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PERIPHERAL AND CENTRAL NERVOUS SYSTEM DRUGS ADVISORY COMMITTEE

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DRISAPERSEN BRIEFING DOCUMENT

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TABLE OF CONTENTS

COVER PAGE....1
TABLE OF CONTENTS....2
LIST OF TABLES....5
LIST OF FIGURES....7
LIST OF ABBREVIATIONS AND ACRONYMS....11
REVIEWER'S GUIDE....14
CORE KNOWLEDGE DOCUMENT....15
1 INTRODUCTION....45
1.1 Indication and Description....45
1.2 Unmet Medical Need....45
1.3 Development Rationale and History....49
1.3.1 Clinical Development Program....51
1.3.2 Regulatory History....56
2 NONCLINICAL OVERVIEW....58
2.1 Mechanism of Action....58
2.2 Primary Pharmacodynamics....59
2.3 Secondary Pharmacodynamics....61
2.4 Nonclinical Pharmacokinetics....61
2.5 Safety Pharmacology....61
2.6 Toxicology....61
3 CLINICAL PHARMACOLOGY....64
3.1 Pharmacokinetics....64
3.1.1 Absorption, Distribution, Metabolism, Elimination....64
3.1.2 Population Pharmacokinetics....66
3.2 Pharmacodynamics and Biomarkers....67
3.2.1 Challenges of Biopsy Analysis and Its Relation to Clinical Function....67
3.2.2 Drisapersen Distribution to Muscle....68
3.2.3 Drisapersen Results in Dystrophin Expression and Exon 51 Skipping....69
3.2.3.1 Dystrophin Expression....69
3.2.3.2 Exon 51 Skipping....70
3.2.4 Serum Biomarkers: Creatine Kinase and Lactate Dehydrogenase....71
3.2.5 MRI Assessments....75
3.3 Drug-Drug Interactions....76
3.4 Dose Rationale....77
4 EFFICACY....78
4.1 Study Designs....79
4.2 Sample Size Determinations....81
4.3 Key Eligibility Criteria....82

4.4 Study Populations 82
4.5 Efficacy Endpoints 87
4.5.1 6MWD as the Primary Endpoint 88
4.5.2 Secondary Endpoints 90
4.6 Statistical Methods 92
4.6.1 Efficacy Studies of Drisapersen in Duchenne Muscular Dystrophy 92
4.6.2 Integrated Analyses 94
4.6.3 Missing Data Handling Conventions 94
4.7 Results 94
4.7.1 Phase II Studies – Primary Endpoint 96
4.7.2 Phase III Study 044 98
4.7.2.1 Primary Endpoint 98
4.7.2.2 Further Evaluation of Study 044 Results 99
4.7.3 Secondary Endpoints 110
4.7.3.1 Studies 117 and 876 110
4.7.3.2 Study 044 112
4.7.4 Long-Term Studies 114
4.7.4.1 Study 349 114
4.7.4.2 Study 673 119
4.8 Efficacy Conclusions 123
5 OVERVIEW OF SAFETY 126
5.1 Clinical Studies with Drisapersen 126
5.2 Overall Safety Analysis Plan 127
5.3 Exposure 128
5.4 Patient Disposition 130
5.5 Concomitant Medications 132
5.6 Adverse Events Overview 133
5.6.1 Placebo-Controlled Studies 133
5.6.2 Repeat-Dose Studies 134
5.7 Common Adverse Events 136
5.7.1 Placebo-Controlled Studies 136
5.7.1.1 Time to Occurrence of Adverse Events 139
5.7.2 Repeat-Dose Studies 142
5.7.3 Long-Term Safety 148
5.7.4 Adverse Events During Follow-Up Period 148
5.8 Deaths 149
5.9 Other Serious Adverse Events 149
5.10 Adverse Events That Led to Discontinuation 151
5.11 Adverse Events of Special Interest 151
5.11.1 Thrombocytopenia 153
5.11.1.1 Laboratory Data Relevant to Thrombocytopenia 155

5.11.2 Renal Abnormalities 156
5.11.2.1 Laboratory Data Relevant to Renal Abnormalities 158
5.11.3 Injection-Site Reactions 159
5.11.4 Hepatic Abnormalities 161
5.11.4.1 Laboratory Values Relevant to Hepatic Abnormities 162
5.11.5 Inflammation Events 164
5.11.5.1 Laboratory Values Relevant to Inflammation Events 166
5.11.6 Coagulation Abnormalities 166
5.11.6.1 Laboratory Values Relevant to Coagulation Abnormalities 168
5.12 Other Laboratory Findings 168
5.13 Electrocardiography 169
5.14 Echocardiography 169
5.15 Vital Signs and Other Observations 170
5.16 Adverse Drug Reactions 170
5.17 Immunogenicity 171
5.18 Conclusions 172
6 BENEFITS/RISKS 174
6.1 Benefits 174
6.2 Risks 175
7 PROPOSED RISK MANAGEMENT PLAN 177
8 PROPOSED POSTMARKETING COMMITMENTS 179
8.1 Registry 179
8.2 Additional Clinical Studies 183
9 CONCLUSION 184
10 REFERENCES 186
11 APPENDICES 197
11.1 Appendix A: Natural History Matches with Patients in Study 673 197
11.2 Appendix B: Patient Narratives: Thrombocytopenia Serious Adverse Events, Adverse Events that Led to Treatment Discontinuation, and Patient with Henoch-Schönlein Purpura 210
11.2.1 Patient 000505: SAE of moderate thrombocytopenia (CTCAE Grade 4) – AE led to treatment discontinuation 210
11.2.2 Patient 000677: SAE of severe thrombocytopenia (CTCAE Grade 3/4) – AE led to treatment discontinuation 211
11.2.3 Patient 000687: SAE of severe thrombocytopenia (CTCAE Grade 3/4) – AE led to treatment discontinuation 212
11.2.4 Patient 001176: SAE of severe thrombocytopenia (CTCAE Grade 4) – AE led to treatment discontinuation 213
11.2.5 Patient 001202: SAE of severe thrombocytopenia (CTCAE Grade 4) – AE led to treatment discontinuation 215

11.2.6 Patient 002000: SAE of severe thrombocytopenia (CTCAE Grade 3) – AE led to treatment discontinuation....216
11.2.7 Patient 003052: SAE of severe thrombocytopenia (CTCAE Grade 3) – AE led to treatment discontinuation....216
11.2.8 Patient 001122: SAE of severe thrombocytopenia (CTCAE Grade 4)....217
11.2.9 Patient 000527: SAE of glomerulonephritis – AE led to treatment discontinuation....218
11.2.10 Patient 001124: SAE of proteinuria – AE led to treatment discontinuation....219
11.2.11 Patient 001270: SAEs of intracranial venous sinus thrombosis and spinal pain – AE led to treatment discontinuation....220
11.2.12 Patient 000511: SAE of injection site edema – AE led to treatment discontinuation....221
11.2.13 Patient 000520: Severe asthenia – AE led to treatment discontinuation....221
11.2.14 Patient 002026: Henoch-Schönlein Purpura....222
11.3 Appendix C: Shift Analysis....225

LIST OF TABLES

Table 1: Key Studies in the Clinical Development of Drisapersen....24
Table 2: Percent of Patients Whose 6MWD Improved in Study 117, 876, and 044....31
Table 3: Mean Change from Baseline of CK in Study 117, 876, and 044 and Mean Change from Baseline of LDH in Study 044....35
Table 1.3.1.1: Clinical Studies of Drisapersen for the Treatment of Duchenne Muscular Dystrophy....52
Table 4.1: Clinical Studies of Efficacy of Drisapersen in Ambulatory Patients with Duchenne Muscular Dystrophy....79
Table 4.4.1: Baseline Demographic Characteristics of Placebo-Controlled Studies (Safety Populations)....83
Table 4.4.2: Baseline Disease Characteristics of Placebo-Controlled Studies (Safety Populations)....85
Table 4.5.1: Primary and Secondary Efficacy Endpoints Assessed in Placebo-Controlled Studies....87
Table 4.7.1: Adjusted Mean Change from Baseline in 6MWD in Placebo-Controlled Studies (ITT Populations)....95
Table 4.7.2.2.1: Adjusted Mean Change from Baseline in 6MWD at Week 48 Adjusted for Age, Baseline 6MWD, and Baseline Rise-from-the-Floor Velocity in Study 044 (ITT Population)....102
Table 4.7.2.2.2: Adjusted Mean Change from Baseline in 6MWD at Week 48 Adjusted for Age, Baseline 6MWD, and Baseline Rise-from-the-

Floor Velocity in Study 044 (ITT Populations Excluding Subjects with Age > 7 and Baseline 6MWD ≤ 330 meters) 107
Table 4.7.2.2.3: Adjusted Mean Change from Baseline in 6MWD at Week 48 Adjusted for Age, Baseline 6MWD, and Baseline Rise-from-the-Floor Time in Study 044 (ITT Populations) 108
Table 4.7.3.2.1: Clinical Global Impression of Improvement by Category in Study 044 at Week 48 114
Table 4.7.4.1.1: Change From Original Baseline in 6MWD in Long-Term Study 349 by Parent Study 044 (ITT Populations) 117
Table 5.1.1: Key Eligibility Criteria Important for Safety Considerations for PRO051-02 and Placebo-Controlled Repeat-Dose Studies 117, 876, and 044 126
Table 5.2.1: Safety Assessments in Drisapersen Studies 128
Table 5.3.1: Overall Cumulative Exposure Duration (Placebo-Controlled Studies) 129
Table 5.3.2: Overall Cumulative Exposure Duration (Repeat-Dose Studies) 130
Table 5.4.1: Patient Disposition (Repeat-Dose Studies) 132
Table 5.6.1.1: Overview of Adverse Events (Placebo-Controlled Studies) 134
Table 5.6.2.1: Overview of Adverse Events (Repeat-Dose Studies) 136
Table 5.7.1.1: On-Treatment Adverse Events (≥5%) (Placebo-Controlled Studies) 137
Table 5.7.1.1.1: Cumulative Incidence of Most Frequent (≥5%) On-Treatment Adverse Events by Time to First Occurrence up to 1 Year of Treatment (Placebo-Controlled Studies) 140
Table 5.7.2.1: Incidence Rates/100 Patient-Years of On-Treatment Adverse Events (≥5%) (Repeat-Dose Studies) 143
Table 5.7.2.2: On-Treatment Adverse Events by System Organ Class and Preferred Term in ≥ 5% of Patients in Drisapersen All Regimen Group (Repeat-Dose Studies) 145
Table 5.9.1: On-Treatment Serious Adverse Events in >1 Patient (Repeat-Dose Studies) 150
Table 5.10.1: Adverse Events That Led to Permanent Treatment Discontinuation (Repeat-Dose Studies) 151
Table 5.11.1: On-Treatment Adverse Events of Special Interest (Placebo-Controlled Studies) 152
Table 5.11.2: On-Treatment Adverse Events of Special Interest (Repeat-Dose Studies) 153
Table 5.11.1.1: On-Treatment Thrombocytopenia Adverse Events by Preferred Term (Repeat-Dose Studies) 154
Table 5.11.1.1.1: Mean Changes in Platelets From Baseline at Weeks 24 and 48 (Placebo-Controlled Studies) 155
Table 5.11.2.1.1: Mean Changes and Shifts From Baseline in Cystatin C at Weeks 24 and 48 (Placebo-Controlled Studies) 159

Table 5.11.3.1: Overview of Chronic, Dermatologically Significant Injection Site Reactions (Repeat-Dose Studies) 161
Table 5.11.4.1: On-Treatment Hepatic Abnormalities by Preferred Term (Repeat-Dose Studies) 162
Table 5.11.4.1.1: Changes in Liver Function Test Results From Baseline at Weeks 24 and 48 (Placebo-Controlled Studies) 163
Table 5.11.4.1.2: Patients With Shifts in GLDH From Normal at Baseline to High or Low On Treatment (Placebo-Controlled Studies) 164
Table 5.11.5.1: On-Treatment Inflammation Events by Preferred Term (Repeat-Dose Studies) 165
Table 5.11.6.1: On-Treatment Coagulation Abnormalities by Preferred Term (Repeat-Dose Studies) 167
Table 5.11.6.1.1: Mean Changes From Baseline in aPTT and INR at Weeks 24 and 48 (Placebo-Controlled Studies) 168
Table 5.12.1: Change in Clinical Chemistry Parameters from Baseline at Weeks 24 and 48 (Placebo-Controlled Studies) 169
Table 5.16.1: Most Common Adverse Drug Reactions: ≥5% Incidence and ≥ Twice Placebo Rate (Placebo-Controlled Studies) 171
Table 7.1: Safety Specification for Drisapersen 177
Table 8.1.1: Recommended Schedule of Events 181
Table 11.2.14.1: Laboratory Results in a Patient with Henoch-Schönlein Purpura 224
Table 11.3.1: CTCAE Criteria for Shifts in Laboratory Values 225

LIST OF FIGURES

Figure 1: T1-Weighted MRI of Thigh Muscles Showing Progression of Duchenne Muscular Dystrophy with Increasing Age 18
Figure 2: Natural History Timeline of Duchenne Muscular Dystrophy 19
Figure 3: Schematic Representation of Exon Skipping Induced by Drisapersen 22
Figure 4: Cumulative Distribution at Week 24 in Study 117 (ITT Population) 28
Figure 5: Cumulative Distribution at Week 24 in Study 876 (ITT Population) 29
Figure 6: Cumulative Distribution at Week 48 in Study 044 (ITT Population) 30
Figure 7: Change from Baseline in 6MWD at Week 48 in Study 044 and Long-Term Follow-Up (Week 48 Completer Analysis) 32
Figure 8: Clinical Global Impression of Improvement at Week 48 in Study 044 (ITT Population) 34
Figure 1.2.1: Function of Dystrophin in Skeletal Muscle 46
Figure 1.2.2: T1-Weighted MRI of Thigh Muscles Comparing Duchenne Muscular Dystrophy Patient With Normal Control 47
Figure 1.2.3: Natural History Timeline of Duchenne Muscular Dystrophy 48
Figure 2.1.1: Schematic Representation of Exon Skipping Induced by Antisense Oligonucleotide Drisapersen 59

Figure 3.1.1.1: Median Plasma Drisapersen Concentration Profiles After SC Injection of 6 mg/kg Drisapersen at Week 29 in Study 117 65
Figure 3.1.1.2: Drisapersen Concentrations in Muscle Biopsies 66
Figure 3.2.1.1: T1-Weighted MRI of Thigh Muscles Showing Progression of Duchenne Muscular Dystrophy with Increasing Age 68
Figure 3.2.3.1.1: Immunofluorescence Analysis of Dystrophin in Study 117 at Week 24 69
Figure 3.2.3.2.1: Exon 51-Skipped Dystrophin Levels in Patients in Study 044 by Nested RT-PCR 71
Figure 3.2.4.1: Mean Serum Creatine Kinase Levels in Study 117 72
Figure 3.2.4.2: Mean Serum Creatine Kinase Levels in Study 876 73
Figure 3.2.4.3: Mean Serum Creatine Kinase Levels in Study 044 73
Figure 3.2.4.4: Mean Serum LDH Levels in Study 117 74
Figure 3.2.4.5: Mean Serum LDH Levels in Study 876 74
Figure 3.2.4.6: Mean Serum LDH Levels in Study 044 75
Figure 3.2.5.1: Rate of Fat Infiltration in Muscles from Patients in Study 876 76
Figure 4.1.1: Designs of Placebo-Controlled Studies 80
Figure 4.7.1.1: Cumulative Distribution Function at Week 24 in Study 117 (ITT Population) 96
Figure 4.7.1.2: Cumulative Distribution at Week 24 in Study 876 (ITT Population) 97
Figure 4.7.2.1.1: Cumulative Distribution at Week 48 in Study 044 (ITT Population) 99
Figure 4.7.2.2.1: Change from Baseline in 6MWD at Week 48 vs. Baseline Age and vs. Baseline 6MWD in Studies 117, 876, and 044 (Placebo ITT Population) 100
Figure 4.7.2.2.2: Change from Baseline in 6MWD at Week 48 vs. Baseline Rise-From-the-Floor Time in Studies 117, 876, and 044 (Placebo ITT Population) 101
Figure 4.7.2.2.3: Proportion of Patients in Categories of Baseline Age and 6MWD by Treatment Group in Study 044 (ITT Population) 102
Figure 4.7.2.2.4: Proportion of Patients in Categories of Baseline Age and 6MWD by Treatment Group in Study 044 Patients with Rise-From-the-Floor Times ≤ 7 seconds 103
Figure 4.7.2.2.5: Density Plot of Baseline Rise from Floor (RFF) Time (in Seconds) – (Study 044 – All Subjects with RFF ≤ 7 Seconds) 104
Figure 4.7.2.2.6: 6MWD over Time by Baseline Age and 6MWD in a Natural History Cohort 105
Figure 4.7.2.2.7: Patients by Age and 6MWD at Baseline in the Placebo-Controlled Studies 106
Figure 4.7.2.2.8: Comparison of Individual Trajectories of Placebo-Treated Patients in Studies 117, 876 and 044 106
Figure 4.7.2.2.9: Change from Baseline in 6MWD at Week 48 in Study 044 and Long-Term Follow-Up (Week 48 Completer Analysis) 109

Figure 4.7.3.1.1: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints at Week 48 in Study 117 110
Figure 4.7.3.1.2: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints at Week 24 in Study 876 111
Figure 4.7.3.2.1: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints at Week 48 in Study 044 112
Figure 4.7.3.2.2: Clinical Global Impression of Improvement in Study 044 at Week 48 113
Figure 4.7.4.1.1: Mean Change from Original Baseline in 6MWD in Long-Term Study 349 for Patients from Parent Study 117 (ITT Population) 115
Figure 4.7.4.1.2: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints at Week 96 in Long-Term Study 349 in Patients from Parent Study 117 116
Figure 4.7.4.1.3: Mean Change From Original Baseline in 6MWD for Patients in Long-Term Study 349 From Parent Study 044 (ITT Population) 117
Figure 4.7.4.1.4: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints in Long-Term Study 349 in Patients from Parent Study 044 at Week 96 118
Figure 4.7.4.2.1: Long-Term 6MWD Results in Study 673 120
Figure 4.7.4.2.2: Long-Term Rise-From-the-Floor Results in Study 673 121
Figure 4.7.4.2.3: Comparison of Individually Matched Drisapersen and Natural History Cohort Patients in Study 673 122
Figure 4.7.4.2.4: Example Patient Trajectories From Study 673 With Matched Natural History Subjects 123
Figure 4.8.1: Summary of Primary and Key Secondary Endpoint Results 124
Figure 5.2.1: Study Groupings for Safety Analyses 127
Figure 5.11.1.1.1: Platelet Levels by Visit in Patients Treated with Drisapersen 6 mg/kg/wk in Their Parent Study (Long-Term Safety) 156
Figure 11.1.1: Patient 673-101 6MWD Trajectory per Matched Natural History Subject 198
Figure 11.1.2: Patient 673-102 6MWD Trajectory per Matched Natural History Subject 199
Figure 11.1.3: Patient 673-105 6MWD Trajectory per Matched Natural History Subject 200
Figure 11.1.4: Patient 673-202 6MWD Trajectory per Matched Natural History Subject 201
Figure 11.1.5: Patient 673-206 6MWD Trajectory per Matched Natural History Subject 202
Figure 11.1.6: Patient 673-207 6MWD Trajectory per Matched Natural History Subject 203
Figure 11.1.7: Patient 673-106 6MWD Trajectory per Matched Natural History Subject 204

Figure 11.1.8: Patient 673-107 6MWD Trajectory per Matched Natural History Subject 205
Figure 11.1.9: Patient 673-205 6MWD Trajectory per Matched Natural History Subject 206
Figure 11.1.10: Patient 673-103 6MWD Trajectory per Matched Natural History Subject 207
Figure 11.1.11: Patient 673-104 6MWD Trajectory per Matched Natural History Subject 208
Figure 11.1.12: Patient 673-201 6MWD Trajectory per Matched Natural History Subject 209
Figure 11.2.1.1: Patient 000505: Platelet Counts 211
Figure 11.2.2.1: Patient 000677: Platelet Counts 212
Figure 11.2.3.1: Patient 000687: Platelet Counts 213
Figure 11.2.4.1: Patient 001176: Platelet Counts 214
Figure 11.2.5.1: Patient 001202: Platelet Counts 215
Figure 11.2.6.1: Patient 002000: Platelet Counts 216
Figure 11.2.7.1: Patient 003052: Platelet Counts 217
Figure 11.2.8.1: Patient 001122: Platelet Counts 218

LIST OF ABBREVIATIONS AND ACRONYMS

6MWD	6-minute walking distance
23AON	mouse-specific antisense oligonucleotide M23D (+02-18)
ADA	anti-drug antibody
ADR	adverse drug reaction
AE	adverse event
AESI	adverse events of special interest
AFF	apparent fat fraction
ALT	alanine aminotransferase
AON	antisense oligonucleotide
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
BLAST	Basic Local Alignment Search Tool
BMD	Becker muscular dystrophy
BUN	blood urea nitrogen
CI	confidence interval
CGI-I	Clinical Global Impression of Improvement
CK	creatine kinase
C_{max}	maximum observed plasma drug concentration
CNS	central nervous system
CRP	C-reactive protein
CSR	clinical study report
CT	computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CYP450	cytochrome P450
DIC	disseminated intravascular coagulation
DMD	Duchenne muscular dystrophy
ECG	electrocardiogram
EEG	electroencephalogram
EF	ejection fraction
EMA	European Medicines Agency
FDA	Food and Drug Administration

FVC	forced vital capacity
GLDH	glutamate dehydrogenase
GGT	gamma-glutamyl transferase
GSK	GlaxoSmithKline
hsCRP	high-sensitivity C-reactive protein
ICSR	individual case safety report
LLN	lower limit of normal
IM	intramuscular
INR	International Normalized Ratio
IP	intraperitoneal
ITT	intent-to-treat
IV	intravenous
LDH	lactate dehydrogenase
MCP-1	monocyte chemotactic protein-1
mdx	Duchenne muscular dystrophy mouse model (dystrophin deficient) with nonsense mutation in exon 23
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	mixed-effect model repeated measure
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
NDA	New Drug Application
Neuro-QOL	Quality of Life in Neurological Disorders
NH	natural history
NOAEL	no adverse effect level
NSAA	North Star Ambulatory Assessment
PBRER	Periodic Benefit-Risk Evaluation Report
PCR	polymerase chain reaction
PD	pharmacodynamics
PedsQL™	Pediatric Quality of Life Inventory
PedsQL™ 3.0 NMM	Pediatric Quality of Life Version 3.0 Neuromuscular Module
PF	peak flow
PK	pharmacokinetics
PODCI	Pediatric Outcomes Data Collection Instrument

PP	per protocol
PSUR	Periodic Safety Update Report
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using Bazett's formula
QTcF	QT interval corrected according to Fridericia's formula
RFF	rise-from-the-floor
RT-PCR	reverse transcription-polymerase chain reaction
SAE	serious adverse event
SC	subcutaneous
SD	standard deviation
SF-36	36-item short-form health survey
SMQ	standardized MedDRA query
SOC	system organ class
ULN	upper limit of normal

REVIEWER'S GUIDE

This document provides 3 levels of review which provide expanding levels of depth of information:

1. Core Knowledge Document (beginning below): Provides a focused review of key program characteristics, results, and conclusions. References are provided to supporting Sections, tables, and figures in the Detail Document.
2. Detail Document (Sections 1 through 9 beginning on page 45): Includes more presentations of findings and detailed discussions in support of the Core Knowledge Document.
3. Appendices (beginning on page 197): Provide plots of natural history matches with patients in Study 673 (Appendix A), narratives for selected patients (Appendix B), and shift laboratory values criteria definitions (Appendix C). These appendices are referenced in the Core Document when relevant.

For those reviewing this document in electronic format, cross-references to tables and figures are electronically linked to the corresponding table or figure. For those reviewing this document in paper format, the page number is provided when the table or figure is in a different Section.

CORE KNOWLEDGE DOCUMENT

Summary

Duchenne muscular dystrophy is a rare, progressive, and lethal neuromuscular disorder that is devastating to the patients, almost exclusively boys, who suffer with this X-linked genetic disorder and to the parents and families who care for them. The course of the disorder starts with early loss of muscular strength and function starting in the lower extremities, leading to wheelchair confinement before age 12. Disability continues to advance throughout the teenage years, proceeding to upper extremities, followed by respiratory and cardiac muscle failure and early mortality, usually by the second decade. Current therapy is primarily symptomatic and supportive.

Duchenne muscular dystrophy results from mutations – usually partial deletions – in the gene coding for the protein dystrophin, which is essential for normal muscular structure and function. To improve the clinical outcomes of a molecularly-defined subset (approximately 13%) of boys with Duchenne muscular dystrophy, BioMarin Pharmaceutical Inc. seeks to introduce drisapersen, a novel, personalized medicine that addresses the most common deletions responsible for the disorder and whose mechanism is uniquely suited to address specific mutations in the dystrophin gene.

Drisapersen is a chemically modified RNA oligonucleotide with a sequence optimized to specifically bind and skip exon 51 in the dystrophin pre-mRNA, allowing synthesis of an internally shortened but largely functional dystrophin protein. Drisapersen is formulated for subcutaneous (SC) administration at a weekly dose of 6 mg/kg of body weight.

The efficacy and safety of drisapersen have been demonstrated in the largest and most comprehensive clinical program ever filed for approval in Duchenne muscular dystrophy. This program includes 326 patients, 312 of whom received drisapersen, comprises 9 clinical studies, including 3 separate randomized placebo-controlled trials, conducted at more than 50 trial sites in 25 countries, and is informed by the findings of a thorough set of nonclinical assessments.

In these trials, drisapersen-treated patients walked farther in the 6 minute walk test than placebo-treated patients, with evidence of persistent benefit seen with long-term treatment. The totality of the available data supports a positive benefit risk assessment in patients with mutations amenable to exon 51 skipping. Important considerations that further support this positive benefit risk assessment include a strong understanding of the disorder and of drisapersen's mechanism of action that targets a well-defined molecular subset of patients, the lack of alternative therapies, the serious and life-threatening nature of this rare condition, and patient and parent input on benefits and risks.

One of the key underlying issues facing the development of orphan drugs is the ability to demonstrate effectiveness when studying the prevalent portion of a rapidly progressing, heterogenous, and exceedingly rare patient population. In a study of the quantum of effectiveness that is required to support approval for rare diseases, the authors studied 135 approvals from 1983 to 2010 (Sasinowski 2012) and updated the review with substantially the same conclusions through 2014 (Sasinowski 2015). The authors state:

> The Federal Food, Drug, and Cosmetic [FD&C] Act provides that for FDA to grant approval for a new drug, there must be 'substantial evidence' of effectiveness derived from 'adequate and well-controlled investigations.' This language, which dates from 1962, provides leeway for FDA medical reviewers to make judgments as to what constitutes "substantial evidence" of a drug's effectiveness, that is, of its benefit to patients.

The authors identified over 100 applications in which the Agency approved new drugs under circumstances in which evidence to support approval was something other than "conventional or traditional showing of effectiveness, which most often is colloquially and commonly referred to as 'the two adequate and well-controlled studies standard'." In these circumstances, evidence was "such that experts qualified by scientific training and experience and to evaluate the effectiveness of the drug could 'fairly and responsibly' conclude that the drug will have the effects …in the sponsor's proposed claim."

The proposed indication for drisapersen is for "the treatment of Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing." Acknowledging that the strongest evidence in support of effectiveness has been obtained in patients with relatively preserved ambulatory capacity, BioMarin seeks a broad label based on: 1) supportive evidence obtained in more advanced stage patients; 2) patient and parent preferences; and 3) the history of labeling similarly developed products in the orphan disease space, where there is a plausible hypothesis that extrapolation beyond the primary population studied is warranted. At the same time, BioMarin recognizes and is undertaking further studies in different segments of the population to fortify knowledge, and guide safe and appropriate use of drisapersen.

