# 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): March 12, 2018**

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

| **Singapore** | **001-37627** | **Not Applicable** |
|---|---|---|
| **(State or other jurisdiction of incorporation)** | **(Commission File Number)** | **(IRS Employer Identification No.)** |

| | |
|---|---|
| **7 Straits View #12-00 Marina One East Tower**<br>**Singapore 018936**<br>**(Address of principal executive offices)** | **018936**<br>**(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))

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 March 12, 2018, Wave Life Sciences Ltd. (the "Company") announced its financial results for the quarter and year ended December 31, 2017. 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 March 12, 2018, 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 this report furnished pursuant to Items 2.02 and 7.01 shall not be deemed "filed" for the 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. It may only be incorporated by reference in another filing under the Exchange Act or the Securities Act of 1933, as amended, if such subsequent filing specifically references the information furnished pursuant to Items 2.02 and 7.01 of this report.*

**Item 9.01 Financial Statements and Exhibits.**

(d) Exhibits.

The following exhibits relating to Items 2.02 and 7.01 shall be deemed to be furnished, and not filed:

| Exhibit No. | Document |
|---|---|
| 99.1 | Press Release issued by Wave Life Sciences Ltd. dated March 12, 2018 |
| 99.2 | Corporate Presentation of Wave Life Sciences Ltd. dated March 12, 2018 |

**SIGNATURE**

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.**

Date: March 12, 2018

/s/ Keith C. Regnante
Keith C. Regnante
Chief Financial Officer

**Exhibit 99.1**

**Wave Life Sciences Reports Fourth Quarter and Full-Year 2017 Financial Results and Provides Business Update**

*Initiated three clinical trials in 2017 and on track to deliver three additional development programs in 2018*

*Neurology pipeline growing; candidate in spinocerebellar ataxia type 3 to be named by year end 2018*

**CAMBRIDGE, Mass., March 12, 2018** – Wave Life Sciences Ltd. (NASDAQ: WVE), a biotechnology company focused on delivering transformational therapies for patients with serious, genetically-defined diseases, today reported financial results for the fourth quarter and full year ended December 31, 2017, and provided a business update.

"2017 was a transformative year for Wave as we transitioned into clinical development by initiating trials for our three lead neurology programs, established our in-house manufacturing capability and made great progress on delivering three more neurology development programs in 2018," said Paul Bolno, MD, MBA, President and Chief Executive Officer of Wave Life Sciences. "Our expertise in designing potentially first-in-class and innovative medicines continues to grow as we generate additional *in vivo* data demonstrating the impressive pharmacodynamic and pharmacokinetic properties of stereopure oligonucleotides in a variety of animal models across multiple organ systems and tissues. We look forward to advancing our existing and planned clinical programs, collaborating with our partners at Takeda and continuing to build our internal capabilities in preparation for the potential commercialization of our lead programs."

**Business Summary and Update**

- **Global strategic collaboration with Takeda to advance therapies for central nervous system (CNS) disorders**

  In February 2018, Wave formed a global strategic collaboration with Takeda Pharmaceutical Company Limited (Takeda) to discover, develop, and commercialize nucleic acid therapies for disorders of the CNS. Under the terms of the agreement, Takeda is obligated to make an initial payment of $110 million to Wave and purchase $60 million of Wave's ordinary shares at $54.70 per share. Takeda is also required to fund at least $60 million of Wave research over a four-year period to advance multiple preclinical targets. Wave's collaboration agreement with Takeda will become effective upon satisfaction of customary closing conditions, including the requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976.

- **Preclinical *in vivo* data supporting amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD) programs presented at 28th International Symposium on ALS/MND**

  In December 2017, Wave announced data from preclinical studies of WVE-3972-01, the company's investigational stereopure antisense oligonucleotide designed to target the pathogenic allele of the *C9ORF72* gene for the treatment of ALS and FTD. In preclinical *in vivo* studies, WVE-3972-01 demonstrated a potent, sustained and preferential knockdown of toxic biomarkers associated with ALS and FTD.

- **Neurology pipeline continues to progress and expand across multiple diseases**

  *Expanding the neurology pipeline into spinocerebellar ataxia type 3 (SCA3)*

  Wave announced today that it expects to name a potential candidate targeting the *ATXN3* gene for the treatment of SCA3 by the end of 2018. This new program will add to Wave's current and planned clinical neurology development programs in Huntington's disease (HD), Duchenne muscular dystrophy (DMD), ALS, and FTD.

SCA3, also known as Machado–Joseph disease, is caused by a CAG-repeat expansion in the *ATXN3* gene, resulting in an abnormally long polyglutamine stretch in the encoded ataxin-3 protein. Mutant ataxin-3 protein is thought to cause widespread neuronal loss in the brain and spinal cord, likely through a toxic gain of function mechanism. SCA3 is the most common dominantly inherited form of ataxia. The prevalence of SCA3 is believed to be one to two cases in 100,000 people with significant geographic and ethnic variations. There are currently no therapies approved for the treatment of SCA3.

*HD: WVE-120101 and WVE-120102*

The PRECISION-HD program, which includes two global Phase 1b/2a clinical trials evaluating WVE-120101 and WVE-120102 for patients with HD, continues to enroll patients and the company is on track to report topline data in H1 2019.

Wave's two programs are allele-specific and differentiated from other investigational therapies currently being studied for the treatment of HD. WVE-120101 and WVE-120102 are designed to selectively silence mRNA transcript produced by the disease-causing mutant *huntingtin* (*HTT*) allele. This personalized approach reduces the mutant HTT protein while leaving the healthy HTT mRNA transcript relatively intact. The healthy transcript is required to produce wild-type, or healthy, HTT protein which is critical for neuronal function, as evidenced by multiple preclinical studies indicating that long-term suppression of healthy HTT protein may have detrimental consequences. Wave's allele-specific approach may also enable the company to address the pre-manifest, or asymptomatic, HD patient population in the future.

*DMD: WVE-210201*

Wave continues to advance its research and clinical efforts in neuromuscular diseases, including WVE-210201, currently in a global Phase 1 clinical trial for the treatment of DMD patients amenable to exon 51 skipping. Safety data from the trial are anticipated in Q3 2018 and expected to facilitate the rapid transition to an open-label extension study and efficacy study. Both studies following the Phase 1 are designed to include an interim efficacy readout of dystrophin expression from muscle biopsies in H2 2019.

*ALS, FTD and exon 53 DMD programs on track to transition to development in 2018*

The company intends to initiate clinical trials of WVE-3972-01 in ALS and FTD in Q4 2018. Wave's next DMD development program will target exon 53, with clinical trials expected to initiate in Q1 2019.

- **New *in vivo* data support ophthalmology franchise**

  Wave is advancing the development of stereopure oligonucleotides to target genetic ophthalmologic diseases, with an initial emphasis on retinal diseases. Using the long-noncoding RNA *MALAT1* as a proof-of concept target, a 10-fold increase in potency was achieved *in vivo* with a stereopure oligonucleotide as compared to a stereorandom oligonucleotide following a single intravitreal injection in the back of a mouse eye. The knockdown of *MALAT1* RNA was sustained through three months after the single injection and the study is scheduled to continue for a total of six months.

  In addition, recent results from a preclinical *in vivo* study in non-human primates demonstrated that a stereopure oligonucleotide achieved a clear dose-dependent knockdown of *MALAT1* mRNA in the back of the eye one week following a single intravitreal injection. A six-month duration of effect study is planned.

  Wave is conducting additional research to develop stereopure oligonucleotides against specific genetic targets to treat diseases of the eye.

- **Pfizer collaboration progress**

  In November 2017, Wave achieved a milestone under its collaboration with Pfizer by demonstrating significant activity of stereopure GalNAc-conjugated APOC3 antisense oligonucleotides over stereorandom oligonucleotides in *in vivo* studies and meeting other milestone criteria. The collaboration continues to make progress on developing genetically targeted therapies for the treatment of metabolic diseases, such as nonalcoholic steatohepatitis.

**Fourth Quarter and Full Year 2017 Financial Results and Financial Guidance**

Wave reported a net loss of $30.2 million in the fourth quarter of 2017 compared to $18.5 million in the fourth quarter of 2016. The company reported a net loss of $102.0 million for the year ended December 31, 2017 as compared to $55.4 million for the year ended December 31, 2016. The increase in net loss for the fourth quarter and year ended December 31, 2017 was mainly due to increases in research and development efforts, infrastructure investments, and employee headcount to support its corporate goals.

Research and development expenses were $25.4 million for the fourth quarter of 2017 as compared to $14.0 million for the same period in 2016. Research and development expenses for the full year were $79.3 million as compared to $40.8 million for the prior year. The increase in research and development expenses for the fourth quarter and full year was primarily driven by increases in research, preclinical and clinical investments, as well as facilities-related expenses to continue to advance Wave's expanding pipeline.

General and administrative expenses were $6.9 million for the fourth quarter of 2017 as compared to $5.2 million for the same period in the prior year. General and administrative expenses were $27.0 million for the full year as compared to $16.0 million for the prior year. The increase in general and administrative expenses in the fourth quarter and full year was primarily driven by the continued growth in Wave's employee headcount, as well as increases in facilities-related expenses and other general operating expenses.

Wave ended 2017 with $142.5 million in cash and cash equivalents compared to $150.3 million as of December 31, 2016. The decrease in cash and cash equivalents was primarily the result of Wave's annual operating loss of $102.0 million partially offset by the $93.5 million in net proceeds from the April 2017 follow-on offering.

The company expects that its cash and cash equivalents, together with the committed cash from its collaboration with Takeda, which is expected to close in the first quarter of 2018, have the potential to fund its operating and capital expenditure requirements to the end of 2020.

**About Wave Life Sciences**

Wave Life Sciences is a biotechnology company focused on delivering transformational therapies for patients with serious, genetically-defined diseases. Our chemistry platform enables the creation of highly specific, well characterized oligonucleotides designed to deliver superior efficacy and safety across multiple therapeutic modalities. Our pipeline is initially focused on neurological disorders and extends across several other therapeutic areas. For more information, please visit www.wavelifesci.com.

