in others discovering, developing or commercializing competitive products before or more successfully than Design; and market conditions. For a more detailed discussion of these and other factors, please refer to Design's filings with the Securities and Exchange Commission ("SEC"), including under the "Risk Factors" heading of Design's Quarterly Report on Form 10-Q for the quarter ended September 30, 2024, as filed with the SEC on November 7, 2024. You are cautioned not to place undue reliance on these forward-looking statements, which speak only as of the date hereof. All forward-looking statements are qualified in their entirety by this cautionary statement and Design undertakes no obligation to revise or update this presentation to reflect events or circumstances after the date hereof, except as required by law.

This presentation discusses product candidates that are under clinical or preclinical study, and which have not yet been approved for marketing by the U.S. Food and Drug Administration. No representation is made as to the safety or effectiveness of these product candidates for the use for which such product candidates are being studied.

"Design Therapeutics," "Design," "GeneTAC®," "D," Design's logos, and other trademarks, trade names or service marks of Design Therapeutics, Inc. appearing in this presentation are the property of Design Therapeutics, Inc. All other trademarks, trade names and service marks appearing in this presentation are the property of their respective owners. Solely for convenience, the trademarks and trade names in this presentation may be referred to without the ® and ™ symbols, but such references should not be construed as any indicator that their respective owners will not assert their rights thereto.

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

DESIGN THERAPEUTICS

Advancing four GeneTAC® molecule programs

	Friedreich Ataxia	FECD	Myotonic Dystrophy 1	Huntington's Disease
Gene	FRATAXIN (FXN)	TCF4	DMPK	HUNTINGTIN (HTT)
Monogenic disease	GAA repeat expansion leads to reduced transcription	CTG repeat expansion causes nuclear foci & corneal endothelial cell dysfunction	CTG repeat expansion causes nuclear foci & cellular dysfunction	CAG repeat expansion leads to toxic mRNA and protein product
Differentiated profile	New drug product DT-216P2 with improved PK and injection site safety profiles observed in nonclinical studies	Allele-selective reduction of mutant transcript (TCF4) DT-168 in an eye drop	Allele-selective reduction of mutant DMPK leads to foci resolution and splicing correction	Allele-selective reduction of mutant HTT
Status	Phase 1 SAD to initiate in 1H 2025	Phase 1 ongoing; data in 1H 2025	Select DC in 2025	Next step: Select DC
Significant market	• Biogen acquired Skyclarys® (REATA) for $7.3B	• 4.6-5.3M US patients with TCF4 repeat expansion • Multi-billion $ oppty	• Estimated >70K cases in US • Multi-billion $ oppty	• In US, >40,000 symptomatic and 200,000 at-risk • Multi-billion $ oppty

GeneTAC® Molecules have several advantages over traditional genomic medicine approaches

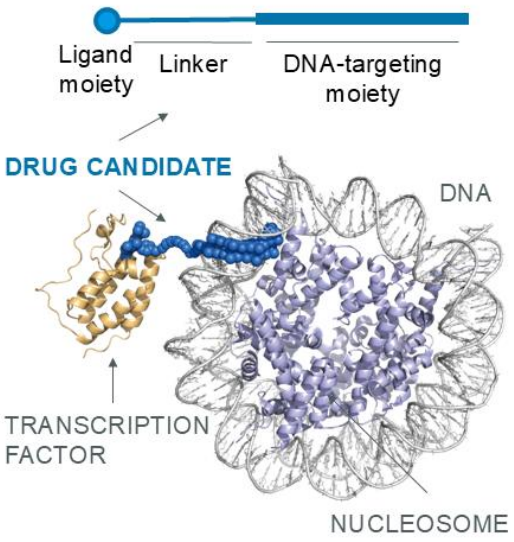
	Simple drug delivery	Working with natural genome	Distribute widely	Low burn rate	Annual R&D spend
Gene editing/ gene therapy	✗	✗	✗	✗	$130-460M[1]
Oligo nucleotide	✗	✓	✗	✗	$50-150M[1]
GeneTAC® platform	✓	✓	✓	✓	$60 - 80M[2]

1. Estimates derived from analysis of R&D spend of select peers in 2022. Gene therapy/gene editing peers included in the analysis: Beam Therapeutics, Crispr Therapeutics, Editas Medicine, Intellia Therapeutics, Sangamo Therapeutics, Verve Therapeutics, Bluebird Bio. Oligonucleotide peers included in the analysis: Avidity Biosciences, Dyne Therapeutics, Entrada Therapeutics, PepGen.
2. Based on analyst consensus forecast for 2024 - 2027

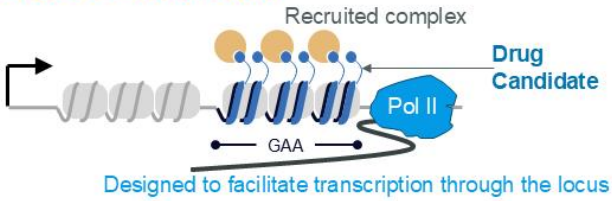
GeneTAC® Molecules can distribute widely overcoming a central challenge for traditional genomic medicines

	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 Successfully targeted cells Native cells	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				

Differentiated mode of action of GeneTAC® molecules

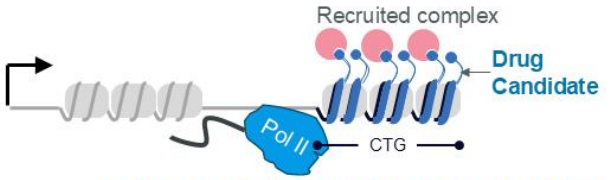


DIAL UP EXPRESSION



Designed to facilitate transcription through the locus

DIAL DOWN EXPRESSION



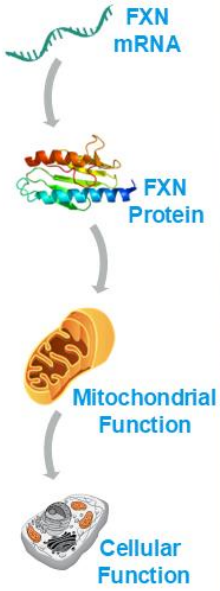
Designed to block transcription at the mutant locus

DT-216P2 for Friedreich Ataxia

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

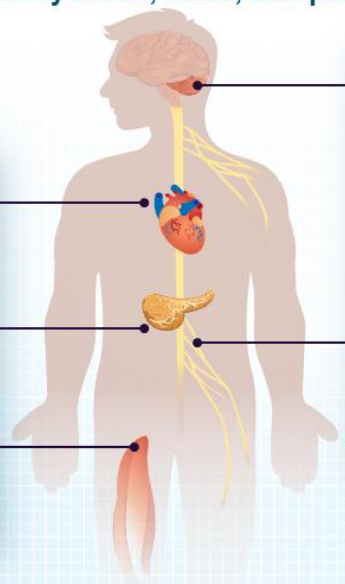


Multi-organ dysfunction: muscle, central and peripheral nervous systems, heart, and pancreas

