



Wave Life Sciences  
Corporate Presentation  
April 2, 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, expected to fund operations to the end of 2020

# 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

# Pipeline spanning multiple modalities, novel targets

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

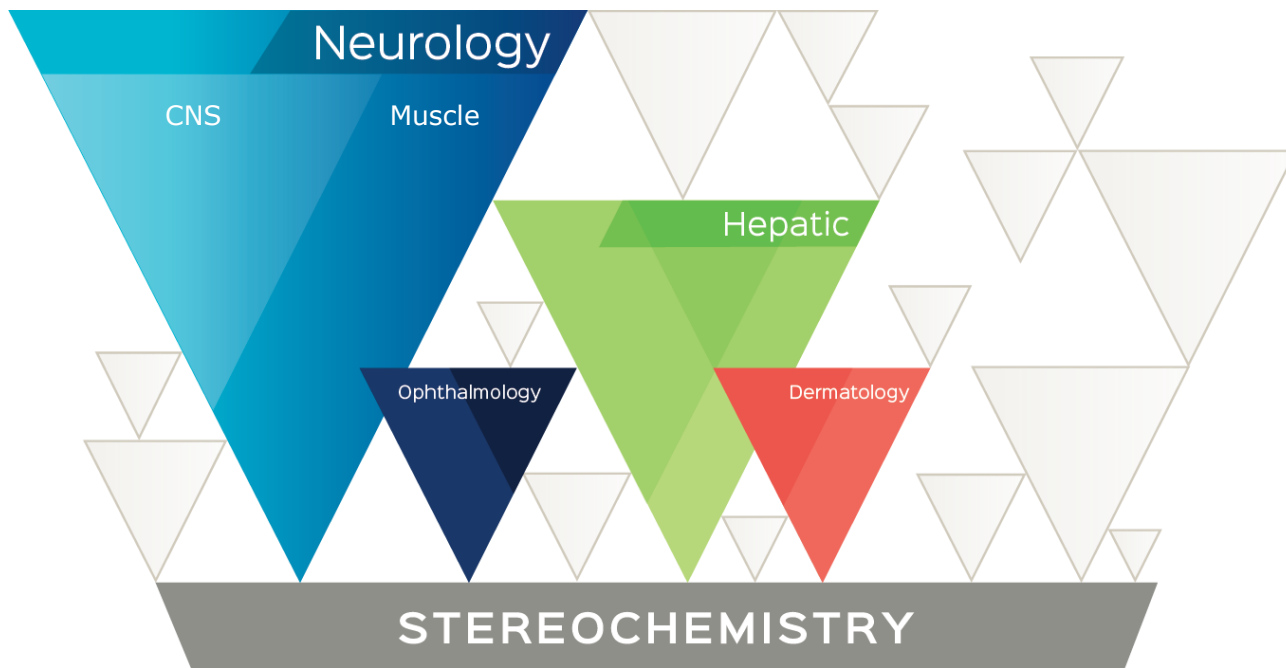
(S) = silencing. (A) = allele-specific silencing. (E) = exon skipping.

\*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.

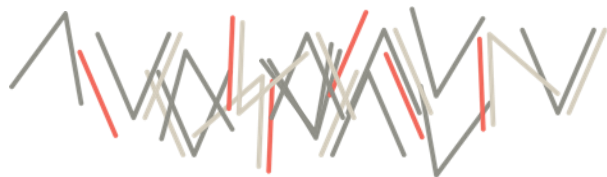
†During a four-year term, Wave and Takeda may collaborate on up to six preclinical targets at any one time.

‡Pfizer has nominated two undisclosed targets in addition to APOC3.

# Broad platform relevance across therapeutic areas



# 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



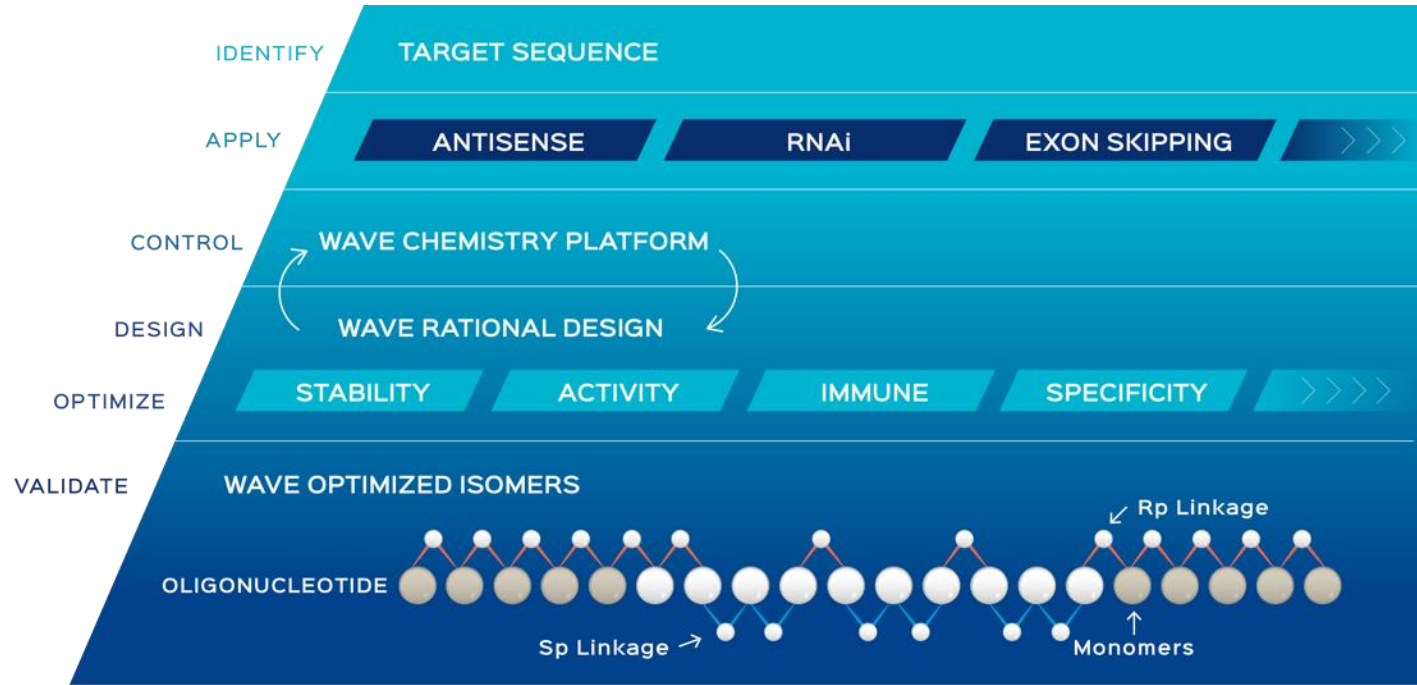
WAVE RATIONAL DESIGN

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

# Creating a new class of oligonucleotides

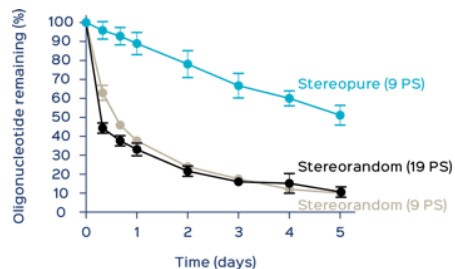




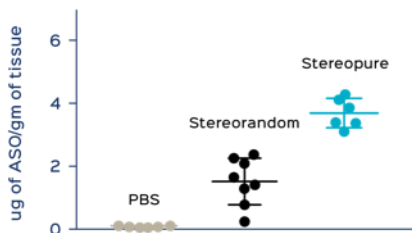
# Chemistry may optimize medicines across multiple dimensions

## Improved Stability

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

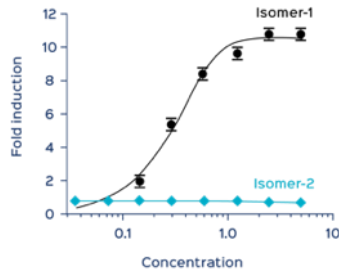


Oligonucleotide exposure (spinal cord)

