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): November 5, 2019

WAVE LIFE SCIENCES LTD.
(Exact name of registrant as specified in its charter)

Singapore	**001-37627**	**00-0000000**
(State or other jurisdiction of incorporation)	**(Commission File Number)**	**(IRS Employer Identification No.)**

7 Straits View #12-00, Marina One East Tower Singapore	**018936**
(Address of principal executive offices)	**(Zip Code)**

Registrant's telephone number, including area code: +65 6236 3388

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 (see General Instruction A.2. below):

☐ 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	Name of each exchange on which registered
$0 Par Value Ordinary Shares	**WVE**	**The Nasdaq Global 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 2.02 Results of Operations and Financial Condition.

On November 5, 2019, Wave Life Sciences Ltd. (the "Company") announced its financial results for the quarter ended September 30, 2019. The full text of the press release issued in connection with the announcement is furnished as Exhibit 99.1 to this Current Report on Form 8-K and is incorporated by reference herein.

Item 7.01 Regulation FD Disclosure.

From time to time, the Company presents and/or distributes slides and presentations to the investment community to provide updates and summaries of its business. On November 5, 2019, the Company updated its corporate presentation, which is available on the "For Investors & Media" section of the Company's website at http://ir.wavelifesciences.com/. This presentation is also furnished as Exhibit 99.2 to this Current Report on Form 8-K.

The information in these Items 2.02 and 7.01 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 in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Item 9.01 Financial Statements and Exhibits.

(d) Exhibits

The following exhibits relating to Items 2.02 and 7.01 are furnished and not filed:

Exhibit No.	Description
99.1	Press Release issued by Wave Life Sciences Ltd. dated November 5, 2019
99.2	Corporate Presentation of Wave Life Sciences Ltd. dated November 5, 2019
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 hereunto duly authorized.

WAVE LIFE SCIENCES LTD.

By: */s/ Paul B. Bolno, M.D.*
Paul B. Bolno, M.D.
President and Chief Executive Officer

Date: November 5, 2019

Wave Life Sciences Reports Third Quarter 2019 Financial Results and Provides Business Update

Fast Track designation for suvodirsen received from the U.S. FDA

Interim analysis of dystrophin expression from suvodirsen open-label extension study expected in 4Q 2019

Topline data from PRECISION-HD2 clinical trial expected by year-end

Key hires and board expansion mark continued progress towards commercial preparedness in the U.S.

CAMBRIDGE, Mass., November 5, 2019 – Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases, today announced financial results for the third quarter ended September 30, 2019 and provided a business update.

"We continued our strong execution in the third quarter and, as a result, we are on track to deliver key clinical data readouts in the fourth quarter from our open-label extension study of suvodirsen in Duchenne muscular dystrophy and from PRECISION-HD2, the first of our two Phase 1b/2a trials in Huntington's disease," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "In anticipation of our potential launch of suvodirsen in the United States and future late-stage programs, we hired a Chief Commercial Officer with proven experience in neurology and rare disease and named three new Board members with deep expertise in clinical development, product commercialization and government and payor relations."

"As we prepare for our near-term milestones, we continue to advance our platform, PRISM, with new preclinical programs such as our SNP3 program in Huntington's disease and our lead ophthalmology program for Usher Syndrome Type 2A," continued Dr. Bolno. "In addition, we're very excited about the latest modality to emerge from PRISM, ADAR-mediated RNA editing, which we presented during our Analyst and Investor Research Day in early October."

Business Update

Wave is committed to building a fully integrated genetic medicines company led by its clinical and preclinical programs for the treatment of neuromuscular, central nervous system and ophthalmologic diseases.

Neuromuscular diseases

Suvodirsen in patients with Duchenne muscular dystrophy amenable to exon 51 skipping

- Suvodirsen, an investigational compound, is currently being studied in an open-label extension (OLE) study and a Phase 2/3 study (as described below) in patients with Duchenne muscular dystrophy (DMD) with mutations amenable to exon 51 skipping. Wave is on track to deliver an interim analysis of dystrophin expression from muscle biopsies in boys receiving suvodirsen, which is expected in the fourth quarter of 2019. This interim analysis will include dystrophin expression from muscle biopsies taken 22 weeks after patients enrolled in the

OLE were transitioned to one of the Phase 2/3 doses of suvodirsen, as well as a safety summary. Pending positive clinical dystrophin expression data, the company expects to file for an accelerated approval of suvodirsen in the United States in the second half of 2020.

- In September 2019, Wave announced that the U.S. Food and Drug Administration (FDA) has granted Fast Track designation to suvodirsen for the treatment of DMD patients with mutations amenable to exon 51 skipping. Fast Track designation is granted for product candidates that are intended for the treatment of serious or life-threatening disease or conditions, which demonstrate the potential to address an unmet medical need. The designation offers the opportunity for frequent interactions with the FDA to discuss the drug's development plan and ensure collection of appropriate data needed to support drug approval, as well as eligibility for rolling submission of a New Drug Application (NDA).
- Suvodirsen is also currently being studied in DYSTANCE 51, a global Phase 2/3, multicenter, randomized, double-blind, placebo-controlled clinical trial that will evaluate the efficacy and safety of suvodirsen in DMD patients with mutations amenable to exon 51 skipping. Patient enrollment in the DYSTANCE 51 trial began in the third quarter and the trial is expected to enroll approximately 150 boys who are between 5 and 12 years of age (inclusive) with a genetically confirmed diagnosis of DMD amenable to exon 51 skipping therapy. The DYSTANCE 51 primary efficacy endpoints will measure change in dystrophin protein level and change in the North Star Ambulatory Assessment score. In addition, the trial will include multiple functional outcome measures as secondary efficacy endpoints.
- DYSTANCE 51 is the first study ever selected by the FDA for its Complex Innovative Trial Design (CID) pilot program, through which Wave will use Bayesian methods to adapt the trial with the aim of maximizing efficiency while ensuring robust clinical results. Results from the DYSTANCE 51 trial are intended to support global regulatory filings for suvodirsen.

Additional exon skipping programs for patients with Duchenne muscular dystrophy

- Wave continues to advance WVE-N531, its preclinical candidate to treat DMD in boys amenable to exon 53 skipping. WVE-N531 induced up to 71% dystrophin protein restoration in DMD *in vitro* patient-derived myoblasts compared with healthy human myoblasts as measured by western blot. Subject to submission of clinical trial applications and approval to proceed, Wave expects to deliver topline clinical data for WVE-N531 in the second half of 2020.
- The company is also exploring exon targets beyond those targeted by suvodirsen and WVE-N531, including exons 44, 45, 52, 54 and 55, with the goal of delivering significant and meaningful levels of dystrophin.

Central nervous system (CNS) diseases

PRECISION-HD clinical program evaluating WVE-120101 and WVE-120102 in Huntington's disease

- Wave's PRECISION-HD program consists of two global, multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials, PRECISION-HD1 and PRECISION-HD2, for patients with Huntington's disease (HD).
- Topline clinical data from the four multi-dose cohorts of the PRECISION-HD2 trial are expected by the end of 2019. In October 2019, Wave initiated an open-label extension (OLE) study open to patients outside of the U.S. who participated in the Phase 1b/2a PRECISION-HD2 trial and patient dosing in the OLE is currently underway.

- Topline data from the four multi-dose cohorts of the PRECISION-HD1 trial are expected in early 2020. An OLE study open to patients outside the U.S. who participated in the Phase 1b/2a PRECISION-HD1 trial is expected to be initiated in 2020.
- PRECISION-HD1 and PRECISION-HD2 are evaluating investigational WVE-120101 and WVE-120102, respectively, which are stereopure oligonucleotides designed to selectively target the mutant huntingtin (mHTT) mRNA transcript of SNP rs362307 (SNP1) and SNP rs362331 (SNP2), respectively. Approximately 50% of the HD population carries SNP1 or SNP2 and, with overlap, up to 70% of the HD population carries either SNP1, SNP2 or both.

Allele-selective approach to treating Huntington's disease

- Wave's HD pipeline includes clinical programs WVE-120101 and WVE-120102 and a third program, which is a preclinical-stage stereopure oligonucleotide designed to target an undisclosed SNP (SNP3). All of these compounds are designed to selectively target the mutant allele of the *huntingtin* (*HTT*) gene, while leaving the wild-type (wtHTT) relatively intact.
- The healthy or wild-type *HTT* transcript is required to produce healthy HTT protein which is important for neuronal function. At Wave's recent Analyst and Investor Research Day, key opinion leaders in HD research presented data suggesting that
  - wtHTT is neuroprotective in an adult brain;
  - transport of key neurotrophic factors such as brain-derived neurotrophic factor (BDNF) are regulated by wtHTT levels; and
  - HD may be caused by a dominant gain of function in mutant HTT *and* a loss of function of wtHTT protein.
- Wave's allele-selective approach may also enable the company to address the pre-manifest, or asymptomatic, HD patient population in the future.
- Also at Wave's recent Analyst and Investor Research Day, the company shared new preclinical data for its SNP3 program. SNP3 represents ~40% of the HD population and, with overlap, up to 80% of the HD population carries at least one of SNP1, SNP2, and/or SNP3. In patient-derived neurons, Wave's allele-selective SNP3 compounds demonstrated more potent knockdown of mutant *HTT in vitro* than a pan-silencing analog of an oligonucleotide currently in clinical development. In addition, Wave's SNP3 compounds demonstrated potent and durable knockdown of mutant *HTT in vivo* for up to 12 weeks.

CNS disease pipeline

- Wave is advancing its C9orf72 preclinical program to potentially treat amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) and expects to initiate clinical development in the second half of 2020, pending the submission of clinical trial applications and approval to proceed. Wave's C9orf72 program preferentially targets the transcript containing the GGGGCC (G4C2) expansion in the *C9orf72* gene.
- The company is leveraging its learnings from PRISM™ to design additional stereopure oligonucleotides with optimized profiles across other CNS diseases as part of its ongoing collaboration with Takeda.

Ophthalmologic diseases

- Wave recently announced that its lead ophthalmology program will use stereopure oligonucleotides to promote *USH2A* exon 13 skipping to address Usher Syndrome Type 2A and presented a poster at the 15th Annual Meeting

of the Oligonucleotide Therapeutics Society (OTS) titled “Stereopure Oligonucleotides that Promote USH2A Exon Skipping for the Treatment of Usher Syndrome Type 2A” on October 14, 2019. In the poster presentation, a stereopure oligonucleotide induced dose-dependent *USH2A* exon skipping that demonstrated enhanced potency over a stereorandom reference compound in Y79 cells and induced dose-dependent *USH2A* exon skipping in the nonhuman primate (NHP) retina and human retina *ex vivo*.

PRISM: next generation modalities

- At its Analyst and Investor Research Day in October 2019, Wave announced that it is leveraging its proprietary PRISM platform to design novel RNA-editing therapeutics. Wave’s technology uses endogenous ADAR (adenosine deaminases acting on RNA) enzymes via non-viral, free uptake of RNA editing oligonucleotides in a variety of primary human cell types *in vitro* with high efficiencies and has potential to be a best-in-class RNA editing modality. Wave observed editing efficiencies of up to 70% in primary hepatocytes and approximately 50% in bronchial epithelial cells without the need for viral or lipid nanoparticle (LNP) delivery vehicles. Wave expects to share *in vivo* RNA editing data generated from ADAR in 2020.

Corporate

- In the third quarter, Wave made several key hires and appointments in anticipation of the company’s potential first commercial launch. This expansion includes Mark Baldry, who was appointed Chief Commercial Officer and is responsible for building Wave’s global commercial strategy and organization, including its sales, marketing and market access and reimbursement teams, as well as launch planning for suvodirsen. Several key hires were also made within the Medical Affairs organization, including the Vice President of Medical Affairs, as well as the global head of Wave’s Medical Science Liaison organization.
- In September 2019, Wave appointed three new directors, Amy Pott, Heidi L. Wagner, JD, and Mark H. N. Corrigan, MD, to its Board of Directors. These new appointments deepen the Board’s expertise in clinical development, product commercialization, and government and payor relations as the company advances its clinical and preclinical pipeline and further develops PRISM.

Third Quarter 2019 Financial Results and Financial Guidance

Wave reported a net loss of $50.7 million in the third quarter of 2019 as compared to $37.6 million in the same period in 2018. The increase in net loss in the third quarter of 2019 was largely driven by increased research and development efforts and continued organizational growth to support Wave’s corporate goals.

Research and development expenses were $44.6 million in the third quarter of 2019 as compared to $32.9 million in the same period in 2018. The increase in research and development expenses in the third quarter of 2019 was primarily due to increased external expenses related to our suvodirsen clinical activities as well as increased investments in PRISM and other research and development expenses.

General and administrative expenses were $12.5 million in the third quarter of 2019 as compared to $9.8 million in the same period in 2018. The increase in general and administrative expenses in the third quarter of 2019 was mainly driven by continued organizational growth to support Wave’s corporate goals.

As of September 30, 2019, Wave had $209.0 million in cash and cash equivalents as compared to $174.8 million as of December 31, 2018. The increase in cash and cash equivalents was mainly due to the $161.8 million in net proceeds from the January 2019 follow-on offering, partially offset by Wave’s year-to-date net loss of $136.9 million. Wave expects that its existing cash and cash equivalents, together with expected and committed cash from existing collaborations, will enable Wave to fund its operating and capital expenditure requirements to the end of 2020.

About PRISM™

PRISM is Wave Life Sciences' proprietary discovery and drug development platform that enables genetically defined diseases to be targeted with stereopure oligonucleotides across multiple therapeutic modalities. PRISM combines the company's unique ability to construct stereopure oligonucleotides with a deep understanding of how the interplay among oligonucleotide sequence, chemistry and backbone stereochemistry impacts key pharmacological properties. By exploring these interactions through iterative analysis of in vitro and in vivo outcomes and artificial intelligence-driven predictive modeling, the company continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles.

About Wave Life Sciences

Wave Life Sciences (NASDAQ: WVE) is a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases. Wave aspires to develop best-in-class medicines across multiple therapeutic modalities using PRISM, the company's proprietary discovery and drug development platform that enables the precise design, optimization and production of stereopure oligonucleotides. Driven by a resolute sense of urgency, the Wave team is targeting a broad range of genetically defined diseases so that patients and families may realize a brighter future. To find out more, please visit www.wavelifesciences.com and follow Wave on Twitter @WaveLifeSci.