**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, data readouts and duration of our clinical trials; the protocol, design and endpoints of our clinical trials; the future performance and results of our programs in clinical trials; the progress and potential benefits of our collaborations with partners, including the expected timing of when our collaboration with Takeda will take effect; the potential of our *in vitro* and *in vivo* preclinical data to predict the behavior of our compounds in humans in clinical trials; our identification of future candidates and their therapeutic potential; the anticipated therapeutic benefits of our potential therapies compared to others; our advancing of therapies across multiple modalities and the anticipated benefits of that strategy; the anticipated benefits of our manufacturing process

and our internal manufacturing facility; our future growth; the potential benefits of our stereopure compounds compared to stereorandom compounds, our drug discovery platform and nucleic acid therapeutics generally; 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: 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 success of our platform in identifying viable candidates; the continued development and acceptance of nucleic acid therapeutics as a class of drugs; our ability to demonstrate the therapeutic benefits of our candidates in clinical trials, including our ability to develop candidates across multiple therapeutic modalities; 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; our ability to finance our drug discovery efforts and to raise additional capital when needed; 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.

**Investor Contact:**

Jillian Connell
Investor@wavelifesci.com

**Media Contact:**

Jose Juves
617-949-4708
jjuves@wavelifesci.com

**Patient Contact:**

Wendy Erler
617-949-2898
werler@wavelifesci.com

**WAVE LIFE SCIENCES LTD.**
**UNAUDITED CONSOLIDATED BALANCE SHEETS**

*(In thousands, except share amounts)*

| | December 31, 2017 | December 31, 2016 |
|---|---|---|
| **Assets** | | |
| Current assets: | | |
| Cash and cash equivalents | $ 142,503 | $ 150,293 |
| Prepaid expenses and other current assets | 7,985 | 1,483 |
| Deferred tax assets | — | 214 |
| Total current assets | 150,488 | 151,990 |
| Long-term assets: | | |
| Property and equipment, net | 27,334 | 8,607 |
| Deferred tax assets | — | 560 |
| Restricted cash | 3,610 | 3,601 |
| Other assets | 411 | 53 |
| Total long-term assets | 31,355 | 12,821 |
| Total assets | $ 181,843 | $ 164,811 |
| **Liabilities, Series A preferred shares and shareholders' equity** | | |
| Current liabilities: | | |
| Accounts payable | $ 7,598 | $ 4,943 |
| Accrued expenses and other current liabilities | 8,898 | 4,434 |
| Current portion of capital lease obligation | 16 | 62 |
| Current portion of deferred rent | 60 | — |
| Current portion of deferred revenue | 2,705 | 2,705 |
| Current portion of lease incentive obligation | 344 | 11 |
| Total current liabilities | 19,621 | 12,155 |
| Long-term liabilities: | | |
| Capital lease obligation, net of current portion | — | 16 |
| Deferred rent, net of current portion | 4,214 | 680 |
| Deferred revenue, net of current portion | 5,607 | 8,311 |
| Lease incentive obligation, net of current portion | 3,094 | 116 |
| Other liabilities | 1,619 | 796 |
| Total long-term liabilities | 14,534 | 9,919 |
| Total liabilities | $ 34,155 | $ 22,074 |
| Series A preferred shares, no par value; 3,901,348 shares issued and outstanding | $ 7,874 | $ 7,874 |
| Shareholders' equity: | | |
| Ordinary shares, no par value; 27,829,079 and 23,502,169 shares issued and outstanding at December 31, 2017 and 2016, respectively | 310,038 | 215,602 |
| Additional paid-in capital | 22,172 | 10,029 |
| Accumulated other comprehensive income (loss) | 116 | (291) |
| Accumulated deficit | (192,512) | (90,477) |
| Total shareholders' equity | 139,814 | 134,863 |
| Total liabilities, Series A preferred shares and shareholders' equity | $ 181,843 | $ 164,811 |

**WAVE LIFE SCIENCES LTD.**
**UNAUDITED CONSOLIDATED STATEMENTS OF OPERATIONS**

*(In thousands, except share and per share amounts)*

| | For the Year Ended December 31, | | |
|---|---|---|---|
| | 2017 | 2016 | 2015 |
| Revenue | $ 3,704 | $ 1,485 | $ 152 |
| Operating expenses: | | | |
| Research and development | 79,309 | 40,818 | 9,057 |
| General and administrative | 26,975 | 15,994 | 10,393 |
| Total operating expenses | 106,284 | 56,812 | 19,450 |
| Loss from operations | (102,580) | (55,327) | (19,298) |
| Other income (expense), net: | | | |
| Dividend income | 1,578 | 255 | — |
| Interest income (expense), net | 6 | 337 | 86 |
| Other income (expense), net | (331) | (50) | 56 |
| Total other income (expense), net | 1,253 | 542 | 142 |
| Loss before income taxes | (101,327) | (54,785) | (19,156) |
| Income tax provision | (708) | (616) | (44) |
| Net loss | $ (102,035) | $ (55,401) | $ (19,200) |
| Net loss per share attributable to ordinary shareholders—basic and diluted | $ (3.85) | $ (2.43) | $ (1.83) |
| Weighted-average ordinary shares used in computing net loss per share attributable to ordinary shareholders—basic and diluted | 26,513,382 | 22,800,628 | 10,501,455 |

Exhibit 99.2

# Wave Life Sciences

## Corporate Presentation

March 12, 2018

# 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.

## Biotechnology company focused on delivering transformational therapies for patients with serious, genetically defined diseases

- Rationally designed stereopure nucleic acid therapeutics
- Utilizing multiple modalities including antisense, exon skipping and RNAi
- 6 neurology development programs by the end of 2018
- Expertise and core focus in neurology
  - 2 Phase 1b/2a trials initiated in Huntington's disease
  - DMD Exon 51 trial initiated
  - Clinical data readouts anticipated in 2019 for first 3 programs
- Robust R&D platform, ability to partner additional therapeutic areas
- Cash, including committed capital from the Takeda collaboration*, has the potential to fund operations to the end of 2020

* Expected to close in Q1 2018, subject to customary closing conditions, including the Hart-Scott-Rodino Antitrust Improvements Act of 1976

WAVE™
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# Paving the way to potentially safer, more effective medicines

**1**
first to design and bring stereopure and allele-specific medicines to clinic

**6**
neurology development programs by end of 2018

**3**
clinical studies initiated in 2017

**10K+**
oligonucleotides created and analyzed to date

**5**
nucleic acid modalities being advanced with Wave stereopure chemistry

**12+**
discovery programs

**5**
therapeutic areas under active investigation

**25M+**
total potentially addressable patients amenable to Wave's partnered and proprietary programs

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# Pipeline spanning multiple modalities, novel targets

| | TARGET | BIOMARKER | ESTIMATED U.S. PREVALENCE [1] | MECHANISM | DISCOVERY | CANDIDATE | CLINICAL | WAVE'S COMMERCIAL RIGHTS | PARTNER | NEXT ANTICIPATED EVENT |
|---|---|---|---|---|---|---|---|---|---|---|
| **CNS** | | | | | | | | | | |
| Huntington's disease | mHTT SNP1 | mHTT | ~10k / ~35k | A | ● | ● | Phase 1b/2a | 50% Global [4] | Takeda [4] | Top line data H1 2019 |
| Huntington's disease | mHTT SNP2 | mHTT | ~10k / ~35k | A | ● | ● | Phase 1b/2a | 50% Global [4] | Takeda [4] | Top line data H1 2019 |
| Amyotrophic lateral sclerosis | C9orf72 | Dipeptide | ~1,800 | A | ● | ● | | 50% Global [4] | Takeda [4] | Trial initiation Q4 2018 |
| Frontotemporal dementia | C9orf72 | Dipeptide | ~7,000 | A | ● | ● | | 50% Global [4] | Takeda [4] | Trial initiation Q4 2018 |
| Spinocerebellar ataxia 3 | ATXN3 | | ~4,500 | ● | ● | ○ | | 50% Global [4] | Takeda [4] | Candidate by YE 2018 |
| CNS diseases | Multiple [2, 4] | | | ○ | ● | ○ | | Milestones & Royalties [4] | Takeda [4] | |
| **MUSCLE** | | | | | | | | | | |
| Duchenne muscular dystrophy | Exon 51 | Dystrophin | ~2,000 | E | ● | ● | Phase 1 | 100% Global | — | Top line data Q3 2018 |
| Duchenne muscular dystrophy | Exon 53 | Dystrophin | ~1,250 | E | ● | ○ | | 100% Global | — | Trial initiation Q1 2019 |
| Neuromuscular diseases | Multiple | | | ○ | ● | ○ | | 100% Global | — | |
| **OPHTHALMOLOGY** | | | | | | | | | | |
| Retinal diseases | Multiple | | | ○ | ● | ○ | | 100% Global | — | |
| **HEPATIC** | | | | | | | | | | |
| Metabolic liver diseases | APOC3 | Triglyceride | | ● | ● | ○ | | Milestones & Royalties | Pfizer | |
| Metabolic liver diseases | Multiple (2) [3] | | | ○ | ● | ○ | | Milestones & Royalties | Pfizer | |

1. 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
2. During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time
3. Pfizer has nominated two undisclosed targets in addition to APOC3
4. Wave's collaboration agreement with Takeda is not effective until satisfaction of customary closing conditions, including the requirements of the Hart-Scott-Rodino Antitrust Improvements Act of 1976

● = silencing. A = allele-specific silencing. E = exon skipping.