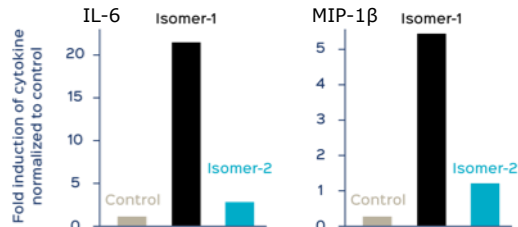


## Controlled Immunogenicity

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

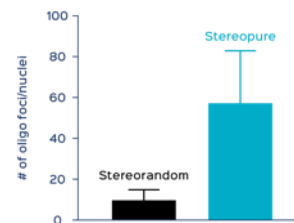


Cytokine induction in human PBMC assay

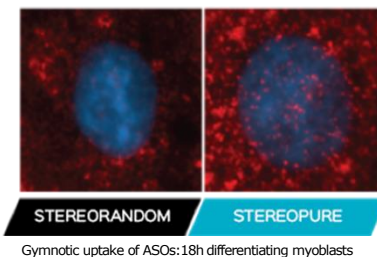


## Enhanced Delivery

Stereochemistry enables enhanced delivery of oligonucleotides



Uptake without transfection agent between a stereopure and stereorandom oligonucleotide

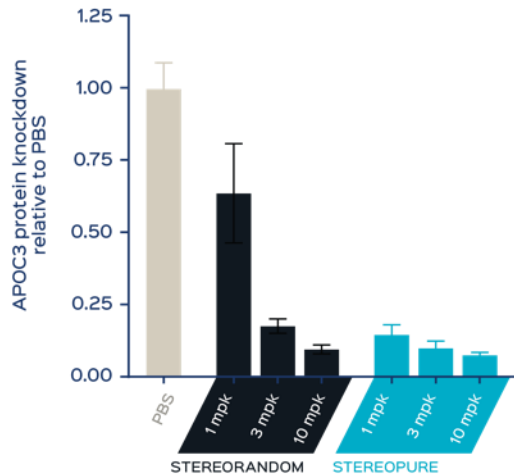


Gymnotic uptake of ASOs: 18h differentiating myoblasts

# Stereochemistry is applicable across modalities

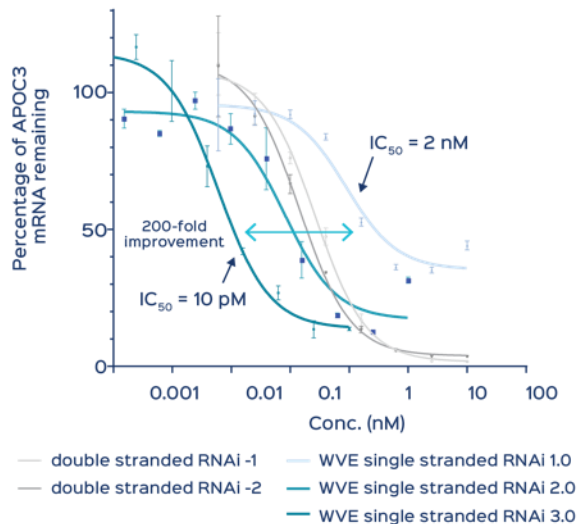
## Antisense

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



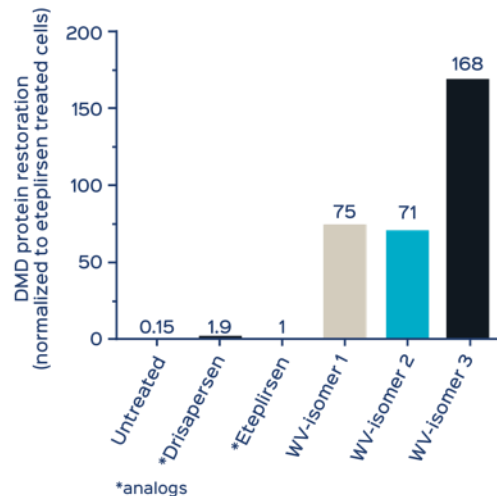
## RNAi

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

# Transforming nucleic acid therapeutics

**SUPERIOR  
PHARMACOLOGY  
+  
SCALABLE  
SYNTHESIS**



## **MULTI-MODALITY**

- Antisense
- RNAi
- Splice Correction
- Exon skipping
- Gene editing



## **BROAD IMPACT**

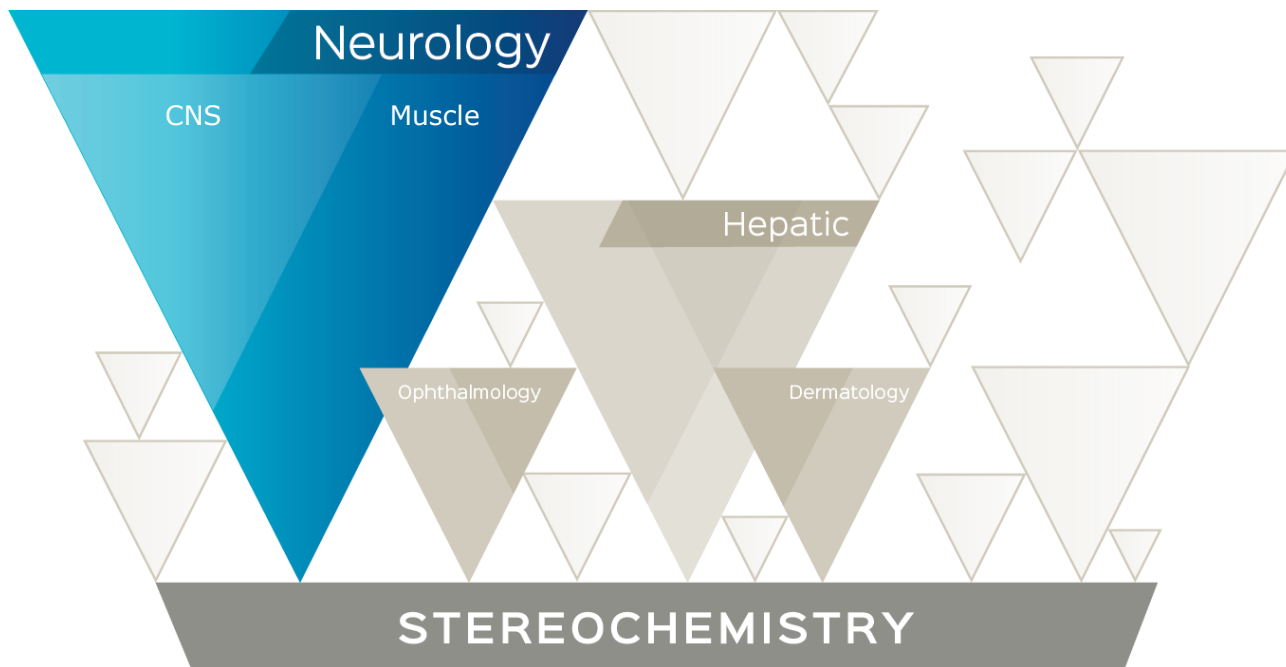
- CNS
- Muscle
- Eye
- Liver
- Skin



## **UNLOCKING THE PLATFORM**

Broad  
addressable  
patient  
population  
across multiple  
therapeutic  
areas

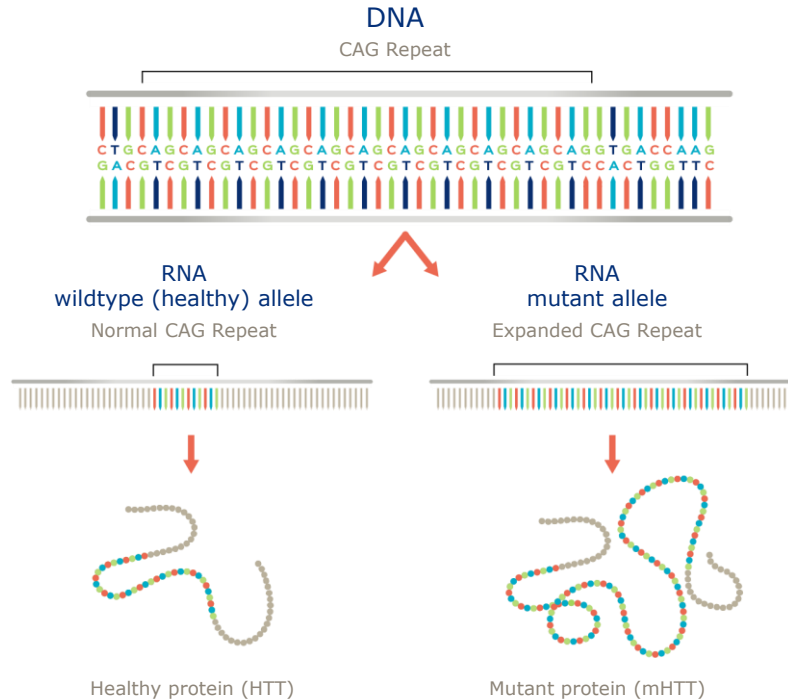
# Neurology



# Huntington's Disease

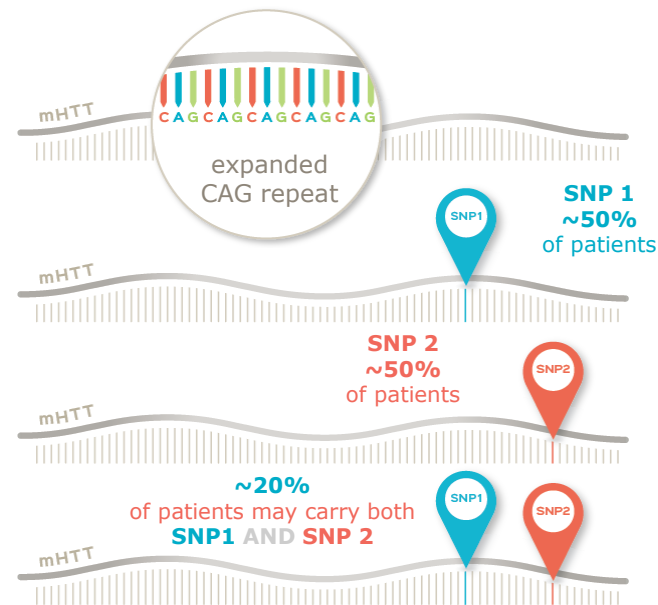
# Huntington's Disease: a hereditary, fatal disorder