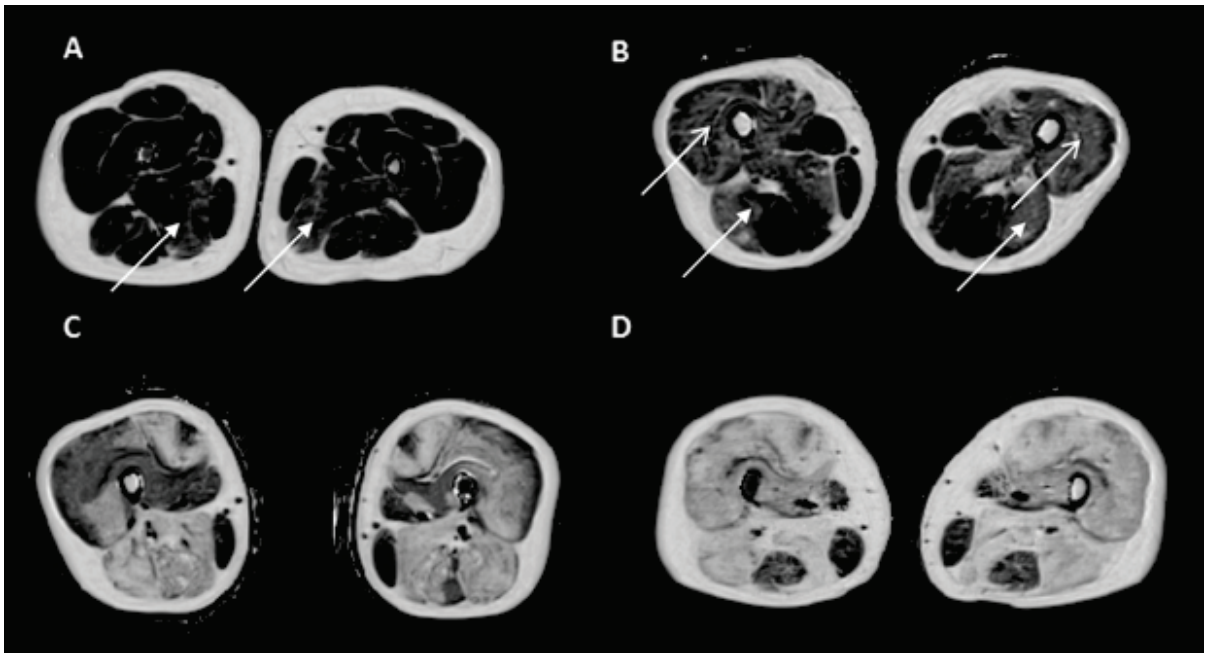
As with BioMarin's other rare disease programs, we are making a long-term commitment to the Duchenne muscular dystrophy community to systematically gather further information regarding the safety and effectiveness of drisapersen in the post-approval setting. These commitments include: 1) a post-approval registry to holistically evaluate long-term outcomes; 2) an enhanced risk management plan tailored to guide safe and appropriate use of drisapersen; 3) a clinical study in younger patients (less than 5 years of age); 4) a clinical study in older, nonambulatory patients to further the understanding of drisapersen's effects in those important patient populations; and 5) a clinical study to examine intravenous dosing as an alternative to subcutaneous administration.

Medical Landscape

Duchenne muscular dystrophy occurs almost exclusively in males (X-linked recessive disorder), with a global incidence of up to 1 in 3,500 male births. The estimated prevalence in the United States is approximately 18,000 cases (McNeil 2010), approximately 2,300 of whom would be amenable to exon 51 skipping therapy based on molecular characteristics of their mutation. Fewer than half of these patients have sufficient ambulatory capacity to participate in clinical trials at any given time. Duchenne muscular dystrophy is caused by genetic mutation resulting in the relative absence of functional dystrophin, a rod-shaped protein necessary for the integrity and function of muscle fibers.

Among other functions, dystrophin anchors the cytoskeleton of muscle fibers to the cell membrane and basal lamina and protects the muscle fibers against contractile stress. Dystrophin also plays a role in cell signaling. The relative importance of these functions is unknown. Dystrophin is not only expressed in skeletal muscle, but also in heart and smooth muscle in for instance the vascular system and lung. Furthermore, other variants of the dystrophin molecule (isoforms) are found in a variety of tissues such as the kidney where its function has not been characterized. Lack of the muscle isoform of dystrophin results in degeneration of muscle fibers, attracting inflammatory cells, and ultimately replacement of muscle by fibrosis and adipose tissue. This process can be visualized through magnetic resonance images (MRIs) (Figure 1), which show the progressive changes to the muscle as boys with Duchenne muscular dystrophy age from 5 to 12 years. Since skeletal muscle is the primary target of the drisapersen, clearly there will be a relationship between the amount of muscle available and the opportunity of therapeutic effect – which will be limited for case C and D in terms of ambulatory function.

Figure 1: T1-Weighted MRI of Thigh Muscles Showing Progression of Duchenne Muscular Dystrophy with Increasing Age



Muscle fat fraction of the thigh muscles in Duchenne muscular dystrophy patients at baseline. Patient A is age 5.0 years; fatty degeneration is most prominent in the adductors (closed arrows). Patient B is age 9.2 years; fatty degeneration now also clearly visible in the quadriceps (open arrows) and hamstrings (closed arrows). Patient C is age 9.8 years; fatty degeneration is visible in all muscle groups. Patient D is age 12.8 years; fatty degeneration is visible in all muscle groups.

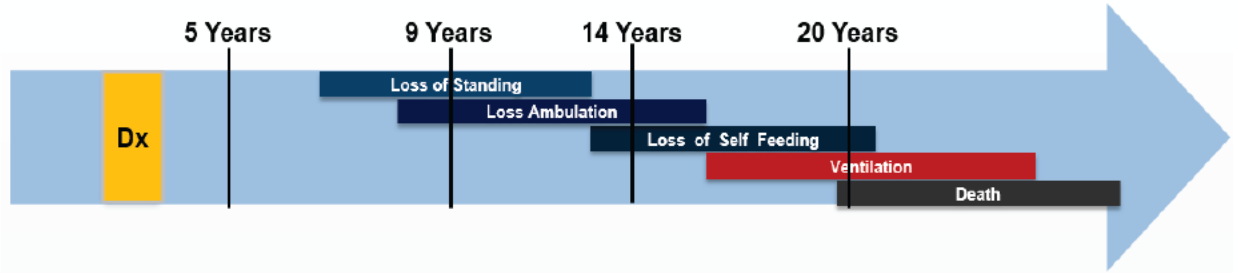
Reprinted from Neuromuscular Disorders, vol. 25/issue 9, Bonati U, Hafner P, Schädelin S, et al. Quantitative muscle MRI: A powerful surrogate outcome measure in Duchenne muscular dystrophy, pp. 679-685 (2015), with permission from Elsevier.

Boys with Duchenne muscular dystrophy may begin to show signs of muscle weakness by 3 years of age. Due to the nonspecific early signs, it may take some time and several doctor visits before a correct diagnosis (usually entailing genetic testing) is made (Figure 2). The mean age of diagnosis is ~5 years (Ciafaloni 2009). All patients experience a progressive weakening of skeletal or voluntary muscles in the arms, legs, and trunk. As a result, the boys may start to show reduced mobility, with difficulty walking or rising from the floor. As the muscle weakness progresses, these boys cannot keep up with their peers; they trip and fall with increasing regularity, often causing bone fractures, and lose the ability to climb stairs. Recently, quantitative evidence on prognostic factors and their impact on 6MWD outcome in Duchenne muscular dystrophy has been published and documents that age and baseline walking distance are prognostic factors in determining change from baseline walking distance. By age 7, many have reached their maximum walking ability as measured by percent-predicted distance in the 6-minute walk test (McDonald 2013a, Pane 2014). Heterogeneity of the disease beyond age and current ambulatory capacity as measured by the 6MWD test is further amplified by differences in the standard of care – not just between

countries, based on their health care systems or region-specific management guidelines, but also between large organized centers with multidisciplinary care teams and peripheral smaller hospitals. This combination of heterogeneity in disease progression and heterogeneity in standard of care leads to a wide variability in age of onset of disease-specific symptoms and passing specific milestones of disease progression. As is often the case in rare disease settings, this heterogeneity poses enormous challenges for the development of new drugs.

Decline in performance on the 6MWD test is correlated with loss of ambulation (Mazzone 2013). Further irreversible loss of function inexorably ensues (Figure 2). By age 12, they are often wheelchair bound; this loss of independence is a life-changing event for the boys and for the parents and families who care for them. The disorder then takes on a new and even more devastating aspect. Flexion contractures develop in elbows, knees, hamstrings, and hips; the ability to raise their arms or to use their hands and wrists becomes increasingly limited as well, further curtailing mobility and the ability to perform activities of daily living and self-care. Severe scoliosis may develop with consequent thoracic deformities. Abnormalities in smooth muscle function of the gastrointestinal tract can lead to digestive symptoms. Cardiac and respiratory muscles typically start to become affected in the early teens (Wagner 2007), ultimately leading to primary cardiomyopathy and respiratory failure requiring ventilator use. In addition, approximately one-third of patients with Duchenne muscular dystrophy experience cognitive impairment, which appears to be independent from the muscular impairment and has been attributed to lack of dystrophin in the central nervous system (Andersen 2002, Bresolin 1994, Zhou 2011).

Figure 2: Natural History Timeline of Duchenne Muscular Dystrophy



Dx, diagnosis. Contemporary treatment with steroids, improved cardiac management, and ventilation. Data from Bushby 2011 and McDonald 2013b. Figure adapted from McDonald DM, et al. Muscle Nerve (2013b);48(1):32-54, with permission (John Wiley and Sons).

Without intervention, Duchenne muscular dystrophy leads to early mortality, usually in the second decade (Bushby 2010). Following the introduction in the 1990s of assisted ventilation in the later stages of the disorder, the mean age of survival (for those patients receiving ventilation who do not develop early and severe cardiomyopathy) improved to 24 years (Rall 2012, Eagle 2002). Current guidelines recommending corticosteroids (though no formal regulatory approval for such use of corticosteroids has been obtained), along with respiratory, cardiac, orthopedic, and rehabilitative interventions, have led to improvements in function, quality of life, and longevity, so that boys diagnosed with the disorder today in

industrialized countries or in the best case have the possibility of survival into their early 30s (Bushby 2010).

There is no cure for Duchenne muscular dystrophy. The goals of treatment are to maintain function for as long as possible and to manage the associated complications of the disorder. Supportive care and off-label use of corticosteroids (usually prednisone or deflazacort) are the primary means to improve the quality of life of affected boys (Emery 2003). However, the risks of chronic corticosteroid administration have led to wide variability in their clinical use (Griggs 2013). Supportive physical therapy can help maintain range of motion and bilateral symmetry to prolong ambulation, but the frequency with which this should be done (at least 4-6 days/week) places great demands on families. Inconsistent use of these measures contributes to the heterogeneity of the Duchenne muscular dystrophy patient population, including those available for clinical trials.

Ataluren is the only disease-modifying agent that has been developed and conditionally approved for Duchenne muscular dystrophy (in Europe). This drug addresses one specific type of underlying genetic defect: nonsense-mediated premature truncation of dystrophin, and is not indicated or appropriate for treatment of patients with exon 51 skipping amenable mutations. Based on a single, completed randomized trial of 174 ambulatory male patients aged 5 to 20 years, ataluren was granted a conditional marketing authorization in Europe in July 2014 (Translarna EPAR 2015). Ataluren has orphan status in the United States but is not currently approved or otherwise commercially available.

There is a clear and urgent unmet medical need for new treatments that provide benefits considered meaningful to patients with Duchenne muscular dystrophy and their caregivers.

Parents of patients with Duchenne muscular dystrophy and parent groups have been active and effective in advocating for greater attention to the clinical development and regulatory consideration of promising new therapies. They have educated themselves on the clinical trials process and the need for objective unbiased assessments of clinical outcomes. They have collaborated with companies developing potential therapies and with regulatory authorities, and they have strongly voiced their preferences for clinical trials that are as inclusive and heterogeneous as possible, even at the risk of reduced precision in the assessment of treatment effects. Their efforts have been instrumental to the issuing in recent years of draft guidances to industry for the development of therapies for Duchenne muscular dystrophy by European Medicines Agency and the US Food and Drug Administration (EMA 2013, FDA 2015) and have championed patient input into regulatory risk-benefit assessments.

Development Rationale and History

The dystrophin gene is the largest in the human genome, with 79 exons covering 2.6 million nucleotide base pairs. This large size makes it prone to rearrangement and recombination events that cause mutations. Boys with a clinical suspicion of Duchenne muscular dystrophy undergo molecular analysis of their dystrophin gene in DNA isolated from a blood sample, which includes characterization of the type and location of mutation through routinely available tests.

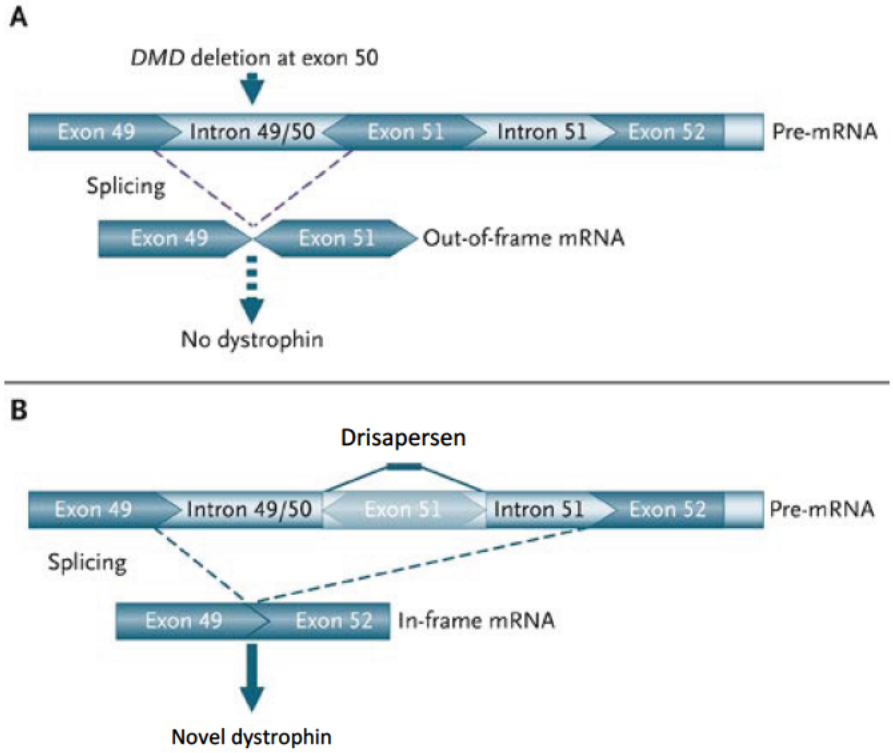
Most (60–68%) of the mutations in the dystrophin gene involve the deletion of one or more exons (Aartsma-Rus 2006, Flanigan 2009). These deletions interrupt the "open reading frame" of the dystrophin transcript, leading to a premature halt in the produced dystrophin protein. However, there are some exon deletions in the dystrophin gene that do not alter the open reading frame but result instead in internally shortened but functional dystrophin proteins. These mutations are associated with Becker muscular dystrophy (BMD), a less severe form of the disorder. Especially when in-frame deletions (that do not disrupt the transcript open reading frame) are located within the central rod domain of the dystrophin protein, clinical manifestations can be quite mild and compatible with a normal lifestyle.

This observation was the basis for the development of exon-skipping strategies designed to restore the open reading frame and thereby convert a Duchenne muscular dystrophy mutation into a BMD mutation at the RNA level. In this approach, antisense oligonucleotides are utilized to target a specific exon that is flanking a deletion. By preventing the binding of splicing factors to that exon, it is skipped during the splicing process. The translation process resumes at the next appropriate exon, producing an internally shortened transcript, which yields a still largely functional dystrophin protein (van Deutekom 2001, Aartsma-Rus 2002, van Ommen 2008, Aartsma-Rus 2010).

Drisapersen is a chemically-modified (2'-O-methyl-phosphorothioate RNA) oligonucleotide with a 20-nucleotide sequence optimized to target a splicing regulatory sequence within exon 51 of the human dystrophin pre-mRNA. Figure 3 provides an example of the drisapersen exon-skipping effect on dystrophin production. The resulting dystrophin protein lacks specific amino acids in the central rod domain, but retains the terminal domains necessary for its structural and signaling roles. Because of its potency and bioavailability, demonstrated in preclinical and pharmacokinetic studies, drisapersen can be administered via SC injection.

Drisapersen-induced exon skipping is a personalized, mutation-dependent corrective approach to Duchenne muscular dystrophy. The majority of Duchenne muscular dystrophy-causing deletions cluster in a hot spot region between exons 45 and 53. Thus, the skipping of one specific exon may apply to a series of different mutations (Aartsma-Rus 2009). For instance, skipping exon 51 would restore the reading frame in patients who carry a deletion of exons 45–50, 47–50, 48–50, 49–50, 50, 52, or 52–63, which comprise 13% of all patients with Duchenne muscular dystrophy.

Figure 3: Schematic Representation of Exon Skipping Induced by Drisapersen



Notes: In a patient with Duchenne muscular dystrophy with a deletion of exon 50, an out-of-frame transcript is generated in which exon 49 is spliced to exon 51 (Panel A). As a result, a stop codon is generated in exon 51 that prematurely aborts dystrophin synthesis. The binding of the antisense oligonucleotide drisapersen to a specific sequence within exon 51 interferes with the correct inclusion of that exon during splicing (Panel B). The skipping of exon 51 restores the open reading frame of the transcript and allows the synthesis of a de novo dystrophin with a deletion of exons 50 to 51.

Figure adapted from The New England Journal of Medicine, Judith C. van Deutekom, Anneke A. Janson, Ieke B. Ginjaar, et al., Local dystrophin restoration with antisense oligonucleotide PRO051, Vol 357, Page 2677-86. © (2007) Massachusetts Medical Society. Used with permission from Massachusetts Medical Society.

Assessments of biomarkers in patients treated with drisapersen provided evidence that drisapersen achieves its intended effect in treated patients and were consistent with results of nonclinical studies. The presence of dystrophin protein and of exon 51-skipped mRNA were demonstrated in muscle biopsy samples from Duchenne muscular dystrophy patients, and was higher in patients who received drisapersen compared with placebo. Studies of therapies directed at dystrophin restoration have not identified a specific parameter that is sufficiently reliable to serve as a surrogate marker of treatment effect. A combination of factors may contribute to this issue: variability in tissue distribution and uptake of drug; variability in muscle responsiveness; heterogeneity of pathological composition of the muscle; small sample size of biopsy compared with total muscle mass; and technical challenges obtaining, storing, and analyzing tissue biopsy samples. Other biomarker evaluations in studies conducted as part of the clinical development program demonstrated a clinical treatment effect of drisapersen. For example, a positive trend in inhibition of adverse structural changes

in the thigh muscles in Duchenne muscular dystrophy patients, determined by MRI analyses, was observed for drisapersen compared with placebo. Furthermore, an investigation of muscle pathology through measurement of serum creatine kinase and lactate dehydrogenase, which can leak from damaged muscles, found these biomarkers decreased following drisapersen treatment compared with placebo. These assessments are further discussed in Section 3.2, page 67.

Clinical Development Program

Clinical development of drisapersen was initiated by Prosensa Therapeutics B.V. with a proof-of concept study (PRO051-01) suggesting that local injection of drisapersen induces exon 51 skipping and results in novel dystrophin production as predicted (van Deutekom 2007). This study was followed by an open-label, dose-escalating study (PRO051-02) that established drisapersen 6 mg/kg/wk by SC injection as an appropriate dose for the subsequent study (Goemans 2011). The 12 patients who took part in this study entered an open-label extension (DMD114673 [Study 673]) investigating the safety and efficacy of continued treatment with drisapersen for up to 188 weeks.

Based on the results of these early studies, and in response to the urgent need for a treatment for Duchenne muscular dystrophy, 3 randomized, double-blind, placebo-controlled studies were designed and implemented nearly simultaneously: Studies 117, 876, and 044 were initiated September 2010, October 2011, and December 2010, respectively (see Table 1 for a summary of key studies).

At that time, data were not available from other development programs (eg, ataluren [Translarna EPAR 2015]); there were no regulatory guidelines for Duchenne muscular dystrophy treatments; and key natural history studies had not yet been published. The drisapersen trials were well under way even as the understanding was still evolving for disease heterogeneity, including key prognostic factors for disease progression, variations in care, the clinical relevance of biomarker assessments, and the relevance of the 6-minute walking distance (6MWD) as a longitudinal endpoint in patients with limited ambulatory capacity.

Study DMD114117 (Study 117) was designed to explore intermittent and continuous drisapersen dosing compared with placebo, with a loading dose to maximize initial tissue uptake. In accordance with early data from Study 673, a relatively homogeneous, early ambulant population was chosen. This population was also selected for the Study DMD114876 (Study 876), which further investigated 2 dose levels (3 mg/kg and 6 mg/kg) of drisapersen compared with placebo, but without a loading dose. Study DMD114044 (Study 044) was initiated within a few months of the start of the Study 117, enrolling a more heterogeneous ambulant population in terms of age and degree of progression. Patients in Studies 117 and 044 were treated with drisapersen through Week 48 while patients in Study 876 were treated only through Week 24, followed by an observational period through Week 48.

Table 1: Key Studies in the Clinical Development of Drisapersen

Study	Study Design	Dosing Regimens	Population
117	• Ph II, randomized, double blind, placebo controlled • 48 wk of treatment	All pts: loading dose of drisapersen 6 mg/kg or placebo SC biw for 3 wk then either: • Continuous drisapersen 6mg/kg/wk SC • Intermittent course alternating drisapersen 6 mg/kg SC biw and 6 mg/kg/wk for 6 wk, then 4 wk off dose • Placebo	• N=53 ambulant pts • 6MWD ≥75 meters • Rise-from-the-floor ≤7 seconds
876	• Ph II, randomized, double blind, placebo controlled • 24 wk of treatment and 24 wk of observational follow-up	• Drisapersen 3 mg/kg/wk SC • Drisapersen 6 mg/kg/wk SC • Placebo	• N=51 ambulant pts • 6MWD ≥75 meters • Rise-from-the-floor ≤7 seconds[a]
044	• Ph III, randomized, double blind, placebo controlled • 48 wk of treatment	• Drisapersen 6 mg/kg/wk SC • Placebo	• N=186 ambulant pts (181 completed study) • 6MWD ≥75 meters
673	• Ph I/II, open-label uncontrolled extension of Study PRO051-02, a Ph I/II 5-wk rising dose (0.5–6 mg/kg) study • Ongoing >3 years	Drisapersen 6 mg/kg/wk SC for 72 wk followed by • 8-wk off-drug period followed by o Intermittent dosing in 12-wk cycles of drisapersen 6 mg/kg/wk for 8 wk then 4-wk off drug up to 188 wk	• N=12 ambulant and nonambulant pts at start of parent study
349	• Ph III, open-label uncontrolled extension of Studies 117 and 044 • Up to 101 wk at termination of dosing (Sept 2013)	• Drisapersen 6 mg/kg/wk SC • Pts with tolerability issues could receive intermittent treatment as in Study 673 • Other pts not wishing to receive drisapersen and withdrawn pts could enter natural history arm	• N=233 pts, ambulant at start of parent study

6MWD, distance walked in 6 minutes in meters; biw, twice per week; Ph, phase; pts, patients; SC, subcutaneous.

[a] The ability to rise from the floor in ≤7 seconds was initially required in Study 876 and changed to ≤15 seconds by protocol amendment 3; however, only 2 patients in Study 876, 1 each in the drisapersen 3-mg and 6-mg/kg/wk groups, were enrolled with a rise-from-floor-time >7 seconds.

Patients enrolled in the 3 randomized, double-blind, placebo-controlled studies were ambulant boys at least 5 years of age with a life expectancy of at least 1 year and with Duchenne muscular dystrophy resulting from a confirmed mutation in the dystrophin gene potentially correctable by drisapersen-induced exon 51 skipping. Consistent with current treatment guidelines, patients were on a stable dose of corticosteroids for a minimum of 6 months before screening. Patients were also required to have a baseline 6MWD, ie, total distance walked within 6 minutes, of 75 meters or more. It was not appreciated at the time that patients whose ambulation was under approximately 330 meters were at substantial, near-term risk for rapid loss of ambulation. Finally, Studies 117 and 876, but not Study 044, required patients to be able to rise from the floor in ≤7 seconds. This criterion was amended to ≤15 seconds in Study 876, but only 2 patients had times >7 seconds. Study 044, with its greater sample size requirement, included patients over a wider range of eligibility (no baseline rise-from-the-floor time) and a greater number and variety of sites and geographical regions than Studies 117 or 876.

The primary efficacy variable of the 3 placebo-controlled studies was the 6MWD, a measure of integrated function that is dependent skeletal muscle function, among other factors. 6MWD has been shown to correlate with patient reported outcomes and also shows that smaller levels of change are associated with meaningful patient benefits as walking impairment progresses (Henricson 2013b). Thus, the 6MWD test respresents a functional benefit that is tangibly meaningful to patients, over a wide range of ambulatory capacity. McDonald demonstrated that 6MWD is more sensitive to detect change in functional status in patients with Duchenne muscular dystrophy compared with other commonly used timed function assessments (McDonald 2010b). In recent years, the 6MWD test has been adapted to evaluate muscle function and endurance in other neuromuscular disorders and has been successfully used as the primary endpoint for regulatory approval of therapies for neuromuscular and pulmonary disorders, such as Pompe disease (Wokke 2008, Van der Ploeg 2010), mucopolysaccharidosis I (Wraith 2004, Clarke 2009), Hunter syndrome (Muenzer 2006), mucopolysaccharidosis IV type A (Hendriksz 2014), and pulmonary arterial hypertension (Rubin 2002, Suleman 2004). A modified version of the 6MWD is used specifically for younger children with Duchenne muscular dystrophy (McDonald 2010b, Henricson 2012). Given the heterogeneity of further disease progression and lack of sensitive endpoints to measure treatment benefit, the primary focus of the development program was based on 6MWD tests.

The primary endpoint was mean change from baseline in the 6MWD in patients treated with drisapersen compared with placebo at Week 24 (Studies 117 and 876) or Week 48 (Study 044). As a secondary endpoint, 6MWD was assessed at Week 48 of treatment in Study 117, and after 24 weeks off treatment in Study 876. Duplicate evaluations of 6MWD were not obtained in these randomized trials unlike in most other pivotal clinical trials in other neuromuscular disorders.

These 3 placebo-controlled studies were supported by robust nonclinical and clinical pharmacology programs that demonstrated the molecular and cellular activity of drisapersen; its distribution and slow accumulation in skeletal muscle tissue; the pharmacodynamic effect on exon 51 skipping, dystrophin expression, and muscle composition; and the validity of

6 mg/kg/wk as a proposed clinical dose. See Section 2 (page 58) and Section 3 (page 64) of this document for discussions of the nonclinical and clinical pharmacology programs, respectively.

Overall, the drisapersen clinical development program consists of 9 clinical studies (see Table 1.3.1.1 in Section 1) in 326 boys with Duchenne muscular dystrophy, 312 of whom received at least 1 dose of drisapersen. At the clinical cut-off date for NDA submission (31 August 2014), 7 of the clinical studies were completed or terminated:

- 2 single-dose Phase I/II studies (PRO051-01 and DMD114118 [Study 118])
- 1 open-label repeat-dose Phase I/II study (PRO051-02)
- 3 randomized, double-blind, placebo-controlled studies (Studies 117, 876, and 044). Of these 3 studies, only Study 117 incorporated a loading dose to accelerate tissue distribution of the drug.
- 1 long-term open-label extension study (DMD114349 [Study 349]), which extends Study 117 and Study 044

Patients continued to be observed in 2 additional long-term, open-label extension studies:

- Study 673 (extension of PRO051-02): Data reported up to Week 188 of SC drisapersen administration are included in this document. In an effort to provide context for these findings, a matched natural history cohort of untreated patients with Duchenne muscular dystrophy with similar baseline characteristics was compared to the Study 673 patients in terms of ambulatory function over time (Goemans 2014; Data on file, BioMarin Pharmaceutical Inc., May 2014)
- Study DMD115501 (Study 501; extension of Study 876): Treatment was suspended with limited patient exposure, therefore, only information on serious adverse events (SAEs) is included in this document.