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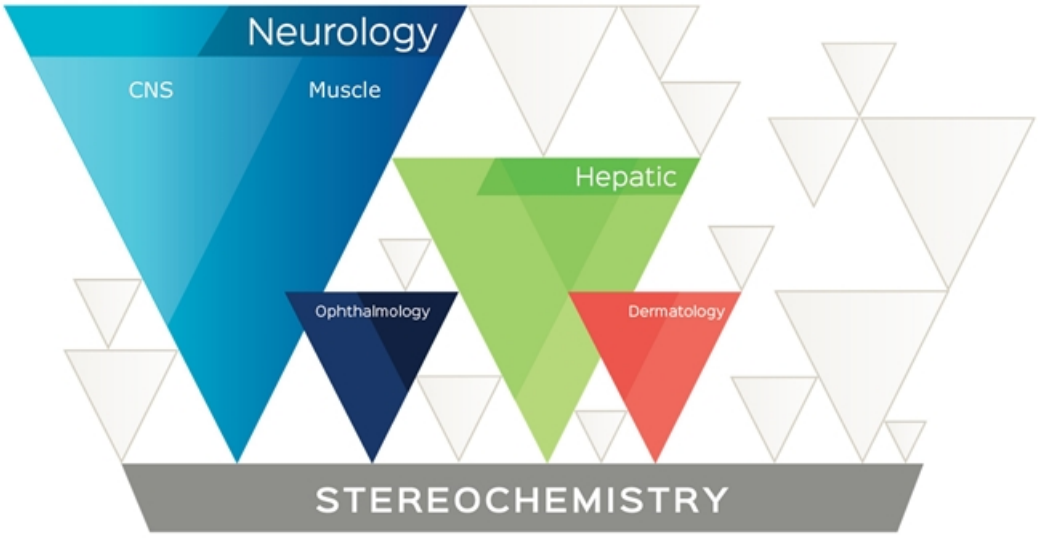
# Broad platform relevance across therapeutic areas

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# Building 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

Stereochemistry enables precise control, ability to optimize critical constructs into one defined and consistent profile

↓

Impact:
Potential for safer, more effective, targeted medicines that can address difficult-to-treat diseases

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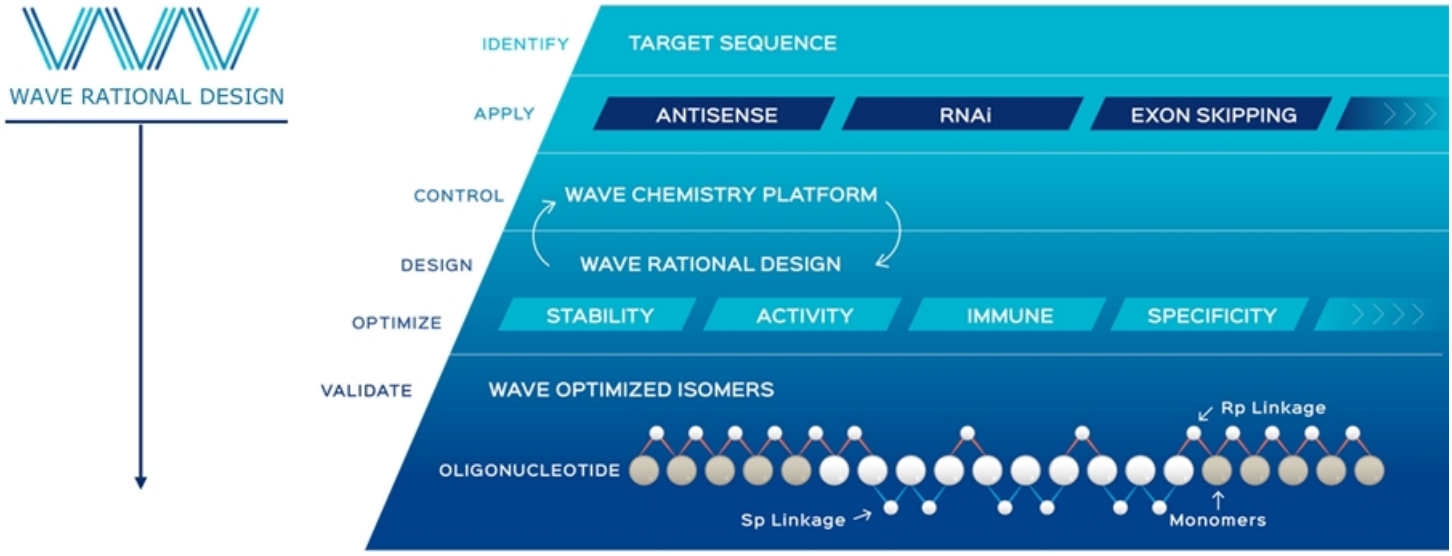
# Creating a new class of oligonucleotides



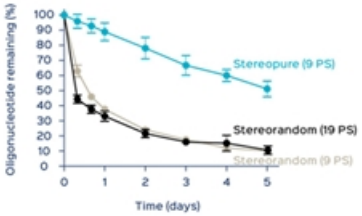

WAVE LIFE SCIENCES

Source: Iwamoto N, et al. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. Nature Biotechnology. 2017.

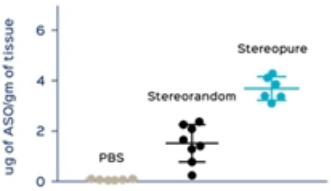
# Chemistry may optimize medicines across multiple dimensions

## Improved Stability

Stability of stereopure molecules with reduced PS content (liver homogenate)

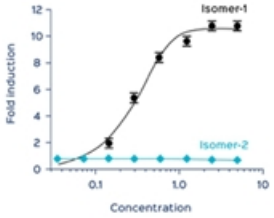



Oligonucleotide exposure (spinal cord)

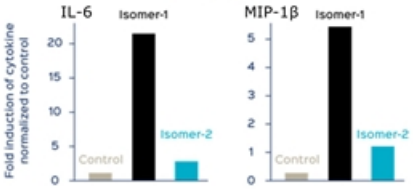



## Controlled Immunogenicity

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

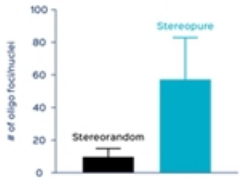



Cytokine induction in human PBMC assay

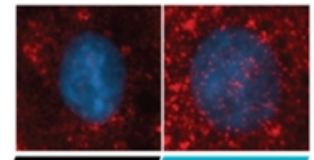



## Enhanced Delivery

Stereochemistry enables enhanced delivery of oligonucleotides




Uptake without transfection agent between a stereopure and stereorandom oligonucleotide




Gymnotic uptake of ASOs:18h differentiating myoblasts

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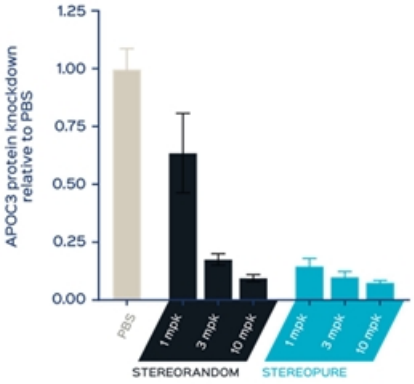
Data represented in this slide from in vitro studies. Experimental conditions: Human TLR9 assay – Source: Ohto U, et al. Structural basis of CpG and inhibitory DNA recognition by Toll-like receptor 9, Nature 520, 702-705, 2015. Intracellular trafficking assay – Cells were washed and fixed and oligos were detected by viewRNA assay and visualized on immunofluorescence microscope with deconvolution capabilities. Z-stacks were taken to eliminate artifacts.

# Stereochemistry is applicable across modalities

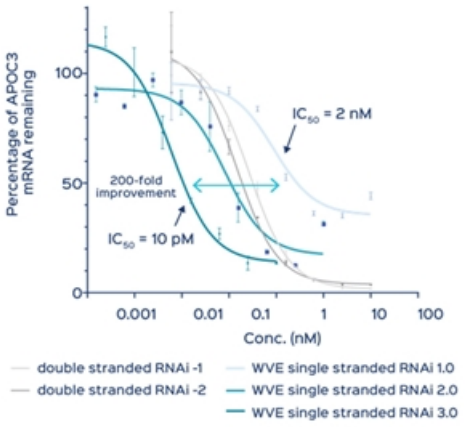
## Antisense

In vivo potency and durability
(APOC3 transgenic mice, day 15)



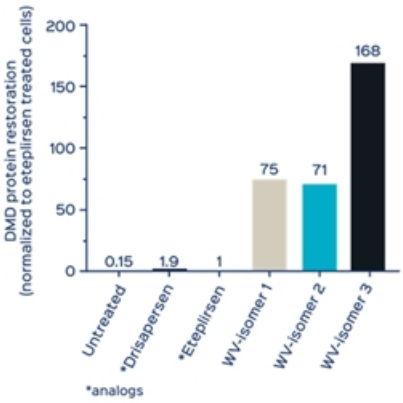

## RNAi

200 Fold Higher Potency from
Original ssRNAi Designs




## Exon skipping

71-168 Fold Increase in
Protein Restoration
Compared to Eteplirsen *




Stereochemistry allows for novel approaches to previously difficult diseases and inaccessible targets