Forward-Looking Statements

This press release contains forward-looking statements concerning our goals, beliefs, expectations, strategies, objectives and plans, and other statements that are not necessarily based on historical facts, including statements regarding the following, among others: the anticipated commencement, patient enrollment, data readouts and completion of our clinical trials, and the announcement of such events; the potential commercial launch of our product candidates; the protocol, design and endpoints of our ongoing and planned clinical trials; the future performance and results of our programs in clinical trials; future preclinical activities and programs; regulatory submissions; the progress and potential benefits of our collaborations with partners; the potential of our in vitro and in vivo preclinical data to predict the behavior of our compounds in humans; our identification of future candidates and their therapeutic potential; the anticipated therapeutic benefits of our potential therapies compared to others; our ability to design compounds using multiple modalities and the anticipated benefits of that model; the anticipated benefits of our proprietary manufacturing processes and our internal manufacturing facility; our future growth and anticipated transition to a fully integrated commercial-stage company; the potential benefits of PRISM and our stereopure oligonucleotides compared with stereorandom oligonucleotides; the benefit of nucleic acid therapeutics generally; the strength of our intellectual property; and the anticipated duration of our cash runway. Actual results may differ materially from those indicated by these forward-looking statements as a result of various important factors, including the following: our ability to finance our drug discovery and development efforts and to raise additional capital when needed; the ability of our preclinical programs to produce data sufficient to support our clinical trial applications and the timing thereof; our ability to continue to build and maintain the company infrastructure and personnel needed to achieve our goals; the clinical results of our programs, which may not support further development of product candidates; actions of regulatory agencies, which may affect the initiation, timing and progress of clinical trials; our effectiveness in managing future clinical trials and regulatory processes; the effectiveness of PRISM; the continued development and acceptance of oligonucleotides as a class of medicines; our ability to demonstrate the therapeutic benefits of our candidates in clinical trials, including our ability to develop candidates across multiple therapeutic modalities; our dependence on third parties, including contract research organizations, contract manufacturing organizations, collaborators and partners; our ability to manufacture or contract with third parties to manufacture drug material to support our programs and growth; our ability to obtain, maintain and protect intellectual property; our ability to enforce our patents against infringers and defend our patent portfolio against challenges from third parties; and competition from others developing therapies for

similar uses, as well as the information under the caption “Risk Factors” contained in our most recent Annual Report on Form 10-K filed with the Securities and Exchange Commission (SEC) and in other filings we make with the SEC from time to time. We undertake no obligation to update the information contained in this press release to reflect subsequently occurring events or circumstances.

WAVE LIFE SCIENCES LTD.

UNAUDITED CONSOLIDATED BALANCE SHEETS

(In thousands, except share amounts)

	September 30, 2019	December 31, 2018
Assets		
Current assets:		
Cash and cash equivalents	$ 209,009	$ 174,819
Current portion of accounts receivable	20,000	10,000
Prepaid expenses and other current assets	21,249	17,454
Total current assets	250,258	202,273
Long-term assets:		
Accounts receivable, net of current portion	30,000	50,000
Property and equipment, net	37,204	39,931
Operating lease right-of-use assets	18,527	—
Restricted cash	3,643	3,625
Other assets	7,580	111
Total long-term assets	96,954	93,667
Total assets	$ 347,212	$ 295,940
Liabilities, Series A preferred shares and shareholders' equity		
Current liabilities:		
Accounts payable	$ 20,219	$ 13,089
Accrued expenses and other current liabilities	13,738	14,736
Current portion of deferred rent	—	115
Current portion of deferred revenue	96,322	100,945
Current portion of lease incentive obligation	—	1,156
Current portion of operating lease liability	3,132	—
Total current liabilities	133,411	130,041
Long-term liabilities:		
Deferred rent, net of current portion	—	5,132
Deferred revenue, net of current portion	59,196	68,156
Lease incentive obligation, net of current portion	—	9,247
Operating lease liability, net of current portion	30,165	—
Other liabilities	1,793	2,142
Total long-term liabilities	$ 91,154	$ 84,677
Total liabilities	$ 224,565	$ 214,718
Series A preferred shares, no par value; 3,901,348 shares issued and outstanding at September 30, 2019 and December 31, 2018	$ 7,874	$ 7,874
Shareholders' equity:		
Ordinary shares, no par value; 34,284,217 and 29,472,197 shares issued and outstanding at September 30, 2019 and December 31, 2018, respectively	$ 538,790	$ 375,148
Additional paid-in capital	52,290	37,768
Accumulated other comprehensive income	282	153
Accumulated deficit	(476,589)	(339,721)
Total shareholders' equity	$ 114,773	$ 73,348
Total liabilities, Series A preferred shares and shareholders' equity	$ 347,212	$ 295,940

WAVE LIFE SCIENCES LTD.
UNAUDITED CONSOLIDATED STATEMENTS OF OPERATIONS AND COMPREHENSIVE LOSS

(In thousands, except share and per share amounts)

	Three Months Ended September 30,		Nine Months Ended September 30,	
	2019	2018	2019	2018
Revenue	$ 2,929	$ 4,493	$ 13,583	$ 10,794
Operating expenses:				
Research and development	44,585	32,876	126,303	94,619
General and administrative	12,523	9,849	35,064	26,755
Total operating expenses	57,108	42,725	161,367	121,374
Loss from operations	(54,179)	(38,232)	(147,784)	(110,580)
Other income, net:				
Dividend income	1,208	1,064	4,176	2,354
Interest income, net	6	5	25	16
Other income (expense), net	2,239	(468)	6,715	(384)
Total other income, net	3,453	601	10,916	1,986
Loss before income taxes	(50,726)	(37,631)	(136,868)	(108,594)
Income tax provision	—	—	—	(172)
Net loss	$ (50,726)	$ (37,631)	$ (136,868)	$ (108,766)
Net loss per share attributable to ordinary shareholders—basic and diluted	$ (1.48)	$ (1.28)	$ (4.06)	$ (3.78)
Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted	34,281,203	29,333,994	33,719,055	28,804,357
Other comprehensive income (loss):				
Net loss	$ (50,726)	$ (37,631)	$ (136,868)	$ (108,766)
Foreign currency translation	2	(20)	129	65
Comprehensive loss	$ (50,724)	$ (37,651)	$ (136,739)	$ (108,701)

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Exhibit 99.2

Wave Life Sciences

Corporate Presentation

November 5, 2019

Forward-looking statements

This document contains forward-looking statements. All statements other than statements of historical facts contained in this document, including statements regarding possible or assumed future results of operations, preclinical and clinical studies, business strategies, research and development plans, collaborations and partnerships, regulatory activities and timing thereof, competitive position, potential growth opportunities, use of proceeds and the effects of competition are forward-looking statements. These statements involve known and unknown risks, uncertainties and other important factors that may cause the actual results, performance or achievements of Wave Life Sciences Ltd. (the "Company") to be materially different from any future results, performance or achievements expressed or implied by the forward-looking statements. In some cases, you can identify forward-looking statements by terms such as "may," "will," "should," "expect," "plan," "aim," "anticipate," "could," "intend," "target," "project," "contemplate," "believe," "estimate," "predict," "potential" or "continue" or the negative of these terms or other similar expressions. The forward-looking statements in this presentation are only predictions. The Company has based these forward-looking statements largely on its current expectations and projections about future events and financial trends that it believes may affect the Company's business, financial condition and results of operations. These forward-looking statements speak only as of the date of this presentation and are subject to a number of risks, uncertainties and assumptions, including those listed under Risk Factors in the Company's Form 10-K and other filings with the SEC, some of which cannot be predicted or quantified and some of which are beyond the Company's control. The events and circumstances reflected in the Company's forward-looking statements may not be achieved or occur, and actual results could differ materially from those projected in the forward-looking statements. Moreover, the Company operates in a dynamic industry and economy. New risk factors and uncertainties may emerge from time to time, and it is not possible for management to predict all risk factors and uncertainties that the Company may face. Except as required by applicable law, the Company does not plan to publicly update or revise any forward-looking statements contained herein, whether as a result of any new information, future events, changed circumstances or otherwise.

Targeting genetically defined diseases with stereopure oligonucleotides

Building fully integrated genetic medicines company led by neurology development programs

Neuromuscular

- ***Lead clinical program:*** **Suvodirsen Phase 2/3 trial ongoing for DMD (exon 51); program on development path toward US and global approvals**
- Advancing additional exon skipping candidates for DMD
- Commercialization activities underway

100% global rights

CNS

- ***Lead clinical program:*** **Two Phase 1b/2a trials ongoing for Huntington's disease using differentiated allele-selective approach**
- Advancing C9orf72 candidate for ALS and FTD
- SNP3 (HD) and ATXN3 (SCA3)

Takeda 50:50 option

Ophthalmology

- Advancing USH2A exon-skipping program for Usher Syndrome

100% global rights

WAVE LIFE SCIENCES

PRISM

DESIGN & OPTIMIZE

Stereopure oligonucleotides across multiple therapeutic modalities

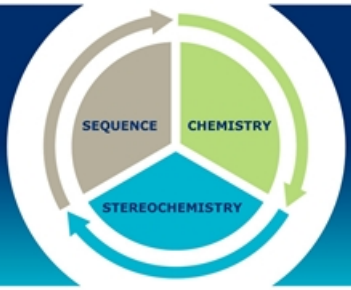
Silencing | Splicing | Editing

PRISM

Enables Wave to target genetically defined diseases with stereopure oligonucleotides across multiple therapeutic modalities

DESIGN

Unique ability to construct stereopure oligonucleotides with one defined and consistent profile



OPTIMIZE

A deep understanding of how the interplay among oligonucleotide sequence, chemistry, and backbone stereochemistry impacts key pharmacological properties

Through iterative analysis of *in vitro* and *in vivo* outcomes and artificial intelligence-driven predictive modeling, Wave continues to define design principles that are deployed across programs to rapidly develop and manufacture clinical candidates that meet pre-defined product profiles

WAVE LIFE SCIENCES

Designing the optimal, stereopure medicine

STANDARD OLIGONUCLEOTIDE APPROACHES

Pharmacologic properties include >500,000 permutations in every dose

↓

Impact:
Unreliable therapeutic effects
Unintended off-target effects

WAVE RATIONAL DESIGN

Control of stereochemistry enables the design and manufacture of oligonucleotides with one defined and consistent profile

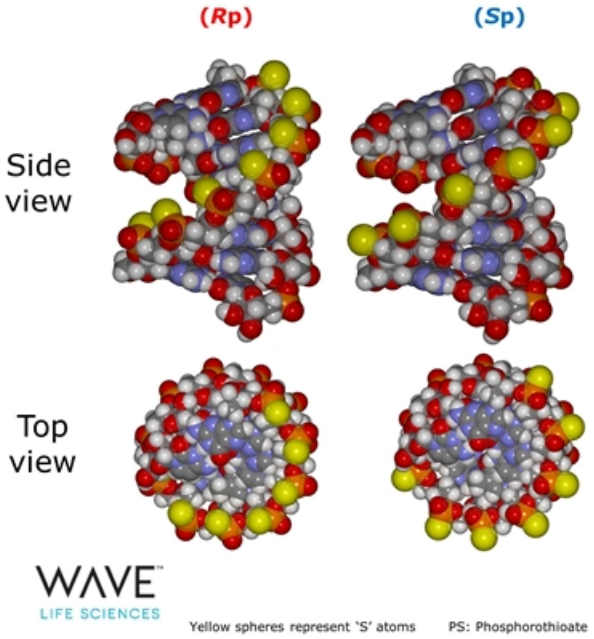
↓

Impact:
Potential for best-in-class medicines that can address difficult-to-treat diseases

WAVE LIFE SCIENCES

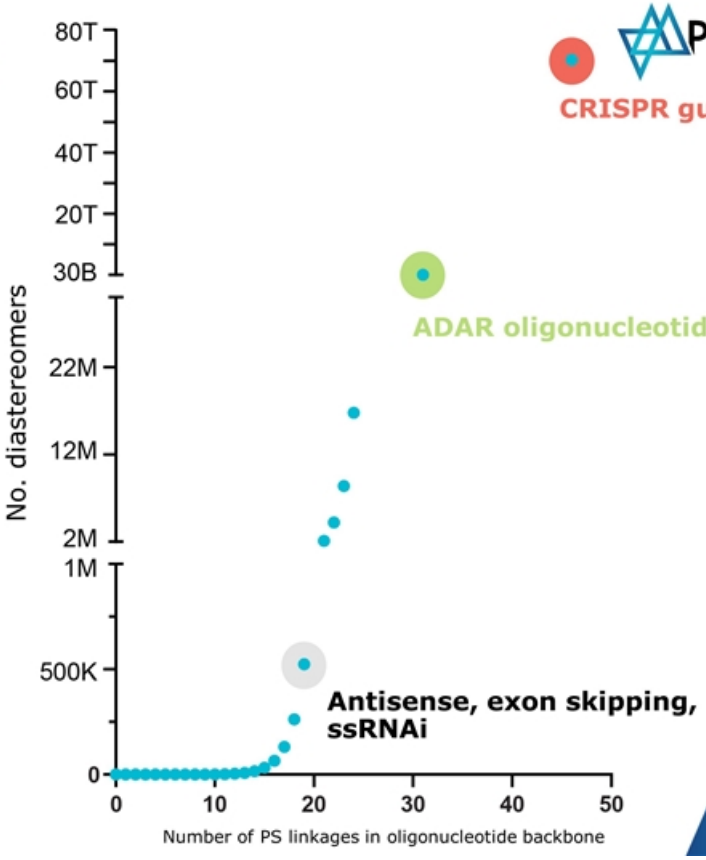
Stereochemical diversity

- Exponential diversity arises from uncontrolled stereochemistry



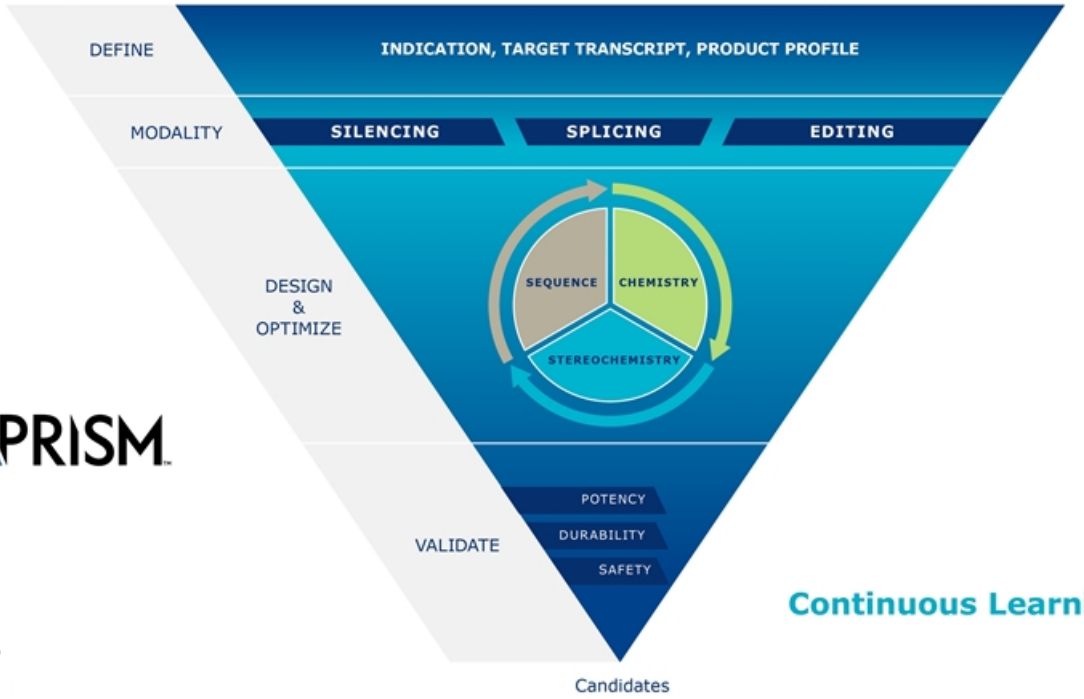
WAVE LIFE SCIENCES

Yellow spheres represent 'S' atoms PS: Phosphorothioate



PRISM CRISPR guide

PRISM platform enables rational drug design



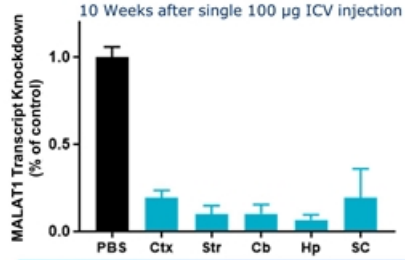
Continuous Learning

Source: Iwamoto N, et al. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. *Nat Biotechnol*. 2017;35:845-851.

