

# **Duchenne Muscular Dystrophy**

## **Clinical and Commercial Strategy**

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# Duchenne Muscular Dystrophy (DMD)

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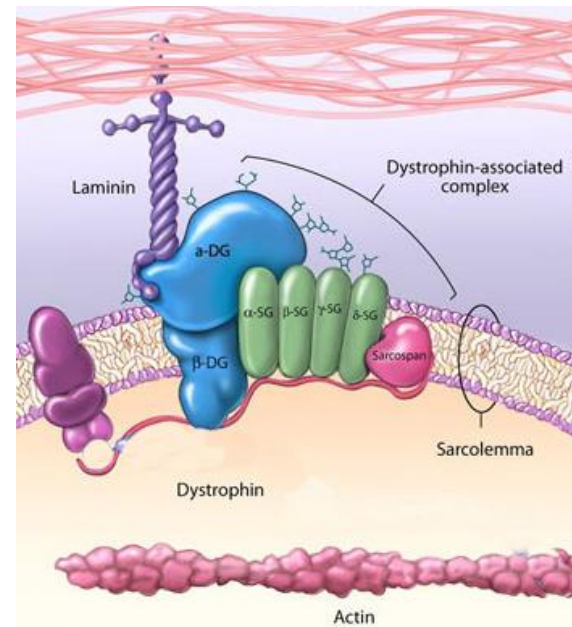
- ◆ Defects in the dystrophin gene; no protein expression
  - X-linked recessive
  - Mutational hot spot: exons 45 and 55: *functionally silent* region
  - 1 in 3 cases arise by spontaneous mutation; limits control via genetic counseling
- ◆ Symptoms present at 3-5 years of age
  - Muscle degeneration overwhelms regenerative capacity
  - Patients restricted to wheelchair by age 12
  - Death from cardiac respiratory complications
- ◆ Effects 1 in 3,500 male births; High yearly cost of care

# Molecular Basis for Exon Skipping

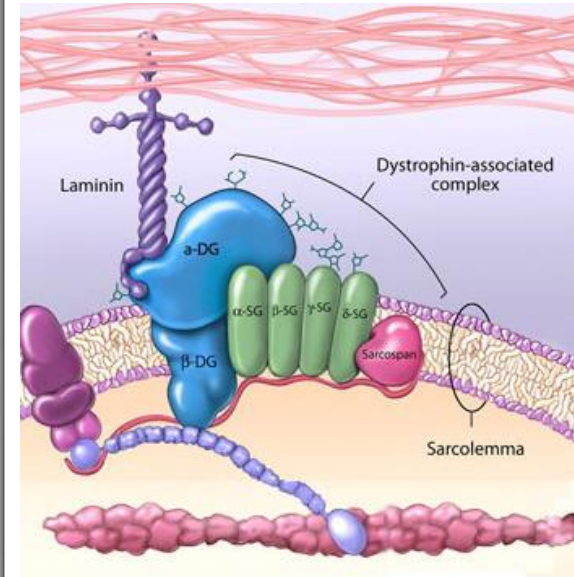
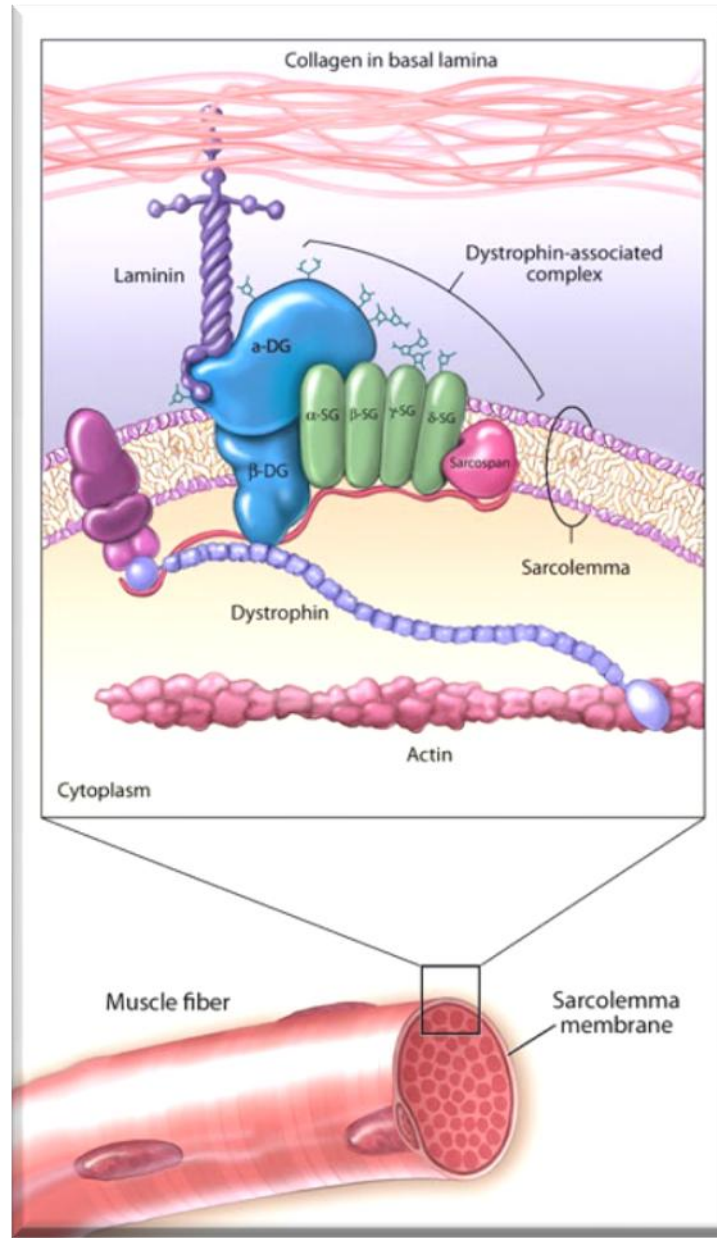
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- ◆ DMD results from mutations which affect critical exons in the dystrophin gene
- ◆ These critical mutations change the reading frame of the gene and so dystrophin protein is not expressed
- ◆ In 17.5% of DMD patients, these mutations might be corrected by removal of exon 51 to restore the reading frame
- ◆ Dystrophin protein would be expressed and functional, but truncated in a functionally silent region
- ◆ In Becker Muscular Dystrophy, loss of the same total exons is related to benign phenotype, normal life expectancy and mild symptoms