- 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



# Wave approach: novel, allele-specific silencing

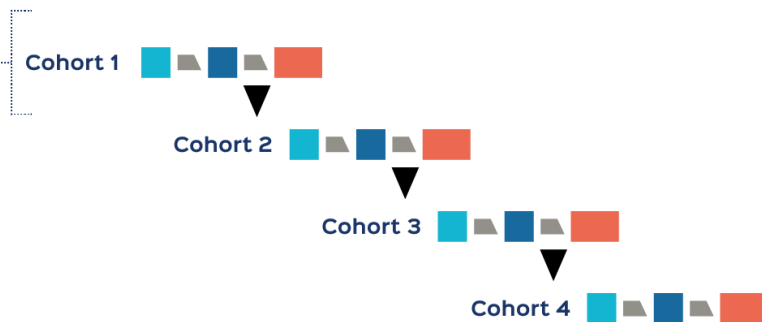
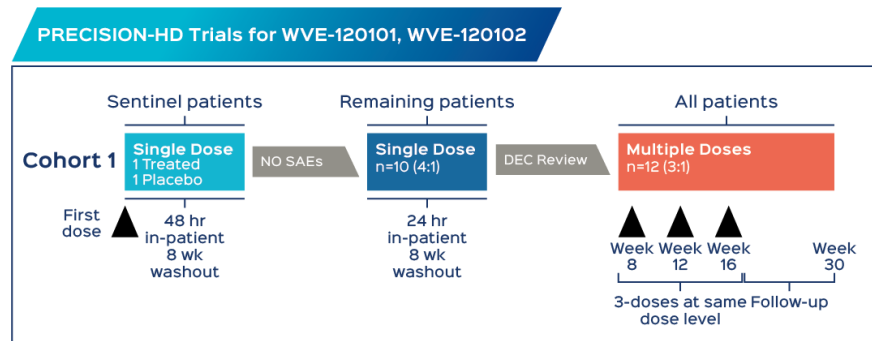
- Utilize association between single nucleotide polymorphisms (SNPs) and genetic mutations to specifically target errors in genetic disorders, including HD.
- Allele-specificity possible by targeting SNPs associated with expanded long CAG repeat in mHTT gene
- Approach aims to lower mHTT transcript while 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

# 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  $\geq 25$  to  $\leq 65$ , stage I or II HD
- Top line data anticipated H1 2019



▲ Indicates dose of WVE-120101/02 or placebo DEC = Dose Escalation Committee



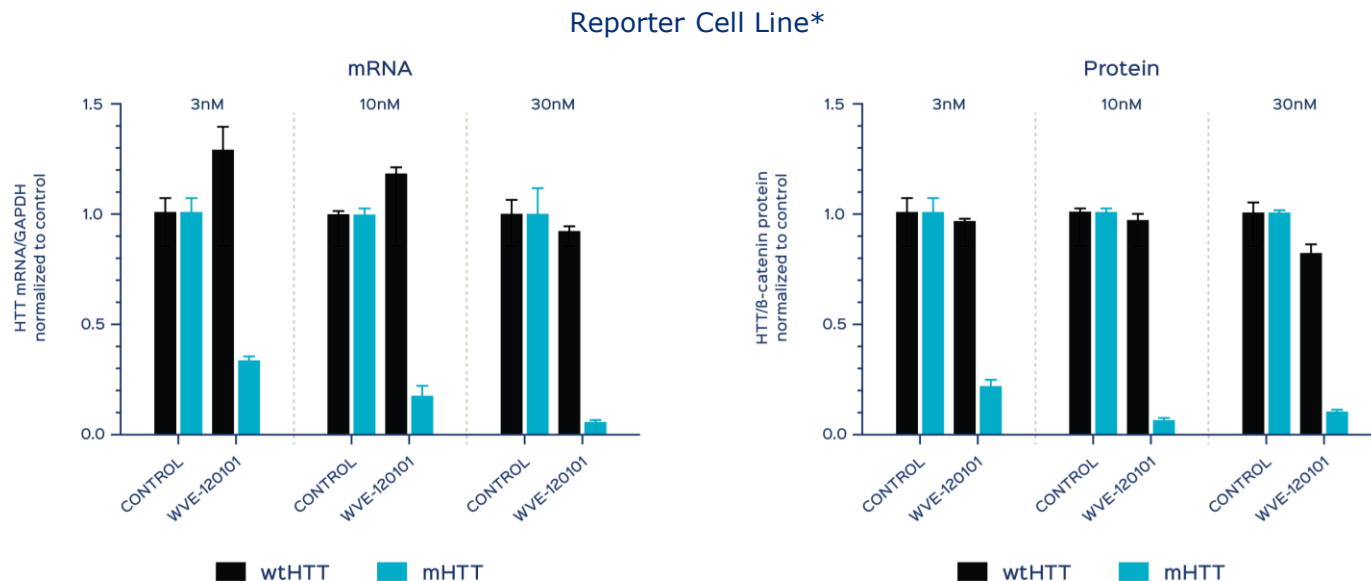
# Mutant huntingtin: a powerful, novel biomarker

- 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**



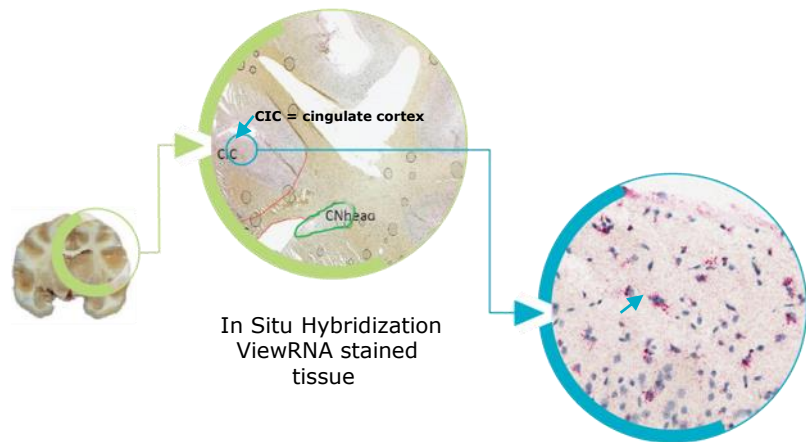
# Selective reduction of mHTT mRNA & protein



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

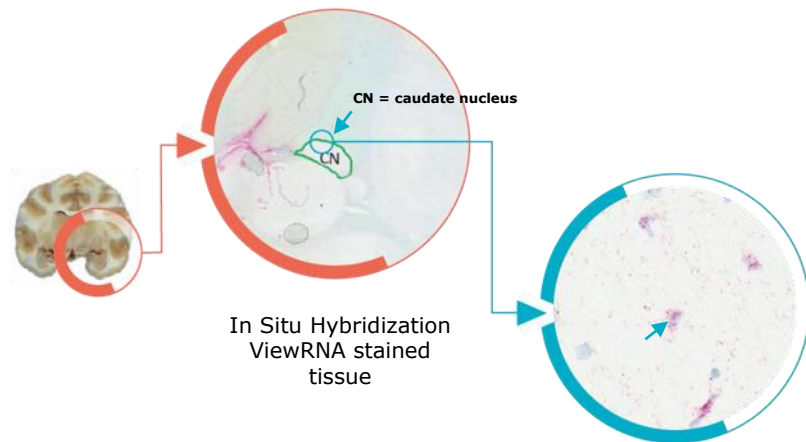
# Demonstrated delivery to brain tissue

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



Red dots are WVE-120101 oligonucleotide.