HEART
cardiomyopathy, arrhythmias

PANCREAS
diabetes

SKELETAL MUSCLE
stiffness, weakness



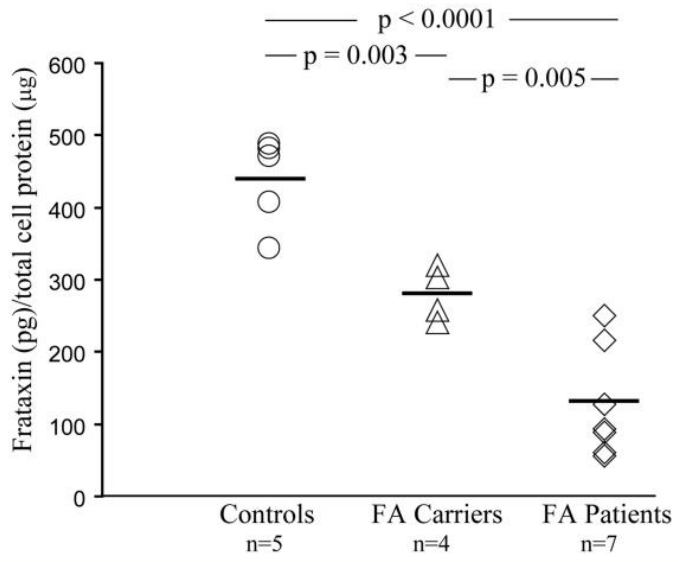
CENTRAL NERVOUS SYSTEM
ataxia, loss of coordination, slurred speech

PERIPHERAL NERVOUS SYSTEM
neuropathy

Therapeutic goal: increase FXN

- FA patients, carriers and controls have different average FXN protein levels
- Carriers are free of FA symptoms
- ~2X increase of FXN protein could potentially bring patients' levels into asymptomatic carrier range

FXN protein level in lymphoblastoid cells

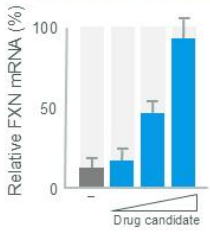


Willis et al. 2008. *Molecular Genetics and Metabolism*

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

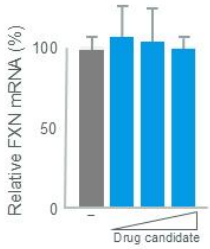
FA PATIENT (two expanded copies)

GeneTAC® molecules normalized levels[1]



HEALTHY INDIVIDUAL (two normal copies)

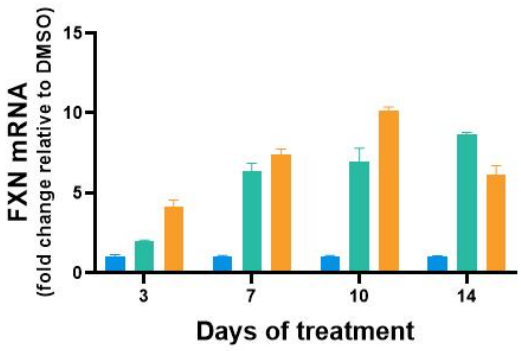
FXN levels unaltered in healthy cells[1]



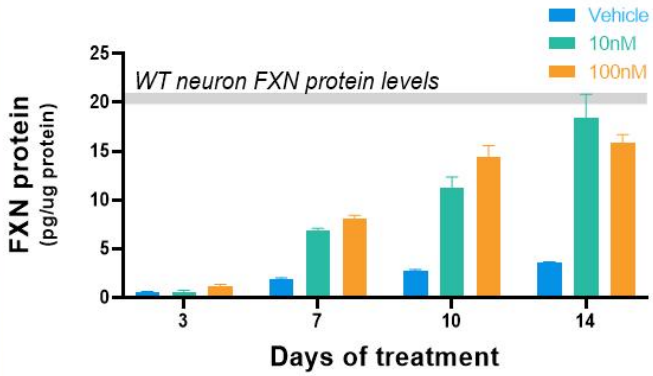
1. Graph x-axis represents increasing levels of cellular exposure to FA GeneTAC® molecules. Bars represent standard error of the mean.

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.

Phase 1 trial with prior DT-216 drug product in FA patients

- **Primary and secondary objectives: evaluate safety, tolerability and pharmacokinetics (PK)**
- **Exploratory objective: evaluate FXN gene expression**

Study Population

- Age 18 to 55
- Genetically confirmed FA
- Stage ≤ 5.5 (Functional Staging of Ataxia*)
- Without clinically significant concomitant medical conditions

Randomization (DT-216 : Placebo)

Single Ascending Dose (SAD)

- 600mg IV x 1
- 400mg IV x 1

Injection site thrombophlebitis observed at 400 and 600mg doses

- 200mg IV x 1
- 100mg IV x 1
- 50mg IV x 1
- 25mg IV x 1
- Placebo IV x 1

Multiple Ascending Dose (MAD)

Selection of MAD doses was based upon anticipated:

- Tissue exposures in therapeutic range at 200-300mg dose levels
- Injection site tolerability

- 300mg IV weekly x 3
- 200mg IV weekly x 3
- 100mg IV weekly x 3

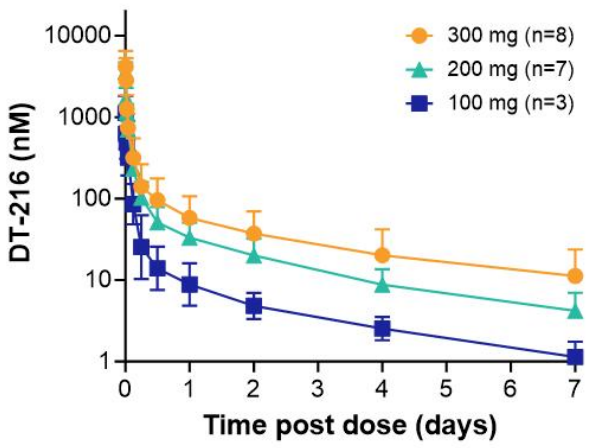
MUSCLE BIOPSIES

- Placebo IV weekly x 3

* FSA; from no disability to severe disability (confined but can navigate a wheelchair; can perform some activities of daily living that do not require standing or walking).

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

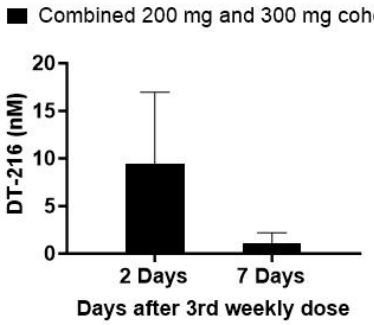
Plasma DT-216 PK after 3rd Dose



Note: Bars represent standard deviation.

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

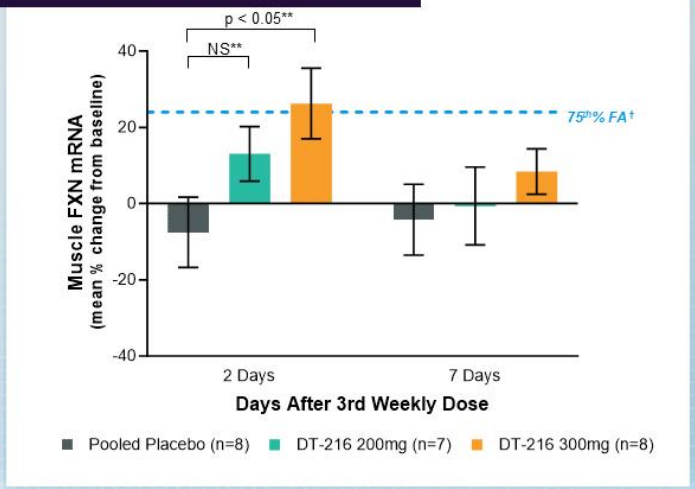


- DT-216 concentrations in muscle were lower than projected based on nonclinical studies in animals

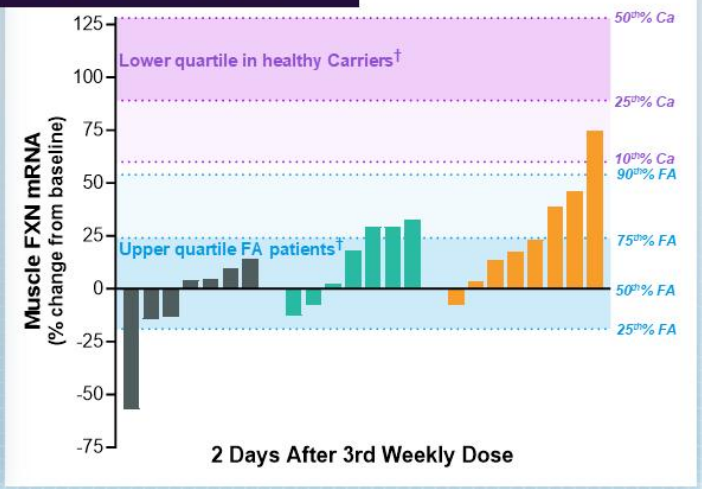
Prior DT-216 drug product Phase 1 MAD study showed FXN expression is dialed up in response to drug exposure in FA Patients

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. 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.