Optimizing potency and durability across multiple tissues

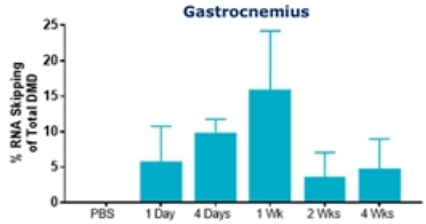
CNS

MALAT1 Transcript Knockdown in Mice
10 Weeks after single 100 µg ICV injection



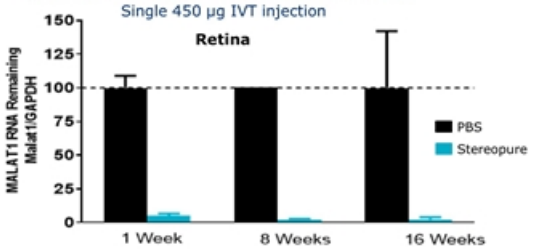
Muscle

DMD: Percent Skipped Transcript in *mdx*23 Mice
Single 150 mg/kg IV injection



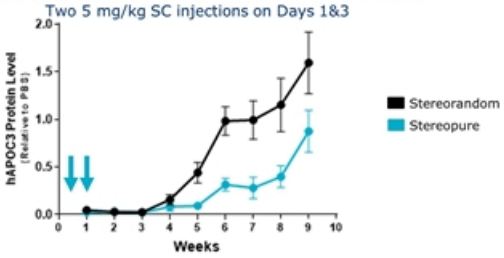
Eye

MALAT1 Knockdown in Non-Human Primates
Single 450 µg IVT injection



Liver

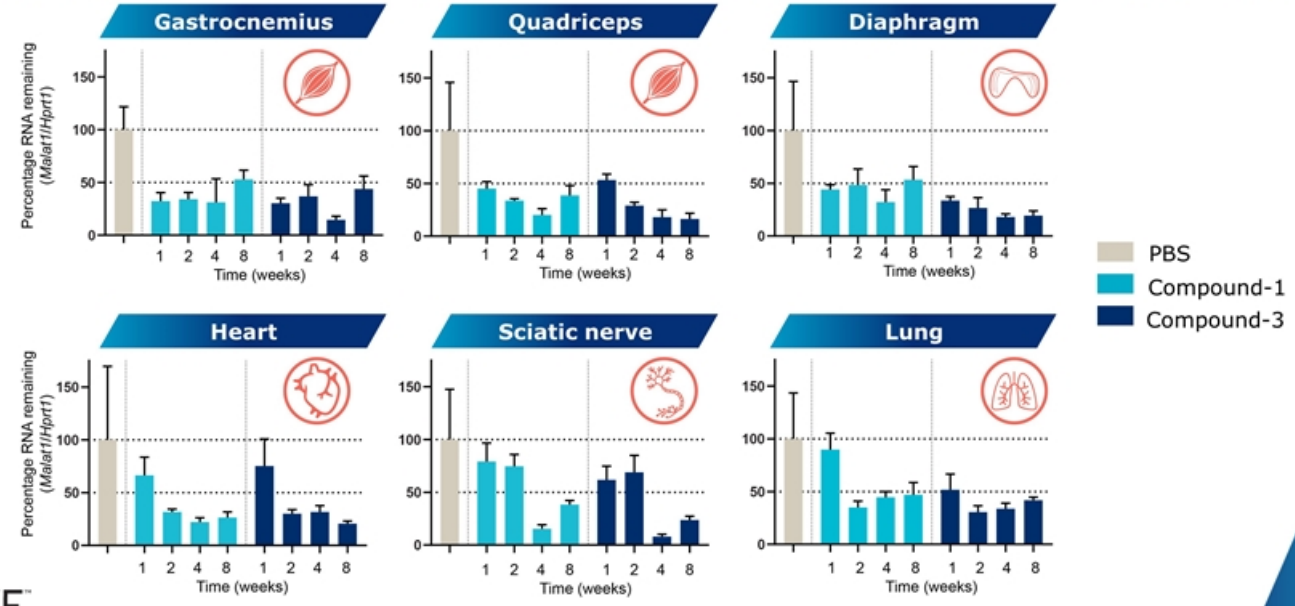
Knockdown of Serum hAPOC3 Protein Levels in Mice
Two 5 mg/kg SC injections on Days 1&3



Data represented in this slide from *in vivo* studies. CNS: PBS = phosphate buffered saline; Ctx = cortex; Str = striatum; Cb = cerebellum; Hp = hippocampus; SC = spinal cord. ICV = intracerebral; IVT = intravitreal; IV = intravenous; SC= subcutaneous.

Broad tissue distribution and durable target engagement

Single IV injection of Wave compounds targeting *MALAT1* (human equivalent of 1.6 mg/kg)

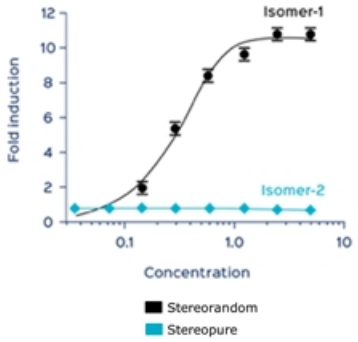


Mice were dosed with a single IV injection (25 mg/kg) of *MALAT1*-targeting compound, and tissues were assessed for RNA expression 1-, 2-. 4-, and 8-weeks post-dose. Relative percentage of *MALAT1* RNA to PBS-treated mice (n=5 per group). *MALAT1* RNA levels are normalized to Hprt1.

Stereochemistry affects immune activation

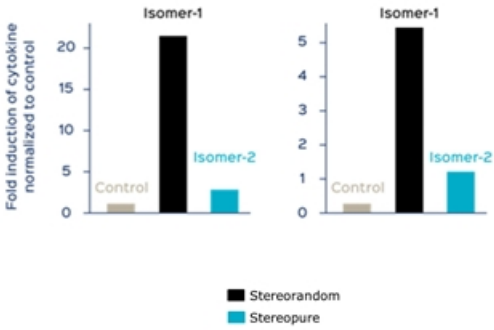
Human TLR9 Activation

Human TLR9 activation assay with 5mC modified CpG containing MOE gapmer



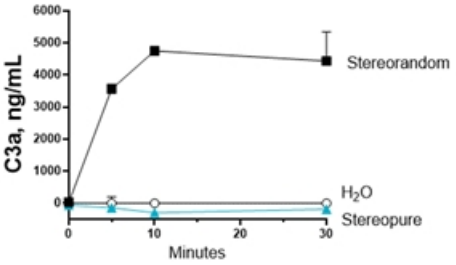
Cytokine Induction

Cytokine induction in human PBMC assay



Complement Activation

Complement activation in non-human primate serum assay



Data represented in this slide from *in vitro* studies. MOE = 2′-O-methoxyethylribose; PBMC = peripheral blood mononuclear cell; TLR9 = toll-like receptor 9.

Pipeline spanning multiple modalities, novel targets

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*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate; for Huntington's disease, numbers approximate manifest and pre-manifest populations, respectively.
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.
A.A.: Accelerated approval; ALS: Amyotrophic lateral sclerosis; FTD: Frontotemporal dementia; CNS: Central nervous system; OLE: Open-label extension

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Suvodirsen
Duchenne Muscular Dystrophy (DMD)

DMD: a progressive, fatal childhood disorder

- Fatal, X-linked genetic neuromuscular disorder characterized by progressive, irreversible loss of muscle function, including heart and lung
- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function
- Symptom onset in early childhood; one of the most serious genetic diseases in children worldwide
- Current disease modifying treatments have demonstrated minimal dystrophin expression and clinical benefit has not been established
- Impacts 1 in every 5,000 newborn boys each year; 20,000 new cases annually worldwide

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Source: Parent Project Muscular Dystrophy. About Duchenne & Becker muscular dystrophy. Available at: https://www.parentprojectmd.org/care/for-healthcare-providers/. Accessed: November 2, 2018.

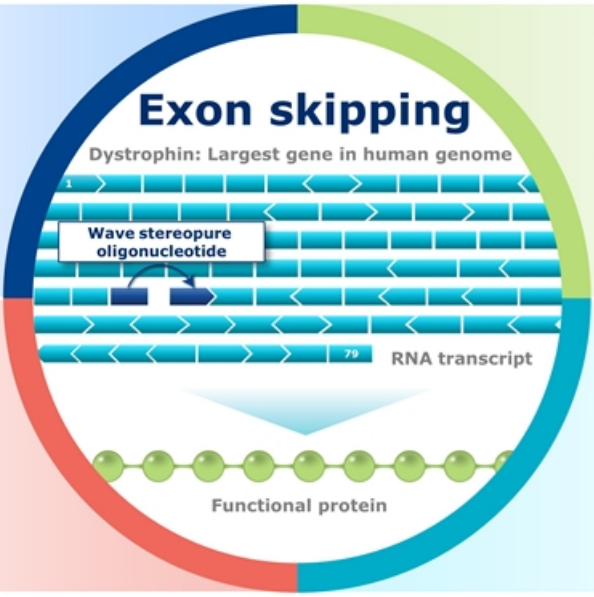
Potential benefits of stereopure oligonucleotide approach to treating Duchenne muscular dystrophy

Delivery

- Entry into cells (including progenitor cells) via free-uptake
- Enhanced nuclear uptake
- Broad tissue distribution

Functional dystrophin

- Production of meaningful levels of functional dystrophin protein
- Expected to result in therapeutic benefit



Repeat administration

- Repeat administration may better address muscle cell turnover and need for broad distribution

Scalable manufacturing

- Scalable manufacturing process to meet clinical and commercial supply requirements
- Cost of goods consistent with conventional oligonucleotide therapies

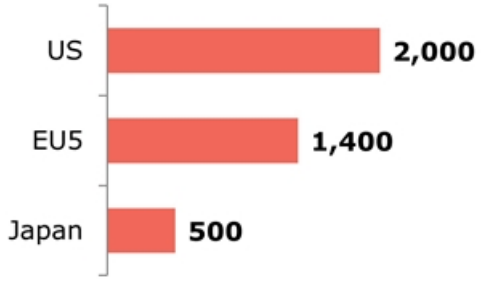
Sources: Arnett ALH, et al. *Mol Ther Methods Clin Dev.* 2014;1:14038. doi:10.1038/mtm.2014.38. Counsell JR, et al. *Sci Rep.* 2017;7:79. doi: 10.1038/s41598-017-00152-5. Duan D. *Mol Ther.* 2018;25:2337-2356. Martinsen B, Dreyer P. *Open Nurs Jrnl.* 2016;10:131-138. Stitelman DH, et al. *Mol Ther Methods Clin Dev.* 2014;1:14040. doi:10.1038/mtm.2014.40; Aartsma-Rus A et al. *J Med Genet.* 2016;53(3):145-151.