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



Red dots are WVE-120102 oligonucleotide.

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

# 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

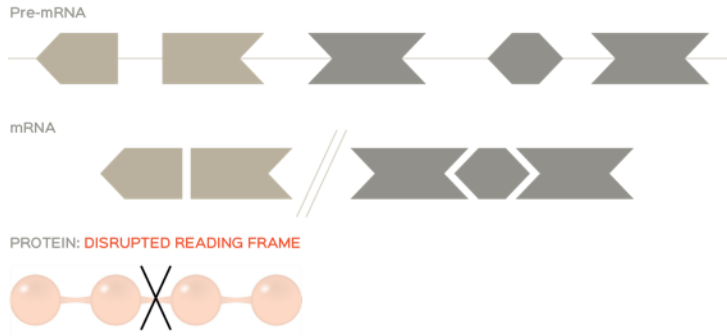


# Wave approach:

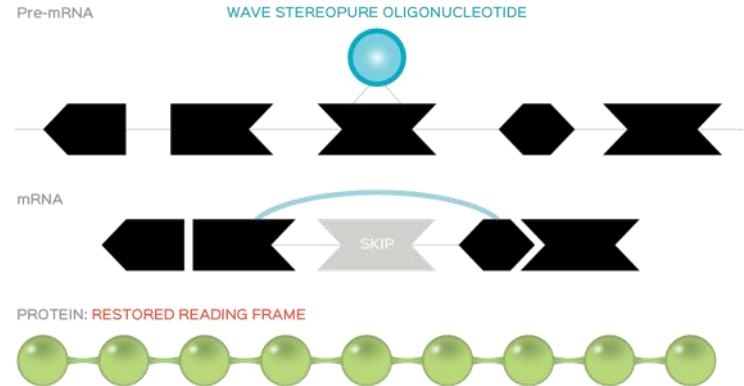
## meaningful restoration of dystrophin production through exon skipping

- 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)

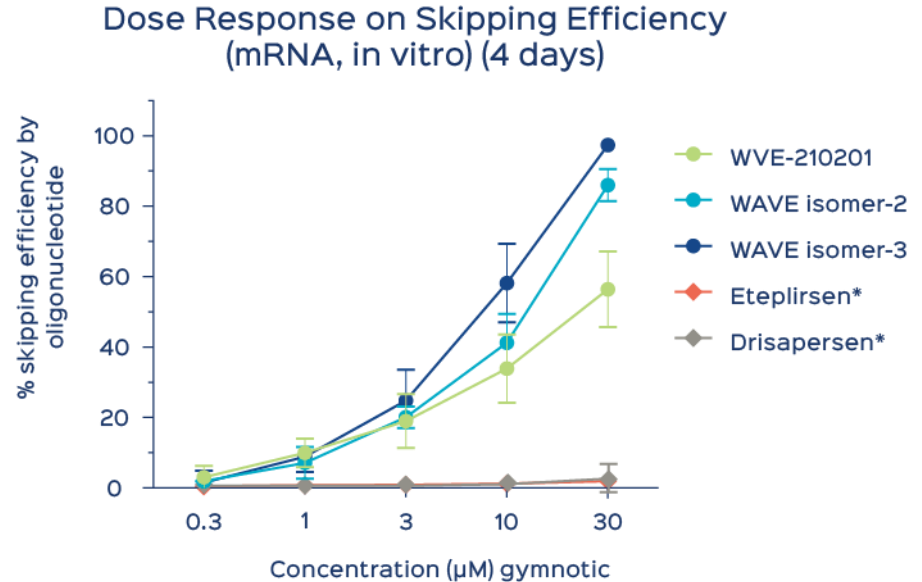


# Exon 51: WVE-210201 clinical program

- 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  $\geq 2$ -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

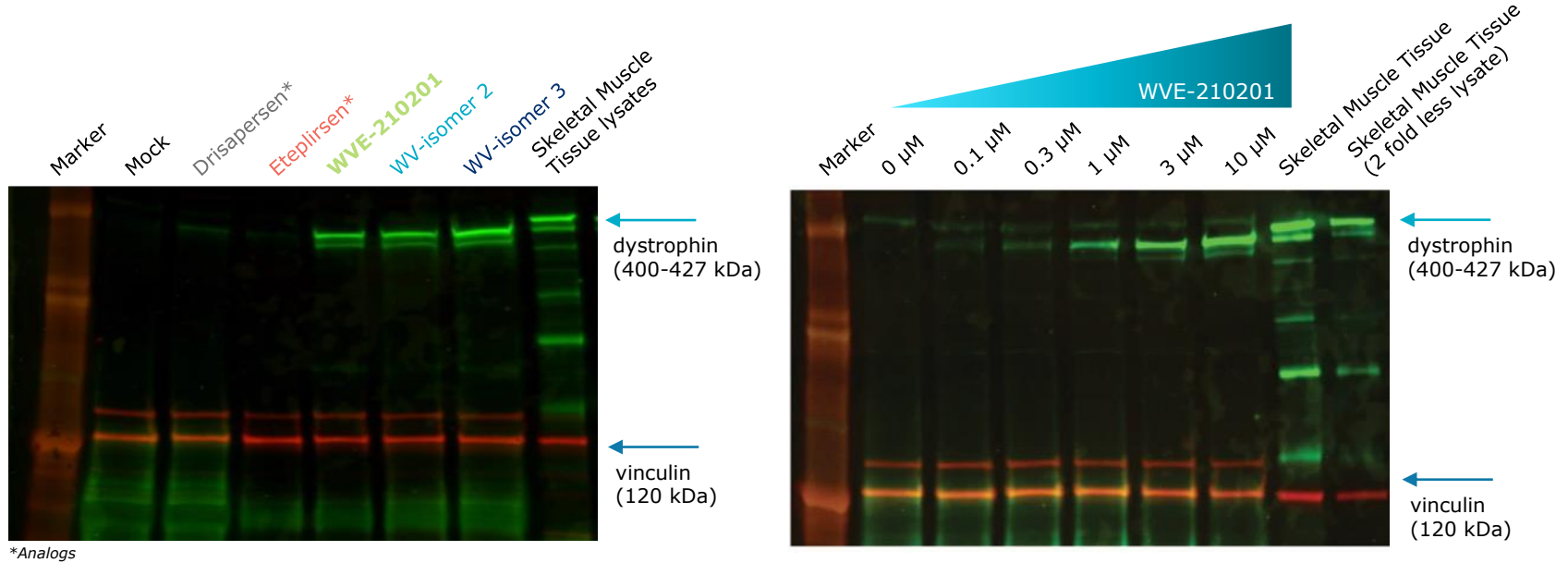
- RNA skipping determined by quantitative RT-PCR
- Wave isomers demonstrated a dose-dependent increase in skipping efficiency
- Free uptake at 10uM concentration of each compound with no transfection agent
- Same foundational stereopure chemistry for Wave isomers; individually optimized to assess ideal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