Injection site thrombophlebitis issue appears addressed with new drug product DT-216P2

Prior DT-216 drug product Phase 1 MAD safety

- No serious or severe adverse events (AEs) and no treatment-related discontinuations (1 unrelated study withdrawal due to COVID infection)
- 5 AEs of injection site thrombophlebitis on DT-216 arm – 100mg cohort (1 mild); 200mg cohort (3 mild); 300mg cohort (1 moderate), none in placebo group

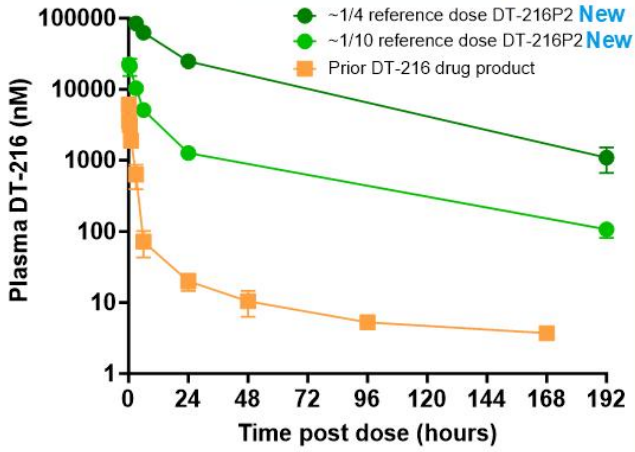
Nonclinical observations with DT-216P2 compared with prior drug product

- Nonclinical studies showed that injection site reactions were attributable to formulation excipients in prior drug product
- DT-216P2 non-GLP animal studies conducted support conclusion that new drug product formulation potentially addresses injection site issues and is suitable for confirmatory GLP studies
- DT-216P2 appears suitable for IV administration (compatible with injections or infusions, peripheral or central with port systems for chronic dosing) or subcutaneous injections or infusions

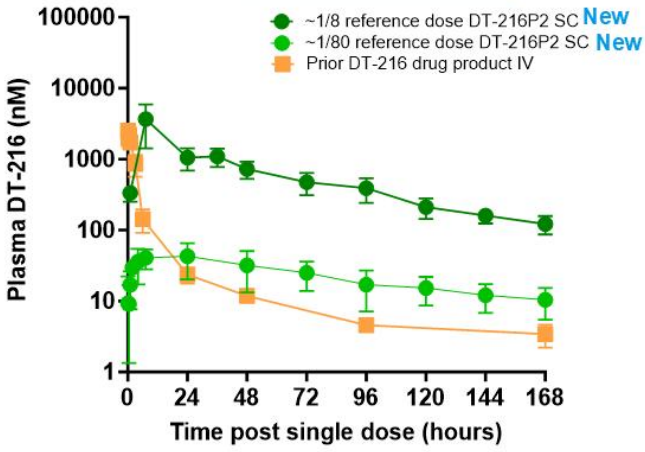
DT-216P2 demonstrates superior product profile in NHPs using a proprietary and novel excipient

NHP

Intravenous



Subcutaneous

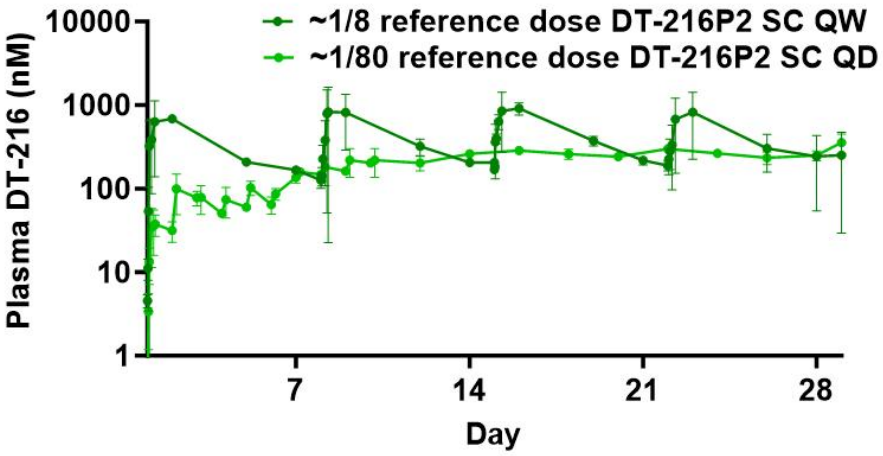


Note: Bars represent standard deviation. Data reflects separate experiments at different times and results were not observed in a head-to-head study. Caution should be advised when comparing different studies.

Daily or weekly administration of DT-216P2 reaches steady state plasma exposure

NHP

Subcutaneous

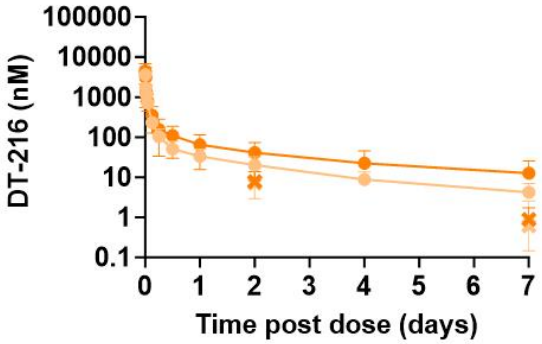


Note: Bars represent standard deviation.

DT-216P2 achieved comparable drug levels in tissue and plasma

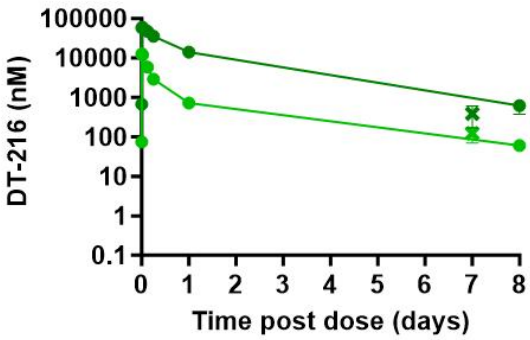
Clinical MAD study
prior DT-216 drug product QW IV

- 300mg cohort plasma PK after 3rd dose
- 300mg cohort muscle biopsy after 3rd dose
- 200mg cohort plasma PK after 3rd dose
- 200mg cohort muscle biopsy after 3rd dose