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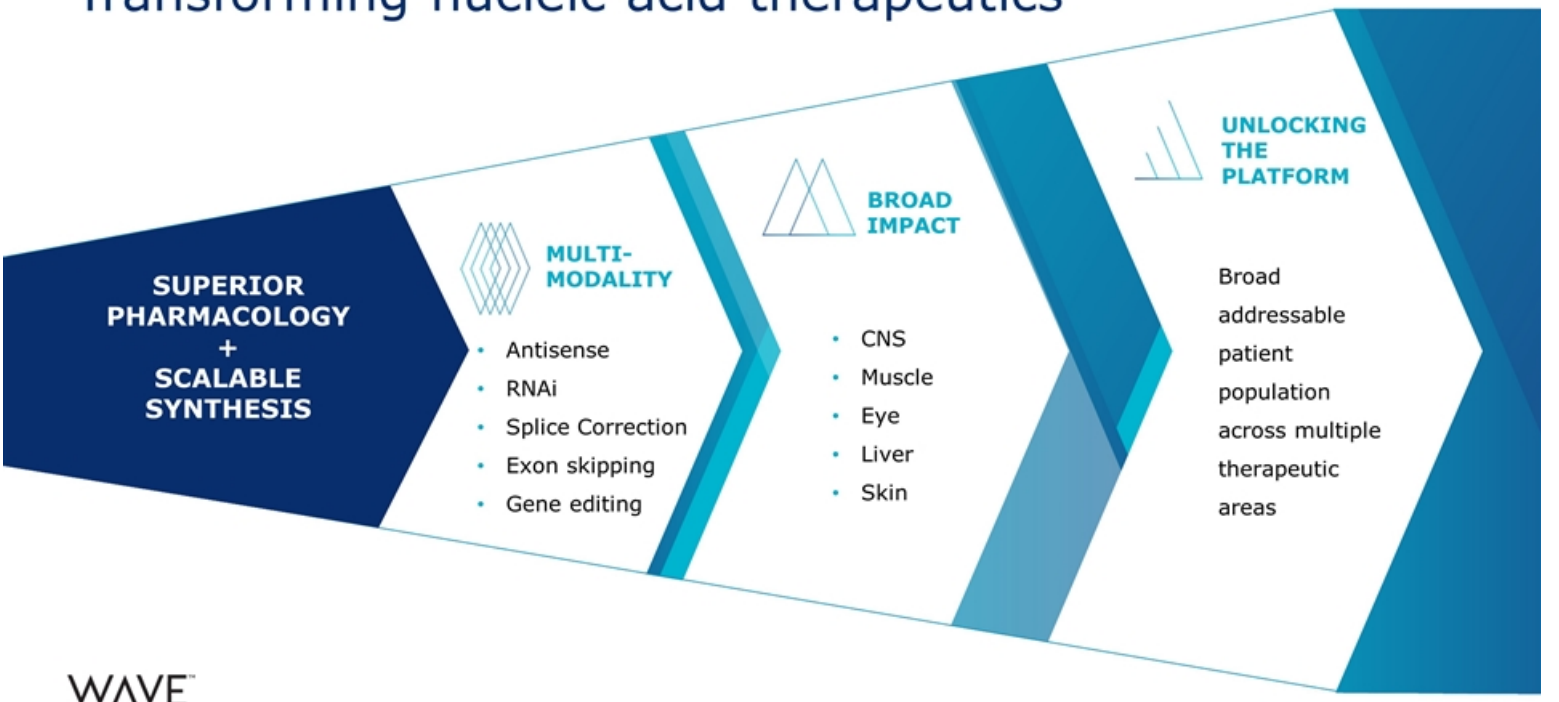
# Transforming nucleic acid therapeutics

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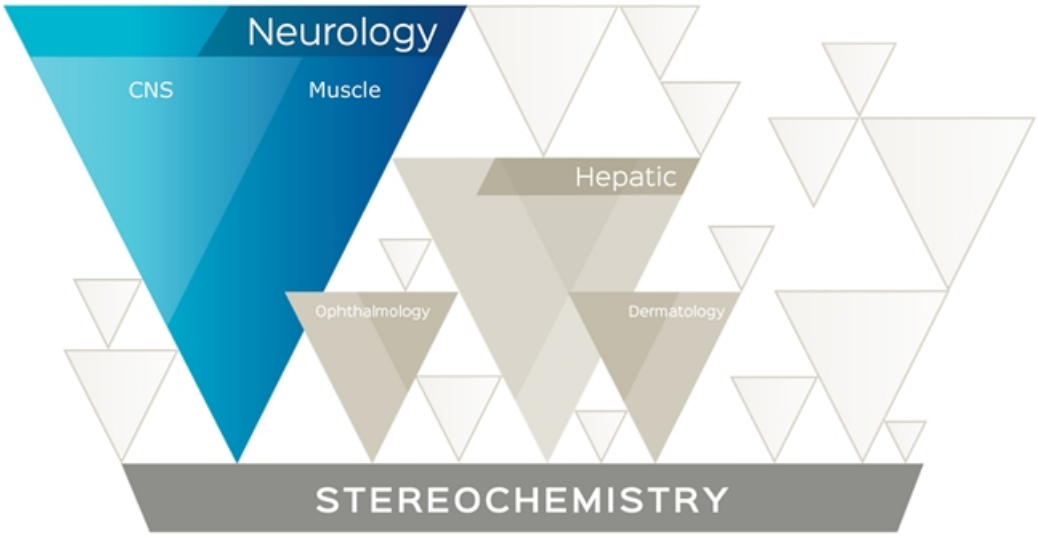
# Neurology

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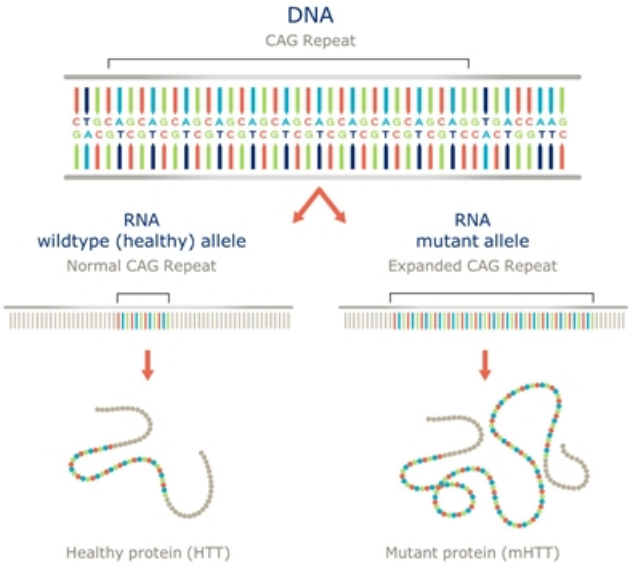
# Huntington's Disease

# Huntington's Disease: a hereditary, fatal disorder

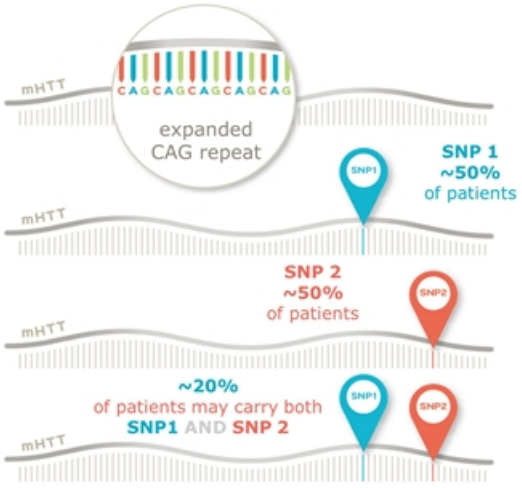
- Autosomal dominant disease, characterized by cognitive decline, psychiatric illness and chorea; fatal
- No approved disease-modifying therapies
- Expanded CAG triplet repeat in HTT gene results in production of mutant huntingtin protein (mHTT); accumulation of mHTT causes progressive loss of neurons in the brain
- Wildtype (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




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.

# Wave approach: novel, allele-specific silencing

- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including HD.
- Allele-specificity possible by targeting SNPs associated with expanded long CAG repeat in mHTT gene
- Approach aims to lower mHTT transcript while leaving healthy HTT relatively intact
- Potential to provide treatment for up to 70% of HD population (either oligo alone could address approximately 50% of HD population)




Total: Due to overlap, an estimated **~70%** of the total HD patient population carry SNP 1 and/or SNP 2

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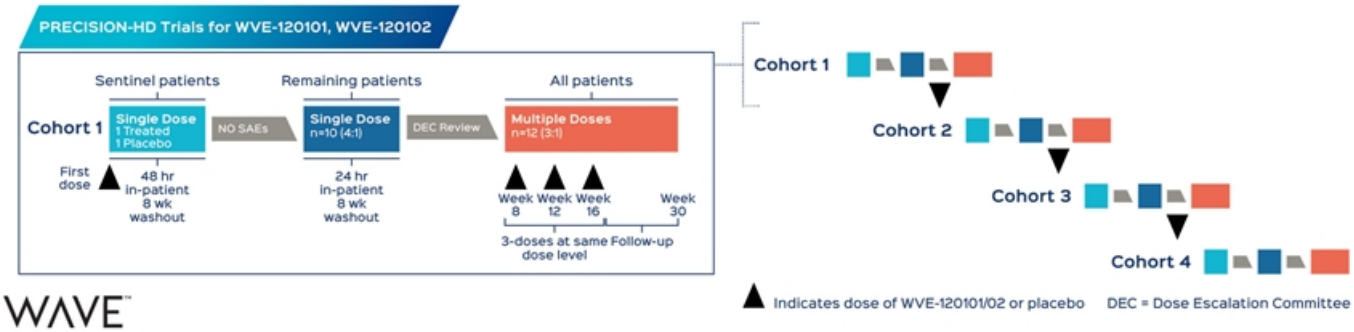
Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. Clin Genet 2014: 86: 29–36

# Two simultaneous Phase 1b/2a clinical trials

- Two parallel global placebo-controlled multi-ascending-dose trials for WVE-120101, WVE-120102
- Primary objective: assess safety and tolerability of intrathecal doses in early manifest HD patients
- Additional objectives: exploratory pharmacokinetic, pharmacodynamic, clinical and MRI endpoints
- Blood test to determine presence of SNP 1 or SNP 2 done at pre-screening
- Approximately 50 patients per trial
- Key inclusion criteria:
  age ≥25 to ≤65, stage I or II HD
- Top line data anticipated H1 2019

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# Mutant huntingtin: a powerful, novel biomarker

- Novel immunoassay allows for quantification of mutant huntingtin, the cause of HD
- Level of mHTT detected is associated with time to onset, increased with disease progression, and predicts diminished cognitive and motor dysfunction
- Assay currently being utilized in clinical studies