Drisapersen was licensed by GlaxoSmithKline (GSK) from Prosensa in 2009, at which time the 2 initial studies (PRO051-01 and PRO051-02) had been completed and the extension study (673) was under way. GSK assumed sole responsibility for clinical development. Following analysis of data from Study 044, which did not achieve statistical significance in the predefined analysis of the primary efficacy endpoint, GSK suspended all administration of drisapersen on 20 September 2013. On 12 January 2014, all rights were returned to Prosensa. In January 2015, BioMarin acquired Prosensa and all of its development programs, including drisapersen. Based on the totality of data from the clinical development program demonstrating a favorable benefit-risk profile, BioMarin submitted a New Drug Application (NDA) for drisapersen in April 2015. No patient received drisapersen from September 2013 up to the cut-off date of 31 August 2014. At present, efforts are under way to meet the demands for resumed dosing by patients who had been in the suspended long-term studies. A total of 54 patients have resumed dosing to date.

Overview of Efficacy

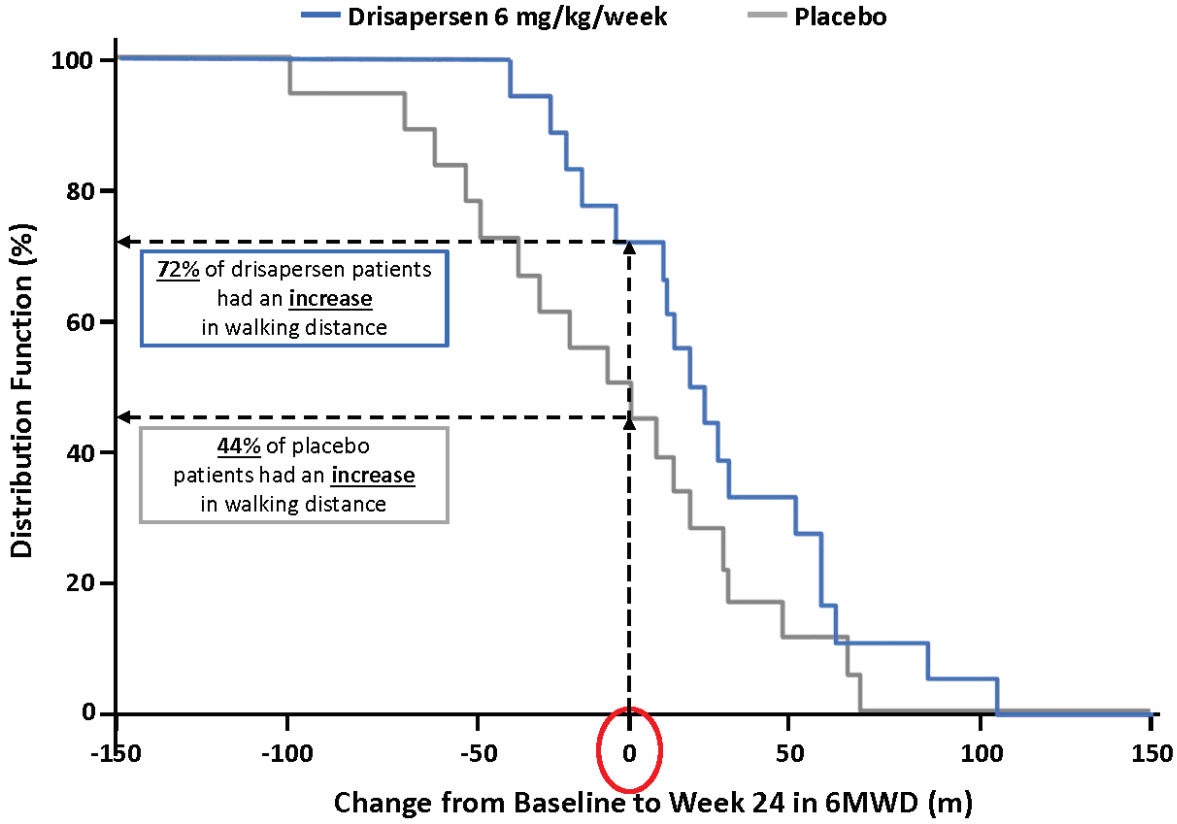
The totality of data from the clinical program demonstrates substantial evidence of efficacy of drisapersen 6 mg/kg/wk administered by SC injection for the treatment of patients with Duchenne muscular dystrophy with mutations amenable to exon 51 skipping. Results of the 3 randomized placebo-controlled studies demonstrated treatment benefits in terms of ambulatory function; long-term extension study data showed durability of drisapersen effect; long-term follow-up data exhibited sustained efficacy and superiority over natural history controls; and supportive evidence was shown in a variety of secondary endpoints.

Primary Endpoint - 6MWD

Studies 117 and 876 demonstrated substantial improvement in 6MWD after 24 weeks of treatment with drisapersen 6 mg/kg/wk compared with placebo. In the Study 117 primary efficacy analysis, a statistically significant (p=0.014) difference in the 6MWD mean change as early as Week 24 of 35.09 meters (95% CI 7.6 to 62.6) was observed between the drisapersen 6 mg/kg/wk and the placebo group. The improvement was sustained through an additional 24 weeks of treatment (mean difference between drisapersen and placebo groups of 35.8 meters; p=0.051). In the Study 876 primary efficacy analysis, a sizeable but not statistically significant (p=0.069) difference in the 6MWD mean change at Week 24 of 27.1 meters (95% CI -2.2 to 56.4) was observed between the drisapersen 6 mg/kg/wk and the placebo group. The increase with drisapersen compared with placebo was maintained through an additional 24 weeks of observation off-treatment (27.9 meters; 95% CI -13.0 to 68.8; p=0.177). In the Study 044 primary efficacy analysis, the estimated treatment difference between the drisapersen 6 mg/kg/wk and the placebo groups at Week 48 was 10.3 meters (95% CI -14.7 to 35.3; p=0.415) (see Table 4.7.1 in Section 4.7, page 95).

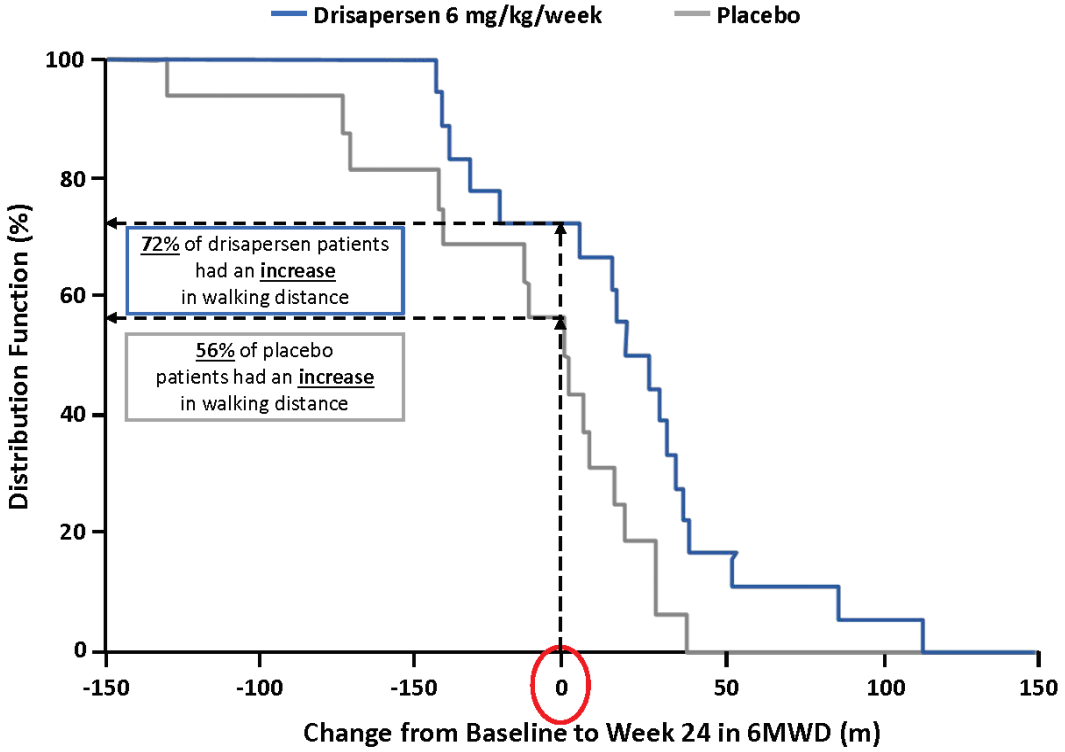
The results of the three studies are presented in the following figures in the form of cumulative distribution function (CDF) plots, depicting all data without statistical modelling (Figure 4, Figure 5, and Figure 6). In this type of plot, the horizontal axis represents the continuum of values of change from baseline in 6MWD, and the vertical axis shows the percentage of patients who had at least that level of change. There is a treatment advantage for drisapersen if the drisapersen curve lies to the right of the placebo curve.

Figure 4: Cumulative Distribution at Week 24 in Study 117 (ITT Population)



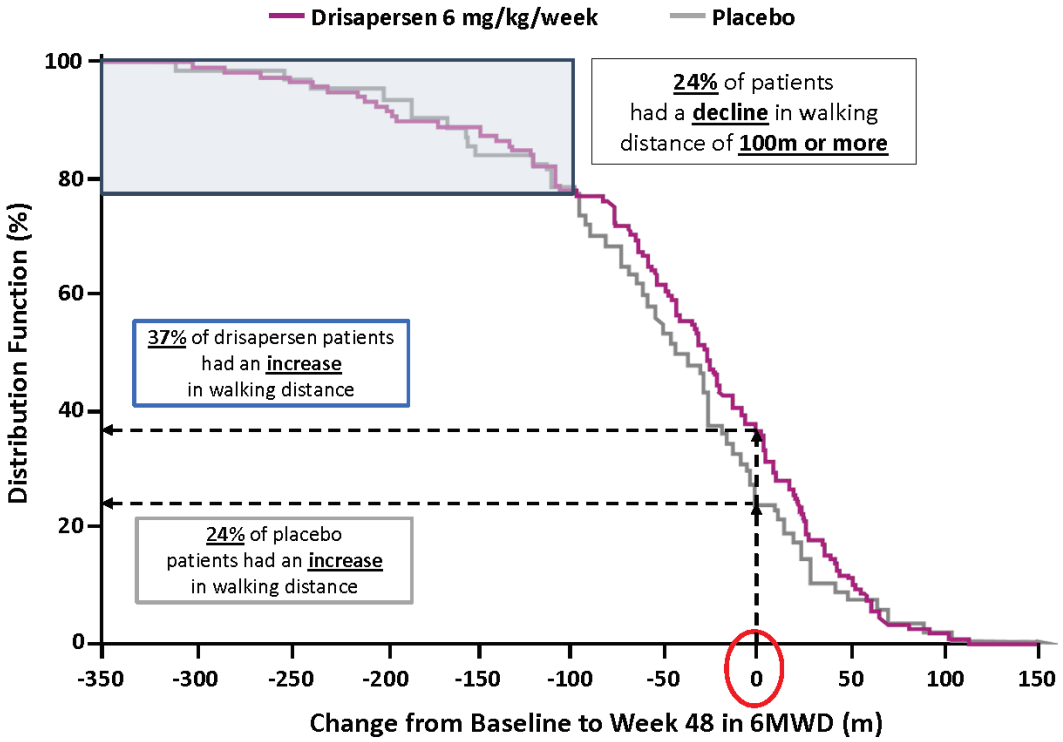
6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population.
Patients in Study 117 received treatment for 48 weeks.

Figure 5: Cumulative Distribution at Week 24 in Study 876 (ITT Population)



6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population.
Patients received study treatment for 24 weeks, followed by a 24-week post-treatment period.

Figure 6: Cumulative Distribution at Week 48 in Study 044 (ITT Population)



6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population.
In Study 044, patients received study treatment for 48 weeks.

In Study 117, there is a clear separation in favor of drisapersen (Figure 4). For example, 44% of placebo patients showed an increase in walking distance, compared to 72% of drisapersen patients. In Study 876, there is again marked separation throughout the curves (Figure 5). In Study 044, a treatment effect is most evident in patients with declines of <100 meters, with a consistent separation from placebo in favor of drisapersen (Figure 6). For example, 24% of placebo patients in Study 044 showed an increase in walking distance, compared to 37% of drisapersen patients.

Table 2 summarizes the differences in Studies 117, 876, and 044 in the percentage of patients (treated with either drisapersen or placebo) whose 6MWD performance improved. It is plainly evident that Study 044 evaluated a more impaired population as evidenced by the proportion of placebo-treated patients who experienced an improvement in the 6MWD test result (24%), as compared to the placebo rate in the other two placebo-controlled studies (44% and 56%, respectively). Nonetheless, the absolute difference in proportion of patients who improve is similar between Study 044 and Study 876, albeit taking longer for that difference to emerge in Study 044. The best results in terms of absolute proportion of patients who improved were observed in Study 117, the only study in which a loading dose of drisapersen was incorporated.

Table 2: Percent of Patients Whose 6MWD Improved in Study 117, 876, and 044

	Study 117 (Week 24)	Study 876 (Week 24)	Study 044 (Week 48)
Drisapersen 6 mg/kg/wk	72%	72%	37%
Placebo	44%	56%	24%
Percentage-point difference in favor of drisapersen	+28%	+16%	+13%

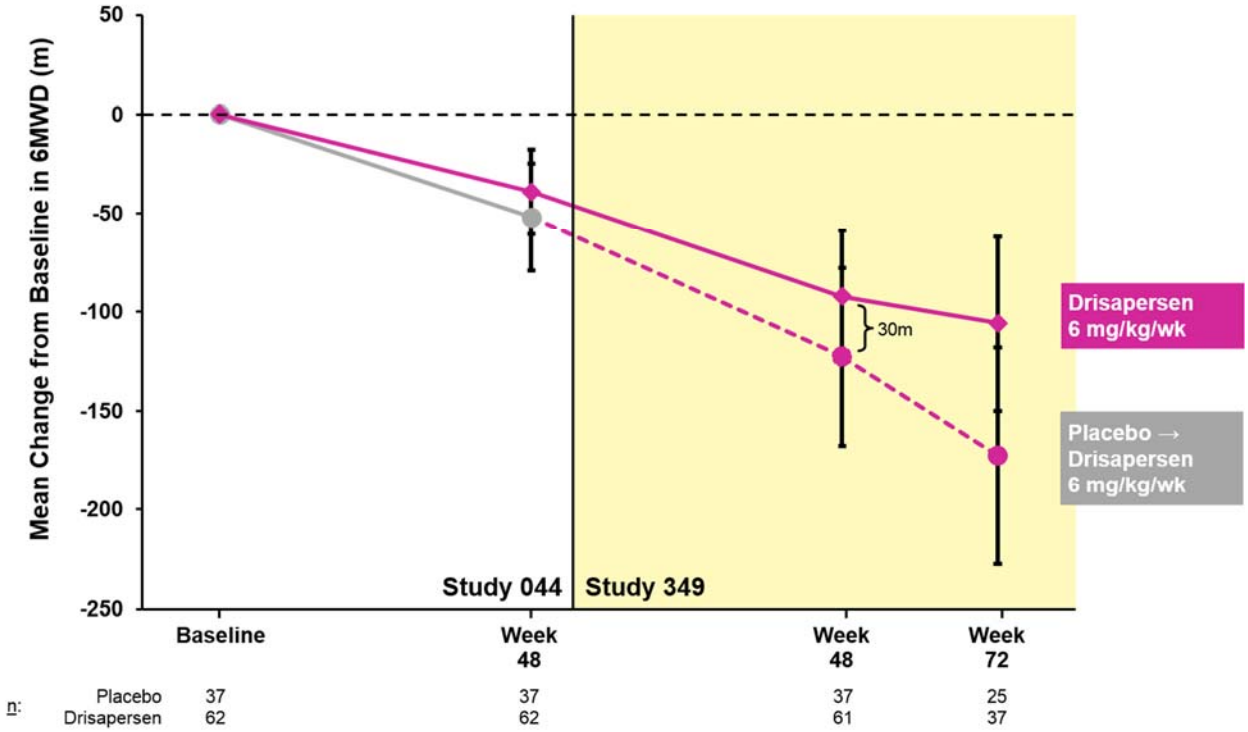
To more fully understand the results of Study 044, it is helpful to understand which factors may have impacted the response (all of which are described in more detail in Section 4.7.2.2, page 99):

1. There was an imbalance between the drisapersen-treated group and the placebo group in certain key prognostic variables, including age, baseline walking ability, and baseline rise-from-the-floor time, none of which were incorporated into the randomization scheme of Study 044. As a result, there was an imbalance in all three parameters in favor of placebo in Study 044. A mixed model repeated measures (MMRM) analysis of 6MWD taking these imbalances into account produced an estimated treatment difference in favor of drisapersen at Week 48 of 15.6 meters (95% CI -8.4 to 39.7), a nearly 60% increase in the estimated magnitude of treatment effect compared with that seen using the original analysis without adjustment of these covariates (Table 4.7.2.2.1, page 102).
2. The treatment effect in Study 044 was diluted by inclusion of an older, more progressed patient population at imminent risk of losing ambulation and ability to complete the 6-minute-walk test; this more severely affected patient population was not represented in the other two randomized placebo-controlled studies. An MMRM analysis excluding patients aged >7 years and with baseline 6MWD ≤ 330 meters, based on literature identifying those patients as vulnerable to accelerated decline (Mazzone 2013, Pane 2014), produced an estimated treatment difference in favor of drisapersen at Week 48 of 23.5 meters (95% CI 0.7, 46.4) (Table 4.7.2.2.2, page 107).
3. Study 044 included a broad range of sites of varying expertise in treating patients with Duchenne muscular dystrophy, including areas such as optimizing the use of physiotherapy, corticosteroid use, and other aspects of patient care An MMRM analysis conducted in the subgroup of patients from centers that also participated in Study 117 produced an estimated treatment difference in favor of drisapersen at Week 48 of 62 meters (95% CI -2, 126) (Table 4.7.2.2.3, page 108).

4. Because steady state tissue concentrations of drisapersen are not reached until after approximately 36 weeks of administration, patients in Study 044 (a 48-week trial without a loading dose) have been at a steady-state tissue concentration for only a short duration when the Week 48 assessments are performed (see Section 3.1.1, page 64). This is especially important in light of data demonstrating a relationship between tissue concentration and dystrophin expression in a parallel randomized, placebo-controlled clinical trial (see Section 4.7.1, page 96). Moreover, this long time to steady-state tissue concentration is exaggerated in the more impaired patient population of Study 044, in which advanced fat and fibrous tissue infiltration reduced the amount of muscle tissue that drisapersen could target.

The issues identified likely caused underestimation of the benefit of drisapersen in patients with preserved ambulatory capacity in Study 044. Nevertheless, with longer-term treatment and follow-up, a greater benefit emerges. In the long-term extension Study 349, patients originally in the placebo arm were switched to active treatment at Week 48. Patients originally in the active treatment arm continued on active treatment. A treatment difference of 30 meters was observed after 96 weeks (Figure 7). This finding suggests that longer duration of therapy may be required to show an effect in ambulatory function in those with more severe disease.

Figure 7: Change from Baseline in 6MWD at Week 48 in Study 044 and Long-Term Follow-Up (Week 48 Completer Analysis)



Similar confirmation of extension of benefit was observed in patients from Study 117 who were treated a further 48 weeks in Study 349.

Secondary Endpoints

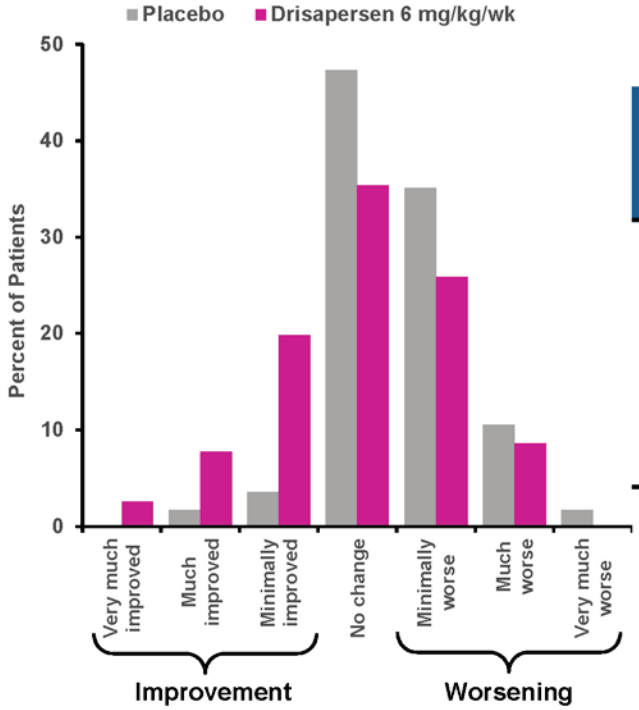
In addition to the 6MWD, several secondary efficacy variables measuring physical and respiratory function, muscular strength, and quality of life were evaluated in the 3 randomized, placebo-controlled studies:

- Timed function tests (rise-from-the-floor, 10-meter walk/run, 4-stair climb/descent)
- North Star Ambulatory Assessment (NSAA)
- Muscle strength testing
- Pulmonary function testing
- Quality of life/functional outcomes testing (done using different instruments in different studies)

Viewed in totality, consistency in direction of effect is seen in some but not all endpoints (Section 4.7.3, page 110). The timed function tests generally agree with the 6MWD in favor of drisapersen. The other endpoints did not demonstrate as consistent of an effect across studies. As with the 6MWD results described above, these endpoints are also affected by imbalance and dilution of effect. For Study 044, some of the secondary endpoint results do not favor drisapersen, but this finding is not surprising and largely uninformative given the heterogeneous patient population. For Study 117 patients enrolled in extension Study 349, most of the positive effects are maintained at the 2-year time point. For Study 044 patients enrolled in extension Study 349, positive results emerged as a result of the longer duration of treatment and follow-up (see Section 4.7.4 for secondary endpoints in Study 349, page 114).

In addition to these secondary clinical endpoints, the Clinical Global Impression of Improvement (CGI-I) scale was used in Study 044. The CGI-I is a single-item question designed to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning after initiating a study medication, compared to the patient's global functioning just prior to initiating treatment. A significant effect in favor of drisapersen was seen with this overall clinician assessment (Figure 8).

Figure 8: Clinical Global Impression of Improvement at Week 48 in Study 044 (ITT Population)



	Placebo N=57 %	Drisapersen 6 mg/kg/wk N=116 %
Any improvement	5	30
Much or very improved	2	10
Any worsening	47	35
Much or very much worse	12	9

These data can be also be expressed categorically, showing that only 5% of patients receiving placebo demonstrated any improvement compared with 30% of patients receiving drisapersen.

Laboratory Evidence of Treatment Effect

Serum CK levels decreased in patients treated with 6 mg/kg drisapersen compared with placebo in the 3 randomized placebo-controlled studies. The reduction was significantly different from placebo at 24 weeks (p=0.049) in Study 117 (Figure 3.2.4.1, page 72) and at Weeks 24 and 48 (p<0.001) in Study 044 (Figure 3.2.4.2, page 73). In Study 876, the CK reduction measured was not significant, but not all patients were sampled (Figure 3.2.4.3, page 73).

Likewise, LDH levels decreased more with drisapersen treatment compared with placebo treatment in Study 044 (Figure 3.2.4.6, page 75). LDH reduction in the drisapersen group was significantly different from placebo at Week 24 (p=0.002 and p<0.001) and 48 (p=0.019 and p<0.001) in Studies 117 and 044, respectively. In Study 876, the difference was not significant, perhaps again reflecting the small sample sizes. The differences between drisapersen- and placebo-treated subjects in change from baseline CK (in Studies 117, 876, and 044) and baseline LDH (in Study 044) are presented in Table 3.

The loss of degenerating muscle fibers with age helps explain the gradual CK level decrease seen in placebo patients over time. The CK and LDH reductions are strongly indicative of improved muscle fiber integrity in drisapersen-treated patients.

Table 3: Mean Change from Baseline of CK in Study 117, 876, and 044 and Mean Change from Baseline of LDH in Study 044

	Mean Change in CK			Mean Change in LDH
	Study 117 (week 24)	**Study 876 (week 24)**	**Study 044 (week 48)**	**Study 044 (week 48)**
Drisapersen 6 mg/kg/wk	-3508.0	-4534.7	-5258.8	-391.2
Mean (SE)	(1241.4)	(1260.6)	(358.4)	(17.3)
Placebo	-0.43	-2482.9	-1217.3	-100.1
Mean (SE)	(1253.9)	(1373.8)	(499.4)	(24.40
Difference (drisapersen – placebo)	-3507.6	-2051.8	-4041.4	-291.1
Mean (SE)	(-6993.5, -21.7)	(-5785.8, 1682.2)	(-5227.7, -2855.2)	(-348.8, -233.4)

In addition, patients in Study 117 demonstrated drisapersen-related increases in dystrophin. Lastly, MRI apparent fat fraction data showed a drisapersen-related reduction in the rate of fat infiltration in muscle in Study 876.

Long-Term Follow-Up Data—Study 673

Long-term data from open-label Study 673 demonstrated a durable treatment effect over three and a half years of treatment. Drisapersen-treated patients with stable ambulatory function at baseline maintained ambulation over the course of the study, whereas 25% of the matched cohort of non-treated patients lost ambulation (see Section 4.7.4.2, page 119).

Summary

In summary, the efficacy of drisapersen is established based on 3 randomized placebo-controlled studies with a relevant clinical primary endpoint, the 6MWD. Consistent important effects across all 3 trials were observed. To observe these effects in the third study required properly accounting for treatment group imbalances as well as population characteristics; however, these issues serve to highlight the importance of early treatment to preserve ambulation. Moreover, the Study 044 6MWD results were confirmed by an advantage of longer-term treatment compared to delayed-start treatment, and by results from a clinician's global assessment. Biomarker data supports these conclusions. Finally, long-term treatment data compared to natural history controls exhibits a treatment benefit for more than 3 years after the start of therapy. Thus the totality of the data provides substantial evidence of the efficacy of drisapersen in Duchenne muscular dystrophy patients amenable to exon 51 skipping.

Overview of Safety

The safety of drisapersen was evaluated in the most extensive database of Duchenne muscular dystrophy patients assembled to date, including 326 patients with the disorder. A total of 312 patients received at least 1 dose of drisapersen, and 302 patients were treated in repeat-dose studies.

The clinical safety database comprises safety results from 9 clinical trials and includes patients between the ages of 5 and 16 years. The total exposure to drisapersen (all regimens) was 490.1 patient-years. The extent of exposure for drisapersen 6 mg/kg/wk was 432.7 patient-years compared with 79.4 patient-years for placebo. A total of 42.8% of drisapersen-treated patients had cumulative exposure duration of at least 96 weeks.

Drisapersen was generally well tolerated. The majority of adverse events (AEs) were reported as mild to moderate in intensity. The most clinically significant risks associated with treatment were thrombocytopenia, renal abnormalities, and injection site reactions, all of which are manageable through close monitoring and risk minimization measures that will be described in the proposed prescribing information (refer to Proposed Risk Management Plan in Section 7, page 177).

Injection site reactions were the most common AEs associated with drisapersen treatment and were reported in 210 of 267 patients (78.7%) who received 6 mg/kg/wk in the repeat-dose studies. Most of these reactions were reported as mild to moderate in intensity and resolved despite ongoing treatment. Analyses to determine whether these injection site reactions caused unintended unblinding of the study corroborated the unbiased nature of efficacy assessments (for example, in Studies 117, 876, and 044, there is no evidence that drisapersen-treated patients had more improvement in their 6MWD than patients who did not have ISRs).

Among the most common events, benign, transient injection site erythema generally occurred within the first month and injection site discoloration within the first 6 months of treatment. Dermatologically significant injection site reactions accumulated with longer-term treatment but still occurred in a minority of patients; injection site induration, injection site atrophy, and injection site edema were reported, mostly after 12 to 24 months of treatment. Injection site reactions including sclerosis, microcalcification, nodules, or ulceration were observed infrequently with longer-term treatment in patients with limited rotation of injection sites. Two patients, both treated with drisapersen 6 mg/kg/wk, had injection site SAEs (both were injection site edema). Ten patients (3.5%) had severe injection site reactions. Only 1 patient (0.4%) discontinued drisapersen treatment for an injection site reaction (injection site edema) in the repeat-dose studies (see Section 5.11.3, page 159); however, longer-term administration of drisapersen may necessitate more frequent discontinuation. Injection site rotation may slow development of such intolerable lesions. Intravenous drisapersen in being investigated in patients as an alternative route of administration to subcutaneous.