Suvodirsen: Wave's lead stereopure exon skipping oligonucleotide for exon 51 amenable DMD

Exon 51: Most frequent mutation among DMD patients

- ~13% of DMD patients amenable to Exon 51 skipping
- One exon-skipping therapy conditionally approved by FDA
  - Minimal increase in dystrophin expression over baseline observed after 48 weeks; **Mean increase 0.28%, Median increase 0.1%**[1]
  - Clinical benefit not established
  - Not approved ex-US
- Demand for additional treatment options remains high
- Established US and EU regulatory paths

Prevalent patient populations amenable to exon 51 skipping[2]

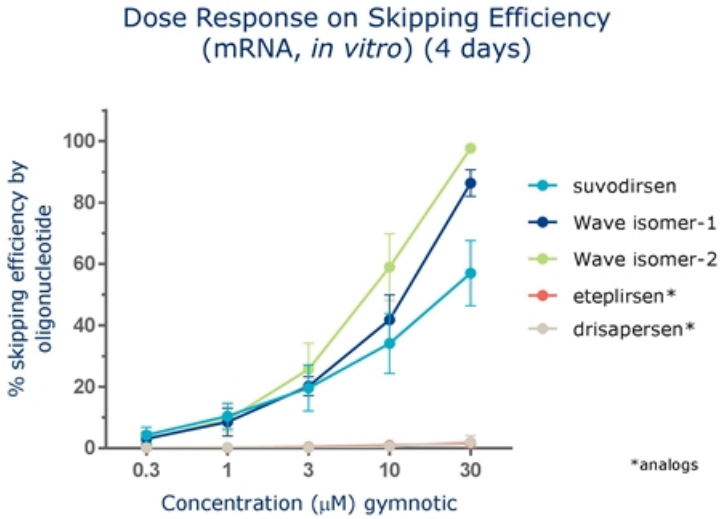


Prevalent patient population represents **>$1.5B** global market opportunity[3]

Annemieke Aartsma-Rus, et al. Theoretic applicability of antisense-mediated exon skipping for Duchenne muscular dystrophy. Hum Mutat. 2009 Mar;30 (3):293-9; Bladen et al , Hum Mutat. 2015 Apr; 36(4): 395–402
[1]eteplirsen label; [2]Decision Resources 2015, [3]US, EU5, Japan; market-based pricing of commercially available DMD treatments

Exon 51: improved skipping efficiency

- RNA skipping determined by quantitative RT-PCR
- Wave isomers demonstrated a dose-dependent increase in skipping efficiency *in vitro*
- Free uptake at 10 µM concentration of each compound with no transfection agent
- Same foundational stereopure chemistry for Wave isomers; individually optimized to select candidate



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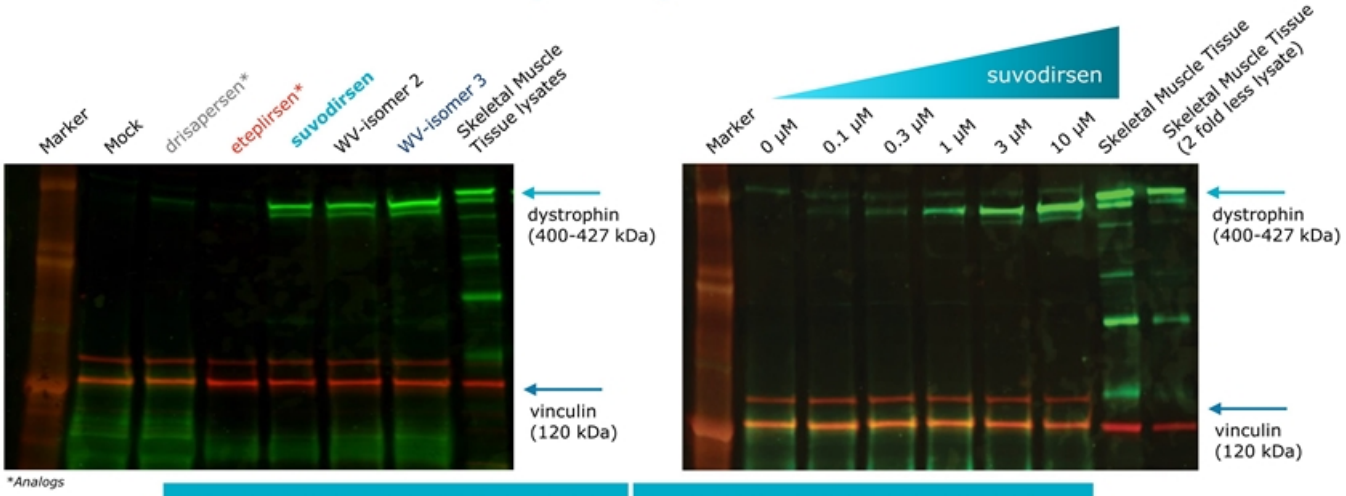
Experimental conditions: Free uptake of ASO in human DMD myoblast cells. Skipping quantified by TaqMan assay.

Exon 51: increased dystrophin restoration *in vitro*



*Analogs

Oligonucleotide at 10 µM concentration	*In vitro* dystrophin restoration
suvodirsen	~52%
drisapersen analogue	~1%
eteplirsen analogue	~1%

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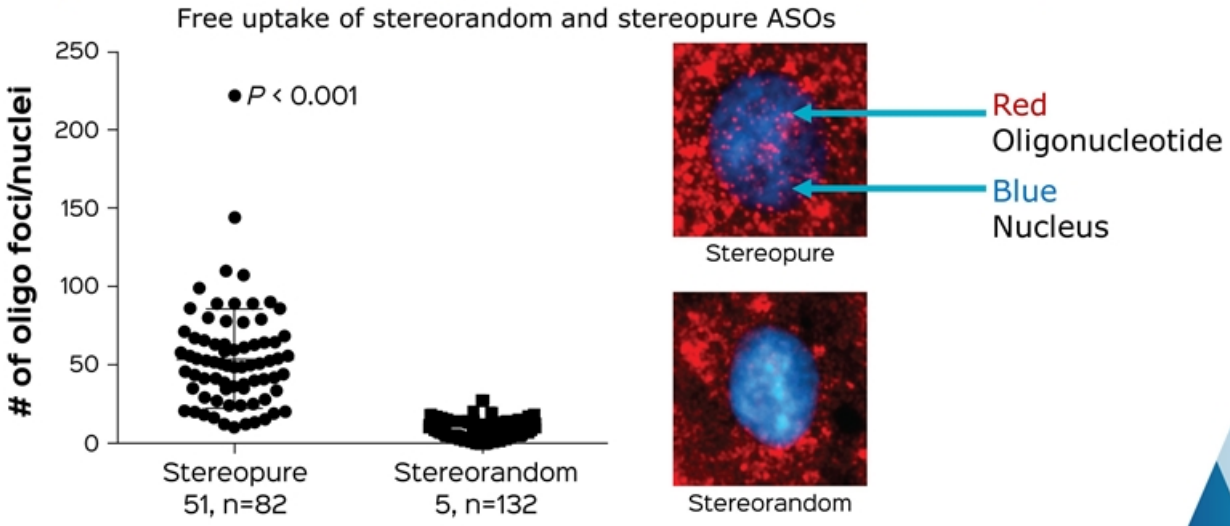
Experimental conditions: DMD protein restoration by Western Blot in patient-derived myotubes with clear dose effect. Free uptake at 10 µM concentration of each compound with no transfection agent.

Exon 51: improved oligonucleotide uptake in the nucleus where splicing occurs

Stereopure oligonucleotides are designed to readily enter the nuclei of cells under free-uptake conditions, which approximates natural delivery in the body



Experimental conditions: Free uptake of ASOs in 18 hour differentiating human DMD myoblasts (Δ48-50).

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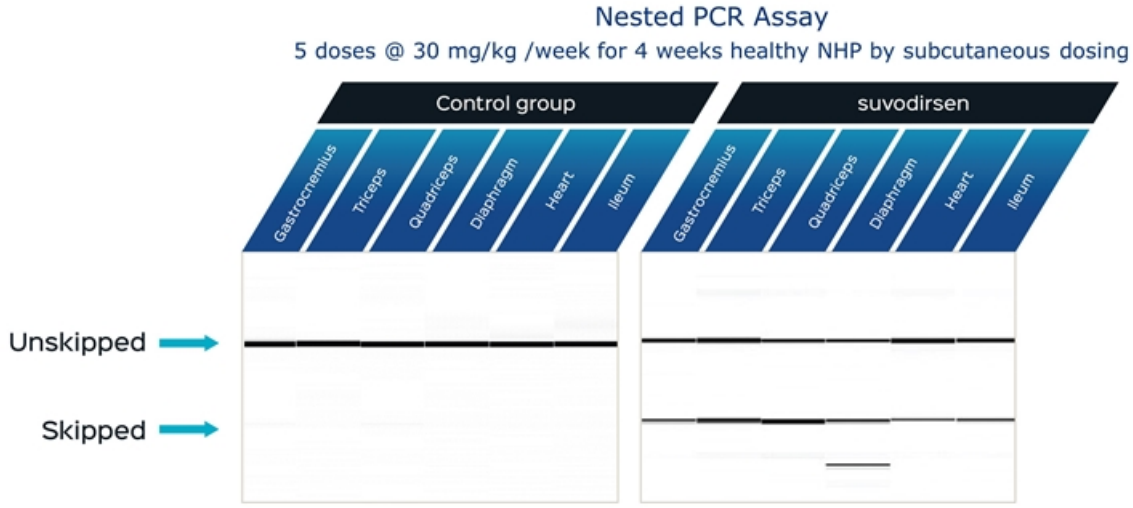
Exon 51: *in vivo* target engagement of suvodirsen in healthy non-human primate



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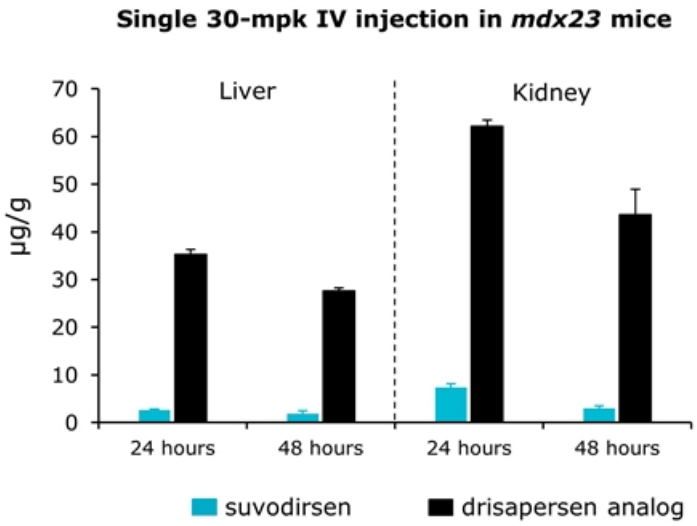
Experimental conditions: Muscle tissues were collected 2 days after the last dose and fresh frozen. Total RNAs were extracted with phenol/chloroform and converted to cDNA using high capacity kit. Nested PCR assay was performed and analyzed by fragment analyzer.

Exon 51: no apparent tissue accumulation observed

- Standard oligonucleotides tend to accumulate in liver and kidney
- Wave rationally designed oligonucleotides optimized to allow compound to clear more effectively
- Suvodirsen demonstrated broad tissue distribution in dose dependent fashion
- No apparent accumulation observed after multiple doses



Experimental conditions: *Mdx23* mice received a single 30-mg/kg intravenous bolus injection of suvodirsen or drisapersen analog (n=3/group), and sacrificed 24 or 48 hours post dose. Oligo quantifications in tissues were performed using hybridization ELISA assay.

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Suvodirsen: Path towards US and global approvals

Phase 1

- Phase 1 single ascending dose clinical trial (40 patients[1])
- ~20% of patients had received eteplirsen previously (following wash out)
- Two suvodirsen doses selected for Phase 2/3 clinical trial
- Suvodirsen had a favorable safety and tolerability profile in context of available treatments for continued development in OLE and Phase 2/3 trial
- **Study complete**

Open-label extension (OLE)

- Multi-dose (3.5 and 5 mg/kg), open-label study with patients from Phase 1 clinical trial ongoing
- Data will be an important component of submission for accelerated approval in US
- **On track to deliver interim analysis of dystrophin expression in 4Q 2019**

Phase 2/3 (DYSTANCE 51)

- Phase 2/3 clinical trial to assess clinical efficacy and dystrophin expression
- Efficacy and safety data to serve as basis of regulatory submissions globally
- **Trial ongoing**

2H 2020: Potential FDA accelerated approval filing in exon 51 amenable DMD

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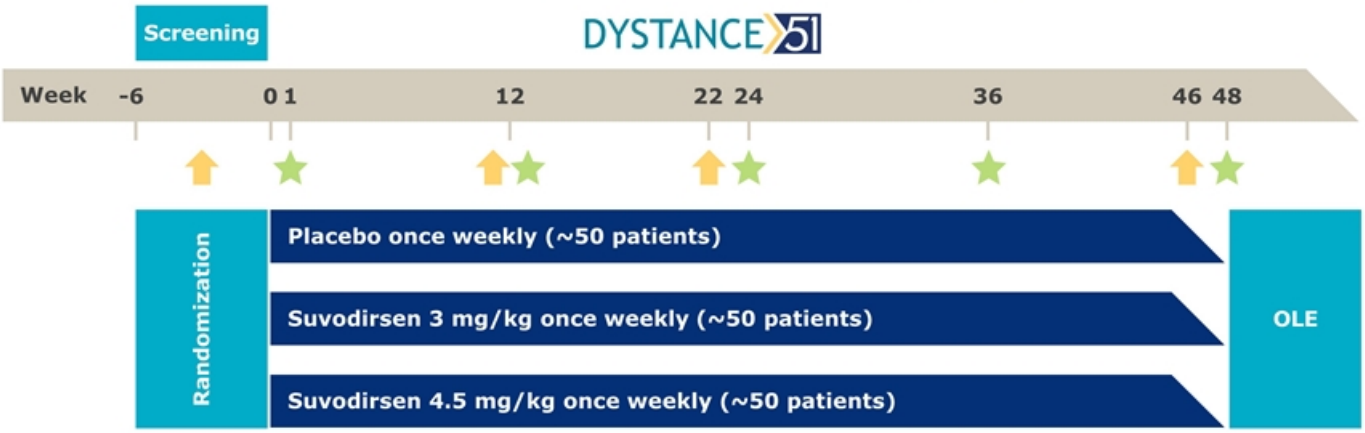
[1]36 patients randomized in Phase 1 and four screened patients expected to enroll directly into Phase 1 OLE
Full Phase 1 Results presented at MDA 2019 Scientific and Clinical Conference.

DYSTANCE 51 study selected for FDA Complex Innovative Trial Design (CID) pilot program



- Phase 2/3 study designed with input from global regulatory communities and DMD patient community
- DMD historical control data will be leveraged to potentially reduce number of patients required to deliver conclusive clinical efficacy results and to potentially accelerate study completion

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Biopsy* = NSAA =

Note: 4.5 mg/kg dose in DYSTANCE 51 provides approximately the same amount of active ingredient as the 5 mg/kg dose in the Phase 1 clinical trial
*Each participant to have only two biopsies (one at baseline, one at either week 12, 22, or 46)

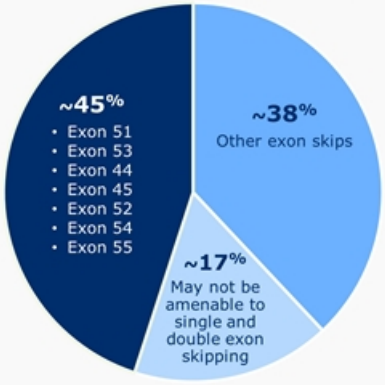
Building a portfolio to transform the care of DMD

Suvodirsen targeting exon 51
- Phase 2/3 trial ongoing for global regulatory submissions
- Potential FDA accelerated approval filing in 2H 2020, pending positive clinical dystrophin expression data

WVE-N531 targeting exon 53
- Topline clinical data expected in 2H 2020

Advancing candidate development for exons 44, 45, 52, 54, 55
- Early leads demonstrated similar *in vitro* exon skipping efficiency as suvodirsen and WVE-N531

Percentage of patients with DMD amenable to exon skipping therapeutic approach



Initiating commercialization activities in anticipation of first potential launch in US

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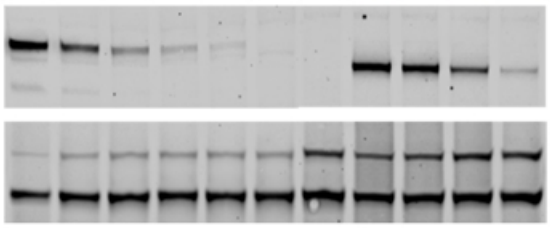
Sources: Aartsma-Rus A, et al. *Hum Mutat.* 2009;30:293-299. Bladen CL, et al. *Hum Mutat.* 2015;36:395–402.