# Clinical Expectations for Exon Skipping



Duchenne muscular dystrophy



Becker muscular dystrophy

# AVI's DMD Exon Skipping Strategy

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- ◆ Clinical trials for exon 51 (17.5% of cases)
  - IM dose escalation on-going in EU
  - CTA for systemic trial approved by MHRA in EU
  - Preclinical pathway in US negotiated with the FDA
- ◆ PMO drug candidate: AVI-4658
- ◆ First generation: 6 single-exon drugs

# DMD – Therapeutic Exon Skipping

Exon to Skip	Therapeutic for Deletions (exons)	% in Leiden Database
51	45–50, 47–50, 48–50, 49–50, 50, 52, 52–63	17.5
45	12–44, 18–44, 44, 46–47, 46–48, 46–49, 46–51, 46–53, 46–55	11.2
44	14–43, 19–43, 30–43, 35–43, 36–43, 40–43, 42–43, 45, 45–54	7.8
53	10–52, 45–52, 46–52, 47–52, 48–52, 49–52, 50–52, 52	7.5
46	21–45, 45, 47–54, 47–56	5.6
50	51, 51–53, 51–55	<u>5.2</u>
	Total top six skipped exons	54.8%

Source: van Deutekom & Ommen, Nature Reviews Genetics **4**, 774, 2003

# Preclinical Findings on AVI-4658

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- ◆ External collaborations and independent validation
  - Professor Francesco Muntoni, University College London
  - Professor Steve Wilton, University of Western Australia
  - Dr. Eric Hoffman in National Children's Hospital, Washington DC
  - And their clinical research networks
- ◆ Comparison of oligomer chemistries
  - PMO is more effective than PNA or 2'-O-Methyl
- ◆ Identify optimal exon 51 sequence
  - AVI-4658 targeted to include exon splicing enhancer sites
- ◆ Pharmacokinetic data supported continued development
- ◆ Pilot toxicology studies had favorable outcome

# AVI-4658 Pre-clinical Efficacy: Two Species

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- ◆ Single treatment in mdx mouse model of DMD leads to 10-100% dystrophin production
- ◆ Mouse dose 36 to 100 mg/kg - human equivalent dosing 2.5 to 8.3 mg/kg
- ◆ Administration of PMO in *mdx* mouse also results in functional improvement
  - Reduced serum CK and improved force measurements
- ◆ Serial injections have cumulative effect on *de novo* dystrophin production and functional improvement
- ◆ Serial IV administration of PMOs to exons 5, 6 and 7 at 20 mg/kg in canine *mdx* model leads to functional improvement



# Exon Skipping “Proof of Concept” Performed by Collaborators in Dystrophic Canine Model



Courtesy of Toshifumi Yokota, Shin'ichi Takeda, National Institute of Neuroscience, Tokyo, Japan and Eric Hoffman, Children's National Medical Center, Washington DC

# Equivalent clinical assessment scales

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# Clinical and Commercial Goals for AVI-4658

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- ◆ Context: Disease invariably lethal; no disease modifying therapies
- ◆ An effective drug must slow the progression of disease through *de novo* dystrophin production ( $\geq 10\%$  fibers showing dystrophin expression)
- ◆ Systemic (intravenous) chronic administration is acceptable in this patient population
- ◆ Once clinical benefit is demonstrated, AVI will commit to life-time treatment of the subject
- ◆ Commercial potential, pricing and market development can be modeled on Genotropin (growth hormone) and disease modifying treatments for other serious genetic diseases