\*analogs



# Exon 51: increased dystrophin restoration



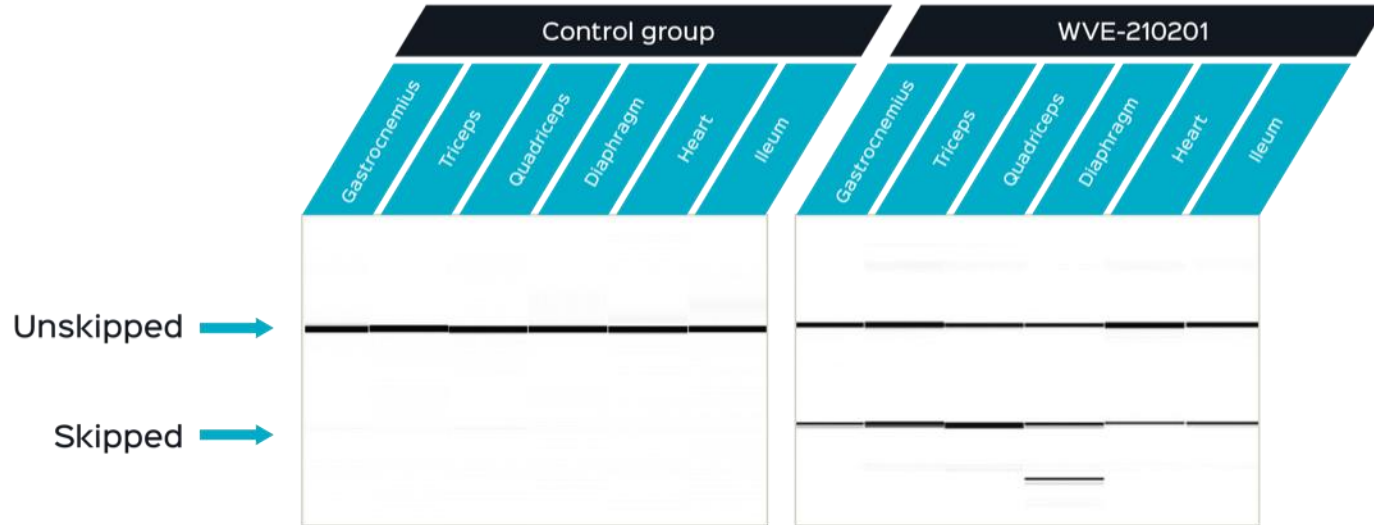
\*Analog

*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*

# Exon 51: in vivo target engagement of WVE-210201 in healthy non-human primate

## Nested PCR Assay

5 doses @ 30 mg/kg /week for 4 weeks healthy NHP by subcutaneous dosing

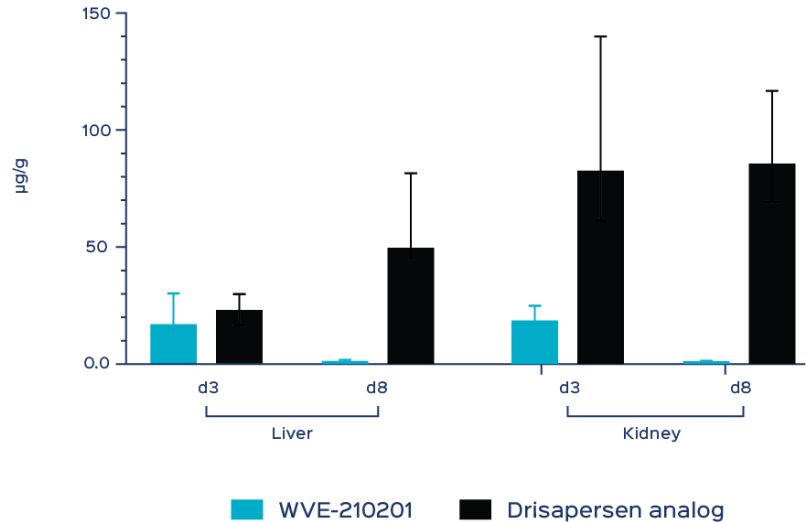


# Exon 51: no apparent tissue accumulation observed

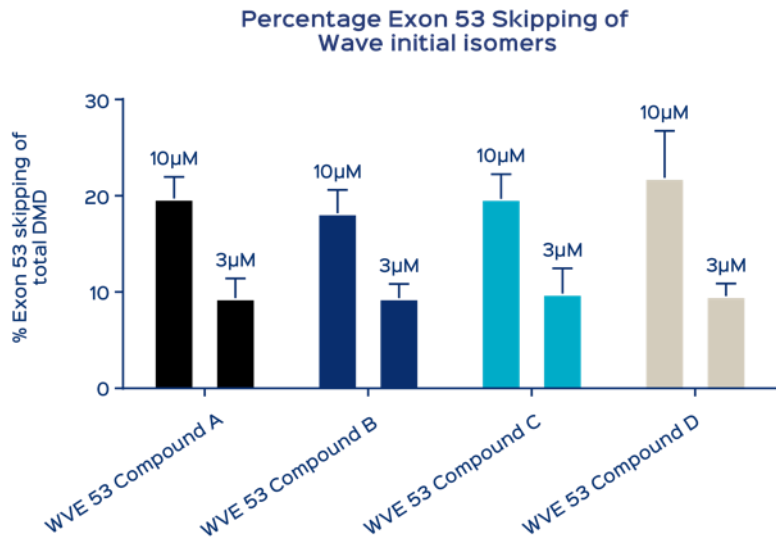
- Standard oligonucleotides tend to accumulate in liver and kidney
- Wave rationally designed oligonucleotides optimized to allow compound to clear more effectively
- WVE-210201 demonstrated wide tissue distribution in dose dependent fashion
- No apparent accumulation observed after multiple doses

## Single in vivo I.V. dose at 30 mpk in MDX 23 mice

I.V. dosing at 30 mpk



# 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%

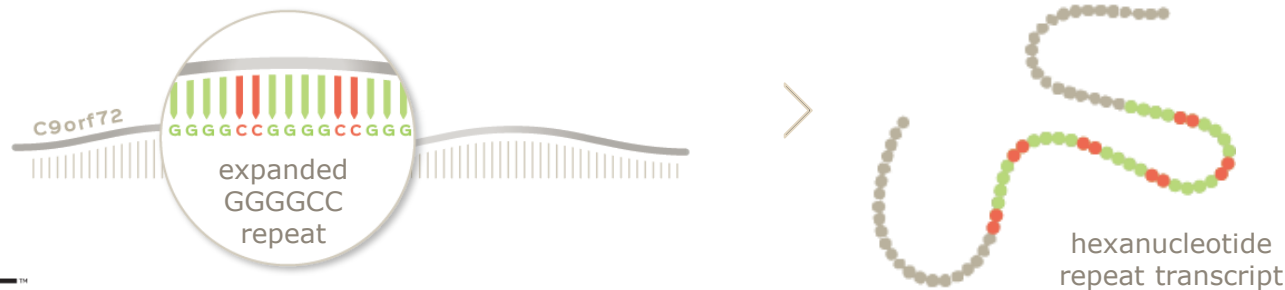
**Early Exon 53 data suggests initial skipping efficiency around 20% pre-optimization**

## C9orf72

Amyotrophic Lateral Sclerosis (ALS)  
Frontotemporal Dementia (FTD)

# C9orf72: a critical genetic risk factor

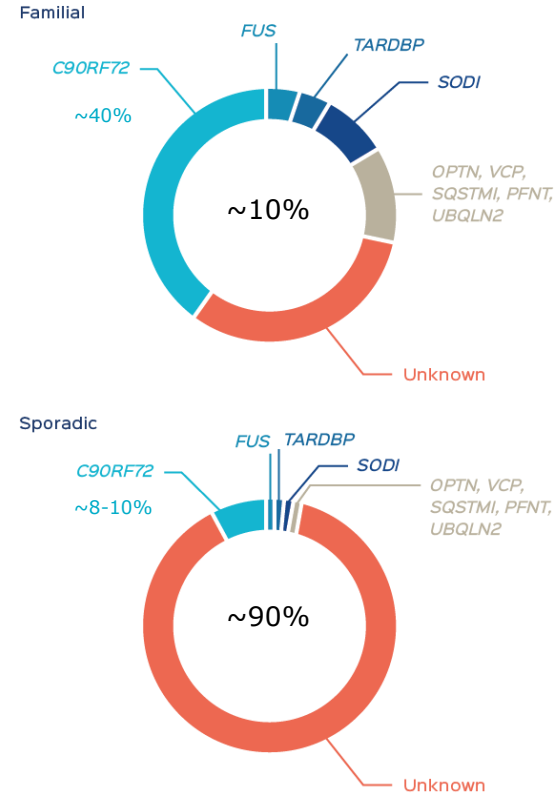
- C9orf72 gene provides instructions for making protein found in various tissues, with abundance in nerve cells in the cerebral cortex and motor neurons
- C9orf72 genetic mutations are the strongest genetic risk factor found to date for the more common, non-inherited (sporadic) forms of Amyotrophic Lateral 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



# 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

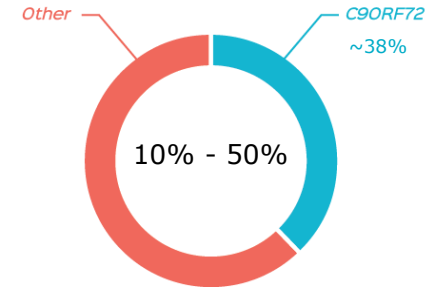


# Frontotemporal dementia

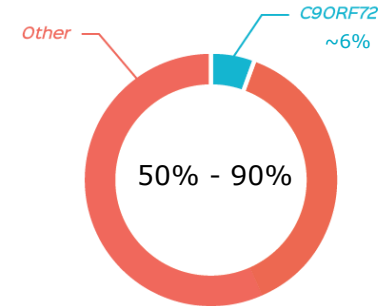
- Progressive neuronal atrophy with loss in the frontal and temporal cortices characterized by personality and behavioral changes, as well as gradual impairment of language skills
- Affects approximately 55,000 people in the US
- Second most common form of early-onset dementia after Alzheimer's disease 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