**Novel approach enables precise measurement of target engagement and effect**


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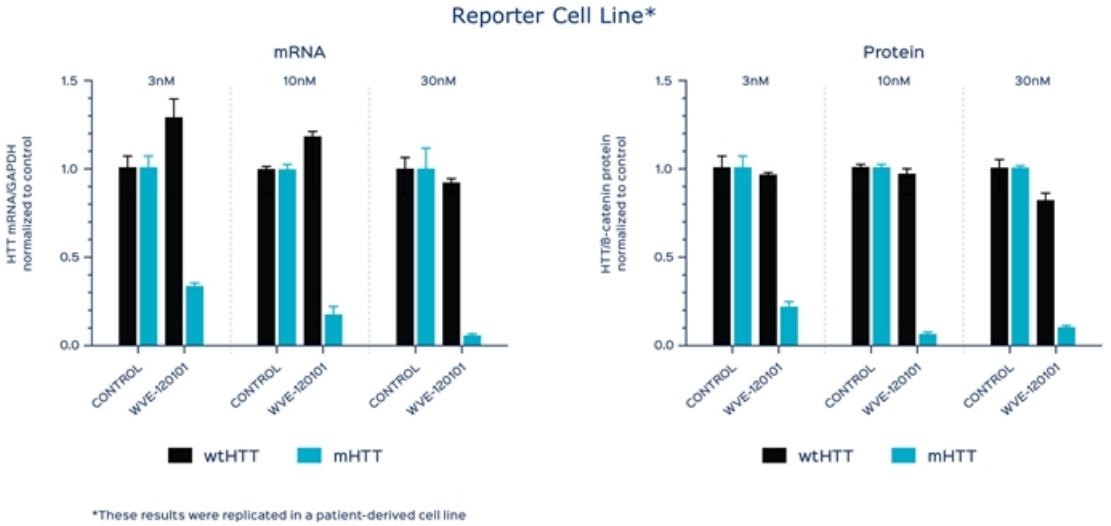
Source: Wild E, et al. Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients. J. Clin. Invest. 2015:125:1979–1986. Edward Wild, MA MB BChir PhD MRCP Principal Investigator at UCL Institute of Neurology and Consultant Neurologist at the National Hospital for Neurology and Neurosurgery, London

# Selective reduction of mHTT mRNA & protein




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

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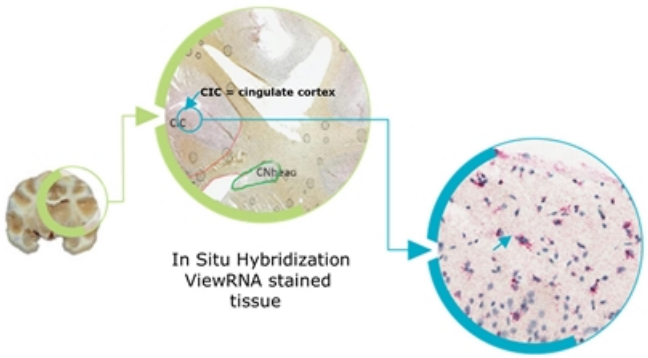
# Demonstrated delivery to brain tissue

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

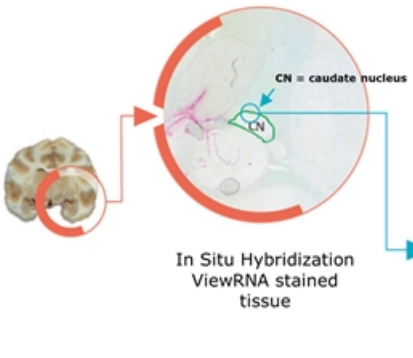



In Situ Hybridization ViewRNA stained tissue

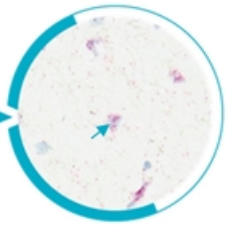


Red dots are WVE-120101 oligonucleotide.

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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CIC = cingulate cortex.
CN = caudate nucleus.

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# 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 3,500 newborn boys each year; 20,000 new cases annually worldwide

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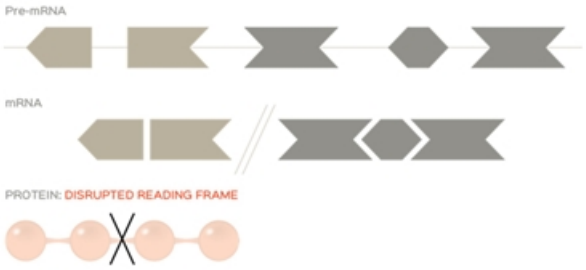
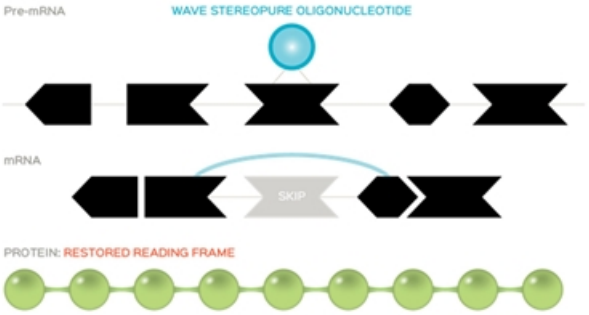
# Wave approach:
## meaningful restoration of dystrophin production through exon skipping

- Meaningful restoration of dystrophin production is expected to result in therapeutic benefit
- Exon-skipping antisense approaches may enable production of functional dystrophin protein
- Initial patient populations are those amenable to Exon 51 and Exon 53 skipping

Dysfunctional splicing (Disease)




Exon skipping (Potential Remedy)

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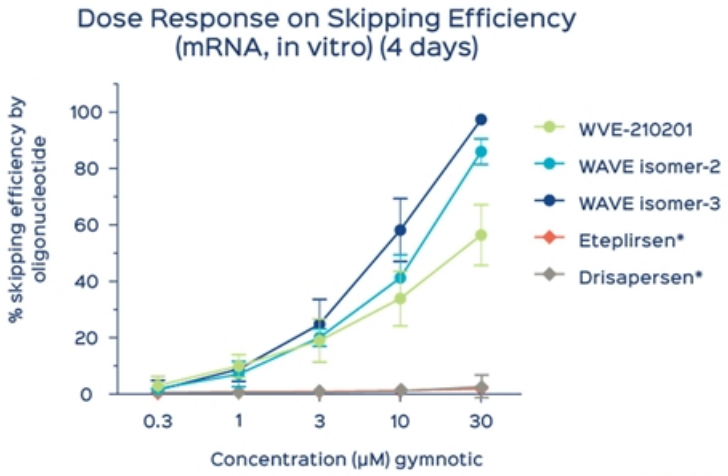
# Exon 51: WVE-210201 clinical program

- WVE-210201 Phase 1 clinical trial initiated November 2017
  - Design: Multicenter, double-blind, placebo-controlled, single ascending dose study with I.V. administration
  - Primary endpoint: Safety and tolerability
  - Inclusion criteria: ages 5 to 18, amenable to exon 51 skipping
    - Ambulatory and non-ambulatory boys eligible, including those previously treated with eteplirsen (following appropriate washout period)
  - Readout expected Q3 2018
  - Planned open-label extension (OLE) with muscle biopsy and ≥2-years of follow-up
- WVE-210201 planned efficacy study
  - Design: Double-blind, placebo-controlled, multi-dose study assessing dystrophin expression and clinical outcomes
  - Measurement of dystrophin via standardized Western Blot
  - Interim analysis of dystrophin expression in muscle biopsies
  - Efficacy readout anticipated H2 2019
- Exploring intravenous and subcutaneous formulations for WVE-210201

# Exon 51: improved skipping efficiency

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




*analogs

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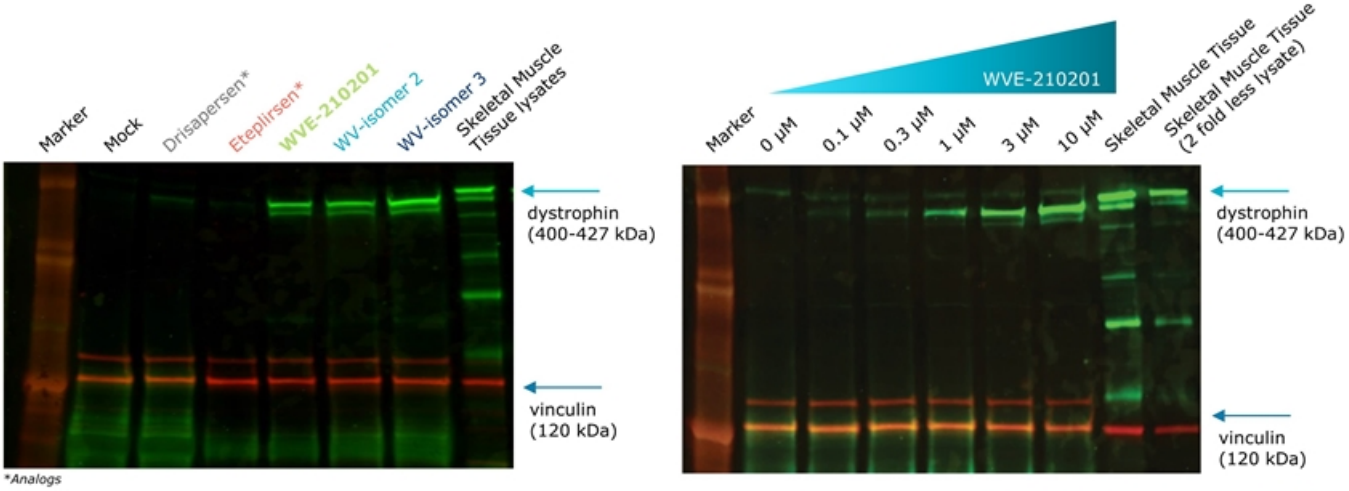
# Exon 51: increased dystrophin restoration




*Dystrophin protein restoration* in vitro *was quantified to be between* ***50-100% of normal*** *skeletal muscle tissue lysates, as compared to about 1% by drisapersen and eteplirsen analogs*