# AVI-sponsored Phase Ib Study on AVI-4658

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- ◆ MHRA has approved an open-label, safety, dose-escalation study; GTAC approval expected in October 2008

# Study 28: Phase 1b, Dose-Ranging Clinical Trial of AVI-4658

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- ◆ Subjects are ambulatory DMD boys, mutations correctable by skipping exon 51
  - Relevant mutation confirmed by DNA sequencing for trial inclusion
  - Virtual absence of dystrophin by immunofluorescence
  - 4 subjects per treatment group (total = 16)
- ◆ Route of Administration: Intravenous
- ◆ Treatment groups: 0.5, 1.0, 2.0, and 4.0 mg/kg
- ◆ Dosing Regimen: IV injection at weekly intervals for 12 weeks

# Study 28 – Clinical Trial Endpoints

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- ◆ Dystrophin production in sentinel muscle (biceps) to achieve a minimum of 10% *de novo* positive fibers by immunofluorescence
  - DMD diagnostic criterion <5% positive fibers
- ◆ Safety
  - Conventional safety laboratory tests
  - Conventional EKG, ECHO, and pulmonary function tests
  - Immunological: cytotoxic T-cell and anti-dystrophin antibodies
  - Quantitative muscle function tests (timed performance test and force evaluations)
- ◆ Tolerability

# European Approval

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- ◆ Option to convert open label study into a double-blind, pivotal trial to demonstrate drug efficacy and sustained clinical benefit
  - Significant reduction in rate of loss of muscle function
  - Minimum of one year clinical study with active surveillance
- ◆ Magnitude of reduction for approval discussed but not negotiated with MHRA
- ◆ EU approval could be on basis of a single pivotal trial

# US Plans for Clinical Development of AVI-4658

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- ◆ Negotiated preclinical requirements with the FDA
- ◆ Have allowance for mechanistic toxicology study in *mdx* mouse model of DMD to support clinical testing of AVI-4658
  - Evaluation of PMO-based exon 23 drug
  - Initiate 3-month *mdx* toxicology study in 4Q 2008
- ◆ Anticipate that UK Phase 1b study results might impact FDA decision making prior to completion of planned pre-clinical GLP agenda for US-based studies
  - Might allow immediate pivotal trial testing in US DMD boys



# Milestones in AVI's DMD Program

		Event
2008	Q4	<ul style="list-style-type: none"><li>• Exon 51 IM AVI-4658 Study completed</li><li>• Exon 51 IV AVI-4658 First patient dosed</li><li>• Exon 23 AVI-4225 Mechanistic toxicology study in <i>mdx</i> mouse</li></ul>
	Q1	Note Filing of IND for exon 50 study in US will await completion of <i>mdx</i> mouse toxicology study
2009	Q2	<ul style="list-style-type: none"><li>• Exon 51 IV AVI-4658 Data on third cohort of patients</li><li>• Exon 23 AVI-4225 Mechanistic toxicology study in <i>mdx</i> mouse study completed</li></ul>

# Economics of DMD

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## ◆ Incidence

- 1 per 3,500 male births
- 600 new cases each year in US
- 700 new cases each year in EU

## ◆ Prevalence

- 12,500 patients US
  - 14,000 patients EU
- ◆ 65% of patients could benefit from exon-skipping therapy
- ◆ Annual cost of care can exceed \$500,000 per non-ambulatory patient

# Precedent for Pricing to Value in Fatal / Debilitating Diseases

Drug	Company	Indication	Annual Price
Vectibix	Amgen	Colon cancer	\$100,000
Kuvan	BioMarin	Phenylketonuria	\$60,000
Cerezyme	Genzyme	Gaucher disease	\$200,000
Fabrazyme	Genzyme	Fabry disease	\$180,000
Myozyme	Genzyme	Pompe disease	\$250,000
Erbix	ImClone	Colon, head and neck cancers	\$120,000
Elaprase	Shire	Hunter syndrome	\$300,000

# DMD Market Opportunity

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- ◆ Sales Potential for Exon-Skipping Drugs:
  - Number of patients in US and EU: 26,500
  - % amenable to exon-skipping therapy: 65%
  - Consensus of analysts' estimates in DMD: \$100,000 revenue per year per eligible patient
- ◆ **US & EU potential market for exon-skipping DMD drugs: \$1.7 billion**
- ◆ Important commercial criteria - true amenable population, optimal time to begin treating, treatment duration, etc. - have yet to be established

# AVI's Potential Franchise Opportunity

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- ◆ BMD phenotype supports belief that exon-skipping in DMD could have good therapeutic outcome
- ◆ Ongoing EU clinical trials supported by favorable efficacy in 2 species and toxicology package
- ◆ Route to clinic in US negotiated
- ◆ First drug for exon 51 is a significant market opportunity
- ◆ First generation exon-skipping drugs will treat over 50% of DMD cases
- ◆ Conservative estimate of overall market addressed by exon skipping is \$1.7 billion