

Wave Life Sciences Corporate Presentation August 9, 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.



Focused on delivering transformational therapies for patients with serious, genetically defined diseases

- Rationally designed stereopure nucleic acid therapeutics
- Platform company utilizing multiple modalities including antisense, exon skipping and RNAi
- 6 neurology development programs by the end of 2018
- Robust R&D platform, ability to partner additional therapeutic areas
- Expertise and core focus in neurology
 - Huntington's disease: Two Phase 1b/2a trials ongoing
 - Duchenne muscular dystrophy: Exon 51 Phase 1 trial ongoing
 - Amyotrophic lateral sclerosis and Frontotemporal dementia for C90rf72: Trials expect to initiate Q4 2018
 - Key data readouts anticipated in 2019 for first 3 programs



Paving the way to potentially safer, more effective medicines





b neurology development programs by end of 2018









5 nucleic acid modalities being advanced with Wave stereopure chemistry



12+ discovery programs



5 therapeutic areas under active investigation







Pipeline spanning multiple modalities, novel targets

CNS	TARGET	BIOMARKER	45 THAT HO US	* *	ARMEN DISCOV	JERY DO	₽ ^{f¢} CLINICAL	WAVE'S COMMERCIAL RIGHTS	PARTNER	NEXT ANTICIPATED MILESTONES
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		\supset		50% Global	Takeda	Candidate by YE 2018
CNS diseases	Multiple ⁺			\bigcirc		\supset		Milestones & Royalties	Takeda	
MUSCLE										
Duchenne muscular dystrophy	Exon 51	Dystrophin	~2,000	E			Phase 1	100% Global	_	Top line data Q4 2018
Duchenne muscular dystrophy	Exon 53	Dystrophin	~1,250	E		\supset		100% Global	_	
Neuromuscular diseases	Multiple			\bigcirc		\supset		100% Global	_	
OPHTHALMOLOGY										
Retinal diseases	Multiple			\bigcirc		\supset		100% Global	_	
HEPATIC										
Metabolic liver diseases	APOC3	Triglyceride		S		\supset		Milestones & Royalties	Pfizer	
Metabolic liver diseases	Multiple $(4)^{\ddagger}$			\bigcirc		\supset		Milestones & Royalties	Pfizer	
	s = silencing.	A = allele-spec	ific silencing.) = exon	skipping.					

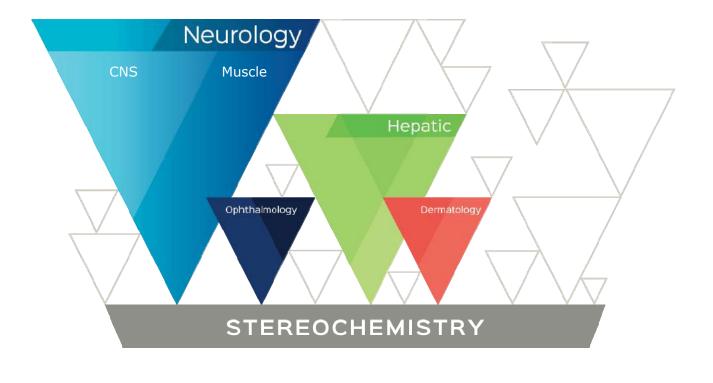


*Estimates of U.S. prevalence and addressable population by target based on publicly available data and are approximate; for Huntington's disease, numbers approximate manifest and pre-manifest populations, respectively.

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

[‡]Pfizer has nominated four undisclosed targets in addition to APOC3.

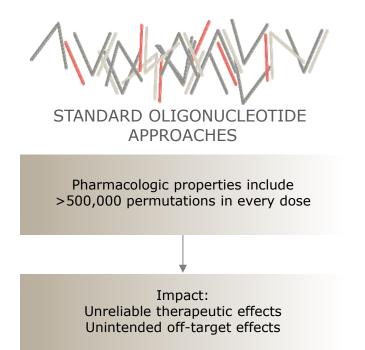
Broad platform relevance across therapeutic areas







Building the optimal, stereopure medicine





WAVE RATIONAL DESIGN

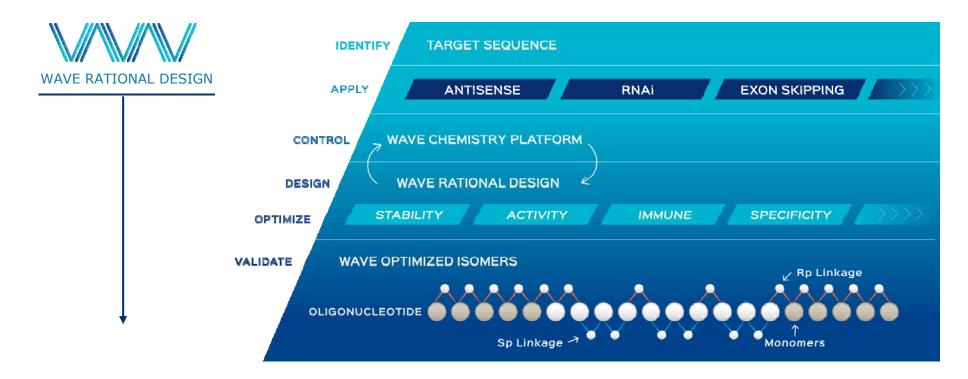
Stereochemistry enables precise control, ability to optimize critical constructs into one defined and consistent profile