NHP
DT-216P2 QW IV

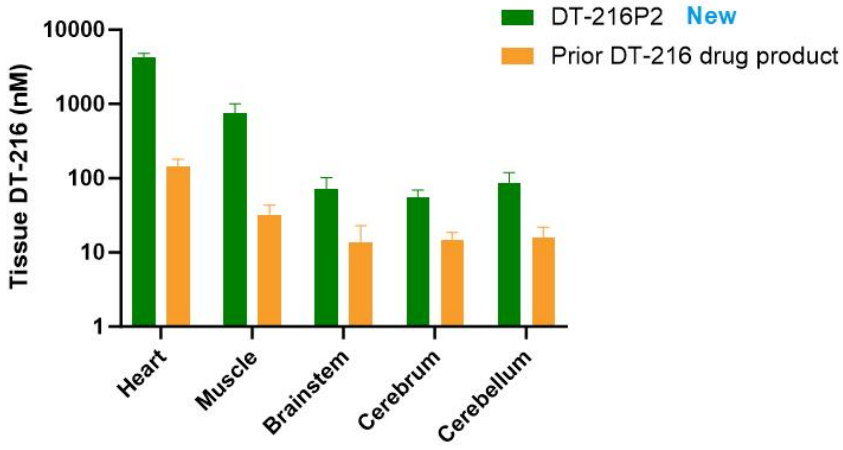
- ~1/4 reference dose plasma PK after 4th dose
- ~1/4 reference dose muscle biopsy after 2nd dose
- ~1/10 reference dose plasma PK after 4th dose
- ~1/10 reference dose muscle biopsy afer 2nd dose



Biodistribution of DT-216P2 IV compared with the prior drug product

Rat

IV



Note: Bars represent standard deviation. Rats received three weekly IV injections of DT-216P2 or prior DT-216 drug product at the same dose level and tissues were collected on day 16 of the study (1 day after the last dose)

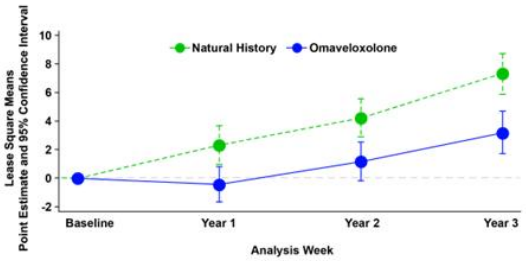
FA program next steps

IND-enabling	Phase 1	Phase 2
• Repeat administration of DT-216P2 in rats and NHPs well-tolerated at doses that achieved higher and more durable exposure than prior DT-216 drug product • GLP animal studies support that DT-216P2 has addressed the injection site reactions seen with prior DT-216 drug product	• Initiate Phase 1 SAD in 1H 2025 to assess PK in healthy volunteers by multiple routes of administration, IV (infusion) and subcutaneous (injection and infusion) - received okay to proceed in Australia • Begin FA patient dosing later in 2025 to understand safety, PK, and pharmacodynamics • Anticipate frataxin data based on 12-weeks of dosing to reach steady state	

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



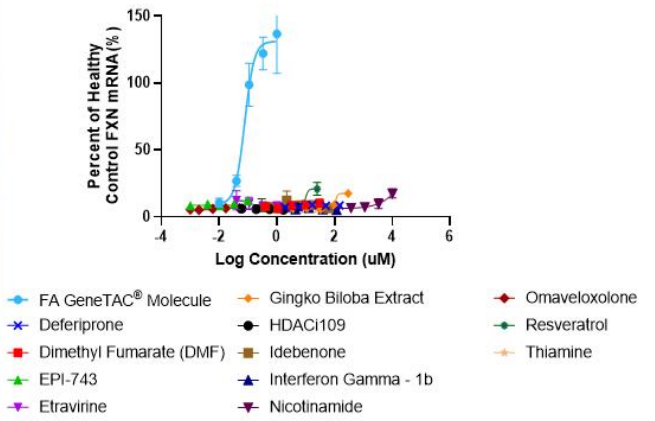
- Other drug candidates in clinical development that aim to address the root cause of FA involve complex modalities
- None of these change endogenous FXN

Larimar Therapeutics — **HIV-TAT-FXN protein**

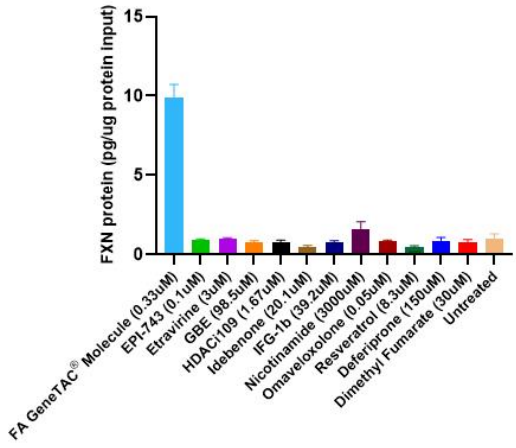
LEXEO therapeutics — **AAV gene therapy targeting cardiac tissue**

Activity of FA GeneTAC® molecules compared with other compounds that have purportedly increased FXN in FA patient LCLs

FXN mRNA (24 hours)



FXN Protein (3 days)



Note: Molecules tested in FA patient lymphoblastoid cells. Bars represent standard deviation. 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.

DT-168 for Fuchs Endothelial Corneal Dystrophy

No disease-modifying options for FECD today, majority of ~5M US patients quietly suffer declining visual function

~5M US FECD patients

18 to 30K
corneal transplant surgeries annually
(0.5% of all FECD)[1]

Increasing Endothelial Dysfunction

- **Diagnosis by optometrist**
- **Loss of visual function**
- **Patient can't stand symptoms**

4.6–5.3M US FECD patients with TCF4 repeat expansion[2]

Surgical Descemet membrane stripping or corneal transplant is limited to 18,000-30,000 by capacity, morbidity and complexity

"If there was something that would halt progression —
I would treat everyone. Even people without symptoms."
- Optometrist

Vision with FECD[1]

Reduced Vision Quality

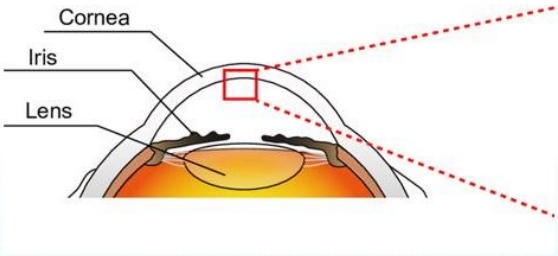
- ↓ vision acuity, esp. low contrast
- Blurriness in the morning
- Glare and halo
- ↓ contrast sensitivity

Discomfort and Pain

- "Grittiness" in the eye
- Floaters
- Episodes of pain

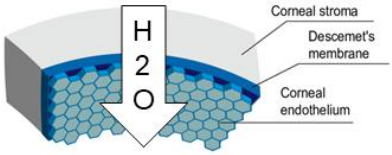
Source: (1) Vianna et al. JAMA Ophthamol (2015), (2) 165.2M people in the US (>40 yrs of age) x 4% FECD prevalence per Lliffe (2012) and Aiello (2022) x 70-80% TCF4 mutations in US per Wieben (2012), Wieben (2014), Vasanth (2015), Eghari (2017), Kinariwali (2021), Xu (2021)

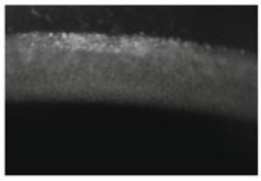
Treatment goal: Restore endothelial function and visual function



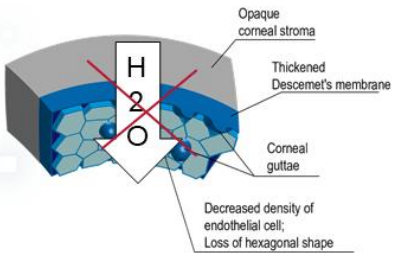
- **Corneal endothelial cells** (CECs) pump water out of the stroma to ensure proper dehydration of collagen fibrils for corneal transparency
- **CEC loss or dysfunction leads to excess hydration of** corneal stroma, resulting in loss of corneal transparency, and visual dysfunction
- As CECs are lost, ECM masses called guttae also form in the basement membrane with **concurrent reduction in cell density, cell shape**, and/or bullae and ultimately fibrosis