Exon 53: WVE-N531 *in vitro* dose-dependent dystrophin restoration

Dystrophin protein restoration of up to 71%

Western Blot normalized to primary healthy human myoblast lysate

Standard Curve (% WT lysate in D45-52 lysate)						D45-52 Cells					
						Mock	WVE-N531				
						0	10	3.3	1.1	0.3	Conc [uM]
100%	50%	25%	12%	6%	0%	0%	71%	65%	37%	9.5%	% Dystrophin



- Free uptake for 6 days in differentiation media with no transfection agent and no peptide conjugated to the oligonucleotide
- Wave stereopure exon 53 candidate demonstrated a dose-dependent increase in dystrophin restoration in DMD patient-derived myoblasts

Topline clinical data expected in 2H 2020

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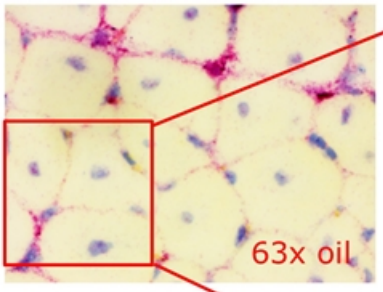
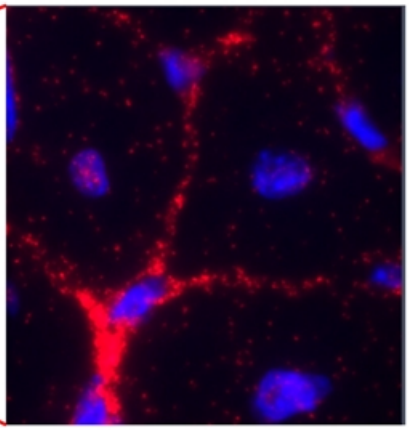
Experimental conditions: Δ45-52 (D45-52) patient myoblasts were treated with oligonucleotide for 6d under free-uptake conditions in differentiation media. Protein harvested in RIPA buffer and dystrophin restoration analyzed by Western Blot. Signal normalized to vinculin loading control and to primary healthy human myotube lysate (pooled from four donors) forming a standard curve in Δ45-52 cell lysate.

Exon 53: targeting oligonucleotide rapidly distributes to muscle within 24 hours after injection



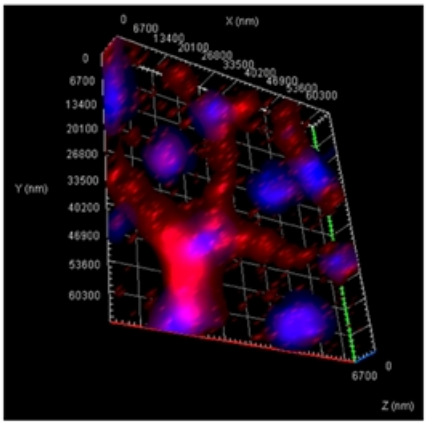
Bright field view

Nucleus: Hematoxylin; Light Blue
Wave oligo: ViewRNA, Fast Red



Fluorescence channel view

Nucleus: Hoechst33342; Blue
Wave oligo: Fast Red/Cy3; Pink Red



Z Stack view

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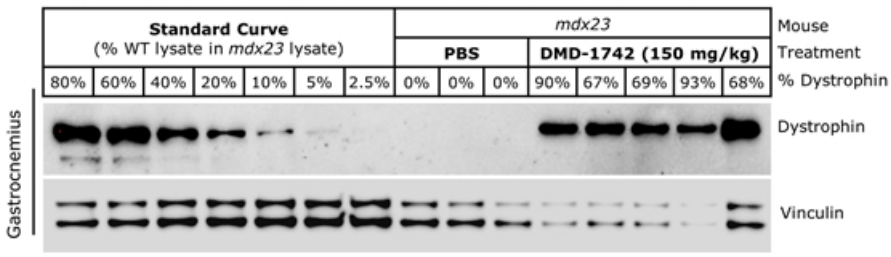
Data derived from *in vivo* preclinical research.

Experimental conditions: A single dose of stereopure oligonucleotide 30 mg/kg IV was administered to *mdx* 23 mice. Tissues collected 24 hours post dose and ASO was detected in muscles using ViewRNA.

In vivo mdx23 dystrophin protein with oligonucleotides

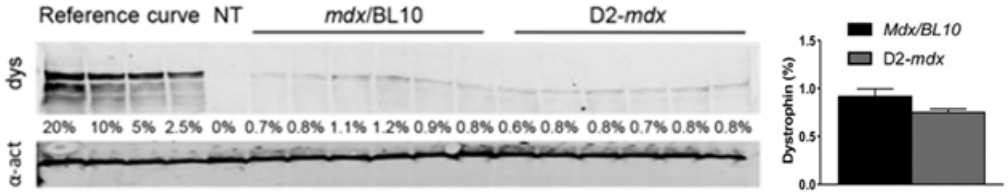
***In vivo* dystrophin protein restoration (stereopure surrogate, 150 mg/kg, 4 weekly IV doses)**



- 70 – 90% dystrophin restoration
- 87% reduction in creatine kinase (CK) levels

Published literature

***In vivo* dystrophin protein restoration (drisapersen surrogate, 200 mg/kg, 8 weekly IV doses)**



- Less than 1.5% dystrophin restoration in two separate studies[1,2]
- No reduction in CK levels[1]

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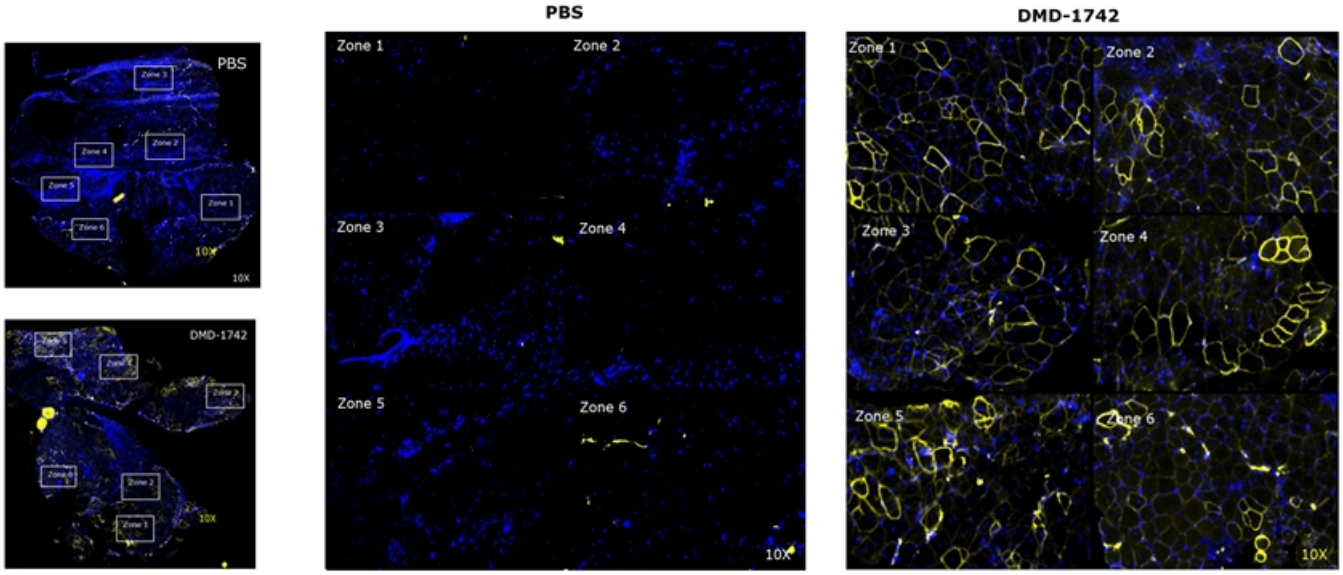
NT = nontreated *mdx* mouse; *mdx*/BL10 = mdx mouse in C57BL/10ScSnJ background; D2-*mdx* = mdx mouse crossed to DBA/2A background resulting in more severely affected model; CK = creatine kinase
Experimental conditions (stereopure surrogate): Tissues collected 96 hours post final dose. Protein expression determined by western Blot.
1. Experimental conditions (drisapersen surrogate): Tissues collected 1 week after the last injection. Protein expression determined by western blot.
van Putten M, Tanganyika-de Winter C, Bosgra S, Aartsma-Rus A. Nonclinical Exon Skipping Studies with 2'-O-Methyl Phosphorothioate Antisense Oligonucleotides in mdx and mdx-utrn-/- Mice Inspired by Clinical Trial Results. *Nucleic Acid Ther.* 2019 Apr;29(2):92-103.
2. Molecular Therapy – Nucleic Acids (2014) 3, e148

Single dose of surrogate results in restoration of dystrophin in muscle fibers

Immunohistochemistry of dystrophin in gastrocnemius in *mdx23* mice at 4 weeks



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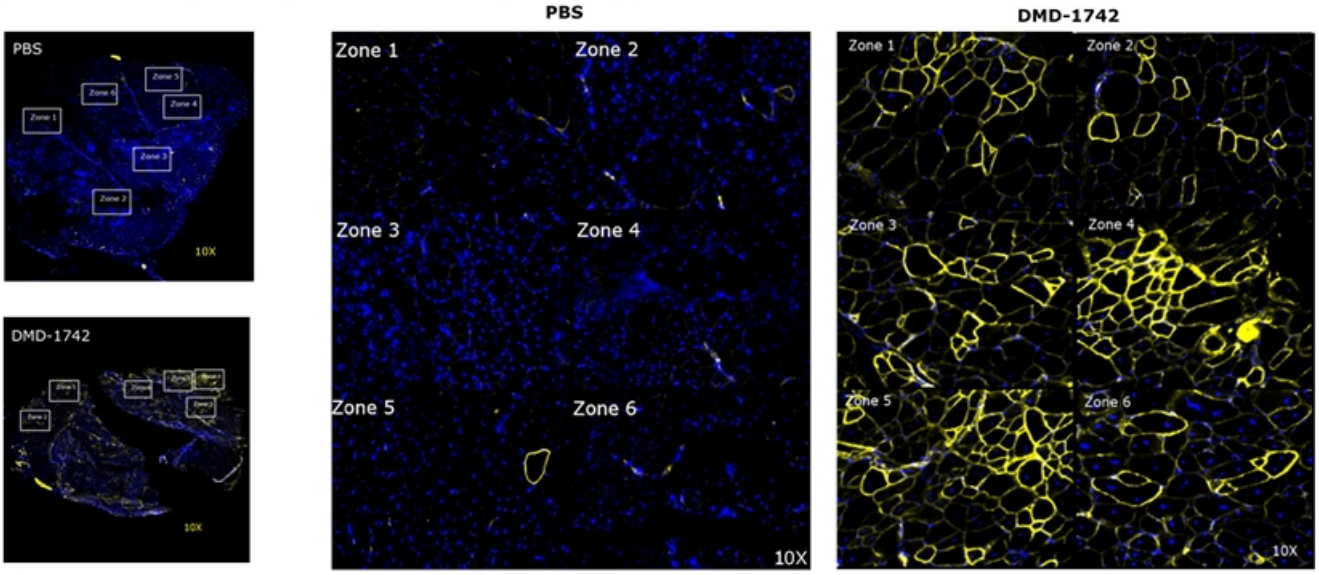
Experimental conditions: *mdx23* mice received a single IV injection of PBS or DMD-1742 (150 mg/kg).
Immunohistochemistry: Blue: Nuclei, Hoechst; Yellow: Rabbit anti-Dystrophin(#ab15277) 1:400 diluent, 555/Cy3, Cy3 staining is represented by the yellow color.
10X magnification.

Multiple doses of surrogate result in further restoration of dystrophin in muscle fibers

Immunohistochemistry of dystrophin in gastrocnemius in *mdx23* mice at 4 weeks



Experimental conditions: *mdx23* mice received 4 weekly IV injections of PBS or DMD-1742 (150 mg/kg).
Immunohistochemistry: Blue: Nuclei, Hoechst; Yellow: Rabbit anti-Dystrophin(#ab15277) 1:400 diluent, 555/Cy3, Cy3 staining is represented by the yellow color.
10X magnification.