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





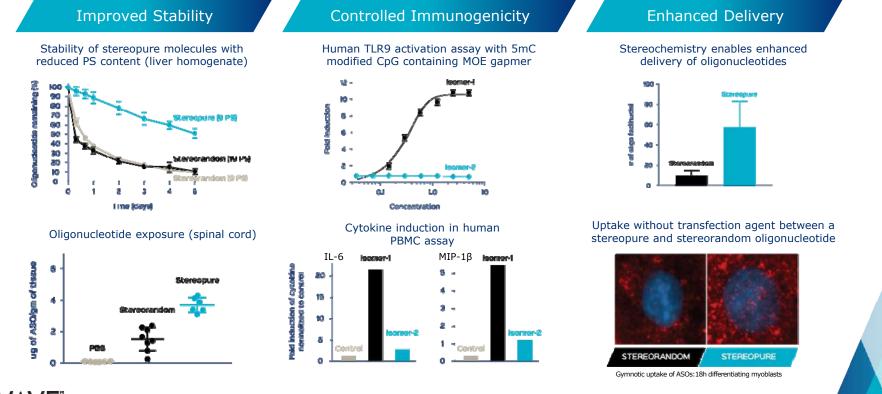
Creating a new class of oligonucleotides





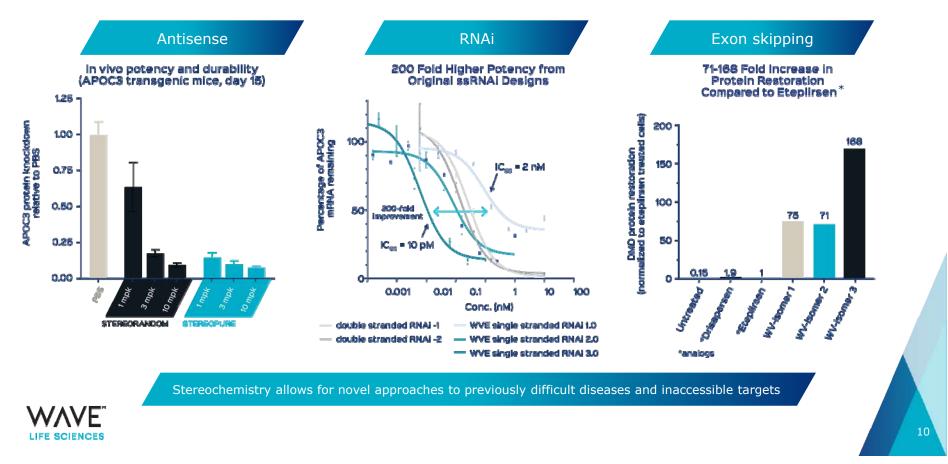
Source: Iwamoto N, et al. Control of phosphorothioate stereochemistry substantially increases the efficacy of antisense oligonucleotides. Nature Biotechnology. 2017.

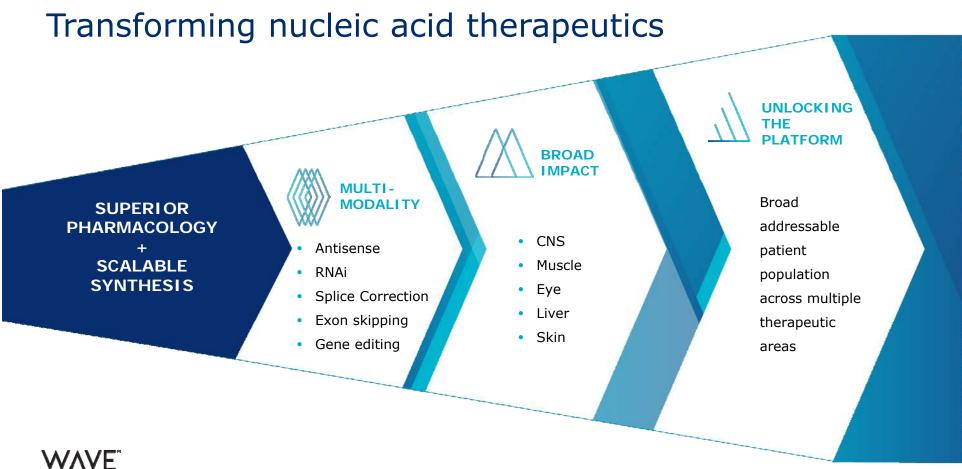
Chemistry may optimize medicines across multiple dimensions