Healthy individuals

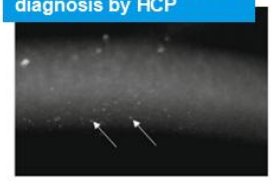




Patients with FECD

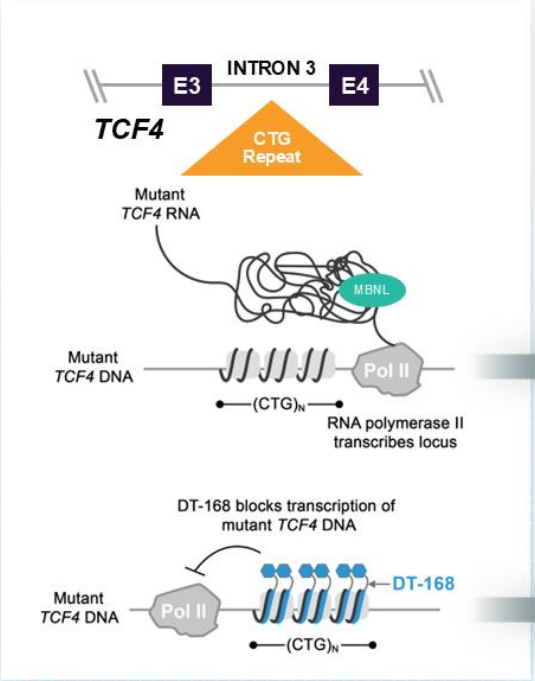


Slit-lamp biomicroscopy diagnosis by HCP



Arrows indicate guttae

FECD GeneTAC® Molecules are designed to suppress transcription of *TCF4* DNA that contains expanded CTG repeats



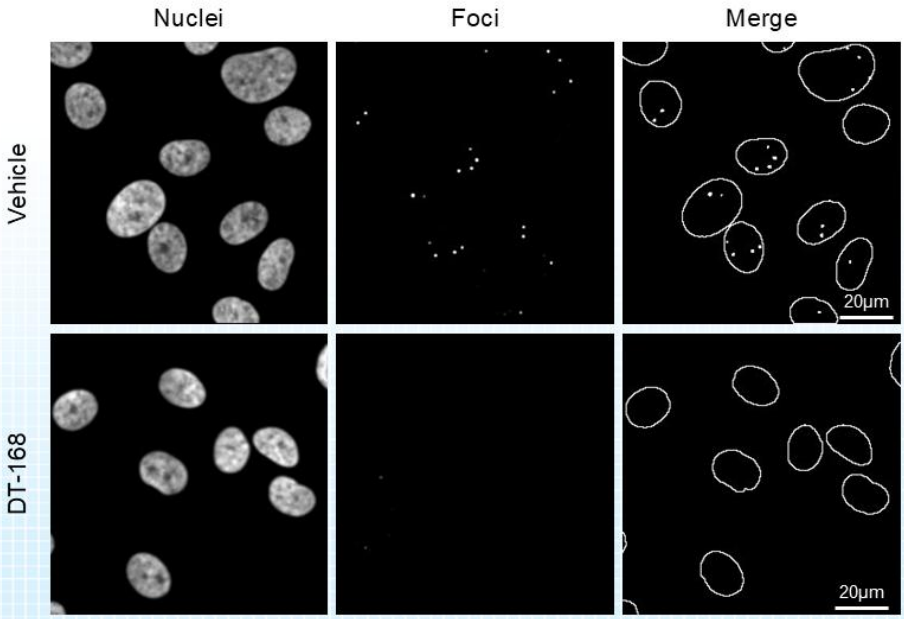
Mutant *TCF4* RNA induces FECD molecular pathology:

Hairpin formation
↓
Nuclear foci
↓
MBNL sequestration
↓
Spliceopathy
↓
CEC dysfunction and loss

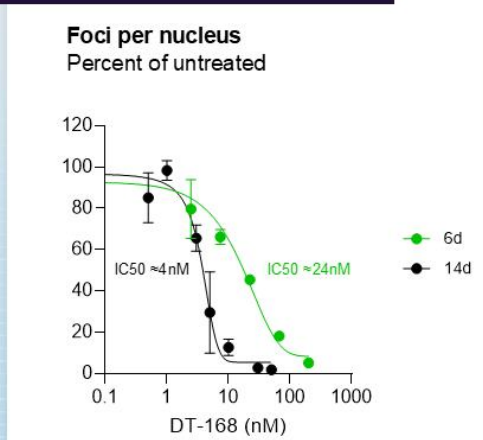
DT-168 designed to suppress initiation of FECD molecular pathology thereby **restoring CEC function and preventing further CEC loss**

Source: Adapted from Fautsch et al. Progress in Retinal and Eye Research (2021)

DT-168 reduces nuclear foci in primary CECs isolated from patients with FECD with high potency (<5nM foci IC_{50})



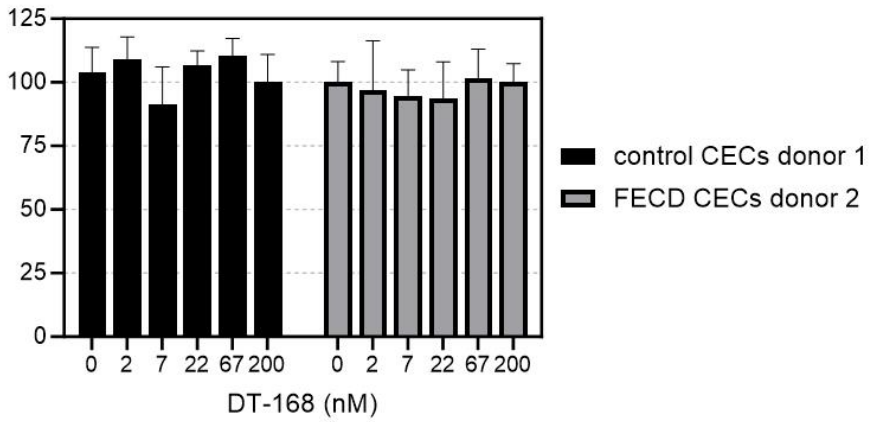
CECs treated daily for 6 or 14 days with DT-168



Note: Bars represent standard deviation.