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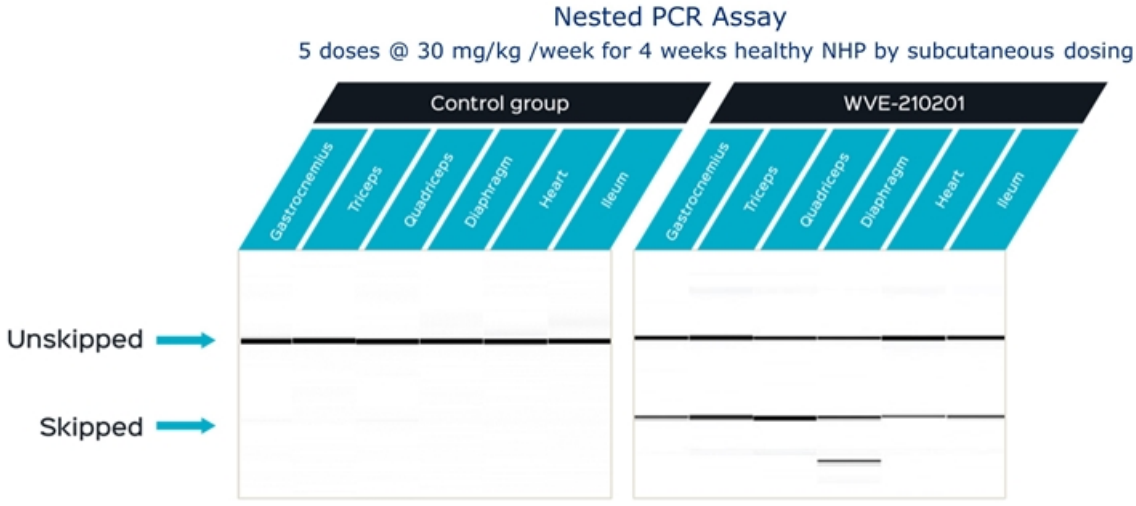
Experimental conditions: DMD protein restoration by Western Blot in patient-derived myotubes with clear dose effect. Free uptake at 10uM concentration of each compound with no transfection agent

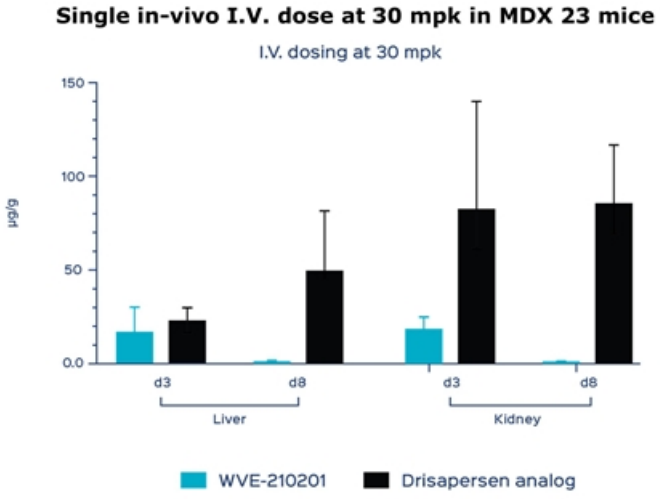
# Exon 51: target engagement in healthy non-human primate




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.

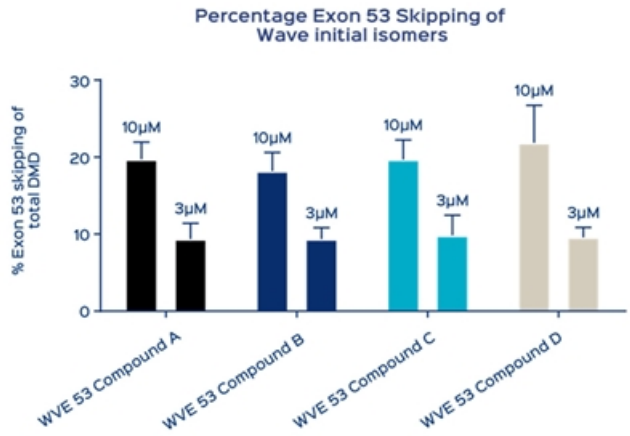
# Exon 51: no apparent tissue accumulation observed

- Standard oligonucleotides tend to accumulate in liver and kidney
- Wave rationally designed oligonucleotides optimized to allow compound to clear more effectively
- WVE-210201 demonstrated wide tissue distribution in dose dependent fashion
- No apparent accumulation observed after multiple doses




Experimental description: Oligo quantifications in tissues were performed using hybridization ELISA assay

# Exon 53: stereopure lead molecules advancing toward candidate




- RNA skipping determined by quantitative RT-PCR
- Free uptake at 10uM and 3uM concentration of each compound with no transfection agent
- Current published clinical dystrophin levels achieved for Exon 53 are ~1%

**Early Exon 53 data suggests initial skipping efficiency around 20% pre-optimization**

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# C9orf72

## 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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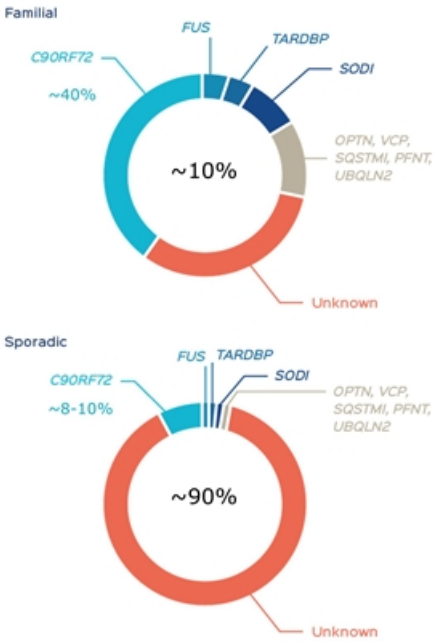
# Amyotrophic lateral sclerosis

- 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 3 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

**Initiation of clinical study expected Q4 2018**

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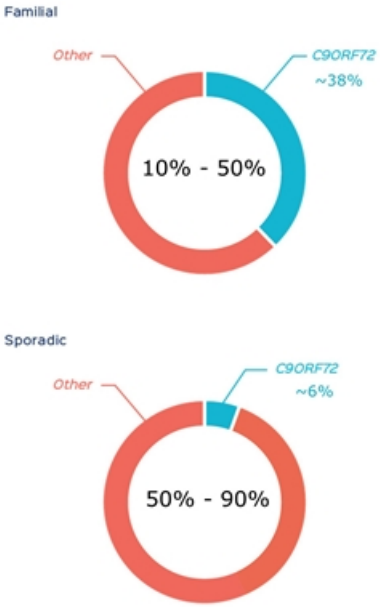
Source: State of play in amyotrophic lateral sclerosis genetics Alan E Renton, Adriano Chiò & Bryan J. Traynor Nature Neuroscience 17, 17–23 (2014) doi:10.1038/nn.3584

# 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

Initiation of clinical study expected Q4 2018

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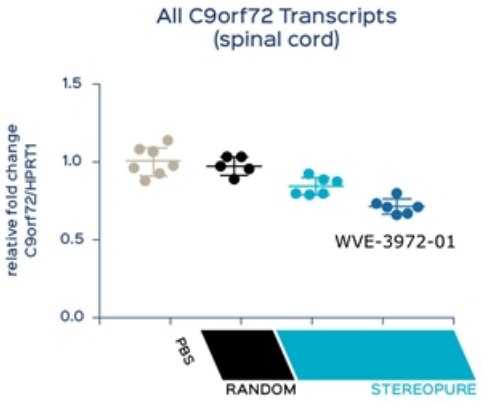
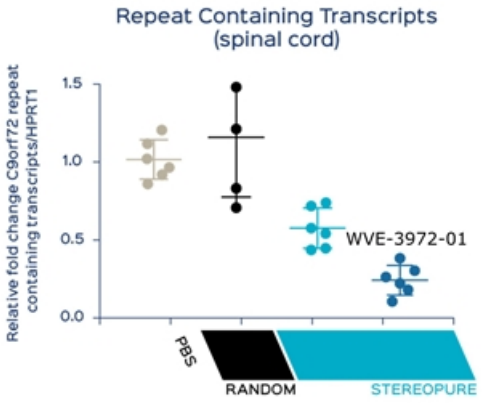
Sources: Familial aggregation in frontotemporal dementia, M. Stevens, MD; C.M. et al, Neurology 1998. Frequency of the C9orf72 hexanucleotide repeat expansion in patients with amyotrophic lateral sclerosis and frontotemporal dementia: a cross-sectional study. Elisa Majounie et al Lancet Neurology March 9, 2012 DOI:10.1016/S1474-4422(12)70043-1

# Selective silencing in vivo of expanded C9orf72 repeat transcripts

- Wave has developed a series of highly optimized antisense compounds which selectively silence the repeat containing transcript in C9orf72 transgenic mice
- These compounds show target engagement across cell types and regions of the nervous system critically implicated in ALS

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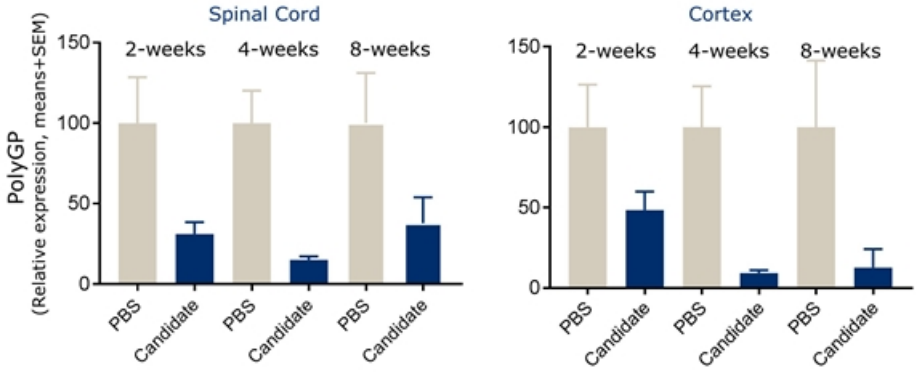
Experimental description: Samples were analyzed using quantitative PCR (Taqman assay)