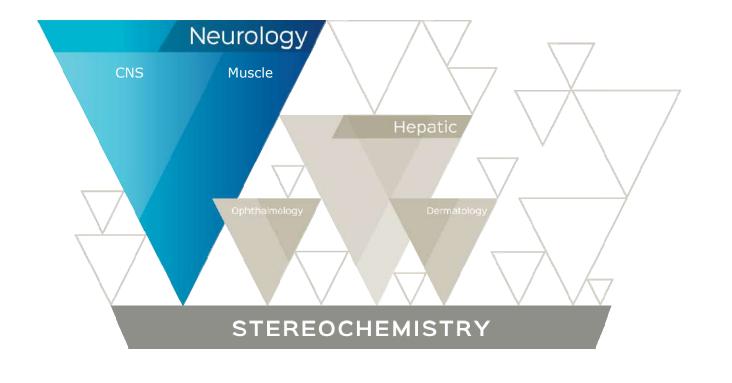
Data represented in this slide from in vitro studies. Experimental conditions: Human TLR9 assay – Source: Ohto U, et al. Structural basis of CpG and inhibitory DNA recognition by Toll-like receptor 9, Nature 520, 702-705, 2015. Intracellular trafficking assay – Cells were washed and fixed and oligos 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





Neurology







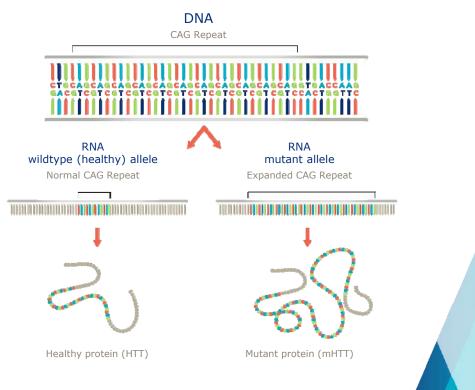




Huntington's Disease

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 longterm consequences
- 30,000 people with Huntington's disease in the US; another 200,000 at risk of developing the condition

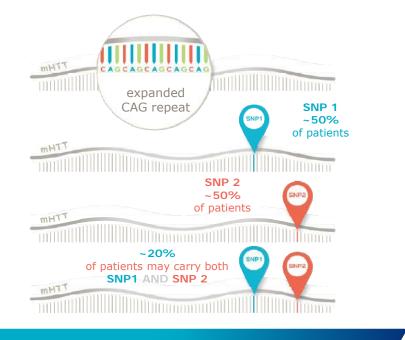




Sources: Auerbach W, et al. Hum Mol Genet. 2001;10:2515-2523. Dragatsis I, et al. Nat Genet. 2000;26:300-306. Leavitt BR, et al. J Neurochem. 2006;96:1121-1129. Nasir J, et al. Cell. 1995;81:811-823. Reiner A, et al. J Neurosci. 2001;21:7608-7619. White JK, et al. Nat Genet. 1997;17:404-410. Zeitlin 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

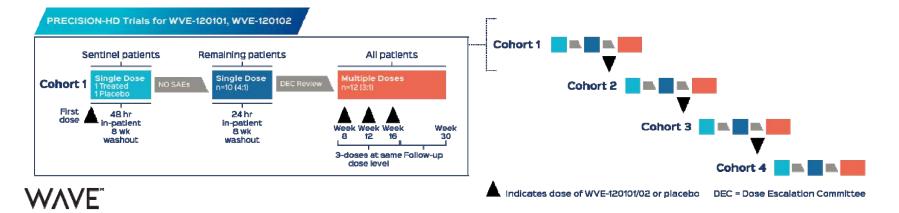


Source: Kay, et al. Personalized gene silencing therapeutics for Huntington disease. Clin Genet 2014: 86: 29-36

Two simultaneous Phase 1b/2a clinical trials

- Two parallel global placebo-controlled multi-ascendingdose 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



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

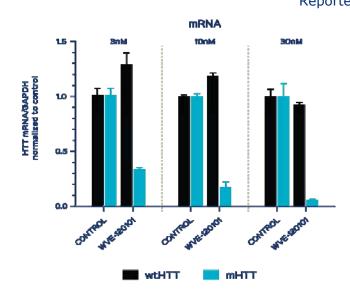
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Source: Wild E, et al. Quantification of mutant huntingtin protein in cerebrospinal fluid from Huntington's disease patients. J. Clin. Invest. 2015:125:1979–1986. Edward Wild, MA MB BChir PhD MRCP Principal Investigator at UCL Institute of Neurology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