Wild-type TCF4 transcripts are unaffected in primary control and FECD CECs following treatment with DT-168

TCF4 mRNA
RT-qPCR; normalized to RPLP0

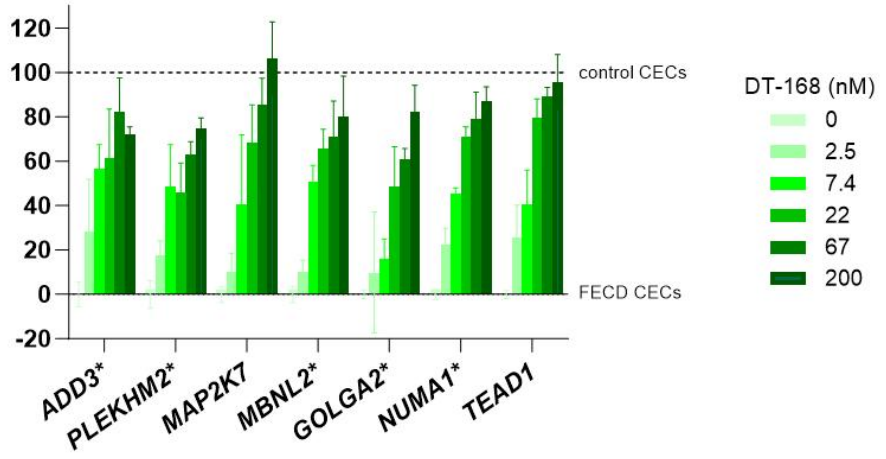


Notes: Control CECs from donor 1 and patient-derived FECD CECs from donor 2 were incubated with DT-168 for 6 d, after which mRNA was purified and used to quantify wild-type *TCF4* transcripts using a primer-probe set targeting exons 18/19. Data represent averages of N=3 replicates, and error bars represent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

DT-168 improves spliceopathy in primary FECD CECs

Top 7 improved genes for FECD CECs derived from donor 2

Patient-derived FECD CECs + DT-168
6d treatment



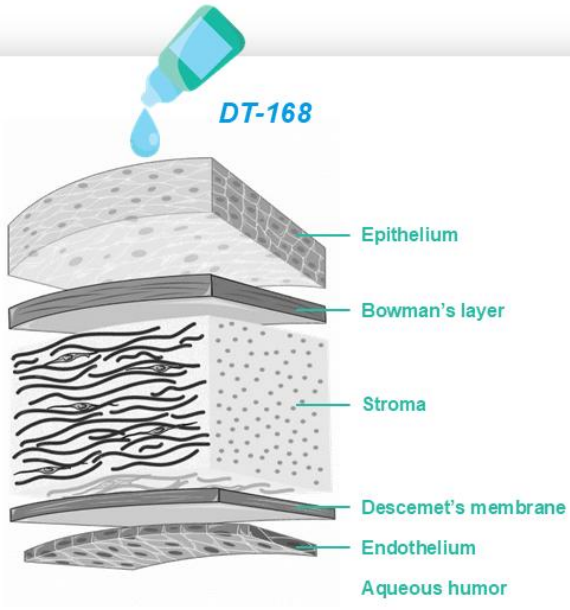
*Previously reported as mis-spliced in primary FECD CECs (Fautsch et al., 2021) Bars represent standard deviation.

DT-168 eye-drops were well-tolerated and readily distributed to CECs

Key observations from nonclinical studies

- Well-tolerated after single and multiple doses per day for 14 days with clean histology
- DT-168 distributed throughout cornea after topical delivery, measurable levels of drug in aqueous humor
- Micromolar DT-168 levels present in cornea at 24 hours post-dose
- Negligible systemic exposure following dosing
- Chronic tox ongoing

Phase 1 MAD trial evaluating 7 days BID dosing in healthy volunteers; data expected in 1H 2025



FECD Observational Study aims to increase probability of DT-168 programmatic success

OBSERVATIONAL STUDY

- Targeting recruitment of 200 patients (~400 eyes) with genetically confirmed TCF4 mutations 2-year follow-up
- Confirm disease characteristics and deterioration in context of running a trial
- Identify characteristics for FECD patients at risk of more rapid disease progression

EVALUATE ENDPOINTS

- Anterior eye tomography
- Corneal endothelium microscopy
- Visual acuity (low luminance, contrast sensitivity, glare disability)
- Visual disability
- Patient reported outcome

REVIEW PROGRESSION

- Measure disease progression in patients with at least 1 tomographic feature of subclinical edema[1]
- Evaluate patient characteristics and obtain satisfactory markers of disease progression and measurable endpoints
- Observational study could expedite recruitment in interventional trials

1) Patel et al. Ophthalmology. 2020

Myotonic Dystrophy Type 1 (DM1)

Myotonic dystrophy type 1 (DM1)

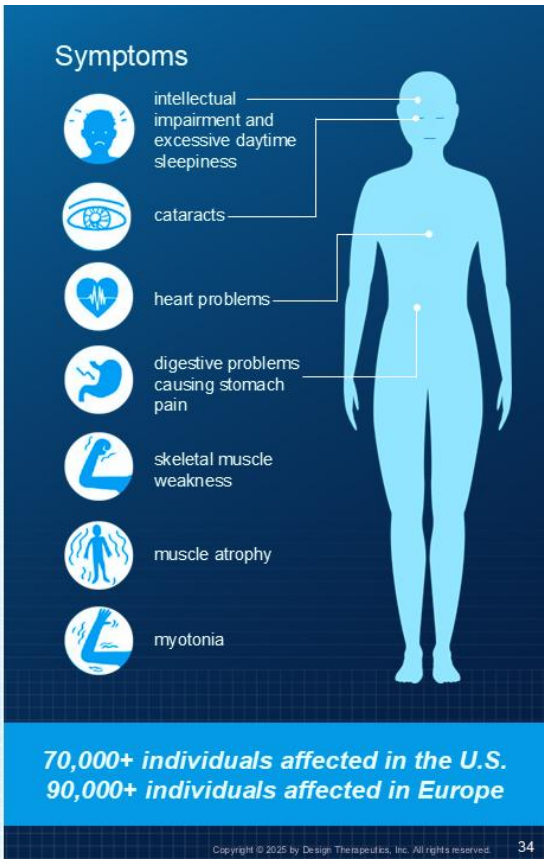
Dominant repeat expansion drive disease

DM1 patients have expanded CTG repeat in the 3' UTR of one copy of their DMPK gene.

Normal

Diseased (one copy)

Expanded CTG repeats in the DMPK mRNA trap MBNL1 splicing factors in CUG foci. Reduced MBNL1 activity leads to improperly spliced genes and cellular dysfunction

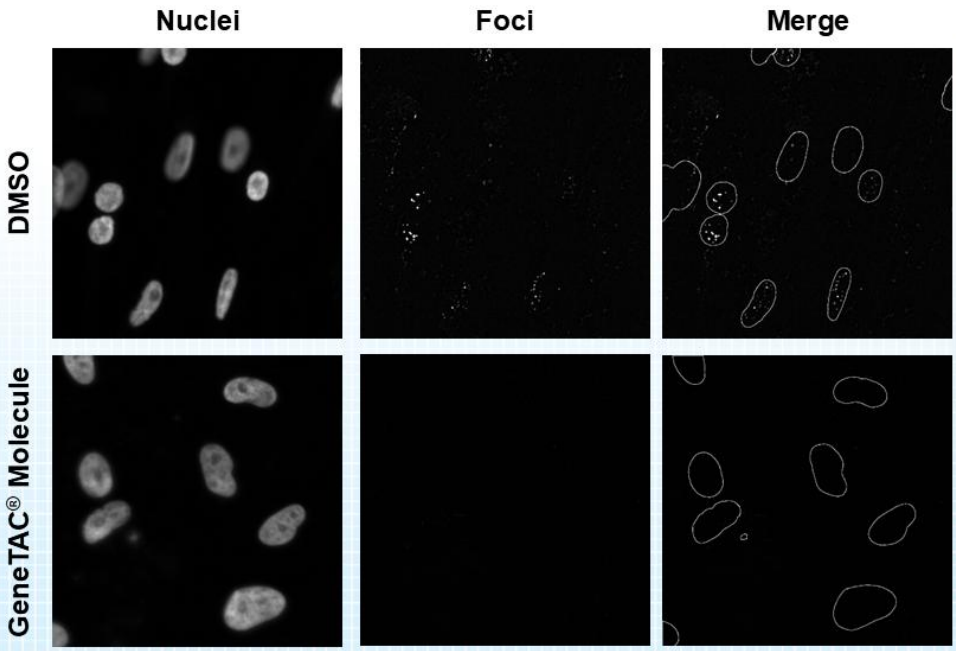


70,000+ individuals affected in the U.S.
90,000+ individuals affected in Europe

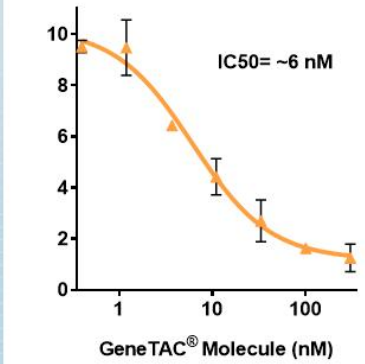
GeneTAC® molecules for DM1 have several advantages