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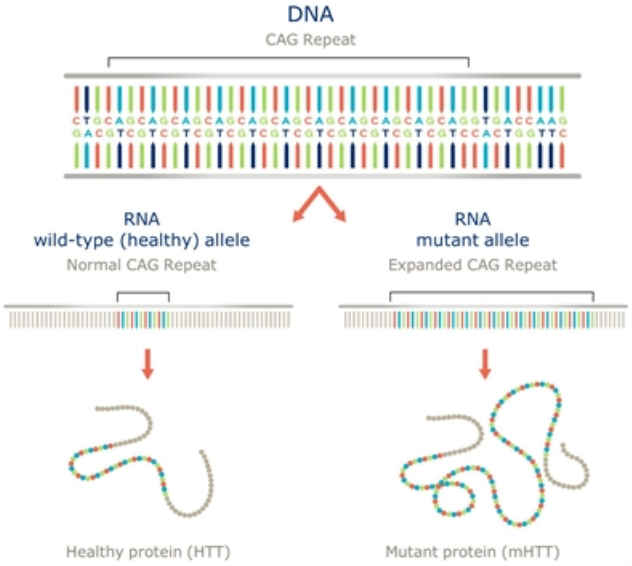
WVE-120101
WVE-120102
Huntington's Disease

Huntington's disease: a hereditary, fatal disorder

- Autosomal dominant disease, characterized by cognitive decline, psychiatric illness and chorea; fatal
- No approved disease-modifying therapies
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT); accumulation of mHTT causes progressive loss of neurons in the brain
- Wild-type (healthy) HTT protein critical for neuronal function; suppression may have detrimental long-term consequences
- 30,000 people with Huntington's disease in the US; another 200,000 at risk of developing the condition



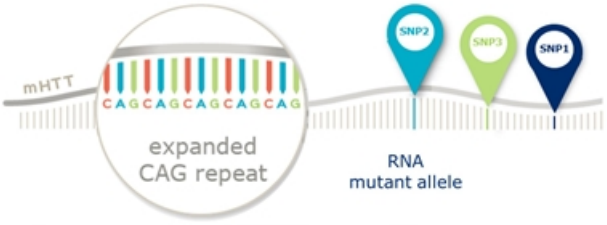
WAVE LIFE SCIENCES

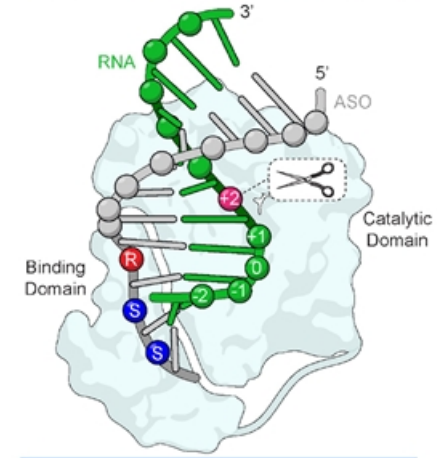
Sources: Auerbach W, et al. *Hum Mol Genet.* 2001;10:2515-2523. Dragatsis I, et al. *Nat Genet.* 2000;26:300-306. Leavitt BR, et al. *J Neurochem.* 2006;96:1121-1129. Nasir J, et al. *Cell.* 1995;81:811-823. Reiner A, et al. *J Neurosci.* 2001;21:7608-7619. White JK, et al. *Nat Genet.* 1997;17:404-410. Zeitlin S, et al. *Nat Genet.* 1995;11:155-163. Carroll JB, et al. *Mol Ther.* 2011;19:2178-2185. Huntington Disease Society of America (HDSA). What is Huntington's disease? Available at: https://hdsa.org/what-is-hd/overview-of-huntingtons-disease/ Accessed: November 2, 2018.

Wave approach: novel, allele-selective silencing

Aims to lower mHTT transcript while leaving healthy wild-type HTT relatively intact

- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including Huntington's disease (HD)
- Potential to provide treatment for up to 80% of HD population





RNase H and ASO:RNA

Allele-selectivity possible by targeting SNPs associated with expanded long CAG repeat in HTT gene

WAVE LIFE SCIENCES

Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. *Clin Genet*. 2014;86:29–36.

Two simultaneous Phase 1b/2a clinical trials

- PRECISION-HD is a global clinical program consisting of the PRECISION-HD1 trial evaluating WVE-120101 targeting SNP1 and the PRECISION-HD2 trial evaluating WVE-120102 targeting SNP2
  - Two parallel, multicenter, double-blind, randomized, placebo-controlled Phase 1b/2a clinical trials for WVE-120101 and WVE-120102, administered intrathecally, with single-ascending dose and multiple-ascending dose portions
  - Primary objective: Assess safety and tolerability of intrathecal doses in early manifest HD patients
  - Key additional objectives: Measurement of total HTT and mHTT; exploratory pharmacokinetic (PK), pharmacodynamic (PD), clinical and MRI endpoints
  - Key inclusion criteria: age ≥25 to ≤65, stage I or II HD who have screened positively for the presence of SNP1 or SNP2
  - Expected to enroll approximately 50 patients per trial
  - **Topline data expected to include: summary of clinical safety results, degree of mHTT protein lowering in CSF at 20 weeks, the ratio of total HTT versus mHTT in CSF at 20 weeks**
- Open-label extension (OLE) study initiated for PRECISION-HD2 outside of the U.S. to allow for continued dosing and clinical assessments
  - PRECISION-HD1 OLE expected to initiate in 2020
- Intend to explore efficacy in early manifest and pre-manifest HD patient populations

Topline data readout for PRECISION-HD2 expected by YE 2019

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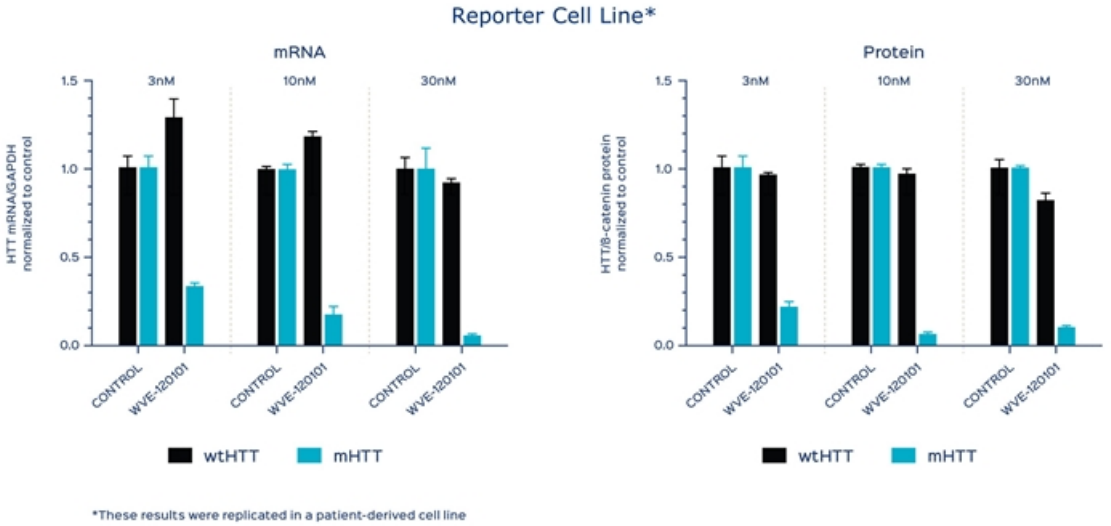
Selective reduction of mHTT mRNA & protein

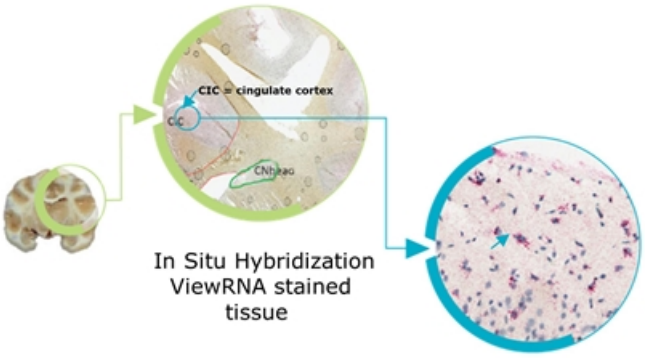


*These results were replicated in a patient-derived cell line

Source: Meena, Zboray L, Svrzikapa N, et al. Selectivity and biodistribution of WVE-120101, a potential antisense oligonucleotide therapy for the treatment of Huntington's disease. Paper presented at: 69th Annual Meeting of the American Academy of Neurology; April 28, 2017; Boston, MA.

Demonstrated delivery to brain tissue

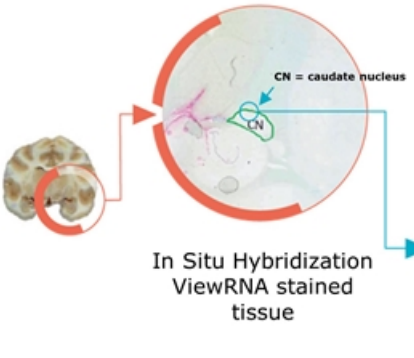
- WVE-120101 and WVE-120102 distribution in cynomolgus non-human primate brain following intrathecal bolus injection



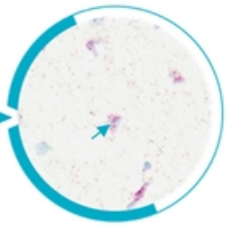
In Situ Hybridization ViewRNA stained tissue

Red dots are WVE-120101 oligonucleotide

Arrow points to nuclear and perinuclear distribution of WVE- 120101 in cingulate cortex



In Situ Hybridization ViewRNA stained tissue



Red dots are WVE-120102 oligonucleotide

Arrow points to nuclear and perinuclear distribution of WVE-120102 in caudate nucleus

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Source: Meena, Zboray L, Svrzikapa N, et al. Selectivity and biodistribution of WVE-120101, a potential antisense oligonucleotide therapy for the treatment of Huntington's disease. Paper presented at: 69th Annual Meeting of the American Academy of Neurology; April 28, 2017; Boston, MA.

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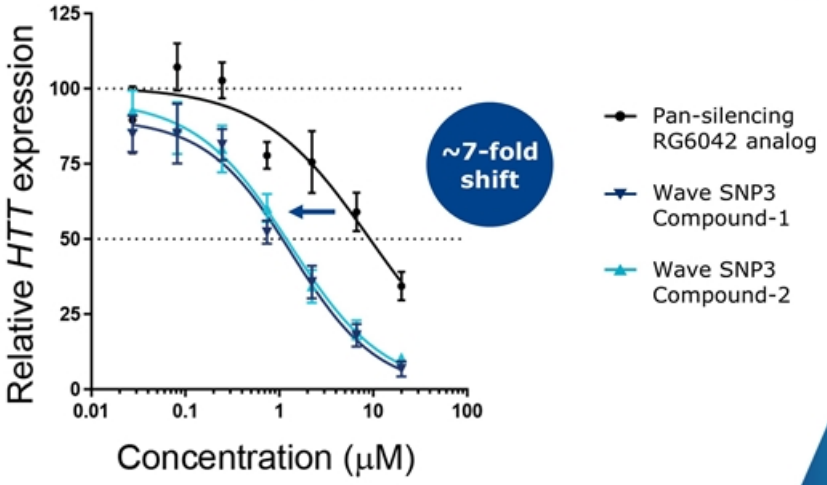
SNP3 Preclinical Program
Huntington's Disease

Potent mutant HTT knockdown activity

Wave allele-selective compounds are more potent than pan-silencing RG6042 analog in preclinical study involving patient-derived neurons

- Greater knockdown of mutant HTT as compared to pan-silencing compound

Homozygous iCell Neurons



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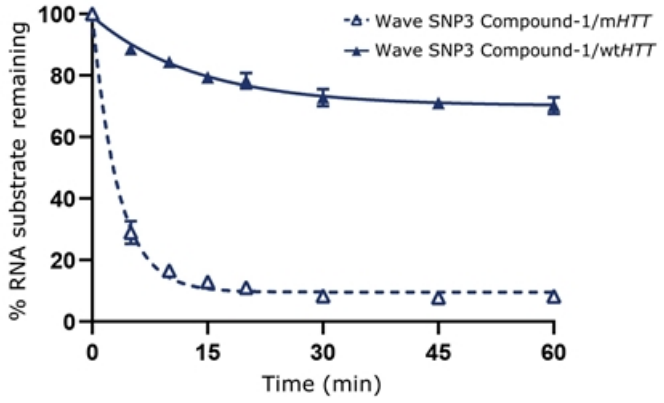
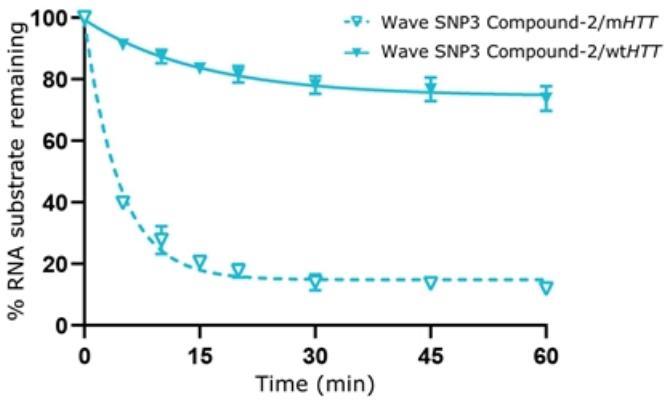
HTT mRNA remaining in iCell neurons (homozygous for SNP) incubated with the indicated ASO under free-uptake conditions. Data show mean ± sem (n=4).

Stereopure oligonucleotides are selective *in vitro*

Stereopure isomers targeting a SNP variant promote RNase H-mediated degradation of mutant *HTT* while sparing wild-type *HTT*

Biochemical RNase H assays





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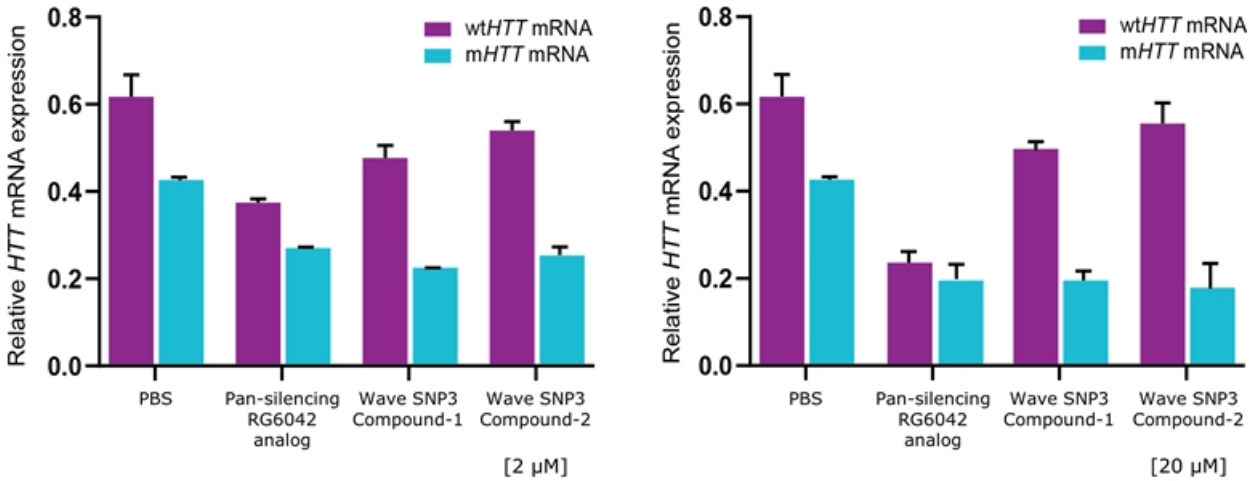
RNase H experiments performed with synthetic RNA substrates corresponding to m*HTT* and wt*HTT* variants (S:E = 100:1; n=2). Percentage of the indicated full-length RNA substrate remaining over time is plotted for the stereopure SNP3 Compound-1 (left) and stereopure SNP3 Compound-2 (right). Abbreviations: S, substrate; E, enzyme.