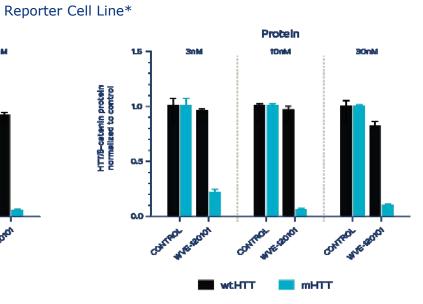


Selective reduction of mHTT mRNA & protein



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



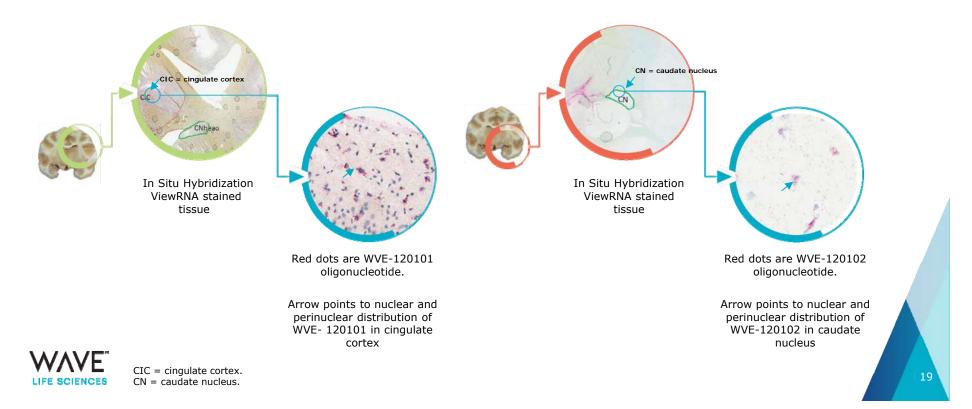






Demonstrated delivery to brain tissue

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





Duchenne Muscular Dystrophy (DMD)



DMD: a progressive, fatal childhood disorder

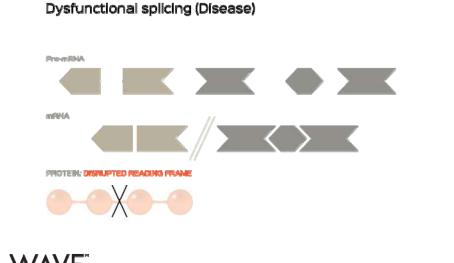
- Fatal, X-linked genetic neuromuscular disorder characterized by progressive, irreversible loss of muscle function, including heart and lung
- Genetic mutation in dystrophin gene prevents the production of dystrophin protein, a critical component of healthy muscle function
- Symptom onset in early childhood;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

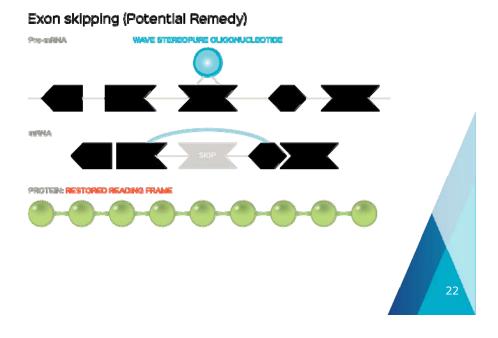




Wave approach: meaningful restoration of dystrophin production through exon skipping

- 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





Exon 51: WVE-210201 clinical program

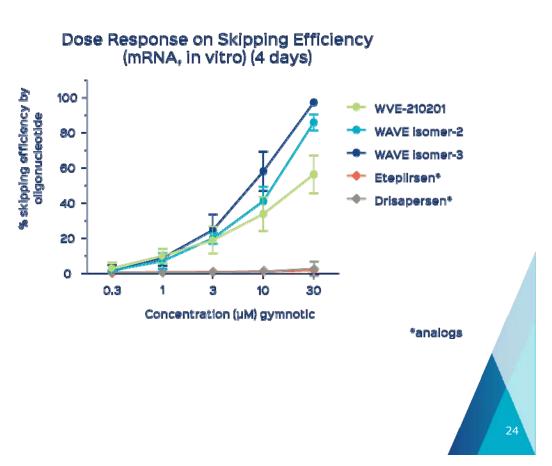
- WVE-210201 Phase 1 clinical trial initiated November 2017
 - Design: Multicenter, double-blind, placebo-controlled, single ascending dose study with I.V. administration
 - Primary endpoint: Safety and tolerability
 - Inclusion criteria: ages 5 to 18, amenable to exon 51 skipping
 - Ambulatory and non-ambulatory boys eligible, including those previously treated with eteplirsen (following appropriate washout period)
 - Readout expected Q4 2018
 - Open-label extension (OLE) with muscle biopsy and \geq 2-years of follow-up
- WVE-210201 planned efficacy study
 - Efficacy readout anticipated H2 2019
 - 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
- Exploring intravenous and subcutaneous formulations for WVE-210201