	GeneTAC® DM1 candidates	AVIDITY BIOSCIENCES AOC 1001	Dyne DYNE-101
Allele selectivity	Allele-selective	Non-selective	Non-selective
Modality	Small molecule	siRNA conjugated to TfR1 targeting mAb	ASO conjugated to TfR1 targeting Fab
Target tissue	Distributes widely to impacted tissues	Muscle	Muscle
In vitro efficacy for foci reduction	~90% foci reduction	"Quantifiable reduction" in nuclear foci	"Approximately 40% reduction in nuclear foci"

GeneTAC® Molecule causes potent foci reduction in DM1 patient-derived cells



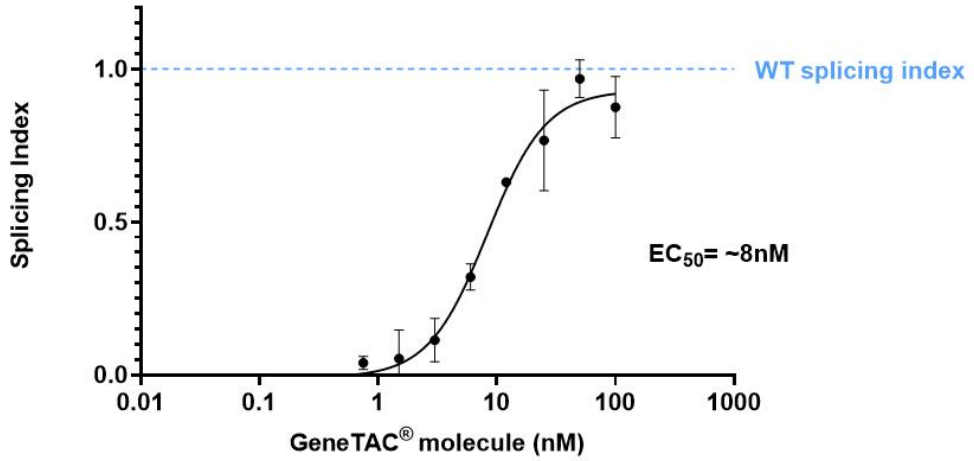
DM1-patient derived cells treated with DM1 GeneTAC® Molecule



Note: Bars represent standard deviation.

GeneTAC® Molecule leads to robust correction of mis-spliced transcripts in patient-derived cells

DM1 patient-derived cells
7d treatment with DM1 GeneTAC® Molecule



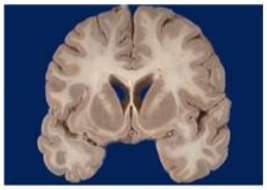
Note: Bars represent standard deviation.

Huntington's Disease (HD)

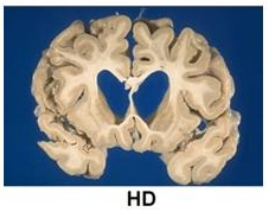
Huntington's Disease (HD)

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



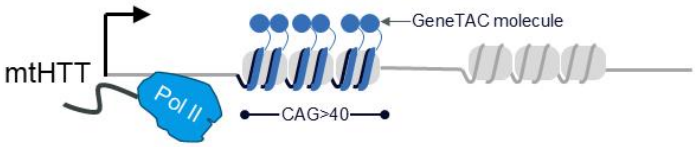
HD

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

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

HTT gene with expansion

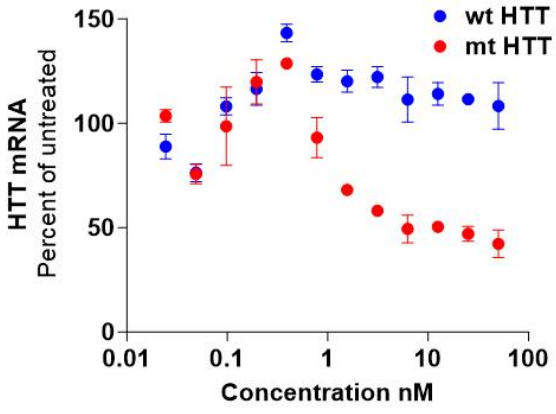
GeneTAC® molecules ***block transcription*** specifically at the ***mutant locus***



GeneTAC® Molecule treatment causes potent, allele-selective reduction of mtHTT mRNA in HD patient fibroblasts

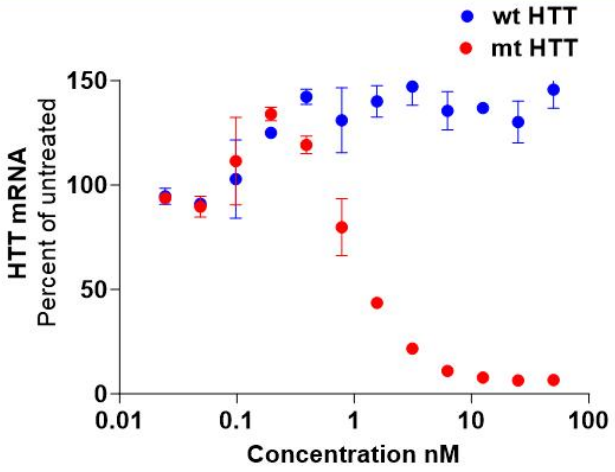
Candidate 1

Normal onset HD patient-derived fibroblasts CAG 18/44



mtHTT IC_{50} 1.3 nM

Early onset HD patient-derived fibroblasts CAG 18/180



mtHTT IC_{50} 1.3nM

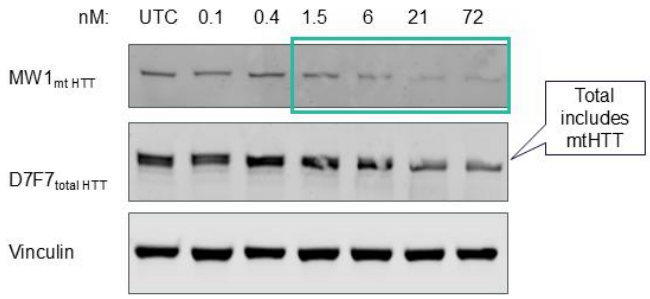
Note: Cells were treated for 4 days. Bars represent standard deviation.