Renal abnormalities were the second most commonly reported AEs occurring in both the placebo and drisapersen groups. In the placebo-controlled studies, renal abnormalities were reported for 98 of 161 patients (60.9%) treated with drisapersen 6 mg/kg/wk and for 32 of 95

patients (33.7%) with placebo. The majority of renal abnormalities were subclinical laboratory findings such as low-grade variable proteinuria, mainly consisting of low-molecular-weight proteins such as α1-microglobulin, which was transient, asymptomatic and nonprogressive; microscopic hematuria; increased cystatin C; and increased urine protein/creatinine ratio. The mild and transient elevations in urinary low-molecular-weight proteins are considered to reflect interference with the tubular reabsorption of proteins from the glomerular filtrate rather than indications of overt renal toxicity. Features of more general tubular dysfunction (such as Fanconi's syndrome) were not observed in patients treated with drisapersen. Most of the renal abnormalities normalized when drisapersen treatment was paused or discontinued. Only 36 (3.2%) of 1,183 renal abnormalities reported in the all drisapersen regimens group, and 1 of 78 (1.3%) in the placebo group (repeat-dose studies), were unresolved at the end of the study. There were 2 SAE reports of severe proteinuria in drisapersen-treated patients: 1 was severe (nephrotic level) proteinuria (no biopsy taken), and the other was associated with stage 1 (stage 1 – least severe, stage 4 – most severe) membranous glomerulonephritis, diagnosed by renal biopsy. These events were considered possibly treatment related although the cause had not been established. The proteinuria resolved in both of these patients following discontinuation of drisapersen treatment (see Section 5.11.2, page 156, for more information about renal abnormalities). The membranous glomerulonephritis was associated with glomerular staining for immunoglobulin (IgG-intense and IgA-very low) and complement (C1q-trace), though complement levels in this patient were normal. This patient also developed thrombosis in the pulmonary and renal veins, a known complication of nephrotic syndrome, before the glomerulopathy resolved.

In repeat-dose studies, AEs of thrombocytopenia were reported in 20 of 285 patients (7%) treated with drisapersen. Most cases were mild to moderate, asymptomatic decreases in platelet count that were self-limiting or resolved with treatment interruption. Eight patients treated with drisapersen 6 mg/kg/wk experienced SAEs with confirmed, severe thrombocytopenia (Common Terminology Criteria for Adverse Events [CTCAE] Grade 3 ($<50 \times 10^9$/L) or Grade 4 ($<25 \times 10^9$/L), with platelet counts decreasing to $<50 \times 10^9$/L (range: 5–48 x 10^9/L). The time to onset from the start of drisapersen treatment to a platelet count $<50 \times 10^9$/L ranged from 9-22 months. These patients had a rapid decline in platelet counts from the lower limit of normal (see graphs in Appendix B, page 210). Five patients with platelet counts $\leq 15 \times 10^9$/L had clinical symptoms including 1 or more of ecchymosis, bleeding gums, bruises on arms or legs, petechiae, and epistaxis. All 8 patients recovered after drisapersen was discontinued, and their platelet counts increased to $>75 \times 10^9$/L with a median time of 3 weeks (range: 1–9 weeks) after discontinuing drisapersen. Six of the patients were treated with 1 or more therapies including tranexamic acid, intravenous immunoglobulin, platelet transfusion, and steroids. Tests for anti-platelet antibodies were reported for 5 of the 8 patients with severe thrombocytopenia and were positive for at least 1 time point in 4 of the 5 patients. No patient experienced a major bleeding episode. Thrombocytopenia is a recognized class effect of antisense oligonucleotides.

Other less common AEs associated with drisapersen treatment were arthralgia, reversible elevations in liver enzymes, including glutamate dehydrogenase and gamma-glutamyl transferase, and alopecia.

Twelve of 267 patients (4.5%) treated with drisapersen 6 mg/kg/wk in repeat-dose studies reported AEs that led to permanent discontinuation of treatment. Of these, only 2 of 161 patients (1.2%) discontinued during the placebo-controlled studies, including 1 for glomerulonephritis (described above). The second patient discontinued treatment during the placebo-controlled phase of the study due to a thrombotic event of intracranial venous sinus thrombosis. This patient may have been in a hypercoagulable state due to his Duchenne muscular dystrophy (Saito 2014). There was no evidence of complement reduction, proteinuria, or vasculitis. This event may also have been due to concomitant use of dipyrone and underlying dehydration. The other 10 AEs leading to treatment discontinuation occurred in extension Study 349. Thrombocytopenia was the only AE that led to discontinuation of more than 1 patient: 7 patients discontinued because of thrombocytopenia, all of whom had been treated with drisapersen for at least 9 months prior to thrombocytopenia onset. Other AEs that led to treatment discontinuation were asthenia, proteinuria, and injection site edema, each in 1 patient (see Section 5.10, page 151; and narratives for patients who discontinued in Appendix B, page 210).

There was no report of Hy's Law (ie, alanine aminotransferase or aspartate aminotransferase increase to >3 times the upper limit of normal [ULN], associated with bilirubin increase ≥2 times the ULN, and no other cause for increase) or of other serious events suggesting meaningful hepatocellular injury. There was no clinically meaningful change in laboratory findings, electrocardiograms, or echocardiograms. No death was reported in the program.

Anti-drisapersen antibodies (ADAs) were tested in patients in Study 044. Of those evaluated, 29.4% (32/109) of treated patients tested positive for ADA during 48 weeks of treatment. Efficacy and safety results in patients who tested positive for ADAs were similar to those in patients who tested negative. See Section 5 for a complete discussion of the safety results (page 126).

Benefits/Risks

Benefits

The studies conducted to date have demonstrated evidence of a treatment difference favoring drisapersen on the 6MWD, the primary measure of ambulatory function. In particular, in two randomized, placebo-controlled studies primarily evaluating patients with preserved muscle strength, meaningful improvements in 6MWD were observed in as little as 24 weeks of therapy. The clinical course of Duchenne muscular dystrophy entails a progressive series of functional losses. Among these, losing the ability to walk represents a major impairment in patient well-being and function in patients with Duchenne muscular dystrophy and their families. It signifies loss of independence for the boys and heightened responsibility for the caregivers. It also heralds further deterioration in other body systems, including respiration and cardiac function, leading to early mortality. Delaying the loss of ambulation has been shown to delay these other disease manifestations (Biggar 2006, King 2007, Machado 2012, Markham 2008, Moxley 2010, Phelps 1995).

Positive trends in secondary endpoints of physical functioning (including timed function tests and the NSAA) were also observed in patients receiving drisapersen, providing supportive evidence of benefits considered meaningful and life changing to patients and their caregivers.

The randomized, double-blind, placebo-controlled Study 044 enrolled an older, more severely affected patient population compared to the randomized, placebo-controlled Studies 117 and 876, including individuals lacking well-preserved muscle and at imminent risk of losing ambulation. Key prognostic factors, which were not yet established at the time of the study design, were not considered in the randomization scheme, producing important imbalances in baseline characteristics between the treatment groups in favor of placebo and a consequently attenuated treatment effect. The overall results demonstrated a modest trend toward improvement in ambulation with drisapersen compared with placebo. However, re-analyses correcting for these baseline imbalances demonstrated a positive treatment effect with drisapersen in the large subgroup of patients with better preserved muscle and ambulatory capacity, consistent with the findings of Studies 117 and 876.

It is reasonable to expect that drisapersen might benefit even a more severely affected group. Evidence supporting this position includes improvement in ambulation in severely affected patients treated at experienced trial sites, improvement in clinical global impression, and consistent reductions in serum lactate dehydrogenase and creatine kinase. Research indicates that in individuals with severely affected ambulatory impairment patients perceive benefit from even relatively small improvements in 6MWD (Henricson 2013b).

The lasting, positive effect of drisapersen treatment on ambulation was shown in long-term extension studies. Patients initially treated in Study 117 showed a durable treatment effect in 6MWD through 120 weeks of treatment. Patients initially treated in Study 044 showed a treatment benefit in 6MWD after 96 weeks that was similar in magnitude to that seen in Studies 117 and 876 at Week 48, suggesting that Duchenne muscular dystrophy patients with greater functional decline can still benefit from drisapersen treatment given over a longer period of time. Patients treated with drisapersen for up to 188 weeks in the long-term Study 673 maintained more ambulatory capacity than their matched natural history comparators, with most of the drisapersen-treated patients performing better than the matched cohorts and none performing worse (see Figure 4.7.4.2.3 in Section 4.7.4.2, page 122).

The placebo-controlled study results also highlight the importance of treating patients early in their disease. Treating a younger patient population, when muscle function is still relatively well preserved, affords a better opportunity to stabilize or even improve function within a relatively short duration of treatment. The replacement of muscle with fat or fibrous tissue in older, more-progressed boys leaves less target tissue available for drisapersen to affect and therefore requires longer time for greater effect to accumulate.

The clinical program provides a large data set relative to the rarity of the disorder, demonstrating that eligible patients with Duchenne muscular dystrophy will see both near-term and long-term benefit with drisapersen treatment. The totality of data shows that treatment with drisapersen provides important benefits in patients with well-preserved muscle. The lasting, positive effect on 6MWD indicates that treatment with drisapersen helps

to prolong the period of independent ambulation, which is relevant to patient well-being and function especially in the absence of alternative therapy.

Risks

The safety of drisapersen was thoroughly evaluated in clinical studies comprising 490 patient-years of exposure. The most clinically significant adverse events associated with drisapersen treatment were infrequent occurrences of severe thrombocytopenia, rare glomerulonephritis and more commonly injection site reactions.

Injection site reactions were the most common AEs associated with drisapersen treatment in the placebo-controlled studies. Injection site reactions were reported in the majority of drisapersen-treated patients. Most were mild or moderate in intensity and resolved. Dermatologically significant injection site reactions occurred in a minority of patients, but were potentially dose-limiting in some patients receiving long-term treatment. Only 1 patient in repeat-dose studies discontinued drisapersen treatment due to an injection site AE. To minimize the potential for injection site reactions, the proposed prescribing information will contain instructions for proper administration of SC injections and rotation of injection sites.

There were two occurrences of severe proteinuria: 1 was asymptomatic proteinuria (up to 11 grams protein excreted in 24 hours; no biopsy taken), and the other was associated with stage 1 membranous glomerulonephritis, diagnosed by renal biopsy. Other renal abnormalities were predominantly subclinical laboratory findings such as mild proteinuria, mainly comprising low-molecular-weight proteins such as α1-microglobulin, which normalized when drisapersen treatment was paused or discontinued. The proposed prescribing information will provide recommendations for monitoring of urinary protein, cystatin C and creatinine, and management guidance for potentially clinically significant renal effects.

Thrombocytopenia AEs were reported during the long-term extension studies. There was no report of thrombocytopenia in the placebo-controlled studies with up to 1 year of treatment. Most cases were mild to moderate, asymptomatic decreases in platelet count that were self-limiting or resolved with treatment interruption. Severe thrombocytopenia was infrequent: 8 patients experienced severe thrombocytopenia with platelet counts decreasing to $<50 \times 10^9$/L, with a time to onset from the first dose of drisapersen of at least 9 months. Five of these patients were tested for anti-platelet antibodies, and 4 had a positive result for at least 1 time point. Recommendations for measurement of platelet count and management guidance for thrombocytopenia will be included in the proposed prescribing information.

Adverse events of special interest observed in nonclinical studies that did not emerge as substantial safety issues in drisapersen-treated patients were hepatocellular damage, coagulation abnormalities, inflammation events (except for injection site reactions), and complement activation with clinical sequelae. These events remain potential risks and will continue to be monitored post-authorization.

In the context of treating a progressively debilitating and universally fatal disorder, in a patient population with a clear and urgent unmet medical need, the benefits afforded by

drisapersen outweigh the known risks, which can be managed through active monitoring and the risk management plan summarized below.

Proposed Risk Management Plan and Postmarketing Commitments

BioMarin is experienced in partnering with regulatory agencies and patient groups to design and conduct appropriate postmarketing studies that strengthen the available data and evaluate long-term outcomes. The plans for drisapersen in Duchenne muscular dystrophy include: a post-approval registry to holistically evaluate long-term outcomes in the real-life practice setting (for more details see Section 8.1, page 179); a post-approval risk management plan to guide safe and appropriate use of the product (see Section 7, page 177); and additional clinical studies in younger patients <5 years of age, as well as older nonambulatory patients to further the understanding of the effects of drisapersen in those important patient populations (see Section 8.2, page 183).

Specifically, BioMarin proposes the following risk minimization and pharmacovigilance activities to ensure safe and effective use of drisapersen, and to gain more knowledge about the safety and long-term use of drisapersen in the post-approval setting:

- *Evidence-based Prescribing Information and Medication Guide* that describes the risks, recommendations for minimizing them, and monitoring guidance
- *Continuous monitoring of the benefit-risk profile* of drisapersen, which includes assessment of aggregate safety data and taking appropriate actions in response, and communicating emerging safety concerns to applicable health authorities
- *Individual case safety report (ICSR) management*, which involves collection, collation, follow-up, assessment, and regulatory reporting of suspected AEs from any source
- *Signal management* to identify, evaluate, validate, and act upon previously unrecognized risks
- Periodic Safety Update Reports (PSUR)/Periodic Benefit-Risk Evaluation Reports (PBRER) to provide periodic benefit-risk evaluations of drisapersen during post-marketing use
- *Study management*, which includes active monitoring of adverse events and relevant laboratory test values in ongoing clinical studies, and planned post-marketing studies/registry. The latter include studies of intravenous dosing as an alternative route of administration; studies of safety, tolerability, and pharmacokinetics in nonambulant patients with Duchenne muscular dystrophy and patients aged <5 years; and an observational, global registry to characterize the population with the disorder as a whole, including the variability, progression, and natural history of the disease, and to evaluate long-term efficacy and safety of drisapersen under standard care practices.

Based on extensive safety evaluation, thrombocytopenia, renal abnormalities, and injection site reactions have been identified as the most clinically significant effects associated with

drisapersen treatment. In consultation with relevant experts, BioMarin has proposed the following risk minimization and management procedures for each of these events.

- Injection site reactions: Only health care professionals should administer drisapersen treatment. Prescribing and educational materials will include instructions for proper subcutaneous injection techniques and strict rotation of injection sites. Patients should receive periodic dermatologic assessments.
- Renal abnormalities: Urine protein by dipstick should be assessed at baseline and monthly, with 24-hour urine collection if the dipstick result is 3+ for protein. Serum cystatin C and serum creatinine levels should be measured at baseline and quarterly. Drisapersen treatment should be interrupted if urine protein measures >1 $g/m^2/24$ hours. Treatment may be resumed based on individual benefit-risk assessment if the urine protein is ≤500 $mg/m^2/24$ hours or after consultation with a pediatric nephrologist. Patients with persistent nephrotic level proteinuria should permanently discontinue drisapersen treatment. If cystatin C level increases to greater than the ULN and > 75% of baseline, drisapersen treatment should be interrupted; treatment may be resumed when cystatin C level returns to normal values.
- Thrombocytopenia: Platelet count measurement is recommended at baseline and at regular intervals, and immediately if a patient develops signs or symptoms of thrombocytopenia. Platelet monitoring should be increased to monthly if any confirmed platelet count is less than the lower limit of normal. Anti-platelet antibody testing is recommended if any platelet count decreases to <75 x 10^9/L. For patients with a confirmed platelet count <75 x 10^9/L, drisapersen treatment should be interrupted. If platelet count recovers to ≥150 x 10^9/L, treatment may be resumed based on benefit-risk assessment for each patient. Drisapersen treatment should be permanently discontinued if the confirmed platelet count is <50 x 10^9/L and/or the anti-platelet antibody test result is positive. In addition, caregivers and health care providers will receive education about the signs and symptoms of thrombocytopenia to help facilitate early recognition of this event. These monitoring recommendations for detection of severe thrombocytopenia in the real world setting were informed by findings from more frequent precautionary platelet count monitoring in the drisapersen clinical trials.

Collectively, the benefits of improved function and well-being exceed the potential for harm as evidenced by these trials. However, individual patients may experience variation in benefit or risk such that benefit-risk scenarios may be unfavorable for certain patients. These proposed risk management activities will help guide safe and appropriate use of drisapersen.

Conclusion

Duchenne muscular dystrophy is a rare, rapidly progressive, and highly heterogeneous disorder, which makes it challenging to study in both the laboratory and the clinical setting. There is an urgent unmet need for effective treatment for Duchenne muscular dystrophy, driven by the devastating nature and uniformly fatal outcome of the disorder. This urgency was reflected in the clinical development of drisapersen, a novel therapy that addresses the

lack of functional dystrophin protein that causes Duchenne muscular dystrophy, specifically in patients with mutations amenable to skipping exon 51.

The efficacy and safety of drisapersen have been demonstrated in the largest and most comprehensive clinical program ever filed for approval with Duchenne muscular dystrophy. The 3 randomized, double-blind, placebo-controlled trials of drisapersen were all initiated within a span of a few months, at a time when limited data and precedent were available to guide the study designs.

Throughout the clinical program, a treatment effect favoring drisapersen was shown on the primary clinical endpoint, the 6MWD, in 3 randomized placebo controlled trials conducted contemporaneously. The 6MWD is widely used and widely accepted in studies of Duchenne muscular dystrophy and other progressive neuromuscular conditions, but has limitations in a heterogeneous patient population that includes individuals with reduced baseline ambulatory capacity. The primary endpoint results of the 3 placebo-controlled trials are impressive considering the long tissue distribution time of drisapersen. Supportive evidence for the efficacy of drisapersen was also demonstrated on secondary endpoints representing a range of other functional domains.

Studies 117 demonstrated improvement in 6MWD after 24 weeks of drisapersen treatment versus placebo, which was statistically significant and sustained through an additional 24 weeks of treatment. The effect was maintained through 48 weeks of the double-blind phase and continued for a further 48 weeks in an open-label extension phase. In Study 117, an increase in dystrophin production was accompanied by reductions in biomarkers of muscle damage. An improvement in 6MWD after 24 weeks of treatment was nearly significant in spite of the absence of a loading dose in Study 876, and the effect was maintained during 24 weeks off drug. A post hoc integrated analysis of Studies 117 and 876 confirmed the beneficial treatment effect of drisapersen at 24 weeks, with a nominal p value of 0.0025. By themselves, these studies can be considered to provide substantial evidence of effectiveness.

Extensive analyses were conducted to understand and explain the attenuated treatment effect observed in Study 044, which enrolled a broader and less randomly distributed patient population than the other placebo-controlled studies, including more severely affected patients with less remaining muscle to support ambulation. These analyses demonstrate a consistent and important benefit with drisapersen in patients with well-preserved muscle across the 3 placebo-controlled trials. They also highlight the importance of early treatment with drisapersen in order to maximize the long-term benefits.

Long-term studies demonstrate a durable treatment effect in 6MWD of up to three and a half years, which compares favorably with data from natural history cohorts and indicates that drisapersen preserves the ability to walk independently.

The safety of drisapersen was evaluated in a comprehensive integrated safety database for a rare disorder which included >300 Duchenne muscular dystrophy patients treated up to three and a half years. Drisapersen was generally well tolerated. Injection site reactions were the most common AEs, but dermatologically significant events occurred in a minority of

patients. Infrequent glomerulonephritis and severe thrombocytopenia were the most clinically significant AEs reported.

The identified and potential risks of drisapersen can be managed through close monitoring and the risk minimization measures that will be described in the proposed prescribing information. BioMarin has a robust post-marketing surveillance and ongoing clinical trial program planned to further quantify and characterize known and potential risks as well as to understand long-term benefits and further the knowledge of drisapersen's effects in a broad range of the patient population. The proposed indication is for all ages of patients and also for ambulatory and nonambulatory patients. This approach is in line with rare disease indications, where extrapolation beyond the primary population studied is warranted where patients are in desperate need, and where there is a plausible hypothesis that extrapolation is justified.

The recently released FDA draft Guidance for Industry for developing drugs to treat Duchenne muscular dystrophy acknowledges that: "When making regulatory decisions regarding drugs for dystrophinopathies, FDA will consider patient and caregiver tolerance for risk, and the serious and life-threatening nature of these conditions" (FDA 2015). Parents of patients with Duchenne muscular dystrophy have clearly stated their urgent support for the development of therapies that may alter or delay the devastating consequences of disease progression (Muntoni 2010, Parent Project Muscular Dystrophy 2014).

The totality of data from the development program demonstrates that drisapersen, at the recommended dose of 6 mg/kg/wk administered by SC injection, provides meaningful and potentially life-changing benefits for patients with an immediate, urgent, unmet medical need.

1 INTRODUCTION

1.1 Indication and Description

BioMarin Pharmaceutical Inc. has developed drisapersen sodium (drisapersen) for the proposed indication of "the treatment of Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing." Drisapersen is formulated for subcutaneous (SC) administration at a weekly dose of 6 mg/kg of body weight.

Duchenne muscular dystrophy is caused by genetic mutations that produce an absence of functional dystrophin, a protein that is essential for muscular strength and function. The majority of these mutations are deletions, and the most common sites of deletions are in the regions flanking exon 51 of the dystrophin gene.

Drisapersen, an antisense oligonucleotide specific for human dystrophin pre-messenger ribonucleic acid (mRNA), is a novel disease-modifying product that induces skipping of dystrophin exon 51. Drisapersen binds to a sequence within the dystrophin mRNA to mask the exon inclusion signals that are used for splicing (Aartsma-Rus 2010, van Deutekom 2007, Hammond 2010, Goemans 2011, Voit 2014), which results in an internally shortened but functional dystrophin protein. Approximately 13% of the Duchenne muscular dystrophy population in the United States, or about 2300 patients, would have the mutations that would make them eligible for drisapersen treatment. Fewer than half of these patients have sufficient ambulatory capacity to participate in clinical trials at any given time.

Drisapersen has been thoroughly evaluated in a comprehensive nonclinical and clinical development program that includes 326 patients, 312 of whom received drisapersen for up to three and a half years. This represents the largest and longest clinical program conducted in Duchenne muscular dystrophy. While most of the clinical program has been focused on evaluating the safety and efficacy of drisapersen in Duchenne muscular dystrophy patients who are ambulant, an inclusive indication is proposed in line with the precedence for rare disease indications where extrapolation beyond the population studied is supported when the patients are in desperate need and where there is a plausible hypothesis that can support extrapolation (FDA 2015, Parent Project Muscular Dystrophy 2014).

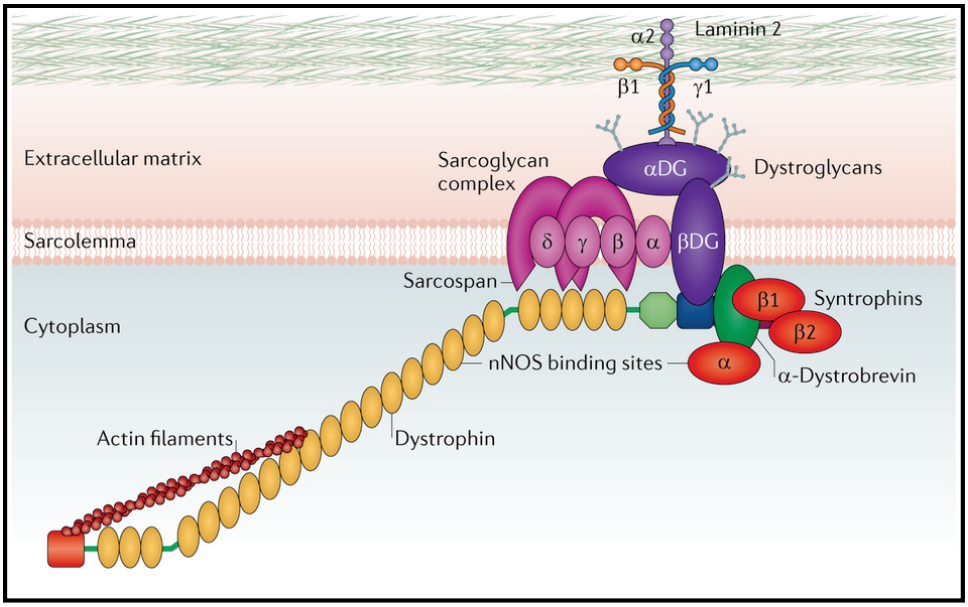
BioMarin acknowledges that further studies in subgroups of patients such as those who are nonambulant and those who are under 5 years of age are needed. BioMarin will conduct these studies in the post-marketing setting to better elucidate the effect of treatment in these additional patient subgroups and to generate further data to add further label guidance for these populations.

1.2 Unmet Medical Need

Duchenne muscular dystrophy is a rare, progressive, and lethal pediatric neuromuscular disorder that is devastating to the patients, almost exclusively boys, who suffer with this X-linked genetic disorder and the parents and families who care for them. Duchenne muscular dystrophy has a global incidence of up to 1 in 3,500 male births. The estimated prevalence in the United States is approximately 18,000 cases (McNeil 2010).

The rod-shaped dystrophin protein anchors the cytoskeleton of muscle fibers to the cell membrane and basal lamina (Figure 1.2.1) and protects the sarcolemma membrane against the stresses imposed by muscle contraction or stretching (Rybakova 2000) and thereby protecting muscle fibers against contraction-induced damage. Dystrophin also interacts with catalyzing enzymes to play a role in intracellular signaling (Brenman 1995). The relative importance of these functions is unknown, and variants of the dystrophin molecule (isoforms) are found in a variety of tissues such as the kidney where its function has not been characterized.

Figure 1.2.1: Function of Dystrophin in Skeletal Muscle



DG, dystroglycan; nNOS, neuronal nitric oxide synthase.

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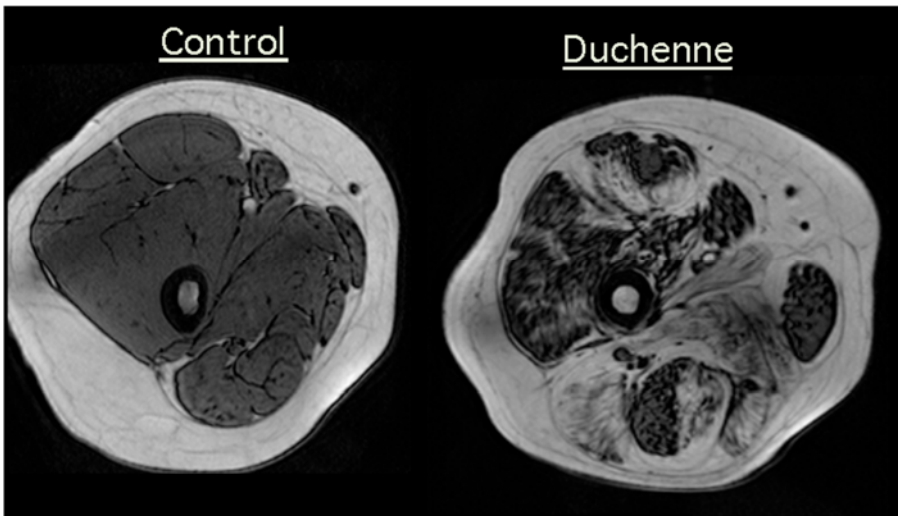
In Duchenne muscular dystrophy, the absence of the muscle isoform of dystrophin results in degeneration of muscle fibers and leads to the replacement of muscle by fibrotic and fatty tissue. Elevated levels of calcium in dystrophic muscle cells are thought to contribute to calcium-dependent proteolysis, facilitating progressive necrosis of muscle fibers (Hopf 2007). Regeneration of tissue is normally facilitated by quiescent satellite cells that are activated in response to trauma; in Duchenne muscular dystrophy, satellite cells are significantly decreased, contributing to reduced regenerative capacity and contractility in skeletal muscle (Jejurikar 2003). Muscle fibers undergo irreversible degradation, releasing cytokines that promote inflammation and activating fibroblasts that promote fibrosis (Ennen 2013). Muscle tissue is steadily replaced by adipose and connective tissues. This myonecrotic process can be visualized through magnetic resonance images (MRIs) (Figure 1.2.2).

Figure 1.2.2: T1-Weighted MRI of Thigh Muscles Comparing Duchenne Muscular Dystrophy Patient With Normal Control



Source: Courtesy of Imaging DMD Project, funded by The National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) & National Institute of Neurological Disorders and Stroke (NINDS).