Exon 51: improved skipping efficiency

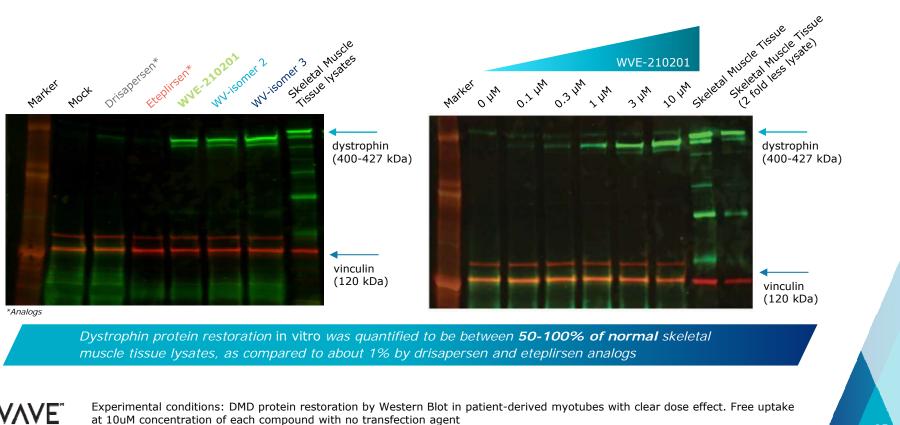
- RNA skipping determined by quantitative RT-PCR
- Wave isomers demonstrated a dose-dependent increase in skipping efficiency
- Free uptake at 10uM concentration of each compound with no transfection agent
- Same foundational stereopure chemistry for Wave isomers; individually optimized to assess ideal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





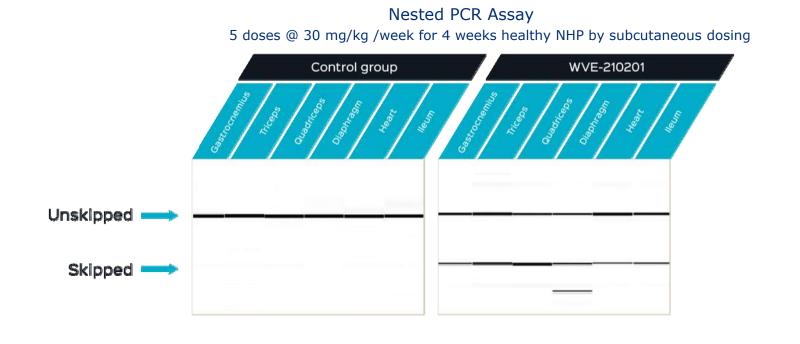
Exon 51: increased dystrophin restoration

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



26



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

B/Bri

- 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



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

Wave stereopure surrogate yields substantial natural dystrophin protein restoration in *mdx 23* mice

70-90% of natural dystrophin production in vivo

	Wild Type/PBS Pool						I	PBS		WV-1							
sn	80%	60%	40%	20%	10%	5%	2.5%	# 1	#2	#3	#1	#2	#3	#4	#5		
Gastrocnemius	-	-	-	-		7					-	-	-	-	-	+	Dystrophin
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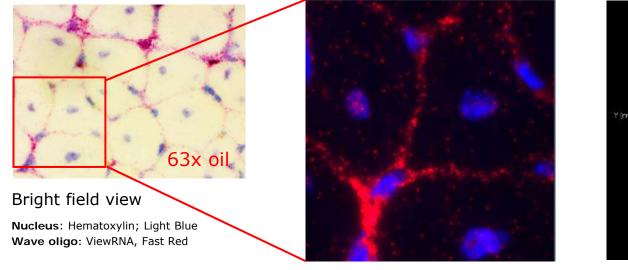
- An exon 23 skipping molecule with a similar profile to WVE-210201
- Level of transcript production observed in vivo correlates strongly to what was observed in vitro at the same 10uM doses
- Protein production after 1 month of treatment (4 weekly doses)



*Numbers indicate individual animals Methods: *mdx* 23 mice received 4 weekly IV doses (150 mg/kg). Tissues collected 96 hours post final dose. Protein expression determined by western blot.