Familial



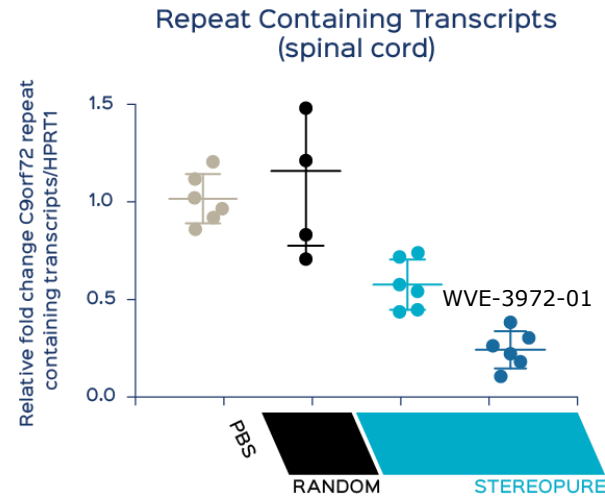
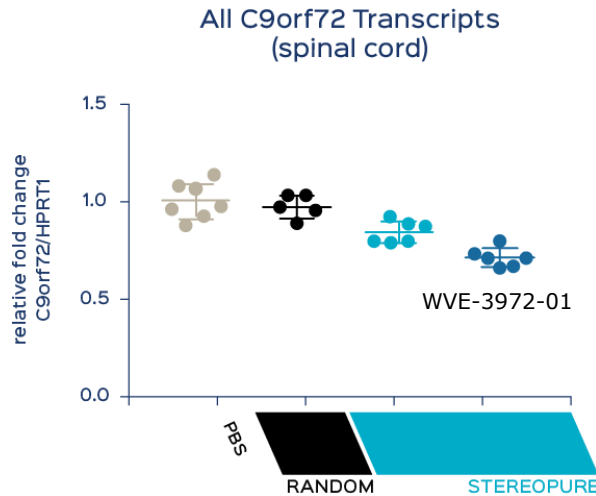
Sporadic





# Selective silencing in vivo of expanded C9orf72 repeat transcripts

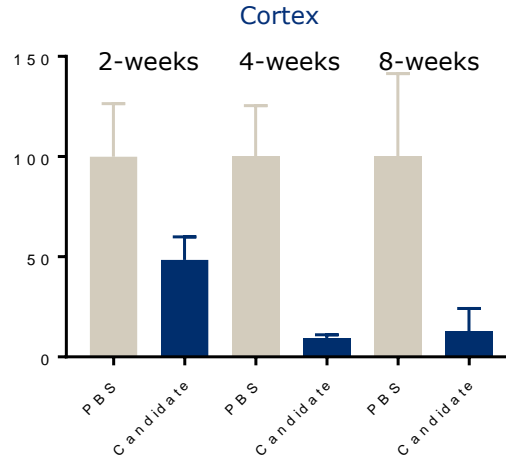
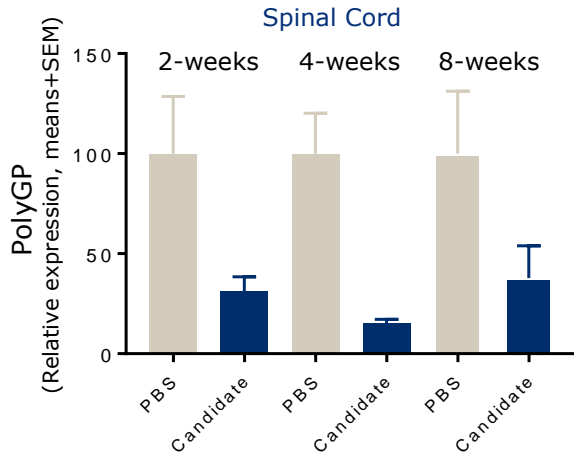
- Wave has developed a series of highly optimized antisense compounds which selectively silence the repeat containing transcript in C9orf72 transgenic mice
- These compounds show target engagement across cell types and regions of the nervous system critically implicated in ALS and FTD



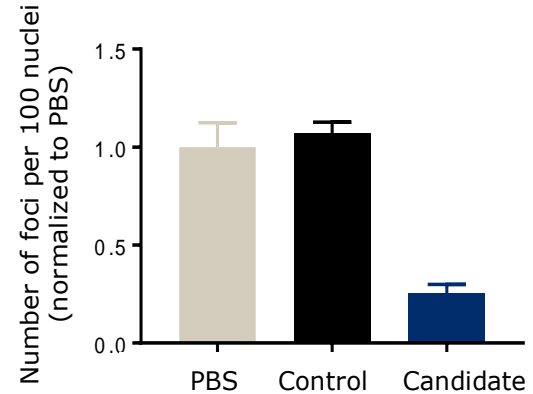
# Durable reduction of dipeptides and RNA foci in vivo

- 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)

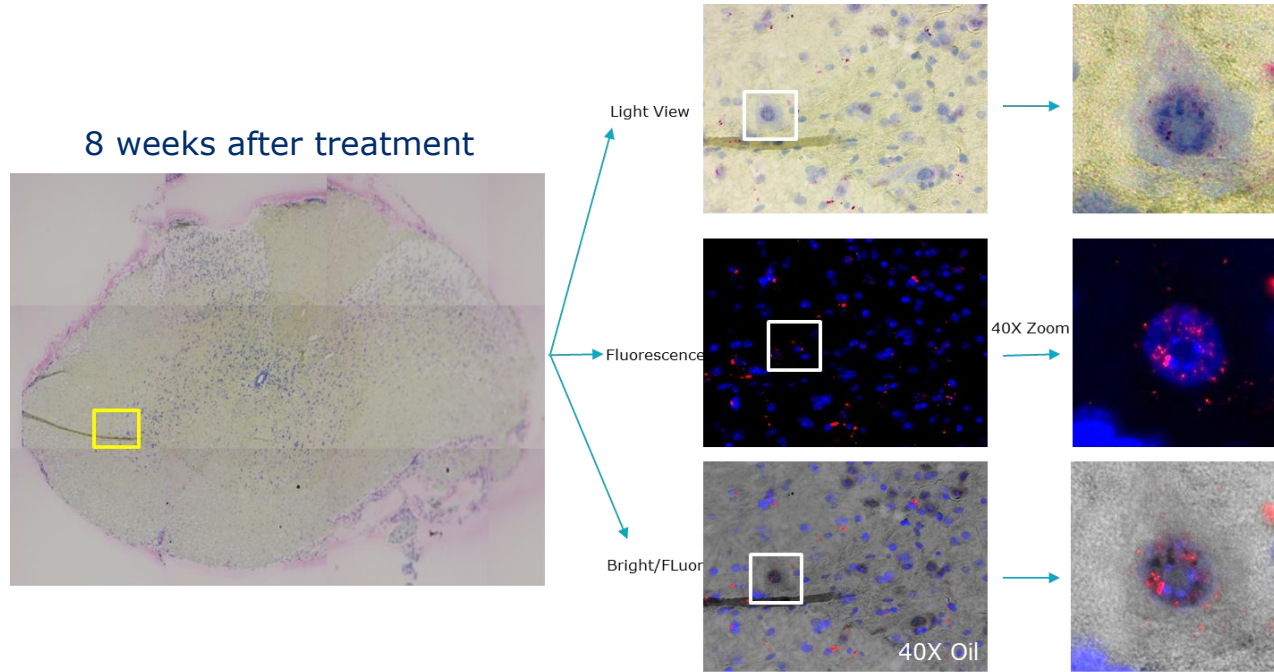
### Durable reduction of dipeptide in vivo



### Reductions in RNA foci in vivo (8 weeks)



# In vivo distribution of WVE-3972-01



Widespread and sustained distribution in nuclei of motor neurons in the spinal cord