GeneTAC® Molecule treatment causes potent, allele-selective reduction of mtHTT protein in HD patient fibroblasts

Candidate 1

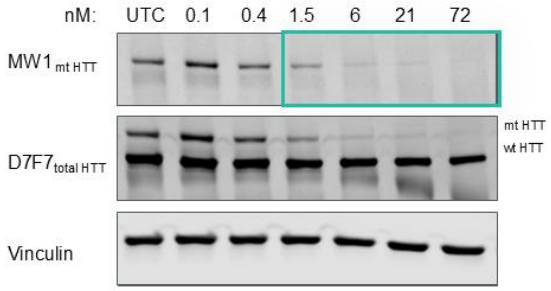
Normal onset HD patient-derived fibroblasts CAG 18/44

Western blot



Early onset HD patient-derived fibroblasts CAG 18/180

Western blot

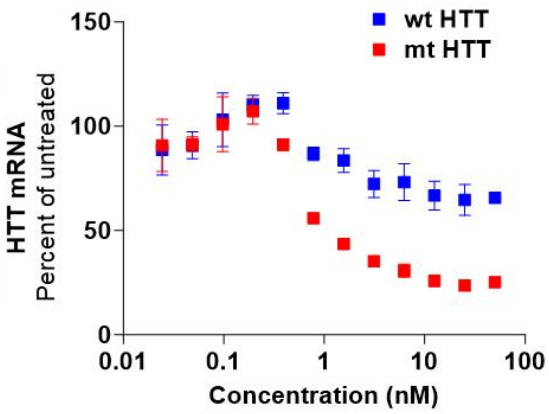


Note: Cells were treated for 7 days

GeneTAC® Molecule treatment causes potent, allele-selective reduction of mtHTT mRNA in HD patient-derived fibroblasts

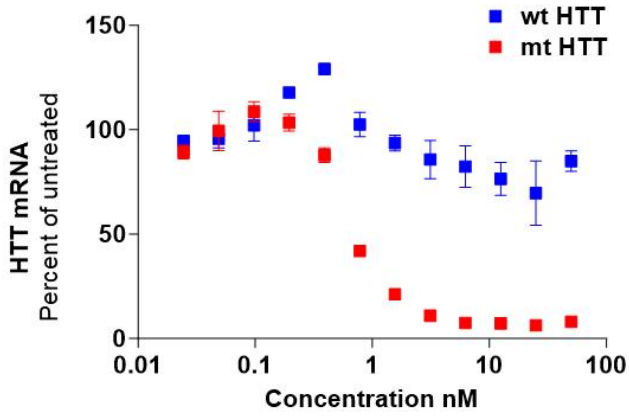
Candidate 2

Normal onset HD patient-derived fibroblasts CAG 18/44



mtHTT IC_{50} 0.8 nM

Early onset HD patient-derived fibroblasts CAG 18/180



mtHTT IC_{50} 0.7nM

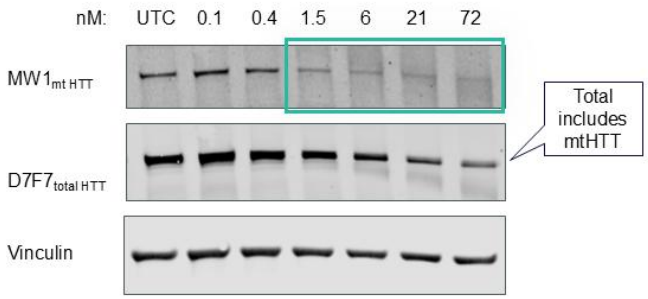
Note: Cells were treated for 4 days. Bars represent standard deviation.

GeneTAC® Molecule treatment causes potent, allele-selective reduction of mtHTT protein in HD patient-derived fibroblasts

Candidate 2

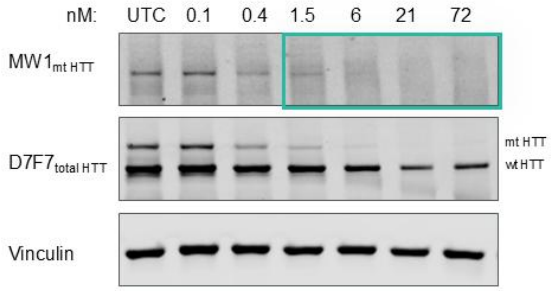
Normal onset HD patient-derived fibroblasts CAG 18/44

Western blot



Early onset HD patient-derived fibroblasts CAG 18/180

Western blot



Note: Cells were treated for 7 days

Candidates well-tolerated in both rodents and NHPs

Rodents

Tested in wild-type rats and mice:

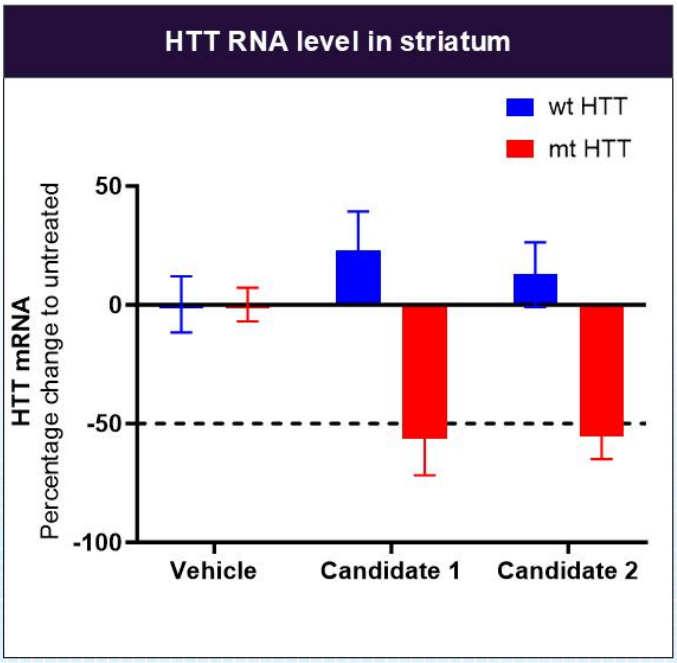
- Well-tolerated in ongoing studies:
  - Weekly doses for three weeks in rats
  - Daily doses for one week in mice
- Tolerability assessed across all macroscopic measures including weight, blood chemistry and liver function tests

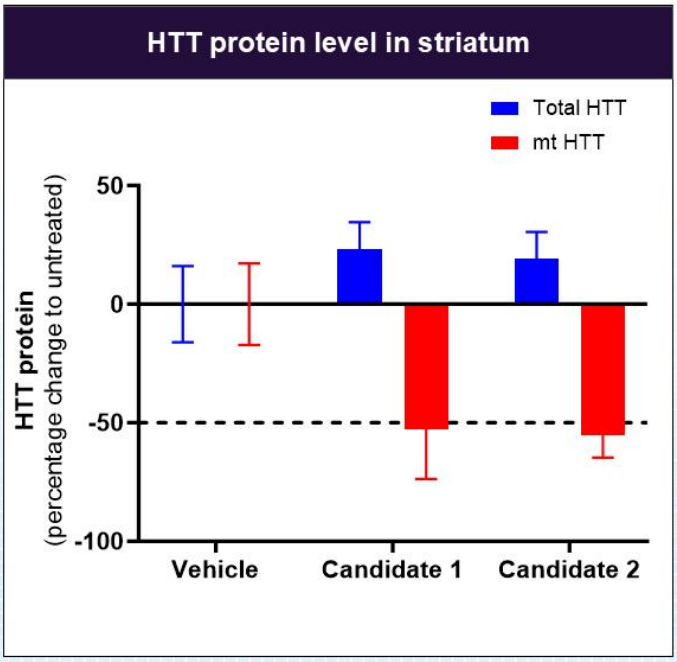
NHP

Tested in wild-type non-naïve NHPs

- Well-tolerated in ongoing studies
- Tolerability assessed across all macroscopic measures including weight, blood chemistry and liver function tests

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





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	**WAVE 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**	
Latest milestone	• **Selective reduction of mtHTT in patient cells (IC50=~1nM)** • **Well tolerated in rodents and NHPs**	**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

- Two clinical-stage programs in 2025 – FA and FECD
- Active research pipeline led by DM1 and HD GeneTAC® programs

PLAN

Balance sheet as of *September 30, 2024*

$254.1 MILLION

Current cash to fund planned operations

INTO 2029

Cash runway enables up to

4 PROGRAMS TO CLINICAL POC*

*Subject to future R&D results and ongoing strategic review