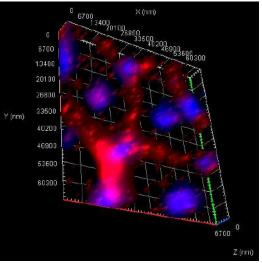


Exon 53: targeting oligonucleotide rapidly distributes to muscle within 24 hours after injection



Fluorescence channel view

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



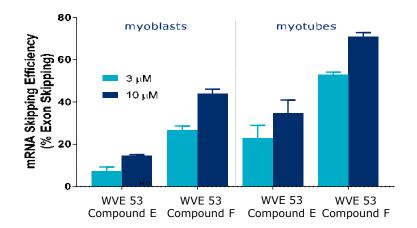
Z Stack view

29

Data derived from *in vivo* preclinical research. Methods: A single dose of stereopure ASO 30 24 hours part dose and ASO was detected in r

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

Exon 53 Program: improved skipping efficiency



Percentage Exon 53 Skipping of Preliminary Wave Isomers

- RNA skipping determined by quantitative RT-PCR
- Free uptake at 10uM and 3uM concentration of each compound with no transfection agent

Wave early Exon 53 data suggests skipping efficiency up to 70%





C9orf72

Amyotrophic Lateral Sclerosis (ALS) Frontotemporal Dementia (FTD)

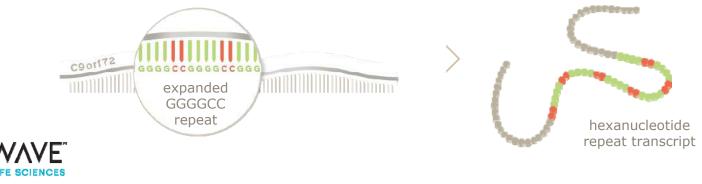
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C9orf72: a critical genetic risk factor

- 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



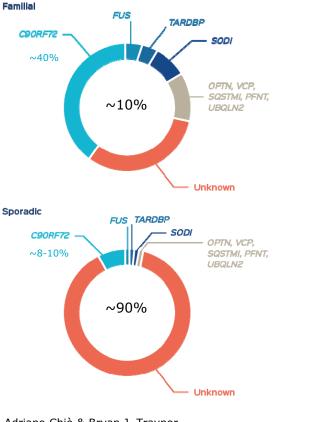




Amyotrophic lateral sclerosis

- 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





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



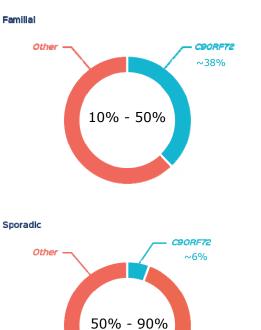
Frontotemporal dementia

- 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



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

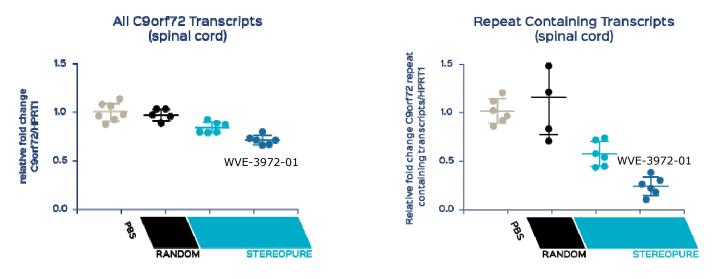






Selective silencing in vivo of expanded C9orf72 repeat transcripts

- 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 and FTD



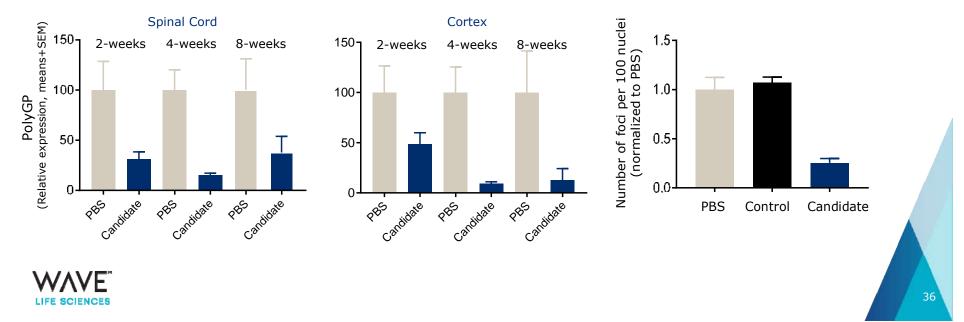


Experimental description: Samples were analyzed using quantitative PCR (Taqman assay)

Neuro C9orf72

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)

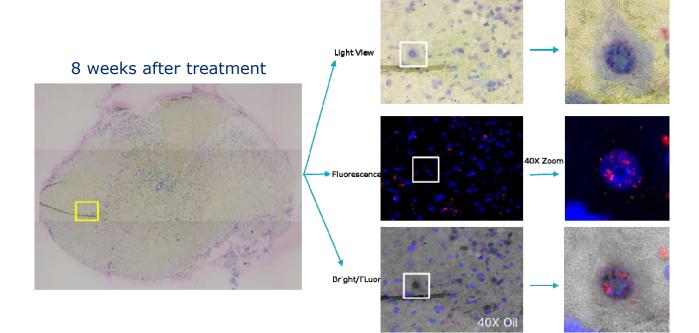


Durable reduction of dipeptide in vivo

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

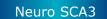


Experimental description: C9-BAC mice were administered $50\mu g$ of WVE-3972-01 ICV on day 1 and day 8; detection using ViewRNA.