Demonstration of allele-selective silencing

Stereopure compounds selectively deplete mutant *HTT* mRNA

No loss of selectivity with increasing concentrations



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Neurons were derived from GM21756 patient-derived fibroblasts (heterozygous for SNP) and treated with 2.2 µM (left) or 20 µM (right) of the indicated ASO under gymnotic conditions for 7 days. RNA was quantified and normalized to *TUBB3*. Data are mean ± sem (n=3). Percentage of remaining wt*HTT* and m*HTT* mRNA is indicated.

In vivo model to assess target engagement and durability

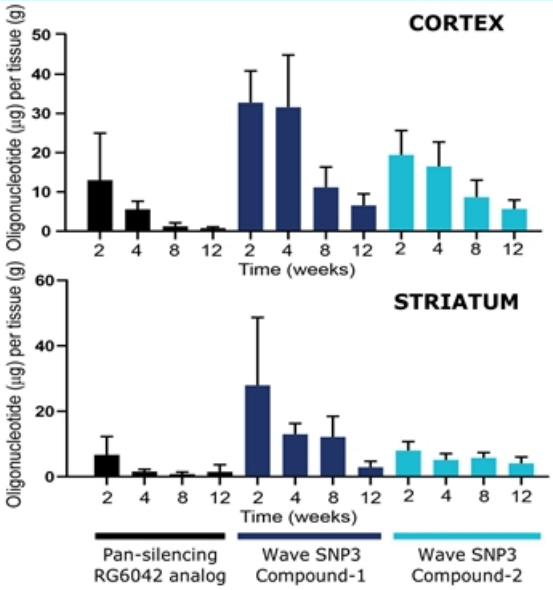
BACHD mouse model

- Expressed transcript includes SNP3 variant that Wave compounds are targeting
- Model is homozygous for mutant *HTT* with SNP3 (only has one type of *HTT*)
- Over-expresses m*HTT* (multiple gene copies)
- No ability to assess allele selectivity

Oligonucleotide concentration in tissues

- Achieved good tissue exposure over 12-weeks in BACHD cortex and striatum

Tissue exposure over time



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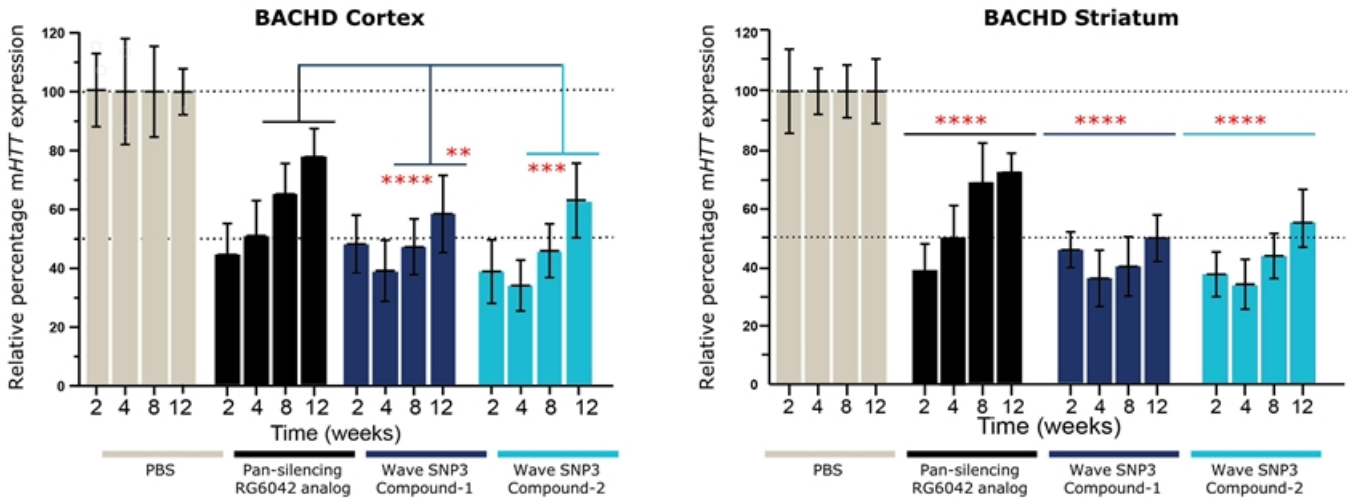
Oligonucleotide or PBS (3 x 100 µg ICV) was delivered to BACHD mice. Oligonucleotides were quantified by ELISA.

Durable *in vivo* mutant *HTT* knockdown with stereopure SNP3 compounds

Knockdown persists for 12 weeks



BACHD model only has mutant HTT (no wild-type HTT)

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Oligonucleotide or PBS (3 x 100 mg ICV) was delivered to BACHD mice. Relative percentage of HTT/TUBB3 mRNA in cortex with respect to levels in PBS-treated mice is shown at 2-12 weeks post-injection. Statistics: All oligo treatment groups are statistically significantly different from PBS; One-way ANOVA ****, P≤0.0001. Wave SNP3 Compound-1 and Compound-2 are also significantly different from RG6042 analog at 8 and 12 weeks ***, P<0.005; **P=0.001.

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C9orf72 program

Amyotrophic Lateral Sclerosis (ALS)

Frontotemporal Dementia (FTD)

C9orf72: a critical genetic risk factor

- C9orf72 gene provides instructions for making protein found in various tissues, with abundance in nerve cells in the cerebral cortex and motor neurons
- C9orf72 genetic mutations are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD); GGGGCC repeat drives the formation and accumulation of dipeptide repeat proteins that accumulate in brain tissue
- First pathogenic mechanism identified to be a genetic link between familial (inherited) ALS and FTD
- Most common mutation identified associated with familial ALS and FTD
- Availability of dipeptide biomarker in CSF has potential to accelerate drug development

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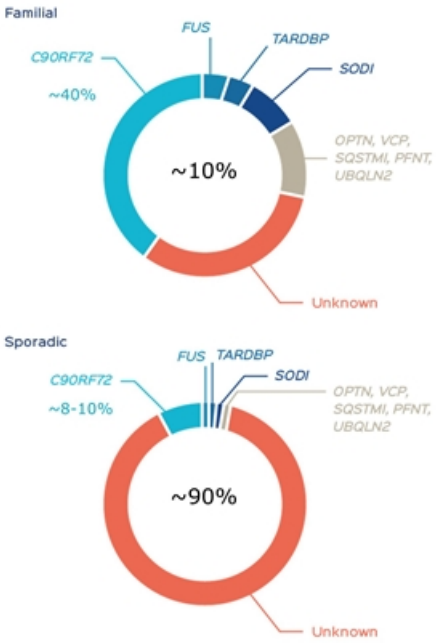
Source: DeJesus-Hernandez M, Mackenzie IR, Boeve BF, et al. *Neuron.* 2011;72:245-256. Renton AE, Majounie E, Waite A, et al. *Neuron.* 2011;72:257-268.

Amyotrophic lateral sclerosis

- Fatal neurodegenerative disease characterized by the progressive degeneration of motor neurons in the brain and spinal cord
- Affects approximately 15,000-20,000 people in the US with a median survival of three years
- C9orf72 is present in approximately 40% of familial ALS and 8-10% of sporadic ALS; currently the most common demonstrated mutation related to ALS, far more so than SOD1 or TDP-43
- Pathogenic transcripts of the C9orf72 gene contain hundreds to thousands of hexanucleotide repeats compared to 2-23 in wild-type transcripts; dominant trait with high penetrance



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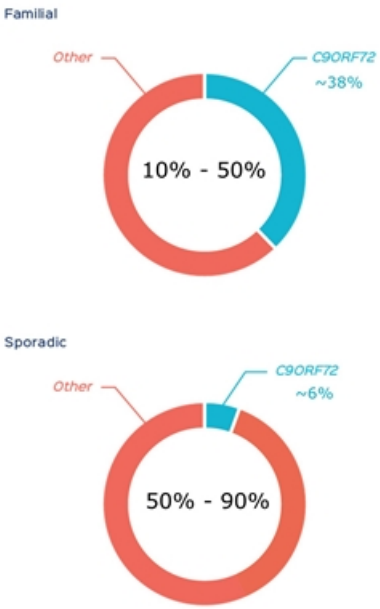
Source: Renton AE, Chiò A, Traynor BJ. State of play in amyotrophic lateral sclerosis genetics. *Nat Neurosci*. 2014;17:17–23.

Frontotemporal dementia

- Progressive neuronal atrophy with loss in the frontal and temporal cortices characterized by personality and behavioral changes, as well as gradual impairment of language skills
- Affects approximately 55,000 people in the US
- Second most common form of early-onset dementia after Alzheimer's disease in people under the age of 65
- Up to 50% of FTD patients have a family history of dementia, many inheriting FTD as an autosomal dominant trait with high penetrance
- Pathogenic transcripts of the C9orf72 gene contain hundreds to thousands of hexanucleotide repeats compared to 2-23 in wild-type transcripts



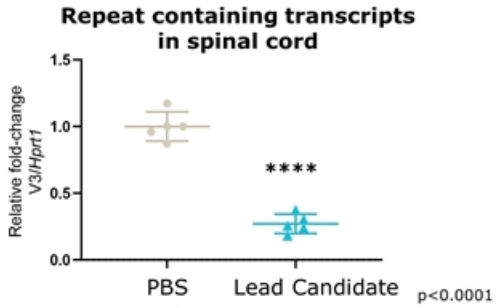
Sources: Stevens M, et al. Familial aggregation in frontotemporal dementia. *Neurology*. 1998;50:1541-1545. Majounie E, et al. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. *Lancet Neurol.* 2012;11:323-330.

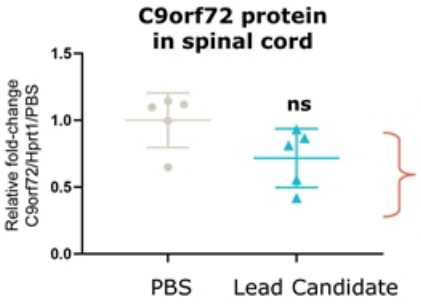
C9orf72 program: Allele-selective silencing *in vivo*

- C9orf72 genetic mutations are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of Amyotrophic Lateral Sclerosis (ALS) and Frontotemporal Dementia (FTD); GGGGCC repeat drives the formation and accumulation of dipeptide repeat proteins that accumulate in brain tissue
- **Wave's approach:** Selectively silence the GGGGCC repeat containing transcript while minimizing the impact on normal C9orf72 protein

Selective silencing of C9orf72 *in vivo* (transgenic mouse)

Reduction of repeat containing transcripts





Protein preservation

Clinical development expected to initiate in 2H 2020

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Experimental description: 2 x 50 ug on day 1 and day 8; mRNA Samples were analyzed using quantitative PCR (Taqman assay), Protein samples were measured by Western Blot.

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Ophthalmology

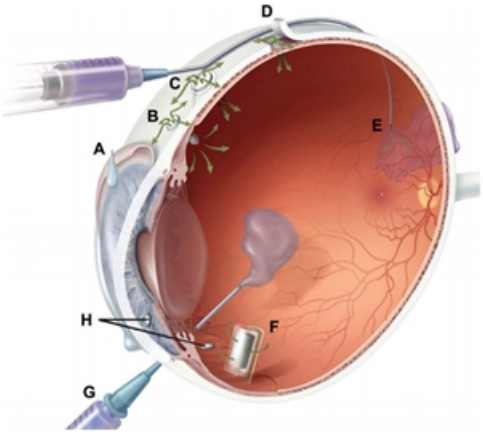
Stereopure oligonucleotides for inherited retinal diseases (IRDs)

Wave ophthalmology opportunity

- Oligonucleotides can be administered by intravitreal (IVT) injection; targeting twice per year dosing
- Stereopure oligonucleotides open novel strategies in both dominant and recessive IRDs; potential for potent and durable effect with low immune response

Successful targeting of *MALAT1* is a surrogate for an ASO mechanism of action

- Widely expressed in many different cell types
- Only expressed in the nucleus



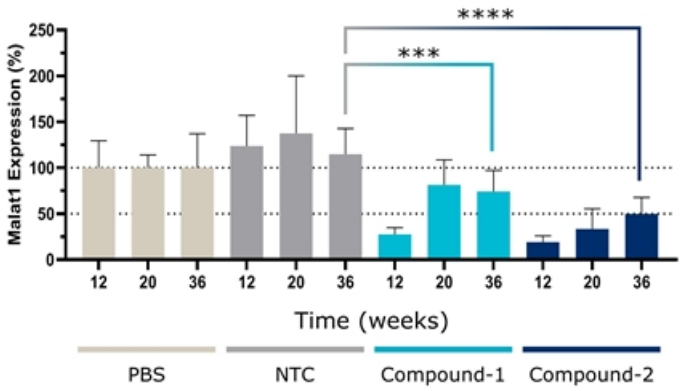
Intravitreal injection

Sources: Daiger S, et al. *Clin Genet*. 2013;84:132-141. Wong CH, et al. *Biostatistics*. 2018; DOI: 10.1093/biostatistics/kxx069. Athanasiou D, et al. *Prog Retin Eye Res*. 2018;62:1–23. Daiger S, et al. *Cold Spring Harb Perspect Med*. 2015;5:a017129. Verbakel S, et al. *Prog Retin Eye Res*. 2018:66:157-186.; Short, B.G.; *Toxicology Pathology*, Jan 2008.