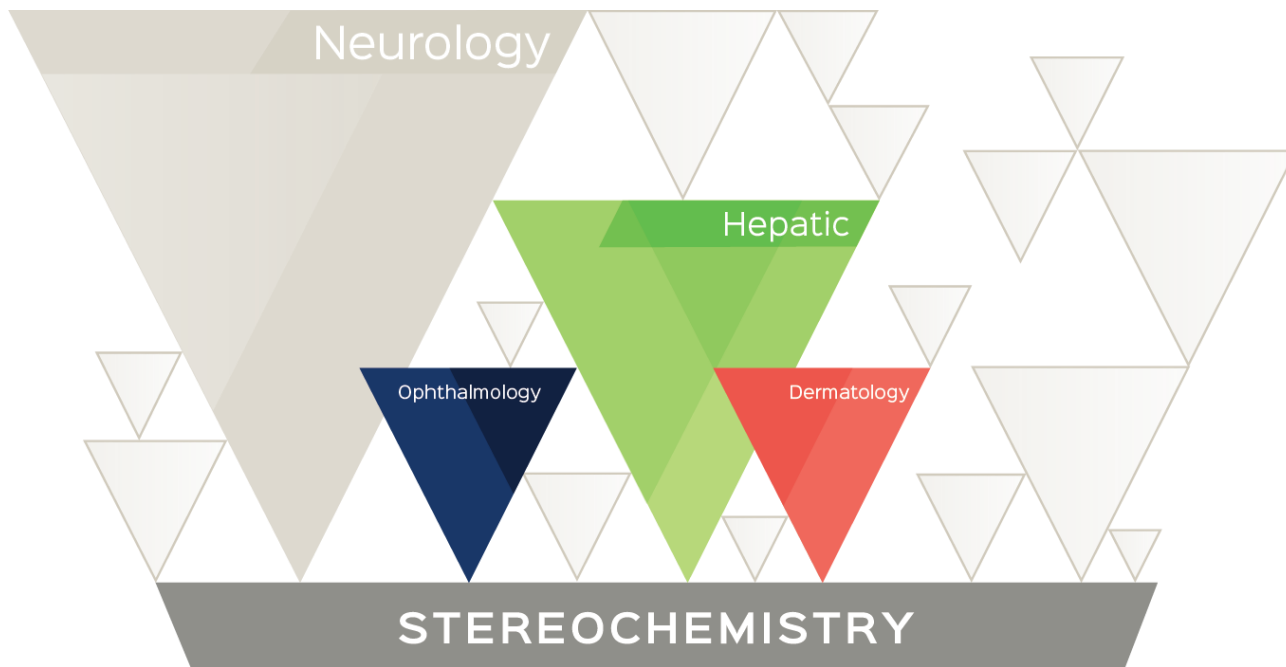
## Spinocerebellar ataxia type 3

# 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

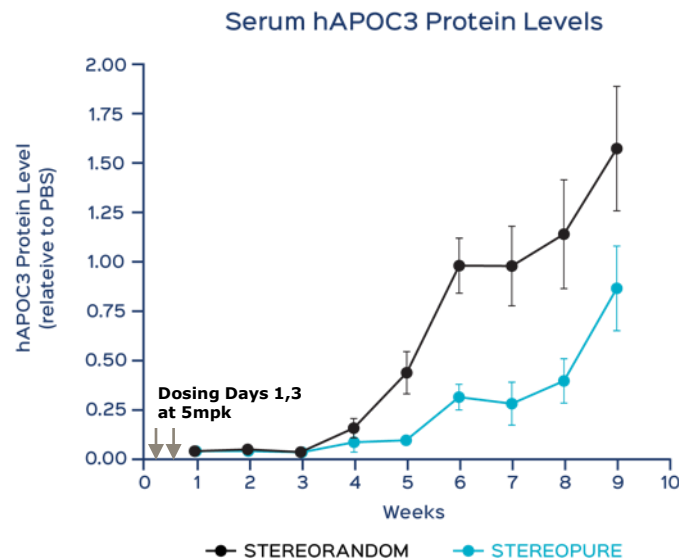
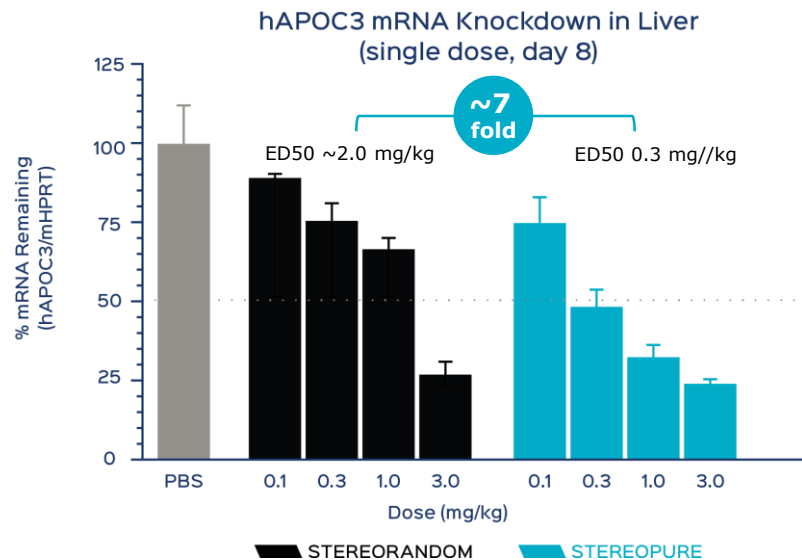
Candidate targeting *ATXN3* expected to be named by YE 2018

# Emerging areas



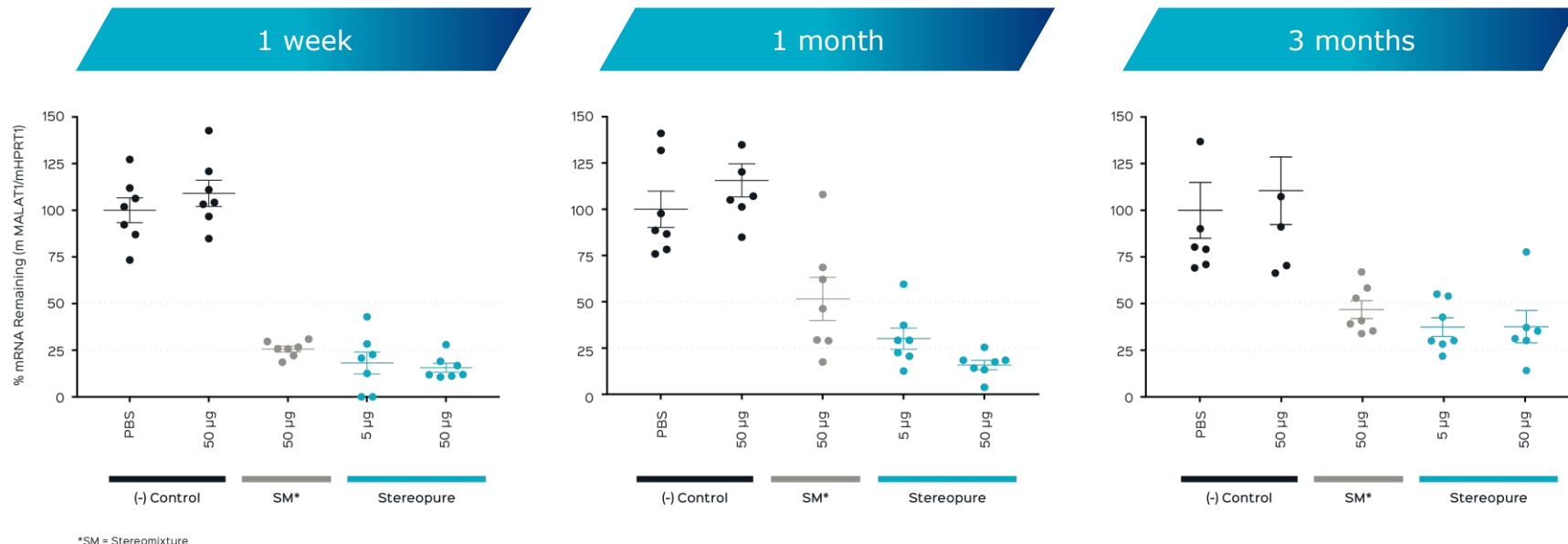
# Stereopure oligonucleotides: improved in vivo potency, extended duration

- 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 oligonucleotide



# Improved in vivo potency, extended duration

## Back of the eye



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



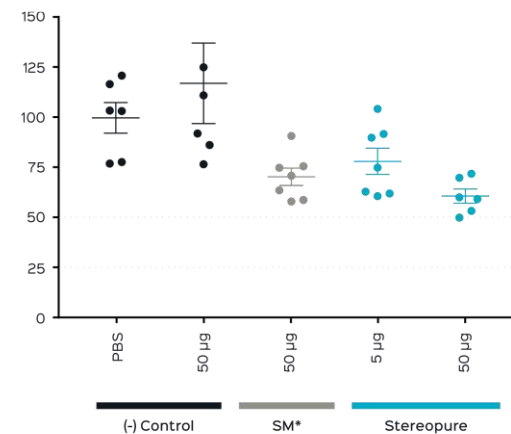
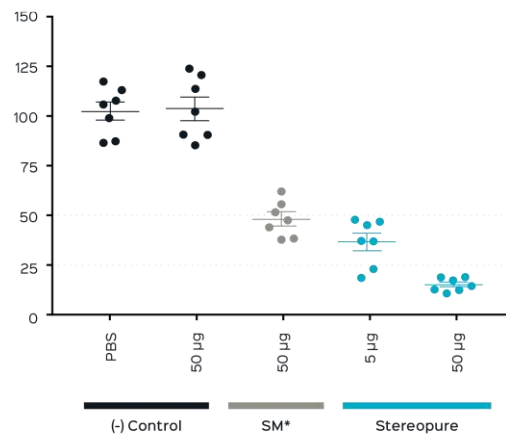
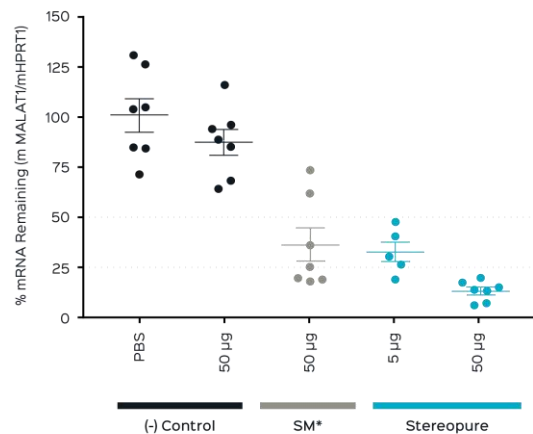
# Improved in vivo potency, extended duration