Spinocerebellar ataxia type 3





Spinocerebellar ataxia type 3

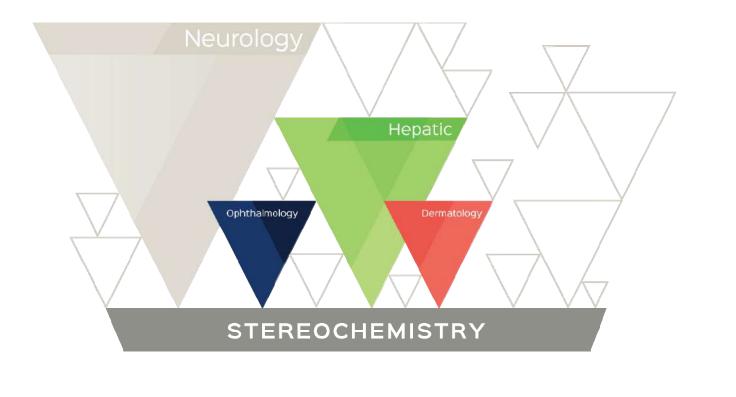
- Also known as Machado-Joseph disease
- Rare, hereditary, progressive neurodegenerative disorder that results in a lack of muscle control and coordination in upper and lower extremities; gradually leads to paralysis and loss of ability to speak or swallow
- Life expectancy is 10-20 years from symptom 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



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: <u>https://ghr.nlm.nih.gov/condition/spinocerebellar-ataxia-type-3</u> on February 15, 2018

Emerging areas



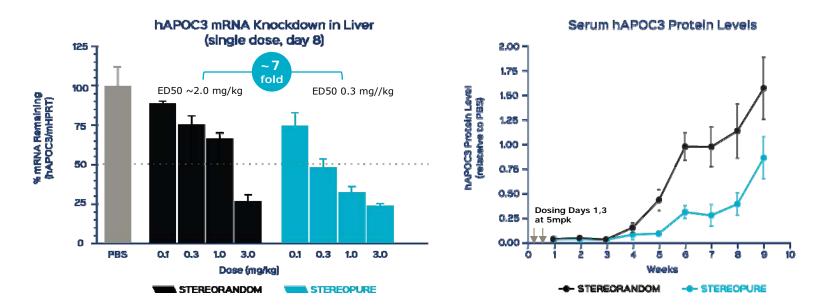


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Liver

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)



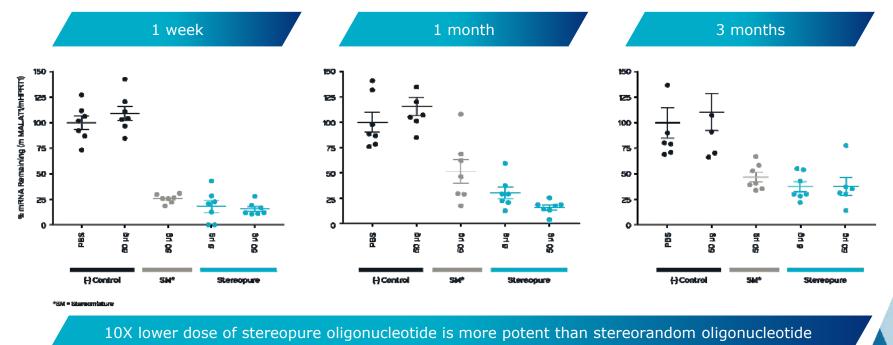
• Demonstrated increase in durability over GalNAc conjugated stereorandom oligonucleotide



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

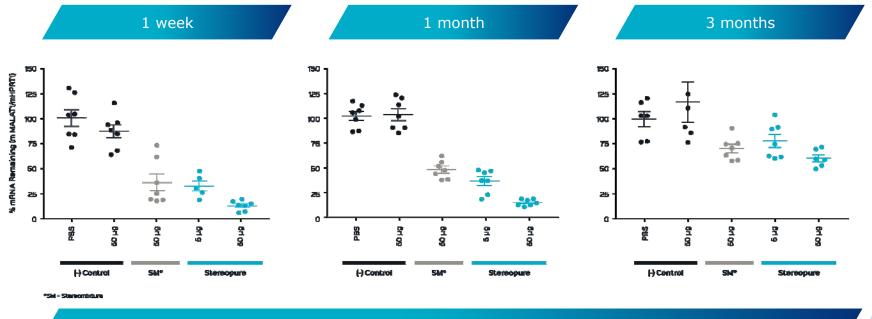




Experimental description: Single intravitreal injection to mouse eye on day 1.