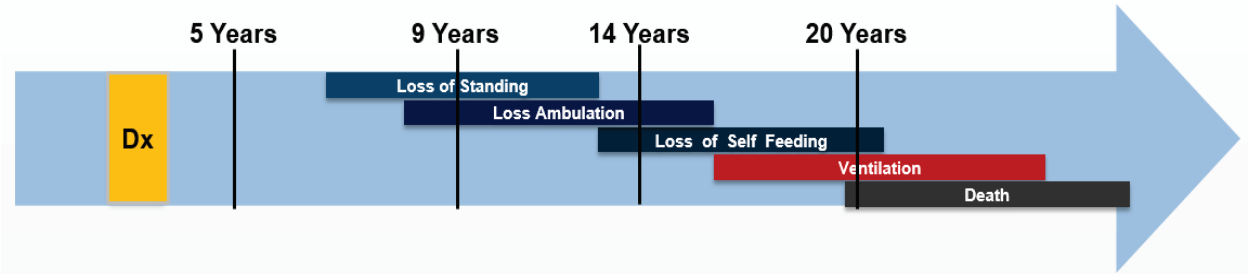
Dystrophin deficiency may also curtail blood vessel formation in muscle tissue through the loss of neuronal nitric oxide synthase, which normally is localized to the sarcolemma as part of the dystrophin–glycoprotein complex (Sander 2000). Skeletal muscle-derived nitric oxide may play a key role in the regulation of blood flow within exercising skeletal muscle through vasoconstriction (Sander 2000, Palladino 2013). Endothelial shear stress in turn regulates adaptive vessel growth and angiogenesis (Ando 1993). In the absence of dystrophin and its mediation of nitric oxide production, new blood vessel formation is downregulated and mismatched to the metabolic need of the muscle tissue.

The net effect is deterioration of the skeletal musculature with subsequent loss of strength and function. Boys with Duchenne muscular dystrophy may begin to show signs of muscle weakness as early as the age of 3. Because the early signs are nonspecific, a correct diagnosis may take some time and several doctor visits (usually entailing genetic testing) (Figure 1.2.3). The mean age of diagnosis is ~5 years (Ciafaloni 2009). All patients experience a progressive weakening of skeletal or voluntary muscles, those in the arms, legs, and trunk, resulting in reduced mobility, with difficulty walking or rising from the floor. As the muscle weakness progresses, these boys cannot keep up with their peers, trip and fall with increasing regularity, often causing bone fractures, and lose the ability to climb stairs. By age 7, many have reached their maximum walking ability as measured by percent-predicted distance in the 6-minute walk test (McDonald 2010a, McDonald 2013a, Pane 2014).

Decline in performance on the 6MWD test is correlated with loss of ambulation (Mazzone 2013). Further irreversible loss of function inexorably ensues. By age 12, they are wheelchair bound; this loss of independence is a life-changing event for the boys and for the

parents and families who care for them. Thereafter, the disorder takes on a new and even more devastating aspect: flexion contractures develop in elbows, knees, hamstrings, and hips, the ability to raise their arms or to use their hands and wrists becomes increasingly limited, which further curtails mobility and the ability to perform activities of daily living and self-care. Severe scoliosis develops with consequent thoracic deformities. Abnormalities in contractile function of the gastrointestinal tract can lead to digestive disorders. Cardiac and respiratory muscles become affected in the early teen years (Wagner 2007), ultimately leading to primary cardiomyopathy and respiratory failure requiring continuous ventilator use. In addition, approximately one-third of Duchenne muscular dystrophy patients experience cognitive impairment, apparently independent from the muscular impairment, attributed to lack of dystrophin in the central nervous system (Andersen 2002, Bresolin 1994, Zhou 2011).

Figure 1.2.3: Natural History Timeline of Duchenne Muscular Dystrophy



Dx, diagnosis. Contemporary treatment with steroids, improved cardiac management, and ventilation. Data from Bushby 2011 and McDonald 2013b. Figure adapted from McDonald DM, et al. Muscle Nerve (2013b);48(1):32-54, with permission (John Wiley and Sons).

Without intervention, Duchenne muscular dystrophy leads to early mortality, usually in the second decade (Bushby 2010). Following the introduction in the 1990s of assisted ventilation in the later stages of the disorder, the mean age of survival (for those patients receiving ventilation who do not develop early and severe cardiomyopathy) improved to 24 years (Rall 2012, Eagle 2002). Current guidelines recommending corticosteroids along with respiratory, cardiac, orthopedic, and rehabilitative interventions have led to improvements in function, quality of life, and longevity, so that boys diagnosed with the disorder today in industrialized countries or in the best case have the possibility of survival into their early 30s (Bushby 2010).

There is currently no cure for Duchenne muscular dystrophy. The goals of treatment are to maintain ambulation for as long as possible and to manage the associated complications of the disorder. Supportive care and corticosteroids (prednisone and deflazacort) are the primary means to help improve the quality of life of affected boys (Emery 2003), though no formal regulatory approval for such use of corticosteroids has been obtained. Corticosteroids have been shown to slow the decline of muscle strength and function in patients with Duchenne muscular dystrophy (Moxley 2010) and are generally offered to boys ≥ 5 years of age whose motor skills are starting to decline. However, the risks of chronic use (including increased

infections, diabetes, Cushingoid appearance, delayed puberty, behavioral changes, obesity, osteoporosis, and increased frequency of long bone and vertebral fractures) and uncertainty about benefits have led to wide variability in corticosteroids use within clinical practice (Griggs 2013). Supportive physical therapy can help maintain range of motion and bilateral symmetry to prolong ambulation, but the frequency with which this should be done (minimum 4–6 days/week) can be demanding on families and also has led to wide variability in clinical practice. Inconsistent use of these measures contributes to the heterogeneity of the population of patients with Duchenne muscular dystrophy, including those available for clinical trials.

Heterogeneity of the disease beyond age and current ambulatory capacity as measured by the 6MWD test is further amplified by differences in the standard of care – not just between countries, based on their health care systems or region-specific management guidelines, but also between large organized centers with multidisciplinary care teams and peripheral smaller hospitals. This combination of heterogeneity in disease progression and heterogeneity in standard of care leads to a wide variability in age of onset of disease-specific symptoms and passing specific milestones of disease progression. As is often the case in rare disease settings, this heterogeneity poses enormous challenges for the development of new drugs.

Ataluren is the only disease-modifying agent that has been developed and conditionally approved for Duchenne muscular dystrophy (in Europe) (Translarna EPAR 2015). Ataluren addresses one specific underlying genetic defect: nonsense-mediated premature truncation of dystrophin, and it is not indicated or appropriate for patients with exon 51 skipping amenable mutations. Based on a single, completed randomized trial of 174 ambulatory male patients aged 5 to 20 years, ataluren was granted a conditional marketing authorization in Europe in July 2014 (Translarna EPAR 2015). Ataluren has orphan status in the United States, but is not currently approved or otherwise commercially available.

There is a clear and urgent unmet medical need for new treatments that provide benefits considered meaningful to patients with Duchenne muscular dystrophy and their caregivers. Parents of patients with Duchenne muscular dystrophy and parent groups have been active and effective in advocating for greater attention to the clinical development and regulatory consideration of promising new therapies. They have collaborated with companies developing potential therapies and with regulatory authorities, and they have strongly voiced their preferences for clinical trials that are as inclusive and heterogeneous as possible, even at the risk of reduced precision in the assessment of treatment effects. Their efforts have been instrumental to the issuing in recent years of draft guidances to industry for the development of Duchenne muscular dystrophy therapies by the European Medicines Agency and the US Food and Drug Administration (EMA 2013, FDA 2015), and these groups have championed patient input into regulatory risk-benefit assessments.

1.3 Development Rationale and History

The dystrophin gene is the largest in the human genome, with 79 exons covering 2.6 million nucleotide base pairs. This great size makes it prone to rearrangement and recombination events that cause mutations. Boys with a clinical suspicion of Duchenne muscular dystrophy

undergo molecular analysis of their dystrophin gene in DNA isolated from a blood sample, which includes characterization of the type and location of mutation through routinely available tests.

Most (60–68%) of the mutations in the dystrophin gene involve the deletion of 1 or more exons (Aartsma-Rus 2006, Flanigan 2009). These deletions are replicated in the initial pre-mRNA transcript, which includes all of the exons and introns, as well as the terminal regions of the original gene. The pre-mRNA transcript is then "read" by regulatory proteins and the introns spliced out in the preparation of the mature mRNA. The deletions characteristic of Duchenne muscular dystrophy alter the "reading frame" of dystrophin, disrupting the regulatory proteins and leading to premature termination of the protein.

Some exon deletions do not disrupt the reading frame entirely but result instead in internally shortened but functional dystrophin proteins. These mutations are associated with Becker muscular dystrophy (BMD), a less severe form of the disorder. Especially when in-frame deletions are located within the central rod domain of the dystrophin protein, clinical manifestations of BMD can be relatively mild and compatible with a normal lifestyle.

This observation was the basis for the development of exon-skipping strategies designed to maintain an open reading frame by bypassing troublesome stretches of pre-mRNA. In this approach, antisense oligonucleotides are utilized to target a specific exon that is flanked on either side by a deletion. Regulatory proteins responsible for RNA splicing are induced to skip over the target exon and thereby restore the reading frame. The reading and splicing process resumes at the next appropriate exon, producing an internally shortened but still functional dystrophin protein (van Deutekom 2001, Aartsma-Rus 2002, van Ommen 2008, Aartsma-Rus 2010).

Proof of mechanism for exon-skipping as a potential therapeutic strategy was provided by multiple laboratory studies, using RNA antisense oligonucleotides to induce novel dystrophin production in cultured muscle cells from Duchenne muscular dystrophy patients with different mutations and in relevant animal models (Aartsma-Rus 2003, Aartsma-Rus 2004a, Aartsma-Rus 2004b, Bremmer-Bout 2004, Lu 2003, Yokota 2009). Even very small increases in dystrophin (<4%) may improve survival in animal models of Duchenne muscular dystrophy (van den Bergen 2014, van Putten 2012, van Putten 2013).

Drisapersen is a 20-nucleotide-sequence oligonucleotide optimized to target a splicing regulatory sequence within exon 51 of the human dystrophin pre-mRNA. This oligonucleotide is chemically modified (fully 2'O-methyl substituted RNA backbone with phosphorothioate linkages) to improve pharmacokinetic (PK) exposure and metabolic stability, promote RNA binding, and prevent activation of ribonuclease H–mediated mRNA breakdown after binding. The newly produced dystrophin lacks amino acids in the central rod domain, but retains the N- and C-terminal domains necessary for its structural and signaling roles.

Drisapersen-induced exon skipping is a personalized, mutation-dependent corrective approach to Duchenne muscular dystrophy. The majority of Duchenne muscular dystrophy-causing deletions cluster in a hot spot region between exons 45 and 53. Skipping 1 specific

exon may apply to different mutations (Aartsma-Rus 2009); for example, skipping exon 51 restores the reading frame in patients who carry a deletion of exons 45–50, 47–50, 48–50, 49–50, 50, 52, or 52–63, which comprise 13% of all patients with the disorder.

1.3.1 Clinical Development Program

Clinical development of drisapersen was initiated by Prosensa Therapeutics B.V. with a proof-of concept study (PRO051-01) verifying that local injection of drisapersen induces exon 51 skipping and results in novel dystrophin production as predicted (van Deutekom 2007). An open-label, dose-escalating study (PRO051-02) followed, which established drisapersen 6 mg/kg/wk SC as an appropriate dose for subsequent study (Goemans 2011) based primarily on what now can be used as "first generation" technology to evaluate dystrophin expression. The 12 patients from this study entered an open-label extension (Study 673) investigating the safety and efficacy of continued treatment with drisapersen for up to 188 weeks.

Based on the results of these early studies, and in response to the urgent need for a treatment for Duchenne muscular dystrophy, 3 randomized, double-blind, placebo-controlled studies were designed and implemented nearly simultaneously (see Table 1.3.1.1 for a complete overview of the clinical studies). Study 117 explored intermittent and continuous drisapersen dosing, with a loading dose to maximize initial tissue uptake in a relatively homogeneous, early ambulant population. This population was also chosen for Study 876, which investigated doses of 3 mg/kg and 6 mg/kg drisapersen without a loading dose. Study 044 was initiated within months of the start of the Study 117, enrolling a more heterogeneous ambulant population in terms of age and degree of disease progression. Patients in studies 117 and 044 were treated with drisapersen through Week 48 while patients in Study 876 were treated only through Week 24, followed by an observational period through Week 48.

At that time, data were not available from other development programs (eg, ataluren [Translarna EPAR 2015]); there were no regulatory guidelines for Duchenne muscular dystrophy treatments; and key natural history studies had not yet been published. The drisapersen trials were well under way even as the understanding was still evolving for disease heterogeneity, including key prognostic factors for disease progression, variations in care, the clinical relevance of biomarker assessments, and the relevance of the 6MWD as a longitudinal endpoint in patients with limited ambulatory capacity.

The placebo-controlled studies were supported by nonclinical and clinical pharmacology programs that demonstrated the molecular and cellular activity of drisapersen; its distribution and slow accumulation in skeletal muscle tissue; the correlation between its pharmacokinetic properties and the pharmacodynamic effect on exon 51 skipping, dystrophin expression, and muscle composition; and the validity of 6 mg/kg/wk as a proposed clinical dose. See Section 2 and Section 3 for overviews of nonclinical and clinical pharmacology programs, respectively.

Table 1.3.1.1: Clinical Studies of Drisapersen for the Treatment of Duchenne Muscular Dystrophy

Study No.	Study Design, No. of Centers and Countries	Study Drug(s), Dosage Regimen, Route of Administration, Treatment Duration	Population	Endpoints
Single-dose studies				
PRO051-01	Phase I/II open-label, single dose Single center: Netherlands	Drisapersen 0.8 mg (4 x 0.2 mg) IM Duration: single dose	N=4 ambulant and nonambulant patients	Single-dose safety and PD
DMD114118 **[Study 118]**	Phase I randomized, placebo-controlled, rising dose 2 centers in 2 countries: United States and France	Drisapersen 3 mg/kg, 6 mg/kg, 9 mg/kg, or 12 mg/kg or placebo SC • No patients received the 12 mg/kg dose due to tolerability issues (acute but self-resolving fever reactions) at the 9 mg/kg dose level Duration: single dose	N=20 nonambulant patients	Single-dose safety and PK
Short-term repeat-dose open-label study				
PRO051-02	Phase I/II open-label, rising dose 2 centers in 2 countries: Belgium, Sweden	Drisapersen 0.5 mg/kg, 2.0 mg/kg, 4.0 mg/kg, or 6 mg/kg SC once weekly Duration: 5 weeks	N=12 ambulant and nonambulant patients	Safety, PK, and PD
Repeat-dose placebo-controlled studies in ambulant boys				
DMD114117 **[Study 117]**	Phase II randomized, double-blind, parallel-group, placebo-controlled 13 centers in 9 countries: Australia, Belgium, France, Germany, Israel, Netherlands, Spain, Turkey, United Kingdom	Placebo OR drisapersen SC 6 mg/kg twice weekly for 3 weeks (loading dose), then either: • Continuous course: drisapersen 6 mg/kg/wk SC; or • Intermittent course: alternating weeks of 6 mg/kg SC twice weekly and 6 mg/kg/wk for 6 weeks followed by 4 weeks off-dose period Duration: 48 weeks	N=53 ambulant patients; 6MWD ≥75 meters, able to Rise from floor ≤7 seconds	Efficacy, tolerability, safety, PD, and PK

Study No.	Study Design, No. of Centers and Countries	Study Drug(s), Dosage Regimen, Route of Administration, Treatment Duration	Population	Endpoints
DMD114876 [**Study 876**]	Phase II randomized, double-blind, parallel-group, placebo-controlled 13 centers in United States	Placebo OR drisapersen 3 mg/kg or 6 mg/kg SC once weekly Duration: 24 weeks, followed by 24-week follow-up with no treatment in either group	N=51 ambulant patients; 6MWD ≥75 meters, able to rise from floor ≤7 seconds[b]	Efficacy, tolerability, safety, PD, and PK
DMD114044 [**Study 044**]	Phase III randomized, double-blind, parallel-group, placebo-controlled 44 centers in 19 countries: Argentina, Belgium, Brazil, Canada, Chile, Czech Republic, Denmark, France, Germany, Italy, Japan, Republic of Korea, Netherlands, Norway, Poland, Russian Federation, Spain, Taiwan, Turkey	Placebo OR drisapersen 6 mg/kg SC once weekly Duration: 48 weeks	N=186 ambulant patients; 6MWD ≥75 meters (181 patients completed the study)	Efficacy, tolerability, safety, PD, and PK

Study No.	Study Design, No. of Centers and Countries	Study Drug(s), Dosage Regimen, Route of Administration, Treatment Duration	Population	Endpoints
Long-term extension studies				
DMD114673[a] (Extension of PRO051-02) [**Study 673**] (Ongoing)	Phase I/II open-label uncontrolled extension of PRO051-02 2 centers in 2 countries: Belgium, Sweden	Drisapersen 6 mg/kg/wk SC for 72 weeks • After an interval of 8 weeks (Weeks 73–80) off drug, patients restarted an intermittent treatment regimen of drisapersen 6 mg/kg/wk for 8 weeks, followed by 4 weeks off treatment (12-week cycles) up to 188 weeks • An IV substudy was also conducted following Week 188 Duration: • Planned: until launch or termination of development • Actual: dosing halted September 2013; restarted after data cutoff for this submission[a]	N=12 ambulant and nonambulant patients at start of parent Study PRO051-02	Long-term safety, efficacy, and PK
DMD114349[c] [**Study 349**]	Phase III open-label extension of Studies 117 and 044 58 centers in 24 countries: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, Czech Republic, Denmark, France, Germany, Hungary, Israel, Italy, Japan, Republic of Korea, Netherlands, Norway, Poland, Russian Federation, Spain, Taiwan, Turkey, United Kingdom	Drisapersen 6 mg/kg/wk SC • Patients with tolerability issues had the option to enter the intermittent arm of 6 mg/kg/wk for 8 weeks followed by 4 weeks off dose • Patients who did not wish to receive drisapersen or who had to withdraw from both active arms during the study had the option to go into a natural history observation arm Duration: • Planned: until launch or termination of development (minimum 104 weeks) • Actual: up to 101 weeks at time of termination of dosing in September 2013[c]	N=233 patients, ambulant at start of parent study[d] (Study 044 or 117)	Long-term safety and efficacy

Study No.	Study Design, No. of Centers and Countries	Study Drug(s), Dosage Regimen, Route of Administration, Treatment Duration	Population	Endpoints
DMD115501[a] **[Study 501]** (Ongoing)	Phase III open-label extension of Study 876 13 centers in United States	Drisapersen 6 mg/kg/wk SC • Patients with tolerability issues had the option to enter the intermittent arm of 6 mg/kg/wk for 8 wk followed by 4 wk off dose/ Duration: • Planned: until launch or termination of development • Actual: Dosing in the study halted in September 2013, but restarted after the data cut off for this submission[a]	N=21 patients, ambulant at start of parent study[e] (Study 876)	Long-term safety and efficacy

6MWD, 6-minute walking distance in meters; IM, intramuscular; IV, intravenous; PD, pharmacodynamics; PK, pharmacokinetics; SC, subcutaneous.

[a] Dosing halted in September 2013 but restarted after data cutoff for this report (31 August 2014).

[b] The ability to rise from the floor in ≤7 seconds was initially required in Study 876 and changed to ≤15 seconds by protocol amendment 3; however, only 2 patients in Study 876, 1 each in the drisapersen 3-mg and 6-mg/kg/wk groups, were enrolled with a rise-from-floor-time >7 seconds.

[c] Study terminated; dosing halted 20 September 2013.

[d] 228 patients enrolled in continuous dosing arm, 4 in intermittent arm, and 1 in natural history arm; at study termination, 205 patients were ongoing in the continuous arm, 11 patients were ongoing in the intermittent arm, and 17 patients were in the natural history arm.

[e] 21 patients entered study; 4 withdrew and 17 were ongoing as of 31 August 2014.

The drisapersen clinical development program consists of 9 clinical studies in 326 boys with Duchenne muscular dystrophy, 312 of whom received at least 1 dose of drisapersen. This global program included more than 50 trial sites in 25 countries on 5 continents. At the clinical cut-off date for NDA submission, 7 of the studies were completed or terminated:

- 2 single-dose Phase I/II studies (PRO051-01 and Study 118)
- 1 open-label repeat-dose Phase I/II study (PRO051-02)
- 3 randomized, double-blind, placebo-controlled studies (Studies 117, 876, and 044). Of these 3 studies, only Study 117 incorporated a loading dose to accelerate tissue distribution of the drug.
- 1 long-term open-label extension study (Study 349) of Studies 117 and 044. The mean duration of treatment was ~ 1 year when dosing was halted on September 20, 2013.

Patients continued to be observed in 2 additional long-term, open-label extension studies:

- Study 673 (extension of PRO051-02). Data reported up to week 188 of SC drisapersen administration are included here. To provide context, a matched natural history cohort of untreated Duchenne muscular dystrophy patients with similar baseline characteristics was compared to Study 673 patients in terms of ambulatory function over time (Goemans 2014; data on file, BioMarin Pharmaceutical Inc., May 2014).
- Study 501 (extension of Study 876). Due to limited patient exposure prior to the suspension of dosing, only information on serious adverse events (SAEs) is included here.

Drisapersen was licensed by GlaxoSmithKline (GSK) from Prosensa in 2009 after 2 initial studies, PRO051-01 and PRO051-02, had been completed and the extension Study 673 was under way. GSK assumed sole responsibility for clinical development. On 20 September 2013, following analysis of data from Study 044, which did not meet its primary endpoint, GSK suspended administration of drisapersen. On 12 January 2014, all rights returned to Prosensa from GSK. In January 2015, BioMarin acquired Prosensa and all of its development programs. Based on the totality of data from the clinical development program which demonstrated a favorable benefit-risk profile, BioMarin submitted a New Drug Application (NDA) for drisapersen in April 2015. The cut-off date for inclusion of data in the NDA was 31 August 2014. No patient received drisapersen from September 2013 up to the cut-off date. At present, efforts are under way to meet the demands for resumed dosing by patients from the suspended long-term studies. A total of 54 patients have resumed dosing to date.

1.3.2 Regulatory History

No published regulatory guidance for Duchenne muscular dystrophy treatment was available when drisapersen clinical development was planned and implemented. Draft guidelines for the clinical investigation of treatments for muscular dystrophies were first released in the European Union in March 2013 (EMA 2013) and in the Unites States in June 2015 (FDA 2015).

The development of drisapersen overlapped substantially with the development of ataluren; therefore, insight gained from the development of other, novel and contemporaneously developed drugs was not possible. Consequently, basic considerations such as eligibility, requirements for concomitant therapy, and choice of supportive endpoints for studies were all uncertain or evolving at critical junctures in the development of drisapersen.

The purpose of the drisapersen development program is to meet a global unmet medical need for a rare disorder. Thus, the Sponsor has conducted a global clinical trial program to support global approval. The sponsor has had numerous interactions with the FDA and EMA to seek guidance on a complementary regulatory approval pathway. In the US, the Sponsor has interacted regularly with the FDA via informal and formal meetings including a Pre-IND meeting (2009), two End-of-Phase 2 meetings (2011 and 2013), additional Type B and Type C meetings (2013, May/Sept/Oct 2014) and a Pre-NDA meeting in January 2015. During these meetings the sponsor gained significant feedback and agreement on several key aspects of the program, including the designs of the placebo-controlled studies, nonclinical toxicology and carcinogenicity studies, and CMC and Quality requirements for drug product approval. In 2013 and 2014, the sponsor met with the FDA to discuss the outcomes of the randomized placebo controlled studies. In early 2015, the sponsor met with the FDA in a Pre-NDA meeting to agree on content and format of the NDA. The submission of the NDA was completed on April 2015 with an associated PDUFA action date of 27 December 2015.

In Europe, scientific advice and pre-submission meetings with EMA were held, the outcomes of which were complementary to and mostly consistent with advice received from the FDA.

The following designations have been received from the FDA: Orphan Drug (2009), Fast Track (2010), Breakthrough Therapy (2013), Priority Review (June 2015) and Rare Pediatric Disease (August 2015). These designations have provided regulatory incentives and expedited pathways for seeking approval of drisapersen for a very challenging, rare, serious, mostly pediatric, unmet medical need, Duchenne muscular dystrophy. Drisapersen is also designated an orphan drug product in the EU.

2 NONCLINICAL OVERVIEW

Drisapersen has undergone a comprehensive nonclinical evaluation, which was performed with doses and dose schedules that mimic or exceed the dosing regimens used in the clinical trials. Proof-of-mechanism was provided by pharmacodynamic (PD) studies in myogenic cell cultures derived from patients with Duchenne muscular dystrophy caused by different relevant dystrophin gene mutations. The results of these investigations were supported by the findings of in vivo PD and PK studies using a surrogate oligonucleotide in the *mdx* mouse, an established model of Duchenne muscular dystrophy.

Secondary pharmacology studies evaluated the safety and target specificity of drisapersen and a battery of safety pharmacology and toxicology studies further elucidated the safety profile. The results confirmed that drisapersen presents negligible risk of central nervous system (CNS)-related adverse effects, and negligible risk of adverse effects on cardiovascular function, respiratory function, and electrocardiographic (ECG) parameters. The risk of hybridization-dependent off-target effects was also negligible with drisapersen and its metabolites, as in silico evaluation confirmed that there was no relevant complementarity to genes other than the intended target in the dystrophin gene. Repeat dose toxicity studies in animals confirmed oligonucleotide-class toxicities, with pro-inflammatory activity and renal toxicity identified as the greatest hazards. Overall, the results provided evidence of favorable PK and overall safety, and supported further development of drisapersen for clinical use in the treatment of Duchenne muscular dystrophy.

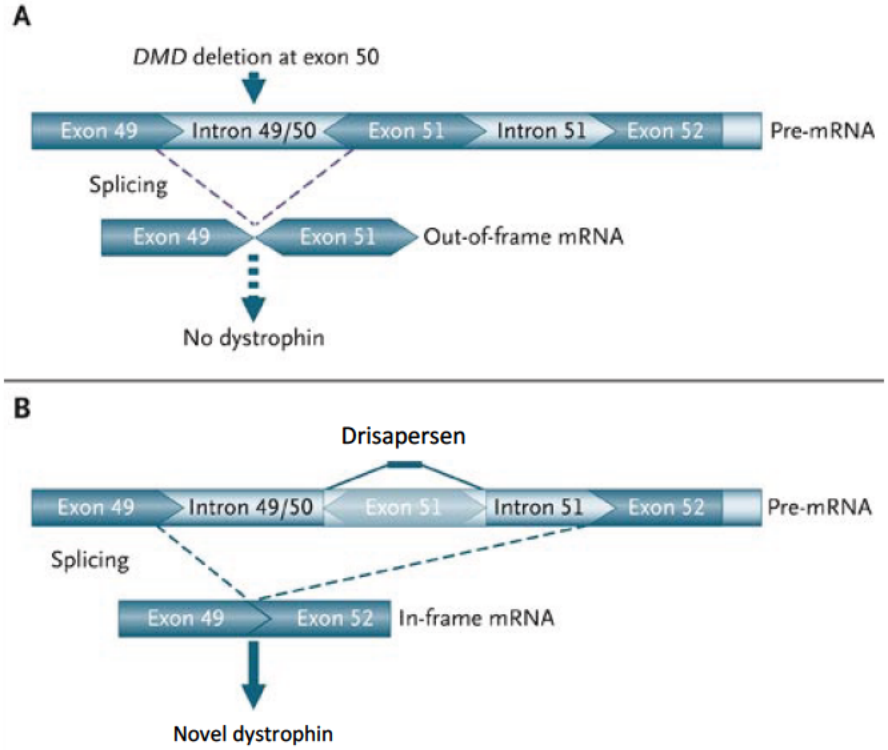
2.1 Mechanism of Action

Duchenne muscular dystrophy results from mutations in the gene coding for the protein dystrophin, which is essential for normal muscular activity. Most dystrophin mutations involve exon deletions that disrupt the mRNA reading frame, leading to loss of dystrophin synthesis. However, some mutations result in exon deletions that do not disrupt the reading frame, producing an internally shortened but functional dystrophin protein, which have been associated with less severe BMD. When in-frame deletions are located within the central rod domain of the dystrophin protein, the clinical manifestations of BMD can be quite mild. This observation was the basis for the development of antisense oligonucleotides that can induce skipping of a specific exon during pre-mRNA splicing, restore the open reading frame, and enable endogenous production of an effective protein (van Deutekom 2001, van Ommen 2008).