Stereopure compound induces potent and durable *MALAT1* knockdown in the eye

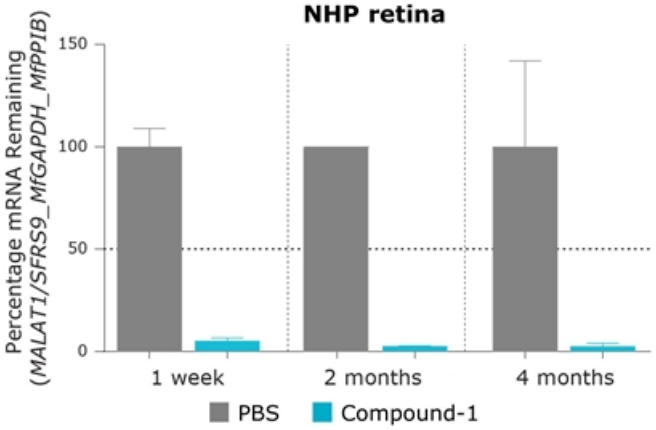
~50% *MALAT1* knockdown at 9 months

***In vivo* duration of effect in the mouse retina**



>90% knockdown of *MALAT1* maintained for 4 months

***In vivo* duration of effect in the NHP retina**



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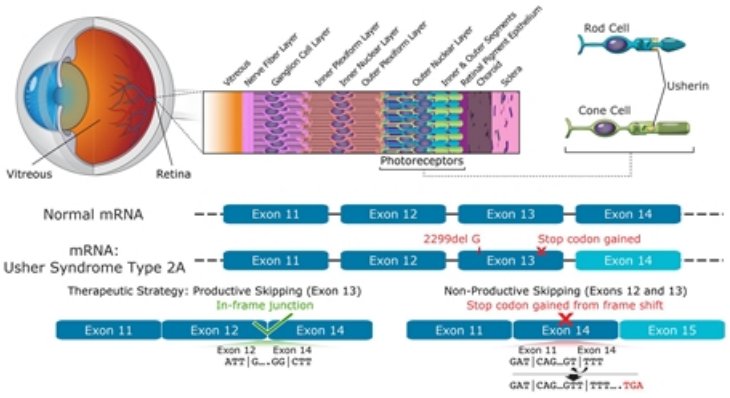
Mouse: Compound or PBS (1 x 50 mg IVT) was delivered to C57BL6 mice. Relative percentage of Malat1 RNA in the posterior of the eye (retina, choroid, sclera) to PBS-treated mice is shown at 12, 20 and 36 weeks post-single injection. Statistics: Compound-2 Malat1 levels are significantly different from NTC at 36 weeks ***, P<0.001; **** P<0.0001, respectively. PBS = phosphate buffered saline; NTC= chemistry matched non-targeting control; Compound-1 and Compound-2 are stereopure MALAT1-targeting antisense oligonucleotide. NHP: Oligonucleotide or PBS (1 x 450 µg IVT) was delivered to NHP. Relative percentage of *MALAT1* RNA in the retina to PBS-treated is shown at 1 week, 2 and 4 months, post-single injection. Compound-1 is a stereopure *MALAT1*-RNA-targeting antisense oligonucleotide.

Usher Syndrome Type 2A: a progressive vision loss disorder

- Autosomal recessive disease characterized by hearing loss at birth and progressive vision loss beginning in adolescence or adulthood
- Caused by mutations in USH2A gene (72 exons) that disrupt production of usherin protein in retina, leading to degeneration of the photoreceptors
- No approved disease-modifying therapies
- **~5,000 addressable patients in US**



Oligonucleotides that promote USH2A exon 13 skipping may restore production of functional usherin protein

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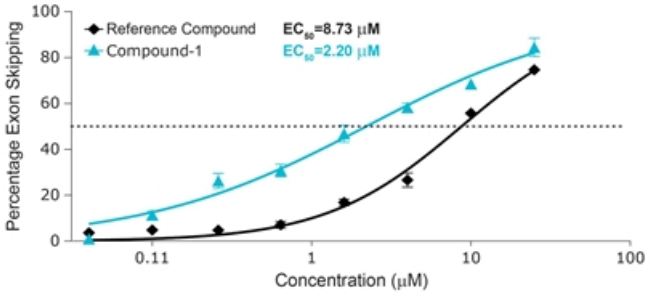
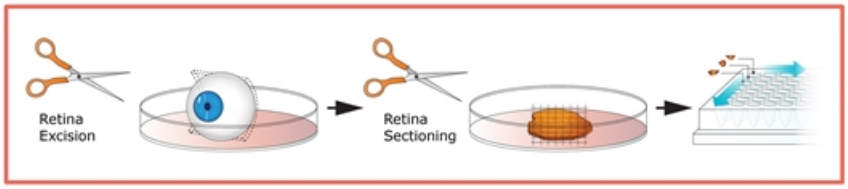
Sources: Boughman et al., 1983. *J Chron Dis.* 36:595-603; Seyedahmadi et al., 2004. *Exp Eye Res.* 79:167-173; Liu et al., 2007. *Proc Natl Acad Sci USA* 104:4413-4418.

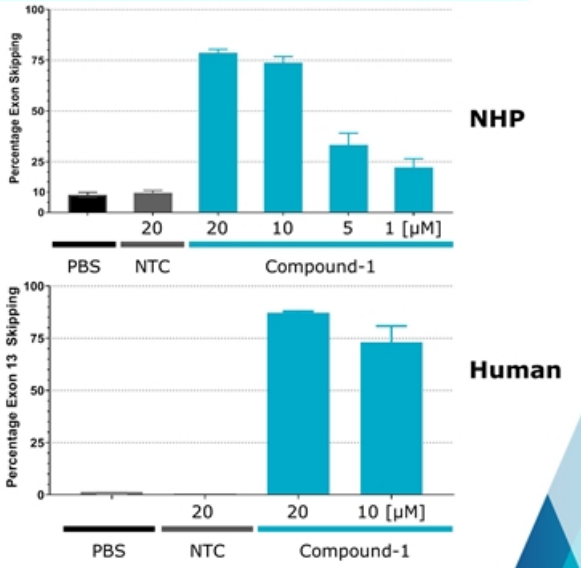
Potent USH2A exon 13 skipping with stereopure compound in *vitro* and *ex vivo*

Enhanced potency over a stereorandom reference compound (*in vitro*)





Target engagement in NHP and human retinas (*ex vivo*)



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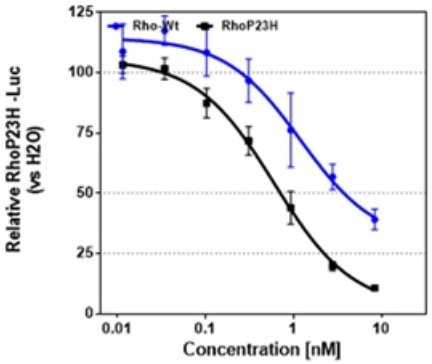
Left: Compounds were added to Y79 cells under free-uptake conditions. Exon skipping was evaluated by Taqman assays. *USH2A* transcripts were normalized to *SRSF9*. Data are mean±s.d., n=2. Reference Compound: van Diepen *et al.* 2018. Antisense oligonucleotides for the treatment of eye disease. W02018055134A1. Compound-1 is a stereopure antisense oligonucleotide. Right: Whole NHP and human eyes were enucleated (n=4 and n=2, respectively) and compounds (1–20 µM) were added to extracted retinas under free-uptake conditions. Exon skipping was evaluated by 48 hrs later by Taqman assays on RNA. USH2A transcript levels were normalized to SRSF9. Data presented are mean± s.e.m.

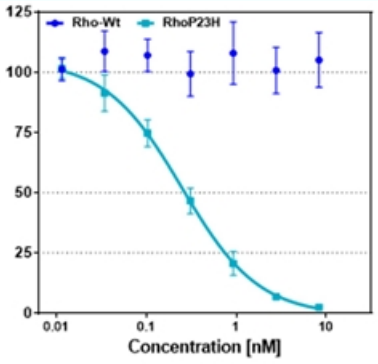
Allele-selective reduction of SNP-containing allele for adRP associated with Rhodopsin P23H mutation

- **Retinitis pigmentosa (RP)**: group of rare, genetic eye disorders resulting in progressive photoreceptor cell death and gradual functional loss; currently no cure
- ~10% of US autosomal dominant RP cases are caused by the P23H mutation in the rhodopsin gene (RHO)
- Mutant P23H rhodopsin protein is thought to misfold and co-aggregate with wild-type rhodopsin, resulting in a gain-of-function or dominant negative effect in rod photoreceptor cells

Stereorandom



Stereopure



In vivo

Collaborations in place for evaluation in transgenic human Rho P23H pig model

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Ferrari et al., *Current Genomics.* 2011;12:238-249.; Reporter assays on a Wave stereopure sequence as well as a sequence described in WO2016138353A1: ASO and luciferase reporter plasmids (wild-type and mutant rhodopsin) are transfected into Cos7 cells. 48-hours later, cells are harvested, and relative luminescence is measured.

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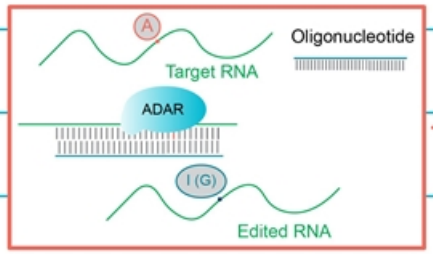
ADAR-mediated RNA editing

RNA-editing can be used for several therapeutic applications and supplement Wave's existing modalities

Strategy	Therapeutic Application	Treatment Modality: Silencing	Splicing	RNA Editing
Silence protein expression	Reduce levels of toxic mRNA/protein	✓		✓
Alter mRNA splicing	Exon skipping/inclusion/ restore frame		✓	✓
Fix nonsense mutations that cannot be splice-corrected	Restore protein expression			✓
Fix missense mutations that cannot be splice-corrected	Restore protein function			✓
Modify amino acid codons	Alter protein function			✓
Remove upstream ORF	Increase protein expression			✓



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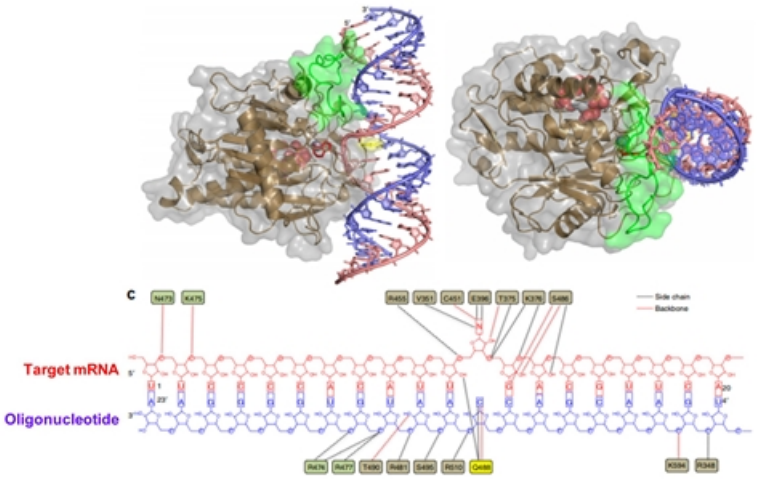
I (G): ADAR converts A>I, I is recognized as G by all cellular machinery; ADAR: Adenosine Deaminase Acting on RNA; ORF: Open reading frame

Using PRISM to unlock ADAR-mediated RNA editing

Structure of ADAR deaminase domain bound to dsRNA substrate



- ADAR makes multiple contacts with oligonucleotide backbone, sugar and bases
- Using PRISM platform, rationally designed and screened oligonucleotides to optimize:
  - 2' sugar chemistry
  - Backbone chemistry and stereochemistry
  - Size and structure
  - Modified nucleobases

~1,000 RNA editing oligonucleotides tested over the last year to develop SAR for editing format

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Structure adapted from Matthews et al., Nat Struct Mol Biol. (2016); SAR = structure-activity relationship; ADAR: Adenosine Deaminase Acting on RNA; dsRNA = double-stranded RNA

Wave's ADAR approach has several potential advantages over existing technologies

PRISM

Existing RNA editing technologies		Wave's RNA editing platform
Use unmodified RNA	Stability	Fully chemically-modified stereopure oligonucleotides
Require AAV or lipid nano particle delivery	Delivery	Free uptake into tissues
Require exogenous protein (e.g. CAS13 or chimeric ADAR)	Editing	Uses endogenous ADAR for editing

Single oligonucleotide through free uptake is sufficient for editing

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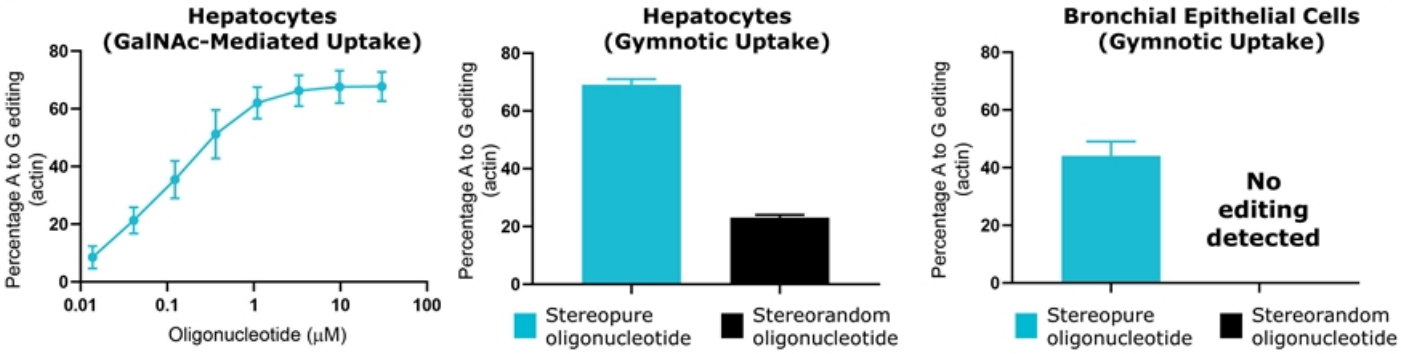
RNA-editing with endogenous ADAR achieved across multiple primary human cell types

Editing UAG Site in Actin mRNA in Primary Human Cell Lines



- Stereochemistry significantly increases editing across all cell lines tested, especially for gymnotic delivery
- GalNAc-conjugated fully-modified stereopure oligonucleotide can be used for targeted editing in hepatocytes; *in vitro* experiments suggest an EC50 of ~100 nM in primary hepatocytes
- *In vivo* editing with fully-modified stereopure oligonucleotide studies underway

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***In vivo* editing data expected in 2020**

Anticipated upcoming Wave milestones

Neuromuscular

- **4Q 2019:** Interim dystrophin data readout for suvodirsen from OLE in DMD (exon 51)
- **2H 2020:** Accelerated approval filing for suvodirsen in DMD (exon 51) in US, pending positive clinical dystrophin expression data
- **2H 2020:** Topline clinical data for WVE-N531 in DMD (exon 53)

CNS

- **By YE 2019:** Topline data readout from PRECISION-HD2 Phase 1b/2a trial in Huntington's disease
- **Early 2020:** Topline data readout from PRECISION-HD1 Phase 1b/2a trial in Huntington's disease
- **2H 2020:** Initiation of clinical development of C9orf72 program in ALS and FTD

Ophthalmology

- **2020:** Advance USH2A exon-skipping program

RNA-editing

- **2020:** *In vivo* ADAR editing data

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Realizing the potential of genetic medicines

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