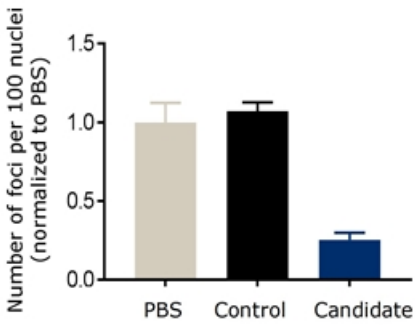
# Durable reduction of dipeptides and RNA foci in vivo

- Wave's candidate (WVE-3972-01) demonstrates durable reduction of dipeptides and reductions in RNA foci
- Data is consistent across blinded studies in independent laboratories (collaboration with Professor Bob Brown, U. Mass)

Durable reduction of dipeptide in vivo




Reductions in RNA foci in vivo (8 weeks)

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# Spinocerebellar ataxia type 3

# Spinocerebellar ataxia type 3

- Also known as Machado-Joseph disease
- Rare, hereditary, progressive neurodegenerative disorder that results in a lack of muscle control and coordination in upper and lower extremities; gradually leads to paralysis and loss of ability to speak or swallow
- Life expectancy is 10-20 years from symptom onset
- Prevalence: 1-2 in 100,000 people; most common dominantly inherited form of ataxia, representing 20% to 50% of all SCAs
- Expanded CAG repeat in *ATXN3* gene results in mutant ATXN3 protein that causes widespread neuronal loss in brain and spinal cord

Candidate targeting *ATXN3* expected to be named by YE 2018

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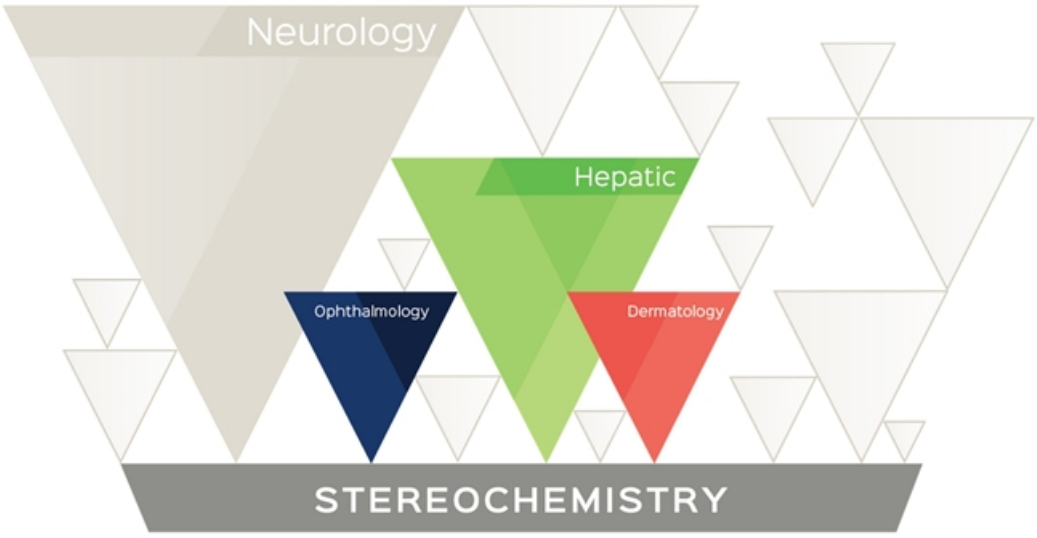
Source: Paulson H. Machado-Joseph disease/spinocerebellar ataxia type 3. Handb Clin Neurol 103, 437—449 (2012).
National Institute of Health. Spinocerebellar ataxia 3. Accessed at: https://ghr.nlm.nih.gov/condition/spinocerebellar-ataxia-type-3 on February 15, 2018

# Emerging areas

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# Pfizer hepatic collaboration

- Initiated May 2016
- Exploring targets across modalities, including ASO and ssRNAi
- Up to 5 hepatic-metabolic programs
  - 3 targets declared; APOC3, 2 undisclosed
  - Option to declare 2 additional targets
- Access to Pfizer's hepatic targeting technology
  - Potentially increasing potency beyond GalNAc
  - Freedom to leverage beyond collaboration targets

**40**

$M upfront payment

**871**

$M in potential milestone payments and royalties

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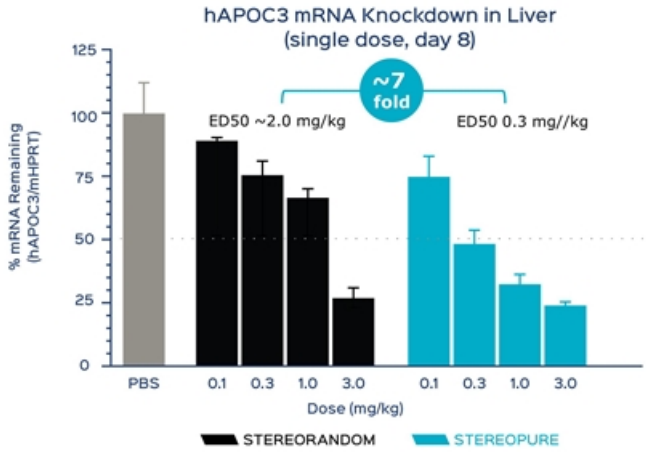
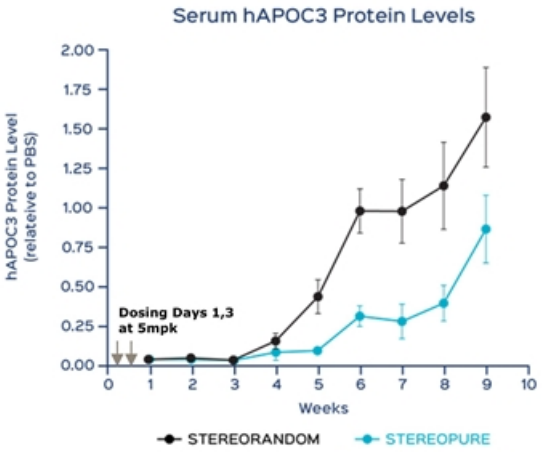
# Stereopure ASOs: improved in vivo potency, extended duration

- Potency equivalent to state-of-the-art GalNAc conjugated double strand RNAi (ED50 0.3 mg/kg)
- Demonstrated increase in durability over GalNAc conjugated stereorandom

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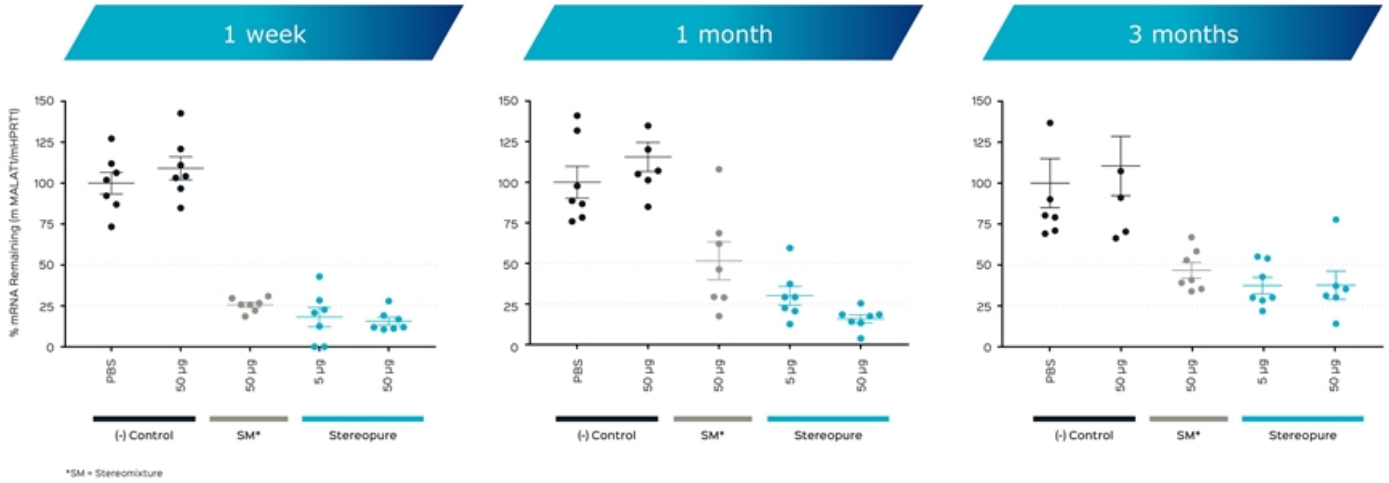
Experimental description: Male human APOC3 transgenic mice were dosed with APOC3 ASOs with indicated doses. APOC3 mRNA quantification in the liver was performed using Taqman assay specific for hAPOC3. For protein analysis, plasma samples were collected weekly and analyzed by ELISA assay specific to human APOC3 protein.