Drisapersen is a 20-mer chemically modified antisense oligonucleotide (fully 2'O-methyl substituted RNA backbone with phosphorothioate linkages) designed to induce the skipping of exon 51 from the human dystrophin pre-mRNA. It is optimized for PK exposure, metabolic stability, RNA binding, and prevention of ribonuclease H–mediated mRNA breakdown after binding. Drisapersen has high sequence specificity to exon 51. The mechanism of action involves disruption of secondary structure and/or interference with the binding of splicing regulatory proteins, resulting in skipping of exon 51 during post-transcriptional splicing. An internally shortened mature mRNA transcript is produced that is capable of dystrophin protein production in Duchenne muscular dystrophy (Figure 2.1.1).

The newly produced dystrophin lacks amino acids in the central rod domain but retains the N- and C-terminal domains necessary for its structural and signaling roles.

Figure 2.1.1: Schematic Representation of Exon Skipping Induced by Antisense Oligonucleotide Drisapersen



In a patient with Duchenne muscular dystrophy with a deletion of exon 50, an out-of-frame transcript is generated in which exon 49 is spliced to exon 51 (Panel A). As a result of this frame shift, an in-frame stop codon in exon 51 prematurely aborts dystrophin synthesis. The binding of the antisense oligonucleotide drisapersen to a specific sequence within exon 51 interferes with the correct inclusion of that exon during splicing (Panel B). The skipping of exon 51 restores the open reading frame of the transcript and allows the synthesis of a de novo dystrophin.

Figure adapted from The New England Journal of Medicine, Judith C. van Deutekom, Anneke A. Janson, Ieke B. Ginjaar, et al., Local dystrophin restoration with antisense oligonucleotide PRO051, Vol 357, Page 2677-86. ©(2007) Massachusetts Medical Society. Used with permission from Massachusetts Medical Society.

2.2 Primary Pharmacodynamics

Exon skipping is induced by the highly sequence-specific binding of an antisense oligonucleotide to a target sequence within an exon of the pre-mRNA. For animal studies, species-specific drisapersen surrogate antisense oligonucleotides were made because the dystrophin gene sequence is not 100% homologous between humans, monkeys, dogs, rats, and mice. In addition, animal models for Duchenne muscular dystrophy do not have mutations that are amenable to correction by drisapersen. Primary PD studies of drisapersen and its metabolites were therefore performed in relevant patient-derived muscle cells, and a

mouse-specific surrogate antisense oligonucleotide was used in Duchenne muscular dystrophy mouse models.

Multiple publications demonstrate the feasibility of specific oligonucleotide-induced skipping of most of the 79 exons of the dystrophin transcript in control myogenic cell cultures (Aartsma-Rus 2002, Aartsma-Rus 2005, Aartsma-Rus 2010, Wilton 2007, Popplewell 2009). The broad applicability of oligonucleotides to induce exon skipping was demonstrated in at least 58 myogenic cell cultures derived from Duchenne muscular dystrophy patients with different relevant mutations (van Deutekom 2001, Takeshima 2001, Aartsma-Rus 2003, Aartsma-Rus 2004b, Surono 2004, Arechavala-Gomeza 2007, Popplewell 2010). For all mutations tested in these studies, exon skipping allowed novel dystrophin restoration to the myotube membranes and co-expression with other proteins of the dystrophin-associated glycoprotein complex.

Multiple in vivo studies of drisapersen were performed using a surrogate mouse-specific antisense oligonucleotide (M23D [+02-18], referred to here as 23AON; Lu 2005) that induces exon 23 skipping in *mdx* mice. The *mdx* mouse is an accepted Duchenne muscular dystrophy model (Bulfield 1984) with a nonsense mutation in exon 23, which results in dystrophin deficiency. The surrogate oligonucleotide 23AON has the same chemical modifications as drisapersen (2-*O*-methyl phosphorothioate oligoribonucleotide; Lu 2005). Previously, 23AON was shown to induce exon 23 skipping and restoration of dystrophin synthesis following either intravenous (IV), SC, intramuscular (IM), or intraperitoneal (IP) administration (Lu 2005, Heemskerk 2010, Tanganyika-de Winter 2012, Verhaart 2013, Verhaart 2014). These studies demonstrated that oligonucleotide-induced exon skipping and restoration of dystrophin expression at the muscle fiber membranes allow pathologic and functional improvement of diseased muscle tissue.

Proof-of-mechanism studies with drisapersen demonstrated expression of newly formed (internally shortened) dystrophin protein in patient-derived cultured muscle cells after treatment in vitro and in tibialis anterior muscle biopsy specimens obtained from patients treated with drisapersen by local IM or systemic SC injection. In addition, improvements were seen in dystrophin-deficient *mdx* mice treated with the mouse-specific surrogate oligonucleotide, suggesting that the exon skipping approach could improve muscle function in Duchenne muscular dystrophy.

Of note in the in vivo studies was the relatively more efficient uptake of the surrogate antisense oligonucleotide 23AON by dystrophic muscle tissue in *mdx* mice than by healthy muscle tissue in wild-type mice (Heemskerk 2010). This enhanced uptake is hypothesized to result from more permeable damaged muscle fiber membranes and/or the activated, proliferating, uptake-permissive muscle satellite cells in regenerative muscle tissue that internalize the oligonucleotide and fuse with surrounding muscle fibers (Aoki 2013). With the variation in the degeneration and regeneration processes between specific muscle groups and over time, the levels of uptake and stability of 23AON in *mdx* mice were found to vary between muscles and between mice at different ages.

2.3 Secondary Pharmacodynamics

Drisapersen and its potential metabolites were examined to estimate the likelihood of off-target effects elsewhere in the human genome and interference with the expression of an unintended target gene by drisapersen-mediated exon skipping. Basic Local Alignment Search Tool (BLAST) searches on drisapersen confirmed the high sequence specificity of drisapersen to exon 51 of the dystrophin gene only (no relevant matches with more than 80% reverse complementarity other than the dystrophin gene), and the risk is considered minimal for sequence-related off-target effects of drisapersen and potential drisapersen 3' metabolites.

2.4 Nonclinical Pharmacokinetics

The PK, absorption, distribution, metabolism, and elimination of drisapersen have been investigated through a series of IV, IM, SC, IP, and in vitro studies in mice, rats, and monkeys. Drisapersen is rapidly absorbed from the SC injection sites followed by plasma clearance with a half-life of less than 1 hour. Clearance from plasma is highly dependent on distribution to tissues and to a lesser extent urinary excretion. Long residence time in tissues with tissue half-lives on the order of weeks supports weekly administration of drisapersen. Protein binding, determined by in vitro plasma protein binding of [^{14}C] drisapersen, was high in all species (> 99.7%). Drisapersen has a characteristic distribution profile of phosphorothioate oligonucleotide, with highest concentrations in kidney, liver, spleen and lymphoid tissues, bone marrow, diaphragm, skin, and rectum mucosa and low to negligible concentrations in the brain. The major drug-related material was unchanged drisapersen. Metabolism was predictable with the sequential loss of nucleotides from the 3' end with decreasing amounts of M1 to M8 (3' N-1 to 3' N-8), suggestive of exonuclease degradation. Overall, the PK and distribution profile supports the safe use of drisapersen for treatment of Duchenne muscular dystrophy at the dosage of 6 mg/kg/wk.

2.5 Safety Pharmacology

Safety pharmacology endpoints assessed included potential effects on central and peripheral nervous system in mice (dosed up to 600 mg/kg), and respiratory function and cardiac function in the monkey (dosed up to 15 mg/kg IV, ~ 84-fold clinical maximum observed plasma concentration [C_{max}] and exposure), which were not affected by drisapersen.

2.6 Toxicology

Drisapersen has undergone a comprehensive toxicological evaluation to support the clinical dosing regimen (weekly, SC). Due to the long tissue half-life of drisapersen, weekly dosing sustains continual exposure to the pharmacological target, skeletal muscle, and recapitulates the dosing regimen evaluated clinically. Single-dose SC, IM, and IV toxicity studies were performed in rodent and non-rodent species. Repeated-dose studies were conducted for up to 27 weeks in mice, 13 weeks in rats, and 39 weeks in monkeys. Treatment-free recovery was assessed for up to 35 weeks in mice and 39 weeks in monkeys.

Nonclinical toxicity findings observed with drisapersen administration were primarily related to drug accumulation in tissues and pro-inflammatory effects. The slow recovery of most of the findings after long term treatment is likely due to the long tissue half-life of several

months for drisapersen. The toxicity profile of drisapersen is typical of the class-related animal toxicities reported for phosphorothioate oligonucleotides with 2' modifications (Kwoh 2008, Levin 2001, Levin 2008, Henry 2008, Engelhardt 2015), which is related to physio-chemical characteristics associated with the polyanionic phosphorothioate backbone, not pharmacologic activity, sequence, or specificity.

The inflammatory effects of drisapersen were the most evident response in animals and stem from activation of the innate immune system (e.g. via complement activation, or via Toll like receptors). Animal species are known to be overly sensitive to the pro-inflammatory effects of oligonucleotides (Henry 2008, Levin 2001). Species differences in cellular distribution and susceptibility of pattern recognition receptors such as toll-like receptors are believed to contribute to the sensitivity of mice. Additionally, monkeys are particularly sensitive to oligonucleotide-induced complement activation, due to direct inhibition of negative regulators like Factor H in the alternative complement pathway. Functional differences between monkey and human factor H have been reported (Henry 2014, Shen 2014), and these may contribute to the more pronounced complement activation in monkeys.

Key toxicities including thrombocytopenia, proteinuria and renal effects, injection site reactions and vascular inflammatory changes seen in animals are addressed in more detail below.

1. Thrombocytopenia

Drisapersen induced a gradual, self-limiting and generally mild decline in platelets in animals, which was reversible during an off dose period. There are no indications of impaired production of platelets by drisapersen. The mild decline in platelets may be due to a drisapersen-induced increase in platelet consumption, without any clinical sequelae. A rapid drop in platelets was seen in a subset of monkeys, associated with typical signs of thrombocytopenia Recovery was apparent within approximately 3 to 4 weeks following cessation of treatment. These more severe platelet drops are likely immune-mediated, in view of the rapid decline in platelet counts which was observed when treatment was restarted in the subset of monkeys.

2. Proteinuria and other renal effects

Mild low molecular weight proteinuria was observed in the majority of monkeys, but was not associated with evidence of renal tubular damage or changes in other serum based markers of renal function (at chronic dosing up to 8X clinical exposure). Oligonucleotides like drisapersen accumulate in the proximal convoluted tubular cells by endocytosis in a similar way as these cells reabsorb low molecular weight proteins from the filtrate. Thus, the frequent, yet reversible, low molecular weight proteinuria with drisapersen treatment reflects (competitive) interference with the tubular protein uptake. Progressive loss of tubular function was not observed in animals.

Upon chronic treatment, inflammatory-mediated glomerular changes were apparent in animals. In monkeys dosed at 2.6X clinical exposure, these were generally minimal to slight and not associated with changes in renal serum biomarkers, but occasionally associated with overt proteinuria (albuminuria). Both the glomerular changes and the

proteinuria were reversible following cessation of treatment. Glomerular deposits of complement C3 fragments, but not C4 or immunoglobulins (IgG, IgM), underscored the immune-mediated pathogenesis. Increased cellularity of affected glomeruli was also noted

Progressive and irreversible renal changes were apparent in mice, but as this was due to a mouse specific glomerulopathy, these findings bear no relevance to the clinic.

3. Injection site reactions

Injection site reactions were evident following SC dosing in all animal species, and are considered to reflect both local accumulation of drisapersen and pro-inflammatory effects that are associated with drug induced activation of innate immunity. Injection site reactions were pronounced in monkeys with minimal rotation (n=2 injection sites), characterized by erythema, edema, induration and eschar formation. With more extensive rotation of sites (n= 8) in long term studies, injection site reactions were less severe (erythema, thickening, dryness and desquamation). Histopathological correlates were primarily mononuclear inflammatory infiltrates and fibrosis/fibroplasia in dermis and subcutis.

4. Vascular inflammatory changes

Following chronic dosing, vascular inflammation was noted in monkeys at and above ~1.7X clinical exposure. Changes were non-necrotic, non-hemorrhagic, and primarily characterized by perivascular mononuclear infiltrates and intimal and/or medial thickening with occasional medial degeneration. In three more severely affected monkeys (of 56 long term treated animals), this was associated with thrombus formation, and this resulted in myocardial infarction and early termination in two of these monkeys. Similar vascular inflammatory lesions in monkeys have been described for other phosphorothioate oligonucleotides (Engelhardt 2015), including Kynamro®, an approved therapy for homozygous familial hypercholesterolemia (FDA 2013). Oligonucleotide-induced vascular inflammation in the monkey is associated with complement activation, for which this species is particularly sensitive. Monkeys with vascular changes had generally more changes in a spectrum of inflammatory biomarkers, including elevated complement split fragments. Since low grade vascular lesions are occasionally observed as spontaneous events in cynomolgus monkeys (Porter 2003, Chamanza 2010), these vascular changes with oligonucleotides in monkeys may occur on a background of species more susceptibility to vascular inflammation.

Overall, the nonclinical findings with drisapersen were useful for hazard identification and subsequent clinical monitoring, but are considered to be less relevant for quantitative risk assessment or mechanistic evaluation since the animal species are known to over predict pro-inflammatory effects of oligonucleotides. As such, the no adverse effect levels (NOAELs) are found at exposures that are at or below the clinical plasma exposure levels. Thus, nonclinical findings identify hazards, rather than provide a customary margin of clinical safety and are expected to be clinically monitorable.

3 CLINICAL PHARMACOLOGY

The clinical PK and PD of drisapersen were assessed in 8 clinical studies in more than 300 patients with Duchenne muscular dystrophy, ambulant and nonambulant (see Table 1.3.1.1 for study descriptions). Of the 9 studies in the drisapersen clinical program, only Study 501 did not contribute to PK and PD assessment of drisapersen. The proposed dose of 6 mg/kg/wk SC was established in early dose-ranging studies and is supported by nonclinical analyses; the slow accumulation and long tissue elimination half-life of drisapersen confirm the weekly dosing regimen. Slow accumulation further suggests that a loading dose would be beneficial by boosting drisapersen muscle levels in the first weeks of treatment.

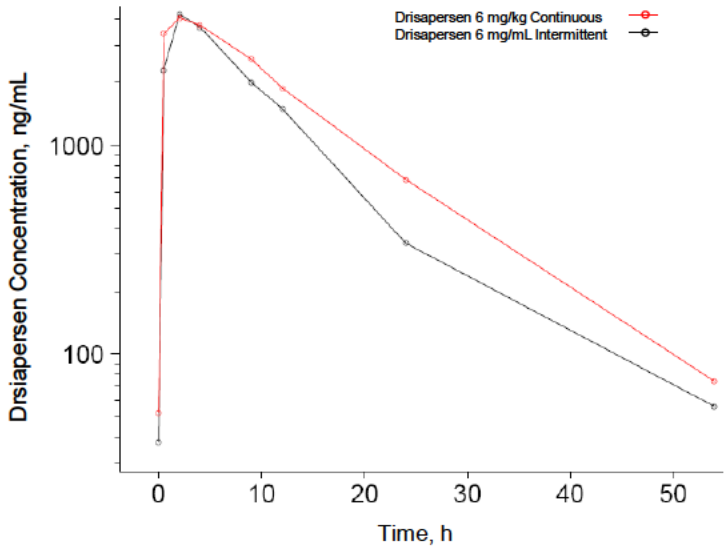
3.1 Pharmacokinetics

3.1.1 Absorption, Distribution, Metabolism, Elimination

Clinical findings indicate that drisapersen displays the PK properties and metabolite profile typical of 2'O-methyl phosphorothioate oligonucleotides (Geary 2009, Levin 2008). These data also are consistent with the results of nonclinical studies of drisapersen.

Maximum plasma levels are generally reached 2 to 4 hours after SC administration, then decline during a rapid initial tissue (re)distribution phase, followed by a slower elimination phase, as shown for patients from study DMD114117 (Study 117) in Figure 3.1.1.1. After 24 hours, plasma concentrations declined to ≤15% of the C_{max}, and after 1 week to ≤0.4% of C_{max}. Most of the plasma exposure occurred during the first 24 hours after SC administration; repeated administration did not significantly affect C_{max}, and increases in area under the plasma concentration versus time curve (AUC) were at most 2-fold. However, plasma trough concentrations increased after repeated weekly dosing, representing equilibrium with tissue exposures. Therefore, increasing trough levels indicate continuous tissue exposure and accumulation of drisapersen during a 1-week dose interval schedule.

Figure 3.1.1.1: Median Plasma Drisapersen Concentration Profiles After SC Injection of 6 mg/kg Drisapersen at Week 29 in Study 117

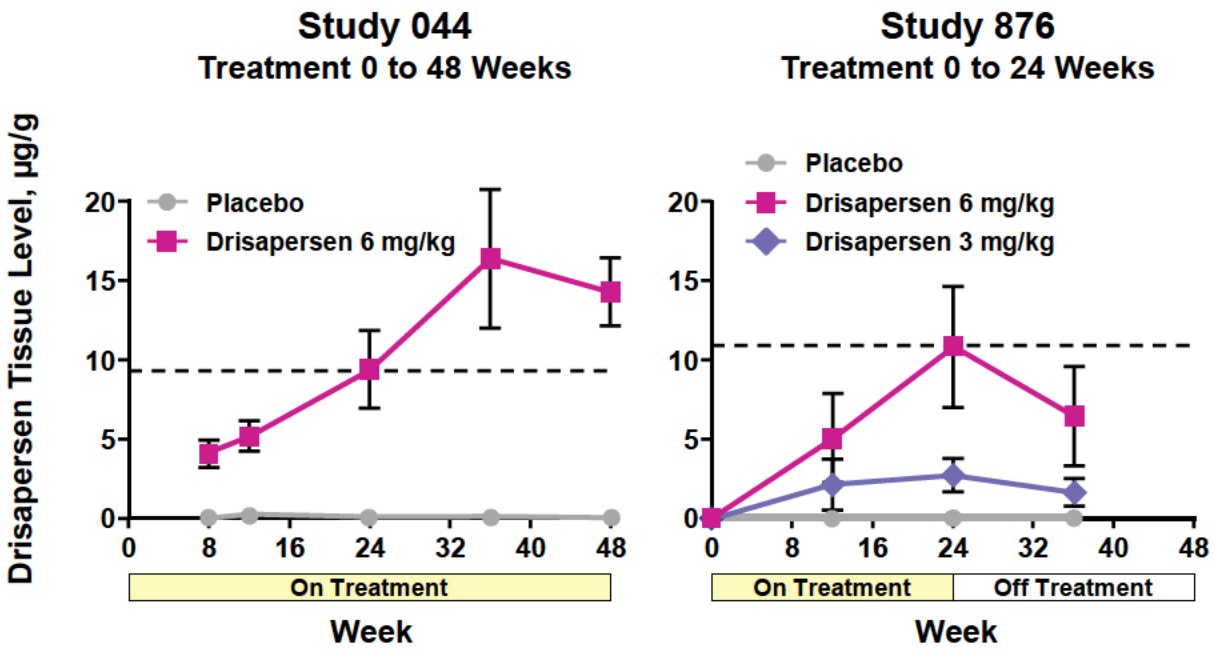


Plasma drisapersen concentrations are shown on a semi-log scale. Patients received weekly treatment (black line) or an intermittent regimen (red line). For the intermittent regimen, the injection was the 7th injection of the 2nd cycle 7 days after the previous injection.

In Study 044, drisapersen levels in tissue homogenates of muscle biopsies continued to increase and maximal tissue levels were measured between Week 36 and 48 of SC administration at 6 mg/kg/wk, suggesting a long tissue elimination half-life for drisapersen and time to reach steady state to be at least 9 months of weekly treatment (Figure 3.1.1.2). Long tissue elimination half-life was also seen in Study 876, where drisapersen tissue levels declined by approximately 40% in 12 weeks during the treatment-free follow-up period. The tissue PK profile of drisapersen supports the weekly dosing regimen, and the slow accumulation indicates that a loading-dose regimen in the first weeks of treatment would be beneficial to reach significant drisapersen muscle levels more rapidly.

In Study 117, tissue drisapersen concentrations were measured at only a single timepoint (Week 25). At Week 25 in patients receiving drisapersen 6 mg/kg/wk, mean tissue drisapersen concentrations (11.0 µg/g) were comparable to those seen in Study 876 at Week 24 (10.8 µg/g), and marginally higher than those seen in Study 044 (9.4 µg/g), though likely arrived at more quickly in 117 because of the inclusion of a loading dose and study of healthier patients. Of note, in Study 117 a weak relation was observed between dystrophin change and drisapersen concentration as measured in muscule biopsies. Drisapersen levels between 5-10 µg/g provided mixed results in terms of increased dystrophin production, with a positive increase in patients in the weekly dose group indicating that these intermediate drisapersen tissue concentrations are still significant. At drisapersen tissue concentrations above 10 µg/g, however, nearly all subjects showed an increase in dystrophin intensity signal when compared with lower levels.

Figure 3.1.1.2: Drisapersen Concentrations in Muscle Biopsies



CI, confidence intervals; SC, subcutaneous.
In Study 044, drisapersen-treated patients received weekly SC injections of 6 mg/kg for 48 weeks and biopsy specimens were collected at Week 48 for all patients (n=54 for placebo and n=109 for drisapersen) and at Weeks 8, 12, 24, or 36 for approximately a quarter of the patients for each time point. In Study 876, drisapersen-treated patients received 24 weeks of treatment with 3 or 6 mg/kg SC and biopsy specimens were collected at baseline, Week 24, and either Week 12 or 36 for all patients (n=16 for placebo, n=17 for drisapersen 3 mg/kg, and n=18 for drisapersen 6 mg/kg). Data depicted as mean with 95% CIs.

The plasma exposure of drisapersen was dose-proportional between 0.5 and 6 mg/kg for SC administration in Study PRO051-02. In nonambulant patients receiving SC drisapersen, a less than dose proportional increase between 6 and 9 mg/kg was observed in plasma, but the small number of patients receiving the higher dose prevents a definitive conclusion. In muscle biopsy specimens, tissue levels appeared to increase a more than dose proportionally 4-fold between 3 and 6 mg/kg (see Figure 3.1.1.2).

In plasma from drisapersen-treated Duchenne muscular dystrophy patients, the major drug-related component was unchanged drisapersen. As predicted by the animal studies discussed in Section 2.4, metabolites were primarily formed by sequential cleavage of nucleotides from the 3' terminus of the molecule. Excretion in humans has not been evaluated in a clinical study. Metabolites of drisapersen, n-1 to n-4, still show significant exon skip activity in a cellular assay compared to drisapersen.

3.1.2 Population Pharmacokinetics

The population PK of drisapersen after SC administration was modeled based on 1,842 plasma samples taken from 270 Duchenne muscular dystrophy patients up to 12 weeks of treatment. Body weight was found to be the only covariate affecting exposure and PK

parameters of drisapersen. Simulations showed that dosing in milligrams per kilogram results in similar maximum concentrations across various body weights and that trough concentrations and $AUC_{0\text{-}168h}$ increase with increased body weight.

3.2 Pharmacodynamics and Biomarkers

3.2.1 Challenges of Biopsy Analysis and Its Relation to Clinical Function

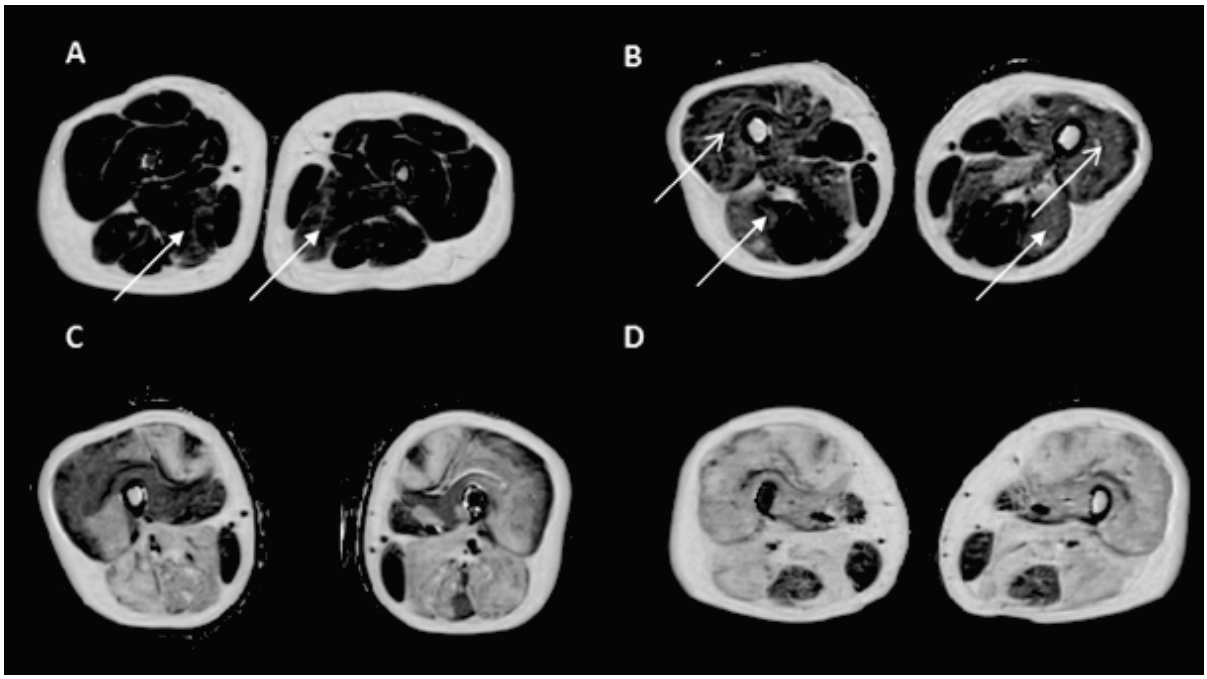
Drisapersen is designed specifically to induce the skipping of exon 51 from the dystrophin pre-mRNA during splicing. This corrects the mutated transcript open reading frame in a subgroup of Duchenne muscular dystrophy patients with deletions of one or more exons flanking exon 51. As a result muscle fibers with drisapersen-positive nuclei will produce novel dystrophin which improves muscle fiber membrane integrity and reduces leakage of creatine kinase (CK) and lactate dehydrogenase (LDH) from damaged muscle tissue into the blood circulation.

Drisapersen-induced exon 51 skipping and dystrophin expression were observed in biopsies from the tibialis anterior muscle of treated patients with Duchenne muscular dystrophy across the studies. The tibialis anterior was selected for practical reasons: it is a large superficial muscle amenable to repeat biopsies and is thought to be reasonably well preserved in Duchenne muscular dystrophy patients. However, drug distribution may be limited in preserved muscle as opposed to diseased muscle samples from tibialis anterior and may not accurately reflect drug-induced change in other muscle groups. Variability in biopsies (choice of muscle, size, quality, heterogeneity in a muscle for sampling), in dystrophin expression (across fibers and muscles and potential muscle-specific response), and in study design (such as pretreatment biopsy comparator or loading dose regimen) did not allow consistency in molecular biopsy results, despite ongoing improvements in methodologies. An important observation was made in the majority of pretreatment and placebo biopsies: a low level of spontaneous exon 51 skipping leads to trace dystrophin expression at the muscle fiber membranes throughout the muscle of patients in this mutational subgroup. This may result in a “positive outcome” of reverse transcription-polymerase chain reaction (RT-PCR) analysis and immunofluorescence or western blot analysis at baseline. The levels of trace dystrophin expression varied between patients. It is therefore essential to carefully compare exon-skipping and dystrophin expression levels in pre- versus post-treatment biopsies, collected from 1 specific muscle group and from 1 patient, and to use sensitive, objective and more quantitative analysis methods. In contrast to RT-PCR and western blot analysis using tissue homogenate samples, immunofluorescence analysis can identify trace and revertant fiber dystrophin expression and differentiate this from a potential pharmacodynamic effect. Conclusions require the detection of an increase in, rather than the presence of, exon 51 skipping and dystrophin intensity levels.

Notwithstanding the limitations noted above, there is clear and consistent evidence that drisapersen creates exon skipping in treated patients, and there is evidence to suggest that drisapersen increases the amount of dystrophin in skeletal muscle. The relationship of the magnitude of such changes and clinical outcomes remains to be determined. As is the case for many biomarkers, iterative evaluation in clinical trials is necessary to establish whether a biomarker can serve as a surrogate of clinical outcome.