## Front of the eye

1 week

1 month

3 months



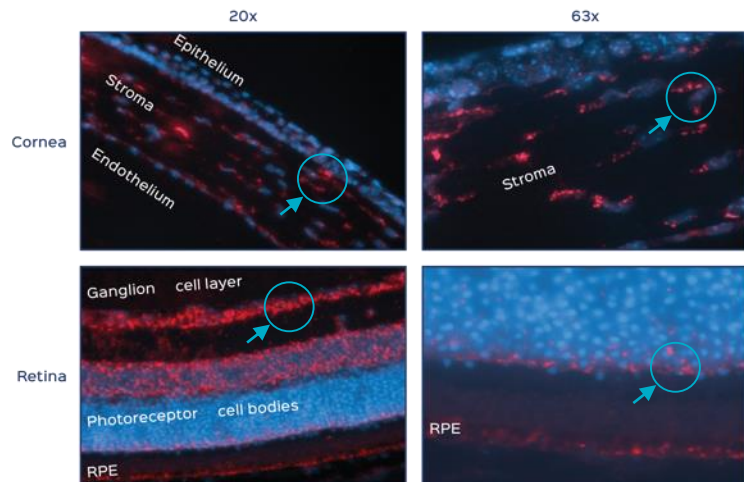
\*SM = Stereomixture

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

# Distribution and target engagement

## Ophthalmology

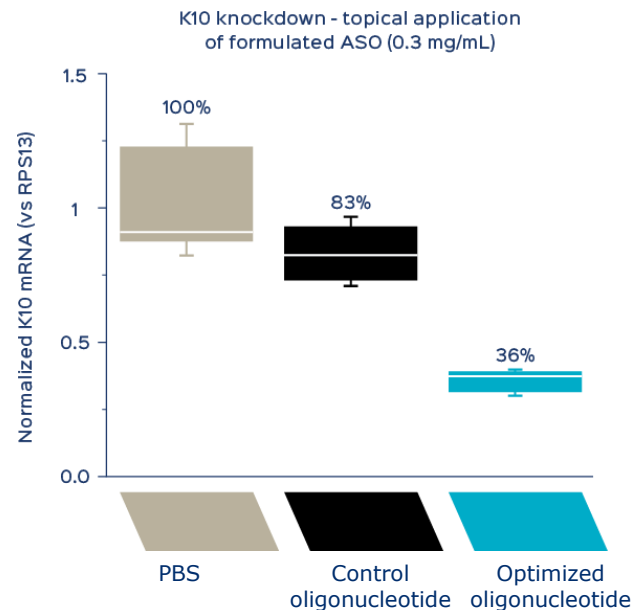
In vivo distribution of oligonucleotide to key cellular compartments following intravitreal injection in murine eye



Red dots = Oligonucleotides

## Dermatology

Target engagement following topical administration on human skin explant model



## Partnerships

# CNS collaboration with Takeda

## Committed capital

**\$230+ million in committed cash; eligible for milestones and royalties in excess of \$2 billion\***

- Expected to fund Wave operations to end of 2020, through multiple data readouts

## Significant value in 50:50 profit share

**Takeda option on global 50:50 share of CNS programs in HD, ALS, FTD and SCA3**

- After opt-in, Takeda to pay 50% of development costs
- Wave will lead manufacturing and joint clinical development; participate in joint co-commercialization in the US

## Fully funded R&D activities in CNS

**Takeda right to license additional preclinical CNS targets over four years**

- Wave CNS R&D fully funded
- Includes potential milestones and royalties in large CNS disorders such as Alzheimer's and Parkinson's diseases

# Hepatic collaboration with Pfizer

- Initiated May 2016
- Exploring targets across modalities, including ASO and ssRNAi
- Up to 5 hepatic-metabolic programs
  - 3 targets declared; APOC3 and 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

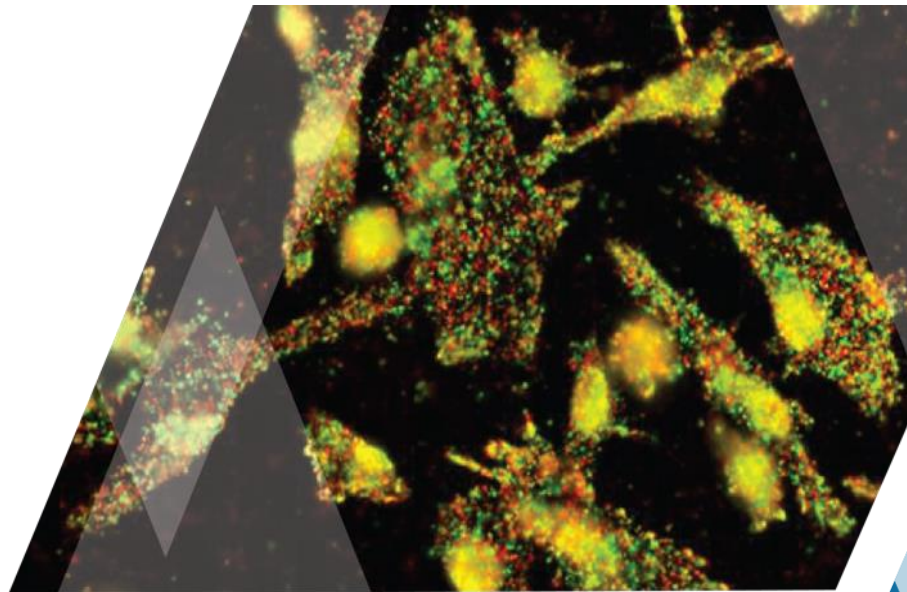
871

\$M in potential  
milestone payments  
and royalties

# Enabling technologies: enhancing stereopure platform



- 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
- Imaging allows for target engagement assessment in specific regions, cell types and subcellular compartments of the brain
- Provides meaningful insight into disease state, treatment effect of oligonucleotides and outcomes at the molecular and cellular level

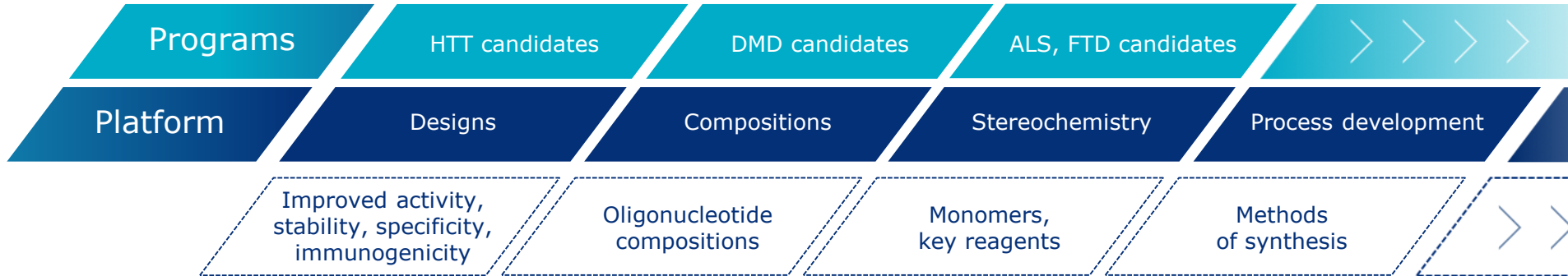


# Manufacturing strength: scalable nucleic acid synthesis

- 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



# Intellectual property strength: breadth and depth of patent portfolio





# 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)**



# Realizing the potential of nucleic acid therapeutics