# Improved in vivo potency, extended duration

## Back of the eye




*SM = Stereomixture

10X lower dose of stereopure oligo is more potent than stereorandom oligo

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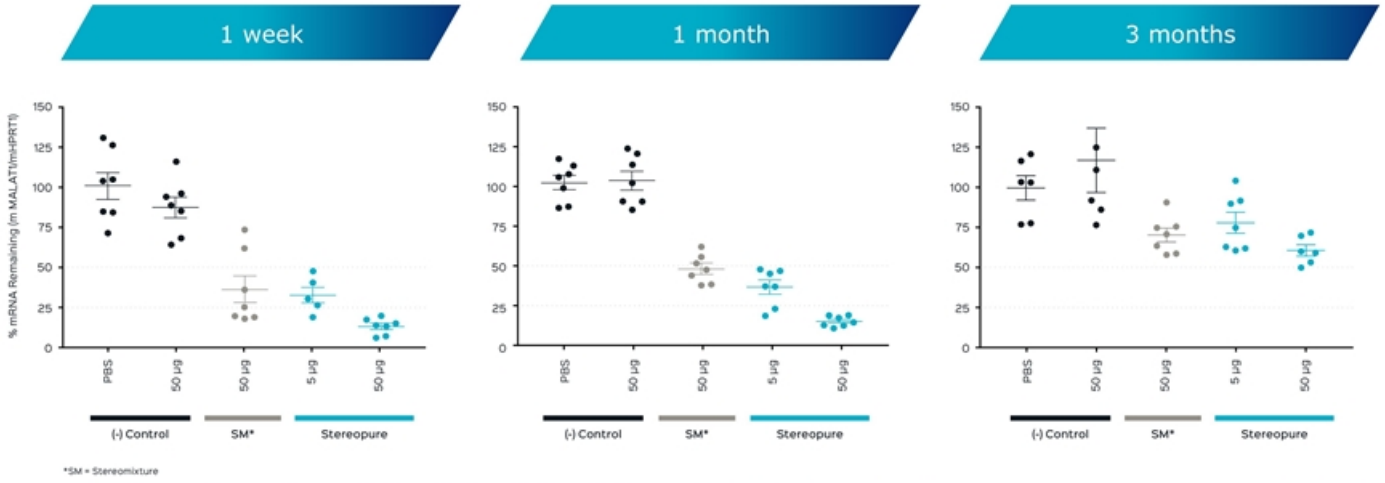
Experimental description: Single intravitreal injection to mouse eye on day 1.

# Improved in vivo potency, extended duration

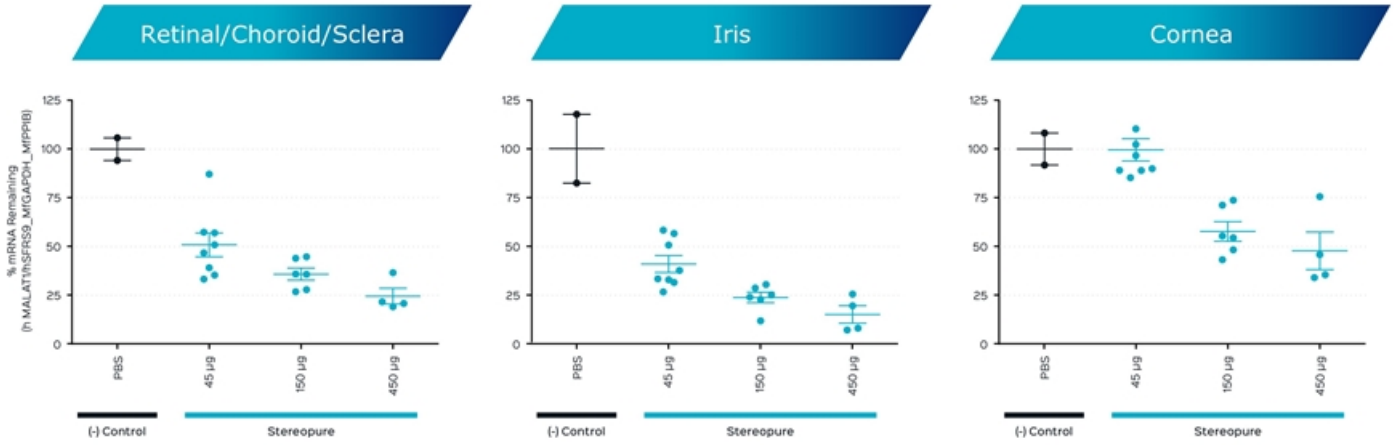
## Front of the eye




10X lower dose of stereopure oligo is more potent than stereorandom oligo

Experimental description: Single intravitreal injection to mouse eye on day 1.

# Knockdown of MALAT1 in non-human primate




Clear dose-dependent knockdown of MALAT1 in mRNA in three separate eye tissues

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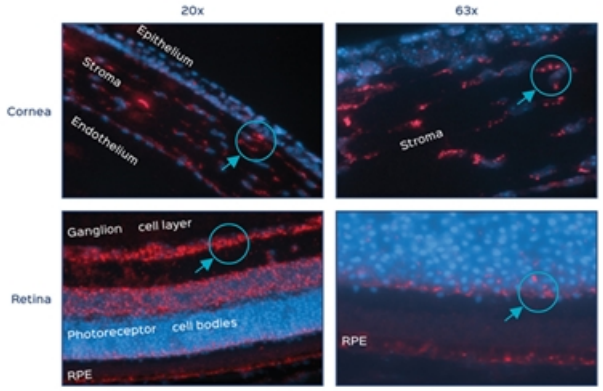
Experimental description: One week following single intravitreal injection.

# Distribution and target engagement

## Ophthalmology

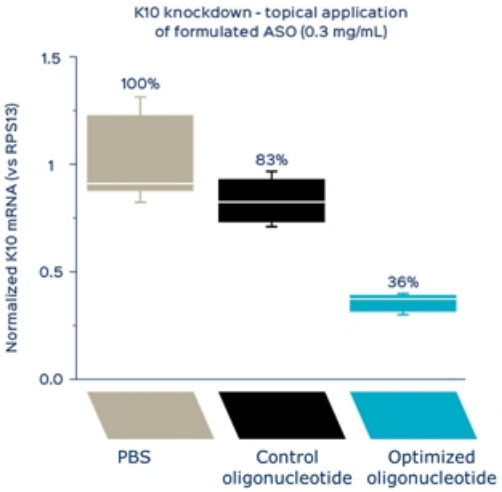
Distribution of oligonucleotide to key cellular Compartments following intravitreal injection in murine eye




Red dots = Oligonucleotides

## Dermatology

Target engagement following topical administration on human skin explant model

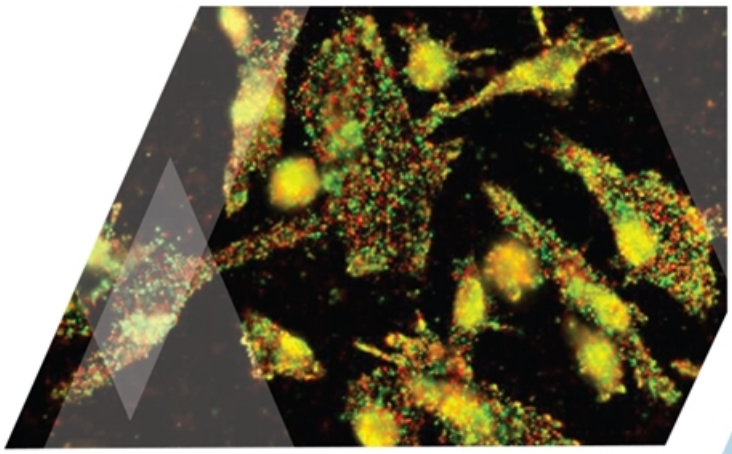



WAVE LIFE SCIENCES

# Enabling technologies: enhancing stereopure platform

READCOOR

- Collaboration leverages ReadCoor's proprietary FISSEQ (Florescent In-Situ Sequencing) platform designed to provide critical spatial data by combining next generation sequencing and three-dimensional imaging
- Developing a registry of brain cell network maps
- Advancing chemistry for targeted delivery to the brain



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# Scalable nucleic acid synthesis

- Oligonucleotide synthesis capacity ranging from high throughput to large scale GMP production
- 90,000 square foot facility
- Ability to continue to meet synthesis demands of growing portfolio and increase control and visibility of product supply chain
- Comparable yield and cost-of-goods to standard stereorandom oligonucleotides
- Industry standard equipment with no biological processing required
- GMP manufacturing capacity potentially available to partners

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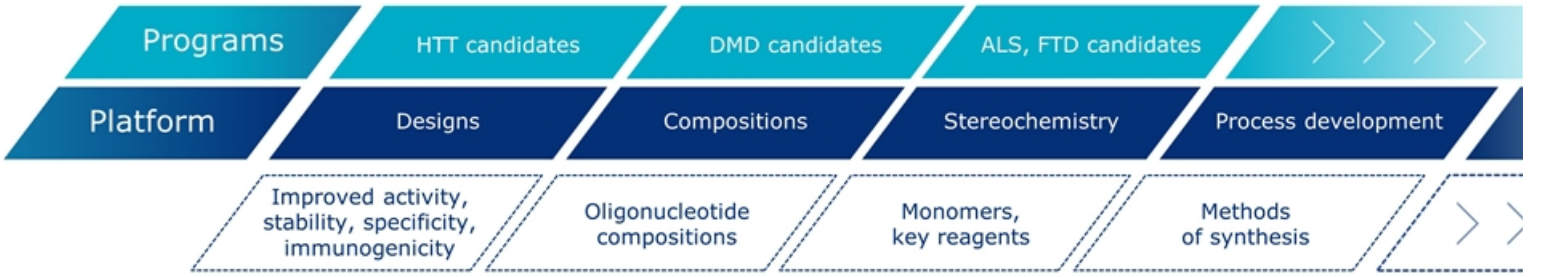
# Secure patent and intellectual property position

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# Wave catalysts

- **Q3 2018: safety data expected in DMD from Phase 1 trial for WVE-210201**
  - Initiated clinical trial in DMD (Exon 51) November 2017
  - WVE-210201 is the first stereopure oligonucleotide targeting Exon 51 with potential to be best-in-class
  - Interim dystrophin readout from planned efficacy and open label extension trials expected in H2 2019

- **Q4 2018: clinical trials expected to initiate in ALS and FTD for WVE-3972-01**
  - WVE-3972-01 is designed to target the pathogenic allele of the C9orf72 gene
  - In vivo animal data demonstrate potent, sustained and preferential knockdown of toxic biomarkers associated with ALS and FTD

- **H1 2019: data expected in HD from Phase 1b/2a trials for WVE-120101 and WVE-120102**
  - Initiated two clinical trials in HD July 2017
  - Potential to be first two allele-specific disease-modifying therapies selectively lowering mHTT
  - Received U.S. orphan drug designation for WVE-120101 and WVE-120102

- **Q1 2019: clinical trial expected to initiate for next DMD program (Exon 53)**

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# Realizing the potential of nucleic acid therapeutics