Figure 3.2.1.**1**, showing disease progression in muscle by MRI, exemplifies the increasing heterogeneity in muscles and the difficulty of representative biopsy sampling. Given the limitations of a local tiny biopsy collected at one specific time point, we further explored serum biomarkers like CK and LDH that can be monitored over time and provide a more systemic response to treatment. Indeed, treatment with 6 mg/kg drisapersen resulted in a reduction in CK and LDH serum biomarkers in all placebo-controlled studies.

Figure 3.2.1.1: T1-Weighted MRI of Thigh Muscles Showing Progression of Duchenne Muscular Dystrophy with Increasing Age



Muscle fat fraction of the thigh muscles in Duchenne muscular dystrophy patients at baseline. Patient A is age 5.0 years; fatty degeneration is most prominent in the adductors (closed arrows). Patient B is age 9.2 years; fatty degeneration now also clearly visible in the quadriceps (open arrows) and hamstrings (closed arrows). Patient C is age 9.8 years; fatty degeneration is visible in all muscle groups. Patient D is age 12.8 years; fatty degeneration is visible in all muscle groups.

Reprinted from Neuromuscular Disorders, vol. 25/issue 9, Bonati U, Hafner P, Schädelin S, et al. Quantitative muscle MRI: A powerful surrogate outcome measure in Duchenne muscular dystrophy, pp. 679-685 (2015), with permission from Elsevier.

3.2.2 Drisapersen Distribution to Muscle

As noted in Section 3.1.1, muscle biopsy studies demonstrate that drisapersen distributes to skeletal muscle and that levels slowly accumulate to steady state. The clinical data also related well to the nonclinical data gathered with drisapersen. Of note, larger samples of whole muscles can be examined in nonclinical samples, compared with smaller, more variable samples in clinical studies. Likewise, clearance from tissues is slow, occurring over a period of months after cessation of treatment.

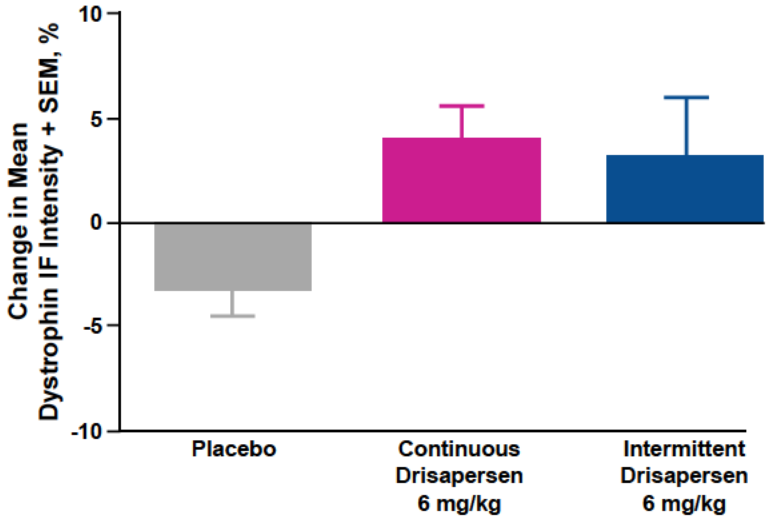
3.2.3 Drisapersen Results in Dystrophin Expression and Exon 51 Skipping

Similar to the nonclinical studies discussed in Section 2.2, the presence of dystrophin protein and of exon 51-skipped mRNA was demonstrated in tibialis anterior biopsy samples from patients with Duchenne muscular dystrophy treated with drisapersen. Dystrophin was assessed by immunofluorescence staining, and the detection of exon 51-skipped mRNA in total RNA isolated from biopsy material was performed using nested RT-PCR methodology with mutation-specific primers. In the placebo-controlled studies, the intensity of the polymerase chain reaction (PCR) exon 51-skipped product band was determined by gel electrophoresis.

3.2.3.1 Dystrophin Expression

In Study 117, which assessed tolerability, safety, PD, and PK, post-treatment muscle biopsy samples were directly compared with specimens obtained at baseline before treatment. In this study, 88% of patients had a biopsy that met quality criteria for acceptance. At 24 weeks, dystrophin expression increased 3.9% ± 1.7 versus baseline (n=15) for continuous drisapersen 6 mg/kg/wk and 3.1% ± 2.9 (n=15) for the intermittent 10-week-cycle treatment compared with a -3.1% ± 1.3 decrease (n=17) for placebo administration (Figure 3.2.3.1.1). Although this analysis was not prespecified, a significant difference was found for the continuous drisapersen regimen compared with placebo (p=0.0026, Student's t-test).

Figure 3.2.3.1.1: Immunofluorescence Analysis of Dystrophin in Study 117 at Week 24



IF, immunofluorescence; SEM, standard error of the mean.

Group change in mean dystrophin signal intensity from Week 1 to Week 25. Result for the 6 mg/kg/wk continuous drisapersen group (mean 3.9%, SEM ± 1.7, n=15) was significantly different (p=0.0026, Student's t test, post hoc analysis) from that for the placebo group (mean -3.1%, SEM ± 1.3, n=17), but not the result for the 6 mg/kg intermittent drisapersen group (mean 3.1%, SEM ± 2.9, n=15) (p=0.069).

Biopsy sample analysis in Study 117 also demonstrated some correlation between drisapersen levels in muscle tissue and change in dystrophin expression. At tissue drisapersen levels >10 µg/g, specimens from nearly all patients showed an increase in dystrophin signal intensity, with levels between 5 and 10 µg/g providing mixed results. Specimens from boys on continuous weekly treatment with 6 mg/kg of drisapersen showed an increase in signal intensity. This study, conducted at a small number of centers of excellence, was the only one in which more frequent administration of drisapersen was undertaken ("loading dose") to facilitate more rapid tissue accumulation.

Due to biopsy quality size and tissue handling in Study 876, only 66% of the patients had biopsies that were acceptable for analysis of dystrophin expression. No significant increase from baseline biopsies was observed with 6 mg/kg/wk drisapersen compared with placebo at Weeks 12 and 24, which may be too early as steady state levels of drisapersen in muscle appear to be reached later and no loading regimen was used in this study. During the off-treatment follow-up period, clinically relevant drisapersen tissue levels (>5 µg/g) were still maintained and simultaneously a trend of increasing dystrophin expression was observed from 12 to 36 weeks in the 6 mg/kg/wk drisapersen group, but not for placebo or drisapersen 3 mg/kg/wk.

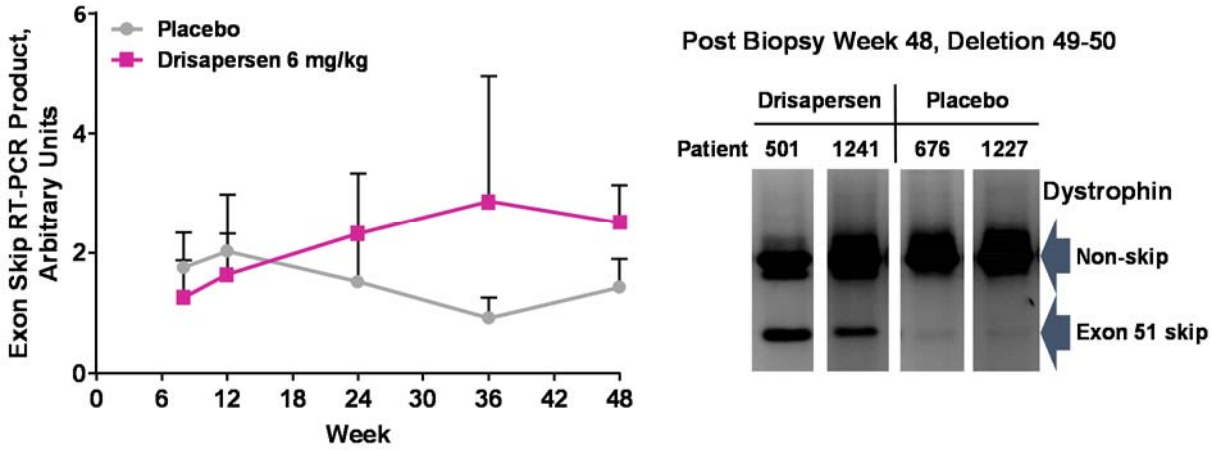
In Study 044, no pre-treatment biopsies were taken; therefore, a relative difference in post-treatment biopsies from baseline could not be ascertained. However, in a pilot study measuring post-treatment biopsies at several time points, a trend for an increase in dystrophin mean membrane intensity was observed from 8 to 48 weeks for 6 mg/kg/wk drisapersen compared with placebo, suggesting a potential underlying treatment effect.

Given the absence of a pretreatment comparator and the inter-patient variability in relation to the potential effect and the high proportion (52% at Week 48) of nonevaluable biopsies in this study (greatly reducing the number of evaluable biopsies in Study 044), no further immunofluorescence assessment was performed.

3.2.3.2 Exon 51 Skipping

In all studies, a majority (>70%) of patients treated with drisapersen or placebo had evidence of exon 51-skipped dystrophin mRNA. This finding in the placebo group indicates some spontaneous exon-skip activity consistent with the presence of trace dystrophin. The intensity of the exon 51-skipped PCR product measured in all 3 placebo-controlled studies generally showed an increase in exon 51 skip post-treatment compared with placebo. A positive trend, with some variability, was observed in the smaller Phase II studies. In Study 044, which assessed drisapersen efficacy, tolerability, safety, PD, and PK, an increase in exon 51-skipped mRNA was observed in a high number of patients and also consistently across biopsy time points (Figure 3.2.3.2.1) and different “exon 51 amenable” deletion groups.

Figure 3.2.3.2.1: Exon 51-Skipped Dystrophin Levels in Patients in Study 044 by Nested RT-PCR



RT-PCR, reverse transcription-polymerase chain reaction.

Mean and upper limit of 95% confidence interval depicted for all patients at Week 48 (n=56 for placebo and n=114 for drisapersen; for earlier time points [sparsely sampled], n ranged from 9–20 for placebo and 26–34 for drisapersen).

3.2.4 Serum Biomarkers: Creatine Kinase and Lactate Dehydrogenase

Placebo-controlled studies in *mdx* mice and mdx/utrn$^{+/-}$ mice treated with mouse surrogate 2-O'-methyl-phosphothiorate AON (Tanganyika-de Winter 2012, Heemskerk 2010) or by phosphorodiamidate morpholino AONs (Wu 2011) have demonstrated exon skipping in various muscles and a related decrease in serum creatine kinase (CK). Creatine kinase was measured in the placebo-controlled drisapersen studies as a secondary efficacy endpoint.

In patients with Duchenne muscular dystrophy, concentrations of CK and LDH increase in serum through leakage from damaged muscle cells; therefore, CK and LDH can serve as biomarkers for muscle fiber membrane integrity. Serum CK is used a diagnostic biomarker for Duchenne muscular dystrophy (Emery 2003, Somer 1976). Creatine kinase levels are lower in BMD (~4-70x normal) than in ambulant Duchenne muscular dystrophy (~10–250x normal) patients, yet are still higher than the CK levels found in healthy boys (Pearce 1964, Zatz 1991, Aston 1984, Zhang 2012). This serum CK elevation starts before clinical symptoms develop and levels gradually decrease with age as a result of the progressive elimination of dystrophic muscle fibers that are the source of the elevated serum CK levels (Zatz 1991). Serum CK levels decreased in patients treated with 6 mg/kg drisapersen compared with placebo in the 3 placebo-controlled studies. The reduction in serum CK upon drisapersen treatment (n=18) was significantly different from placebo (n=18) in Study 117 at 24 weeks (p=0.049**)** **(**Figure 3.2.4.1). In Study 876, the CK reduction measured was not significant, yet the data are limited to 13 of 16 patients in the placebo-treatment group and to 16 of 18 patients in the drisapersen-treatment group (Figure 3.2.4.2**)**. In Study 044, in which a larger number of patients were studied, a statistically significance difference was observed:

48% decrease from baseline (-5270 IU/L, n=118) for 6 mg/kg/wk drisapersen versus a 10% decrease from baseline (-1230 IU/L, n=60) for placebo (p<0.001) (Figure 3.2.4.3). The loss of degenerating muscle fibers with age helps explain the gradual CK level decrease seen in placebo patients over time.

Likewise, LDH levels decreased more with drisapersen treatment compared with placebo treatment as shown for Study 044 in Figure 3.2.4.6. Several studies have shown that LDH is elevated in serum of patients with Duchenne muscular dystrophy compared with healthy controls (Somer 1973, Yasmineh 1978, Pearson 1965, Hathout 2015). LDH isoform expression has been shown to be dysregulated in muscle from patients with Duchenne muscular dystrophy (Yasmineh 1978, Pearson 1965) and LDH in circulation is a marker of muscle damage. LDH reduction in the drisapersen group was significantly different from placebo in Study 117 at 24 and 48 weeks of treatment (p=0.002, 0.019, respectively) (Figure 3.2.4.4). In Study 876, the difference was not significant, perhaps again reflecting the small sample sizes (

Figure 3.2.4.5). A larger number of patients were studied in Study 044 and serum LDH reduction reached statistical significance compared to placebo as early as 12 weeks. The difference remained significant at 24 and 48 weeks (p<0.001).

Figure 3.2.4.1: Mean Serum Creatine Kinase Levels in Study 117

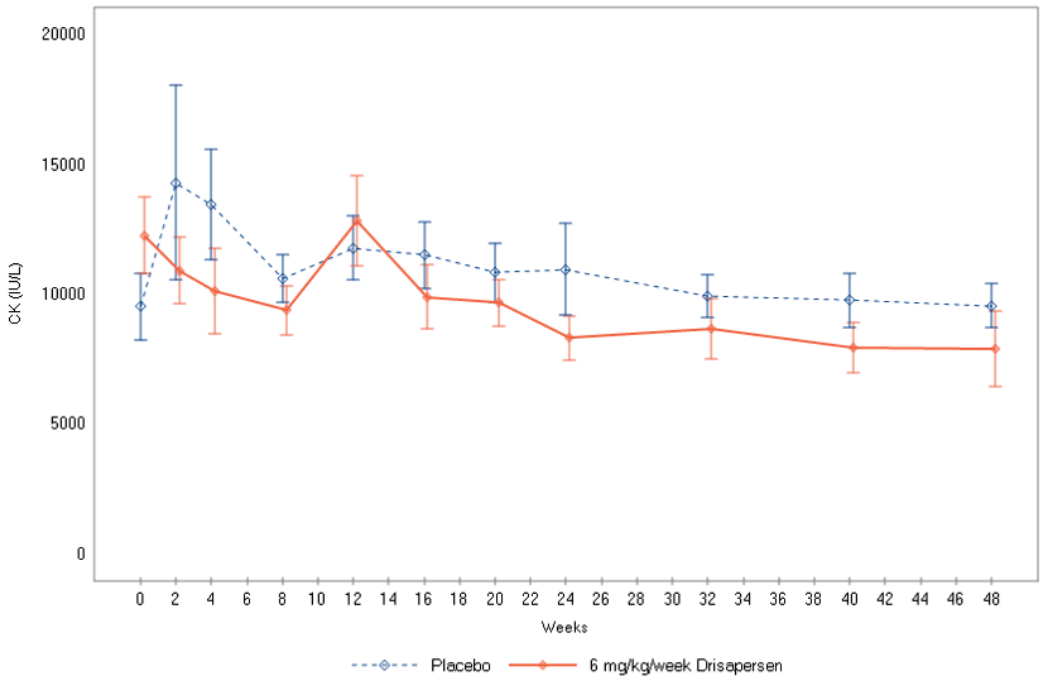


Figure 3.2.4.2: Mean Serum Creatine Kinase Levels in Study 876

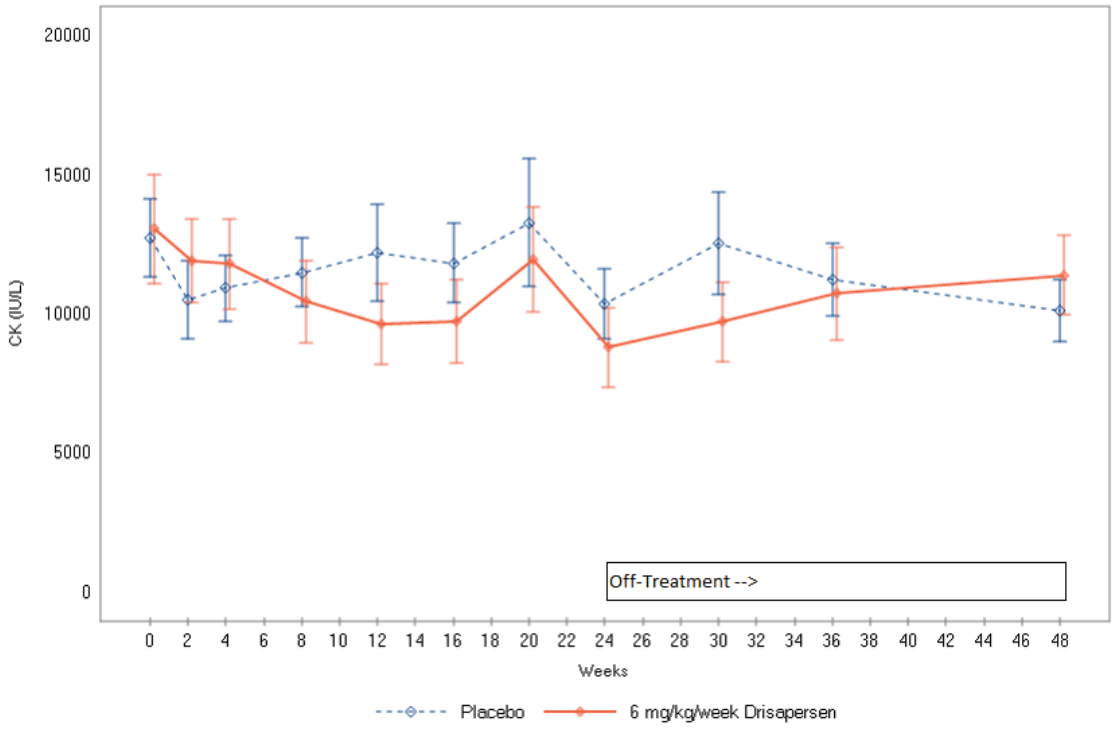


Figure 3.2.4.3: Mean Serum Creatine Kinase Levels in Study 044

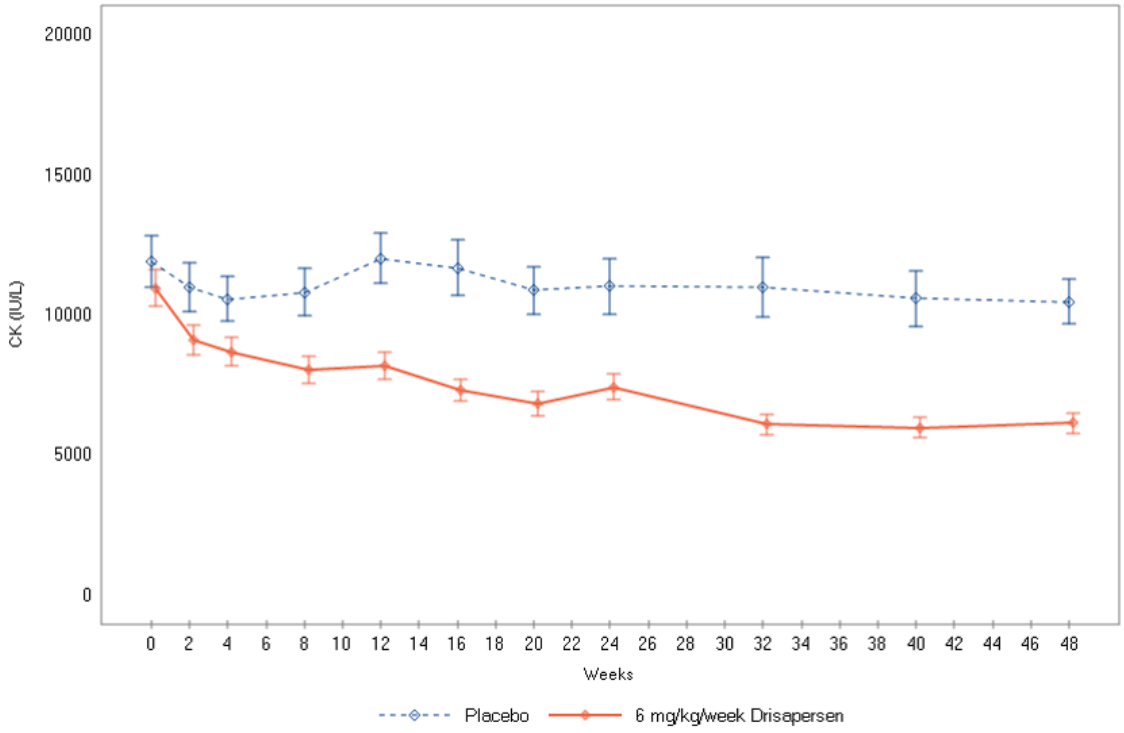


Figure 3.2.4.4: Mean Serum LDH Levels in Study 117

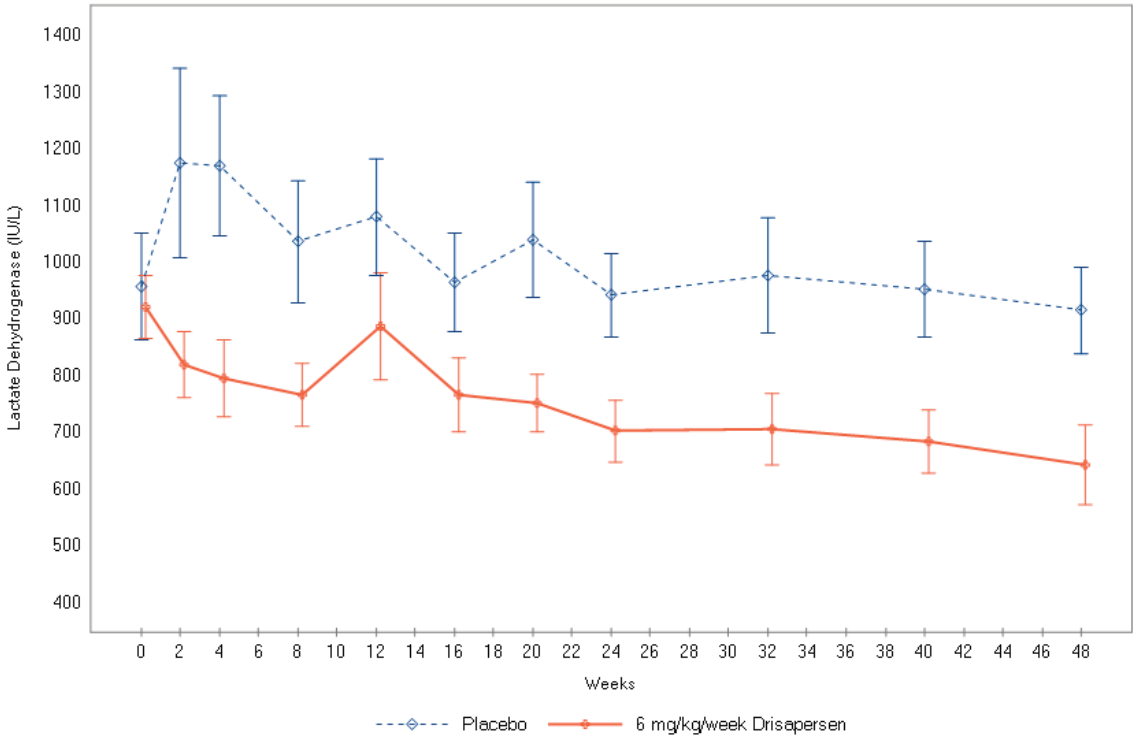


Figure 3.2.4.5: Mean Serum LDH Levels in Study 876

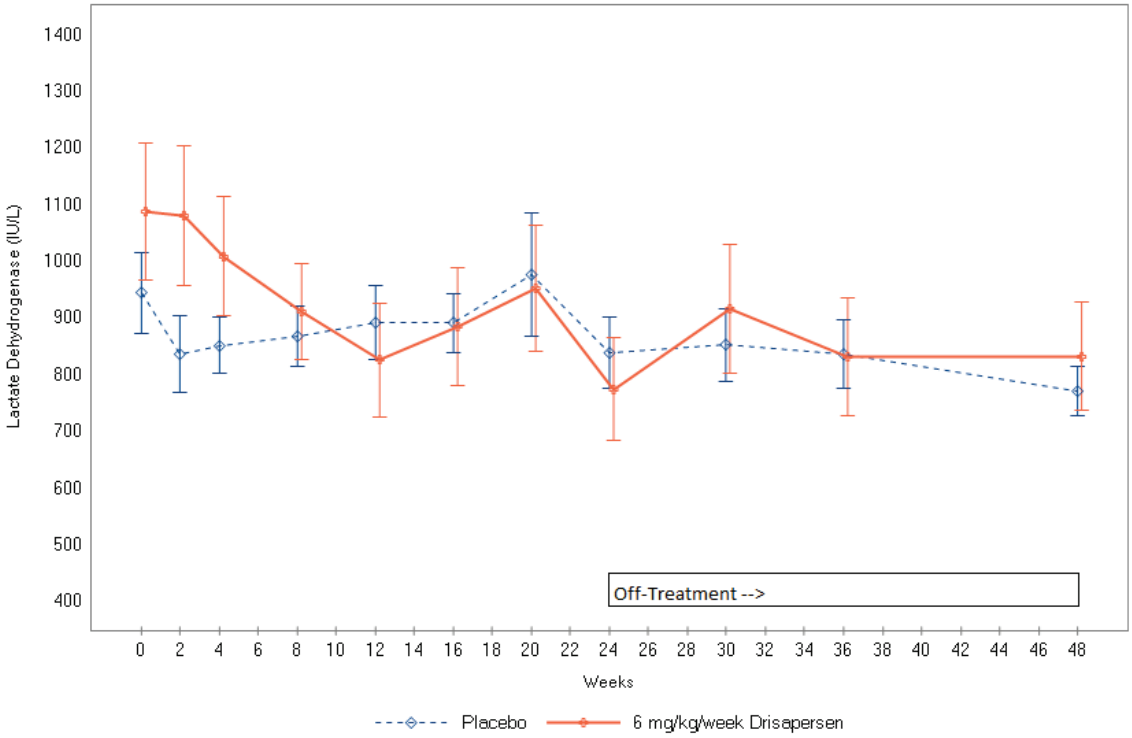
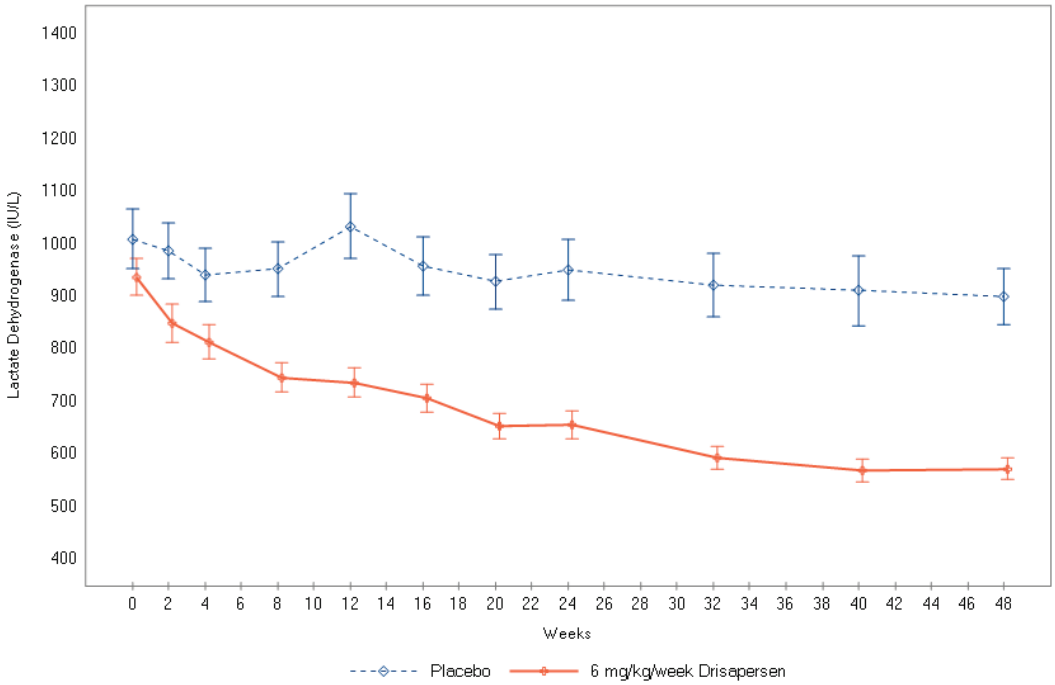


Figure 3.2.4.6: Mean Serum LDH Levels in Study 044

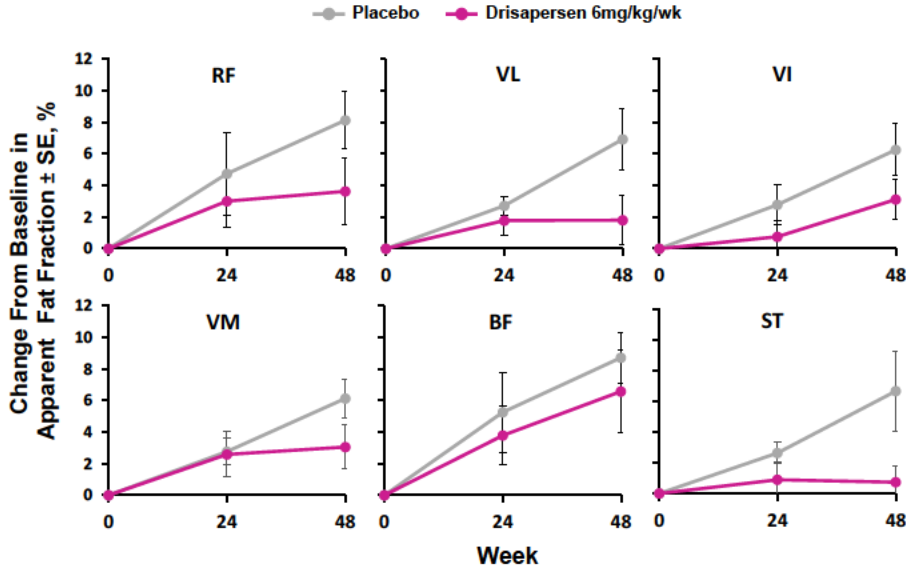


Taken together, these results are strongly indicative of improved muscle fiber integrity in drisapersen-treated patients.