Improved in vivo potency, extended duration Front of the eye



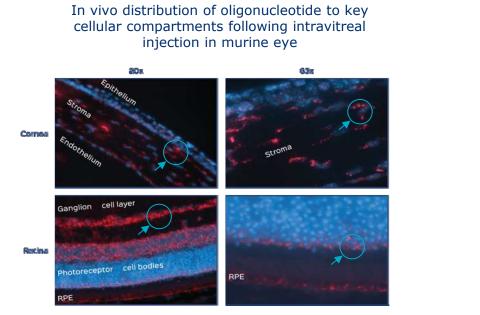
10X lower dose of stereopure oligonucleotide is more potent than stereorandom oligonucleotide



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

Eye Skin

Distribution and target engagement



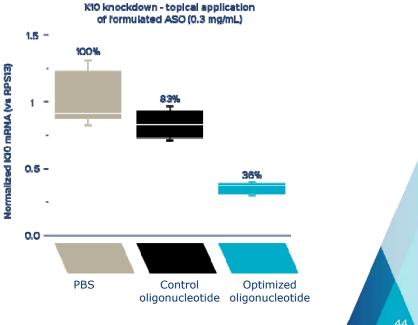
Ophthalmology

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 	



* Assuming Takeda advances six programs that achieve regulatory approval and commercial sales, Wave will be eligible to receive up to \$2 billion in cash milestone payments, of which more than \$1 billion would be in precommercial milestone payments.

Hepatic collaboration with Pfizer

- Initiated May 2016
- Exploring targets across modalities, including ASO and ssRNAi
- Up to 5 hepatic-metabolic programs
 - 5 targets declared; APOC3 and 4 undisclosed
- Access to Pfizer's hepatic targeting technology
 - Potentially increasing potency beyond GalNAc
 - Freedom to leverage beyond collaboration targets

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\$M upfront payment

871 \$M in potential milestone payments and royalties





Enabling technologies: Applying artificial intelligence to discover novel therapies for genetic neuromuscular disorders



- Deep Genomics is a world leader in artificial intelligence with a platform that combines automation, advanced biomedical knowledge, high volume data acquisition and machine learning
- Wave is collaborating with Deep Genomics to predict the impact of genetic mutations and oligonucleotide approaches to splicing
- The goal is to identify new targets and optimal regions or sequences within those targets to be addressed by Wave's rationally designed oligonucleotides



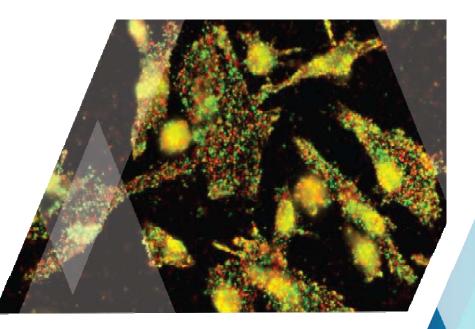
Understanding splicing biology to illuminate new approaches to increase size of addressable patient populations



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





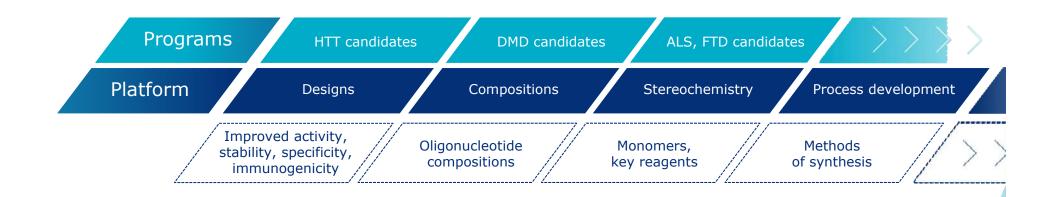
Manufacturing strength: scalable nucleic acid synthesis

- 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





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Upcoming Wave catalysts

- Q4 2018: safety data expected in DMD from Phase 1 trial for WVE-210201
 - WVE-210201 is the first stereopure oligonucleotide targeting Exon 51 with potential to be best-in-class
 - Received EU orphan drug designation
- 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
- H1 2019: data expected in HD from Phase 1b/2a trials for WVE-120101 and WVE-120102
 - Potential to be first two allele-specific disease-modifying therapies selectively lowering mHTT
 - Received U.S. orphan drug designation
- H2 2019: Interim dystrophin readout from ongoing open label extension and planned efficacy trials expected for WVE-210201
- 2020: DMD Exon 53 Program clinical data readout expected





LIFE SCIENCES

Realizing the potential of nucleic acid therapeutics