3.2.5 MRI Assessments

In an exploratory substudy of Study 876, improvements in muscle structure after drisapersen treatment were evaluated by MRI. Six different thigh muscles in 6 patients treated with drisapersen and 6 treated with placebo were assessed by MRI at baseline, 24 weeks after start of treatment, and 24 weeks after the last treatment (Week 48). The normalized T2-weighted signal (indicative of edema and inflammation) showed an increase from baseline in patients given placebo and a noticeable decrease in the 6 mg/kg/wk drisapersen-treated patients (range of T2-weighted signal in 6 muscles was 0.07 to 0.14 [n=10] and -0.07 to -0.23 [n=14], respectively). Also, a slower progression from baseline across the 6 muscles in apparent fat fraction (AFF), a marker of Duchenne muscular dystrophy progression (Gaeta 2012), was observed in patients treated with drisapersen (Figure 3.2.5.1). In placebo patients, the AFF increased to 2.7–5.2% (n=5) for the 6 muscles, and decreased to 0.9–3.8% (n=6) for patients receiving drisapersen 6 mg/kg/wk with an approximately 50% overall reduction in the fat fraction. In general, these effects persisted up to 24 weeks post-treatment. Slow elimination of drisapersen from muscle tissue may have contributed to this prolonged effect.

Figure 3.2.5.1: Rate of Fat Infiltration in Muscles from Patients in Study 876



SE, standard error. 6 muscle groups were examined: BF, bicep femoris; RF, rectus femoris; ST, semitendinosus; VL, vastus lateralis; VI, vastus intermedius; VM, vastus medialis. Apparent fat fraction determined for all patients with evaluable data at each visit; placebo group n=5 and 5; 6 mg/kg/wk group n=6 and 5 at Week 24 and 48, respectively.

3.3 Drug-Drug Interactions

Similar to other second-generation antisense oligonucleotides in previously reported in vitro studies is not expected to be a substrate of CYP450 enzymes, and indeed drisapersen did not inhibit or induce cytochrome P450 (CYP450) enzymes in vitro in human hepatocytes and. Clinical studies evaluating potential metabolic-based drug-drug interactions of drisapersen with concomitant medications were not conducted or deemed warranted.

Although plasma protein binding is high for drisapersen, no drug-drug interaction is expected because the reported binding of similar oligonucleotides has been relatively weak (Kd ~ µM); the binding sites for these hydrophilic oligonucleotides differ from those of low-molecular-weight hydrophobic compounds; and little saturation of binding would be expected to occur at the peak plasma concentration of drisapersen (low µM range), which is well below those of plasma proteins such as albumin (~600 µM).

The probability of pharmacodynamic drug-drug interactions is also low. The drisapersen sequence is highly specific, reducing the likelihood of molecular interactions with other molecules acting on RNA. Due to its size and charge, drisapersen is unlikely to interact with the cell-surface and intracellular receptors of co-medications, such as corticosteroids.

Phosphorothioate oligonucleotides can cause transient prolongation of activated partial thromboplastin time (aPTT) at high plasma concentrations and also decrease platelet count; therefore, the use of anticoagulant drugs has been an exclusion criterion in clinical studies. Concomitant use of anticoagulants, thrombolytics, or other antiplatelet agents by patients taking drisapersen is not recommended.

3.4 Dose Rationale

The drisapersen 6 mg/kg/wk dose was chosen as the primary dose for the placebo-controlled studies based on nonclinical modelling and findings from study PRO051-02, which tested doses of 0.5–6 mg/kg/wk. A dose-proportional increase was shown for C_{max} and AUC parameters. Because of the long term stability of drisapersen in tissue, exposure in muscle tissue was expected to further increase with continuous weekly dosing, so higher doses were not explored in this study. In Study 118 with nonambulant patients, single doses of 3 and 6 mg/kg SC did not result in significant safety concerns, but tolerability issues were reported for 9 mg/kg.

The drisapersen tissue PK profile supports weekly dosing. The majority of drisapersen plasma exposure occurs during the first 24 hours after SC injection and the C_{max} remains similar after repeated dosing. However, plasma trough concentrations increase, which indicates continuous tissue exposure during the 1-week dose interval and accumulation of drisapersen in tissues. Muscle homogenates showed increasing levels of drisapersen and maximum levels were measured between 36 and 48 weeks after weekly 6 mg/kg SC injections. A long tissue elimination half-life was also suggested from tissue results in Study 876; tissue levels declined by less than half in 12 weeks without treatment. This slow decrease in muscle exposure off-treatment contributed to maintenance of effects. Intervals longer than 1 week combined with higher dose levels have not been evaluated due to limitations in injectable volume by SC administration.

In Study 876, patients receiving the 3 mg/kg dose had numerically worse 6-minute walk distance (6MWD) results than placebo at Week 24 with additional decline off treatment. The muscle tissue exposure between the dose groups was also well separated: drisapersen tissue levels were 6.3–13.4 µg/g (for the first and third quartile) for 6 mg/kg compared with 1.4–3.1 µg/g for 3 mg/kg at Week 24. The differing clinical response can be explained by a low exposure at 3 mg/kg within the 24-week treatment period.

The exposures and tissue concentrations of drisapersen did not differ significantly between the intermittent and continuous 6 mg/kg dosing regimens in Study 117. The drisapersen intermittent group did not separate from the placebo group at Week 24, had less improvement than the drisapersen continuous arm at Week 48, and showed a response similar to the placebo group at Week 96.

In Study 117, a loading dose regimen of twice-weekly dosing for the first 3 weeks was administered for faster tissue accumulation, and the continuous treatment arm demonstrated a significant change in 6MWD compared with placebo at 24 weeks.

Based on the results of the Phase II and Phase III studies showing treatment differences in 6MWD with drisapersen compared with placebo, an acceptable safety profile, the potential added benefit shown in patients who received the loading dose, and the lack of a treatment effect with the 3 mg/kg dosing regimens, the proposed dose of drisapersen for patients with Duchenne muscular dystrophy is a loading dose (3 weeks of twice weekly 6 mg/kg), followed by drisapersen 6 mg/kg/wk.

4 EFFICACY

Overall, the totality of the efficacy data from the drisapersen clinical program provides substantial evidence of the benefit of drisapersen 6 mg/kg/wk SC treatment for up to three and a half years in boys with Duchenne muscular dystrophy. In all studies conducted to date, the results indicated a treatment difference in favor of drisapersen on the 6MWD, the primary measure of ambulatory function. Results of the randomized placebo-controlled studies demonstrated additional treatment benefit in terms of ambulatory function; long-term extension study data showed durability of drisapersen efficacy; long-term follow-up data exhibited sustained efficacy and superiority over natural history controls; and supportive evidence was shown in a variety of secondary endpoints.

Of the 9 clinical studies of drisapersen (see Table 1.3.1.1), 5 investigated the efficacy of drisapersen SC in patients with Duchenne muscular dystrophy and are included in this efficacy summary. The 5 studies include 2 Phase II placebo-controlled studies (Studies 117 and 876), Phase III placebo-controlled Study 044, and 2 long-term extension studies (Studies 673 and 349). As can be seen from the study dates in Table 4.1, the studies were essentially implemented in parallel, not sequentially.

The primary objectives of the 3 placebo-controlled clinical studies were to assess the efficacy of:

- Continuous or intermittent dosing of drisapersen 6 mg/kg/wk SC versus placebo administered over 24 weeks in ambulant patients with Duchenne muscular dystrophy in Study 117. Efficacy over 48 weeks was a secondary objective of this study.
- 3 mg/kg/wk and 6 mg/kg/wk of drisapersen SC versus placebo administered over 24 weeks in ambulant patients with Duchenne muscular dystrophy in Study 876. Some efficacy measures were also assessed at Week 48, following 24 weeks with no drisapersen treatment.
- Drisapersen 6 mg/kg/wk SC versus placebo administered over 48 weeks in ambulant patients with Duchenne muscular dystrophy in Study 044.

The clinical development program focused on treatment of ambulant patients. Management of Duchenne muscular dystrophy aims for the highest possible levels of independent function, quality of life, and life expectancy; treatment prior to loss of ambulation offers the best opportunity to meet these goals.

Four studies were not included in the evaluation of efficacy. Proof-of-concept, single-dose study PRO051-01 did not investigate efficacy parameters. Although some efficacy variables were measured, dose-finding study PRO051-02 was uncontrolled, included a nonambulant patient, and few patients received the 6 mg/kg/wk dose. Study 118 was a single-dose, placebo-controlled study in nonambulant patients, which did not include evaluation of efficacy. Ongoing, open-label, long-term extension study DMD115501 enrolled 21 patients from Study 876, who had been on treatment for a maximum of 14 weeks when GSK suspended dosing in September 2013, well before the first scheduled efficacy assessments at Week 24.

Table 4.1: Clinical Studies of Efficacy of Drisapersen in Ambulatory Patients with Duchenne Muscular Dystrophy

Study	Study Objectives	Study Design	Study Dates / Status[a]
Placebo-controlled studies			
Phase II Study 117	Efficacy, tolerability, safety, PD, and PK	Double-blind, exploratory, randomized, parallel-group, placebo-controlled study	01 Sep 2010 – 12 Sep 2012 Completed
Phase II Study 876	Efficacy, tolerability, safety, PD, and PK	Double-blind, exploratory, randomized, parallel-group, placebo-controlled study	26 Oct 2011 – 04 Nov 2013 Completed
Phase III Study 044	Efficacy, tolerability, safety, PD, and PK	Double-blind, randomized, parallel-group, placebo-controlled study	02 Dec 2010 – 28 Jun 2013 Completed
Long-term extension studies			
Phase I/II Study 673	Long-term safety, efficacy, and PK	Open-label, uncontrolled extension study in patients who had completed PRO051-02	30 Jul 2009 – 25 Jun 2013 (interim CSR) Ongoing (no treatment)[a]
Phase III Study 349	Long-term safety, efficacy, and PK	Open-label, uncontrolled extension study in patients who completed the treatment phase in Studies 117 or 044	19 Sep 2011 – 17 Mar 2014 Terminated[b] (no dosing after 20 Sep 2013)

CSR, clinical study report; PD, pharmacodynamics; PK, pharmacokinetics.

[a] Status as of the cut-off date for preparation of efficacy summary (31 August 2014); dosing in Study 673 has subsequently been restarted.

[b] Dosing was suspended on 20 September 2013 and the study formally terminated on 17 March 2014.

4.1 Study Designs

The designs for the placebo-controlled studies are shown in Figure 4.1.1. All 3 studies were multicenter, randomized, double-blind, parallel-group, placebo-controlled studies in ambulant boys with Duchenne muscular dystrophy resulting from a mutation which could be corrected by exon 51 skipping. Study 044, with its greater sample size requirement, included a greater number and variety of sites and geographical regions than Studies 117 or 876.

Each study included a continuous drisapersen 6 mg/kg/wk treatment group. Patients were randomized 2:1 to drisapersen or placebo in these studies; for the Phase II studies, the randomization ratio was 2:1 within each cohort and the placebo groups were combined for analysis, resulting in a 1:1:1 ratio (2 active treatment arms and 1 combined placebo arm). Placebo consisted of vehicle alone and was volume matched to drisapersen dose. To maintain the blind with differing volumes between doses, the personnel who were responsible for preparation and administration of the doses were not involved in efficacy assessments.

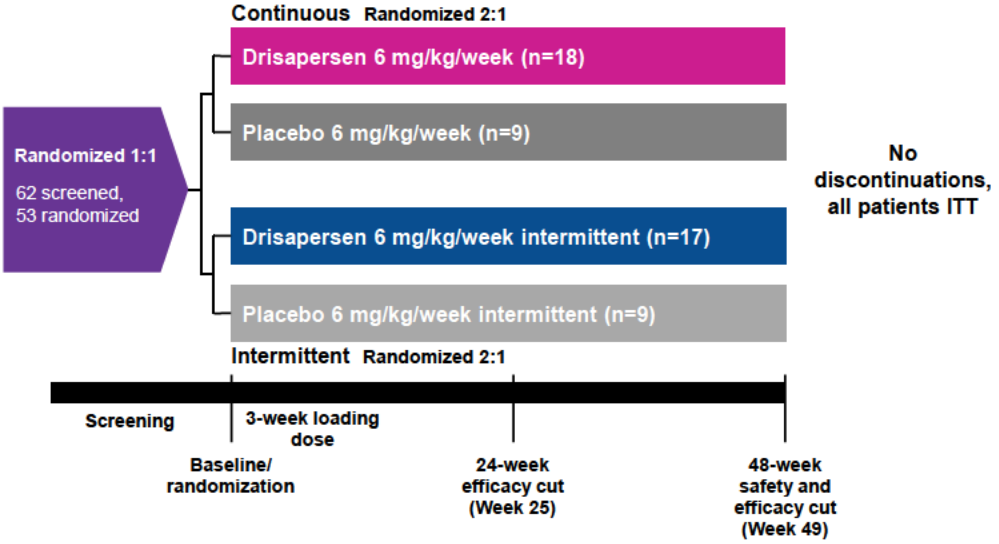
The study period of all 3 placebo-controlled studies was 48 weeks: patients received treatment for 48 weeks in Studies 117 and 044 and for 24 weeks followed by a 24-week post-treatment period in Study 876 during which no drug was administered. This post-treatment

phase was designed to model the half-life of dystrophin, assess maintenance of response, and provide information about resolution of adverse events (AEs) and laboratory abnormalities following cessation of treatment.

Only Study 117 included a loading dose regimen of twice-weekly dosing with 6 mg/kg drisapersen (or volume matched placebo) for the first 3 weeks of treatment. Thereafter, patients received their once-weekly regimen based on their assigned treatment group.

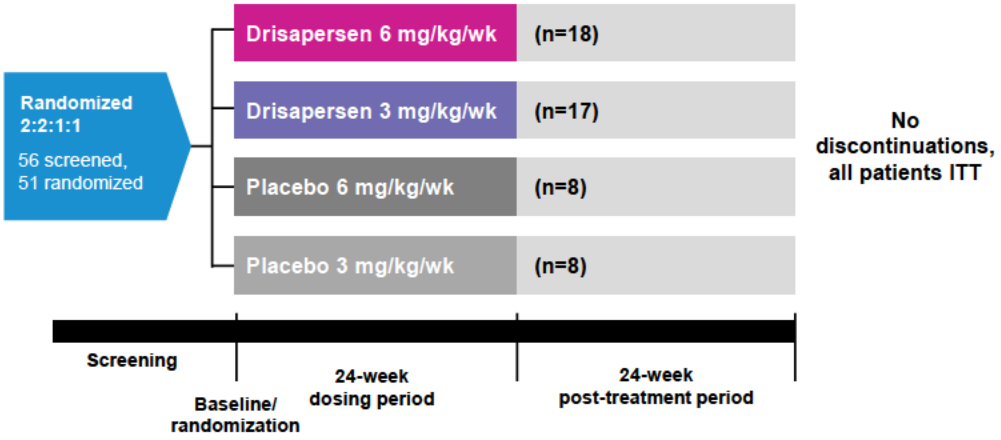
Figure 4.1.1: Designs of Placebo-Controlled Studies

Study 117



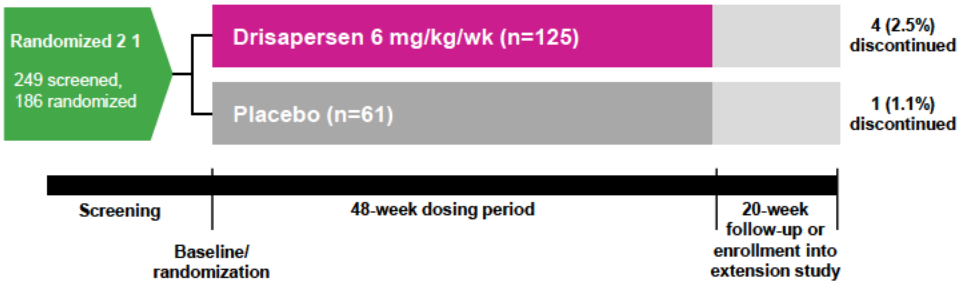
ITT, intent-to-treat.
All patients received a loading dosing regimen of twice weekly dosing with drisapersen 6 mg/kg for the first 3 weeks of treatment only. Study conducted in 13 centers in 9 EU countries.
Intermittent dosing: 10-week cycles of twice-weekly dosing in 1st, 3rd, and 5th weeks, once-weekly dosing in 2nd, 4th, and 6th weeks, no dosing in 7th to 10th weeks.

Study 876



ITT, intent-to-treat.
Study conducted in 13 centers in the US.

Study 044



ITT, intent-to-treat.
Study conducted in 44 centers in 19 ex-US countries.

4.2 Sample Size Determinations

The planned enrollment of 54 patients in both Study 117 and Study 876, allowing for 10% dropout, was considered appropriate for PK analysis and indication of trends in safety and efficacy.

Study 044 was designed to have sufficient power to show a treatment effect for drisapersen compared with placebo. With a 10% dropout rate from the planned 180 patients, 162 evaluable patients, allocated 2:1 for drisapersen to placebo, would provide 90% power to detect a difference in the mean change from baseline 6MWD of 30 meters between drisapersen and placebo with a common standard deviation of 55 meters (effect size 0.545 using a 2 group t-test with a 0.05 two-sided significance level).

4.3 Key Eligibility Criteria

Key eligibility criteria for the placebo-controlled studies included ambulant male patients aged ≥5 years, a life expectancy of ≥1 year, and Duchenne muscular dystrophy resulting from a confirmed dystrophin gene mutation, potentially correctable by drisapersen-induced exon 51 skipping.

All patients were receiving corticosteroids (continuous or intermittent regimens) for ≥6 months prior to screening, with no significant change in total daily dosage or dosing regimen for ≥3 months. Enrolled patients continued use of corticosteroids with an expectation for continued treatment for the duration of the study. Changes to their regimen were at the discretion of the principal investigator in consultation with the patient/parent and the medical monitor.

Available natural history data and ongoing open-label Study 673 informed the design of all 3 placebo-controlled studies. The natural cohort data suggested that setting an eligibility criterion for baseline 6MWD of ≥75 meters would minimize the loss of ambulation within a 1-year period (Mazzone 2011) and this minimum performance was an entry requirement for all 3 placebo-controlled studies. More recently published data indicate the risk for a precipitous loss of ambulatory function in patients with an absolute 6MWD of <325 meters and percent-predicted 6MWD of <50–55% (McDonald 2013c), a distance much greater than the 75 meter inclusion threshold for the drisapersen studies. Other recently published studies have confirmed that baseline 6MWD <330 or <350 meters predicts loss of ambulation (Mazzone 2013, Pane 2014).

In Studies 117 and 876, an additional eligibility criterion of ≤7 seconds for rise-from-the-floor performance was required based on observations from the long-term Study 673. This criterion was later amended to ≤15 seconds in Study 876; however, only 2 enrolled patients, 1 each in the 3 mg- and 6-mg/kg/wk treatment groups, had times >7 seconds. A minimal rise-from-the-floor performance was not required in Study 044; this less stringent criteria enabled a greater number of patients to enroll, in order to power the study, but also resulted in a population that was older and functionally more impaired compared with Studies 117 and 876, including more patients who were already in the decline phase of their ambulatory capacity.

4.4 Study Populations

As a result of the eligibility criteria differences, patient populations in Studies 117 and 876 differed from Study 044, as shown in the baseline demographic characteristics summarized in Table 4.4.1. The mean age was 7.8 years with median (range) of 8 years (5–11) in Study 117, and 7.3 years with median of 7 years (5–13) in Study 876. Patients in Study 044 study were older, with a mean age of 8.2 years and median (range) of 8 years (5–16). In Study 044, 3 patients in the placebo group and 8 patients in the drisapersen group were aged ≥13 years, which exceeds the range of the Study 117 and at minimum matches the oldest patients in the range for the Study 876.

Table 4.4.1: Baseline Demographic Characteristics of Placebo-Controlled Studies (Safety Populations)

	Phase II Study 117			Phase II Study 876			Phase III Study 044	
	Placebo (Combined) (n=18)	**Drisapersen 6 mg/kg/wk (n=18)**	**Drisapersen 6 mg/kg Intermittent (n=17)**	**Placebo (Combined) (n=16)**	**Drisapersen 3 mg/kg/wk (n=17)**	**Drisapersen 6 mg/kg/wk (n=18)**	**Placebo (n=61)**	**Drisapersen 6 mg/kg/wk (n=125)**
Age, years								
Mean ± SD	6.9 ± 1.18	7.2 ± 1.66	7.7 ± 1.49	8.0 ± 1.79	7.8 ± 1.91	7.6 ± 2.70	8.0 ± 2.37	8.3 ± 2.43
Median (min, max)	7.0 (5, 9)	6.5 (5, 11)	8.0 (5, 10)	8.0 (5, 11)	8.0 (5, 11)	6.5 (5,13)	8.0 (5, 16)	8.0 (5, 16)
Sex, n (%)								
Male	18 (100)	18 (100)	17 (100)	16 (100)	17 (100)	18 (100)	61 (100)	125 (100)
Ethnicity, n (%) [a]								
n	16	17	15	16	17	18	61	125
Hispanic/Latino	0	0	1 (7)	4 (25)	1 (6)	1 (6)	10 (16)	23 (18)
Non-Hispanic/Latino	16 (100)	17 (100)	14 (93)	12 (75)	16 (94)	17 (94)	51 (84)	102 (82)
Race, n (%) [a]								
n	16	17	15	16	17	18	61	125
African American/African heritage	0	0	0	1 (6)	1 (6)	1 (6)	1 (2)	0
American Indian/Alaskan Native	0	0	1 (7)	0	0	0	0	0
Asian, Central/South Asian heritage	0	0	0	0	0	0	1 (2)	3 (2)
Asian, East Asian heritage	0	0	0	0	0	1 (6)	3 (5)	6 (5)
Asian, Japanese heritage	0	0	0	0	0	0	5 (8)	9 (7)
Asian, South East Asian heritage	1 (6)	0	0	0	0	1 (6)	0	2 (2)
Native Hawaiian/Pacific Islander	1 (6)	0	0	0	0	0	0	0
White, Arabic/North African heritage	0	2 (12)	0	0	0	0	4 (7)	5 (4)
White, Caucasian/European heritage	13 (81)	15 (88)	14 (93)	14 (88)	16 (94)	15 (83)	46 (75)	95 (76)
White, mixed race	0	0	0	0	0	0	0	1 (<1)
Mixed race	1 (6)	0	0	1 (6)	0	0	1 (2)	4 (3)
Height, cm								
Mean ± SD	118.69 ± 8.14	118.42 ± 10.46	120.60 ± 10.27	122.65 ± 6.43	119.76 ± 8.11	120.40 ± 13.51	122.03 ± 9.58	123.96 ± 10.78
Median (min, max)	119.50 (98.5, 132.0)	119.05 (102.0, 139.0)	119.50 (105.6, 139.0)	122.25 (109.0, 133.3)	120.00 (101.5, 130.0)	116.80 (100.5, 146.0)	122.00 (101.6, 145.0)	122.60 (100.7, 148.0)
Weight, kg								
Mean ± SD	25.03 ± 5.23	25.05 ± 7.39	28.39 ± 9.81	30.23 ± 8.53	28.91 ± 6.49	29.51 ± 12.53	26.86 ± 7.58	30.06 ± 10.25
Median (min, max)	24.25 (15.5, 34.5)	23.20 (16.0, 41.5)	26.40 (18.0, 51.4)	28.20 (18.6, 50.5)	31.30 (18.2, 41.5)	24.85 (16.9, 64.5)	24.50 (16.8, 45.9)	27.00 (17.0, 68.2)

SD, standard deviation.

[a] Race and ethnicity were not collected in Study 117 for patients from France per country-specific clinical trial guideline.

As shown in Table 4.4.2, the baseline disease characteristics of patients in Studies 117 and 876 were similar in terms of time since diagnosis and time since the start of steroid treatment. For patients in Study 044, time since first symptoms and diagnosis were generally longer than in Studies 117 and 876, whereas time since first steroid treatment was roughly similar.

Fewer patients in Study 117 received a continuous regimen of corticosteroids (53–67%) than in Study 876 (88–100%) or Study 044 (85–86%).

On average, patients in Study 044 had more functional impairment than in the other studies, partially due to the differing inclusion criteria. The mean 6MWD across all patients in Study 044 was 341 ± standard deviation (SD) of 94.4 meters (range 107–566 meters) compared with 409 ± 62 meters, (range 238–561 meters) and 409 ± 58.3 meters (range 298–532 meters) in Studies 117 and 876, respectively. The minimum baseline 6MWD in Study 044, 107 meters, was much lower than the lowest baseline 6MWD in either Study 117 or 876 (238 meters), and 6 of 61 patients (9.8%) in the placebo group and 19 of 125 patients (15.2%) in the drisapersen group in Study 044 had an equally low or lower baseline 6MWD than the Phase II minimum baseline 6MWD.

Average baseline rise-from-the-floor time was also notably longer in Study 044 than Studies 117 and 876. More drisapersen-treated patients (19/125, 15.2%) in Study 044 could not complete the rise-from-the-floor test at baseline compared with placebo-treated patients (6/61, 9.8%). The average rise-from-the-floor results are reported only for patients who could complete the test.

All patients in all studies had Duchenne muscular dystrophy confirmed by genetic testing with no major differences observed between the studies with respect to the distribution of patients by exon mutation.

Table 4.4.2: Baseline Disease Characteristics of Placebo-Controlled Studies (Safety Populations)

	Phase II Study 117			Phase II Study 876			Phase III Study 044	
	Placebo (Combined) (n=18)	**Drisapersen 6 mg/kg/wk (n=18)**	**Drisapersen 6 mg/kg Intermittent (n=17)**	**Placebo (Combined) (n=16)**	**Drisapersen 3 mg/kg/wk (n=17)**	**Drisapersen 6 mg/kg/wk (n=18)**	**Placebo (n=61)**	**Drisapersen 6 mg/kg/wk (n=125)**
Time since first symptoms, months[a]								
n	18	18	17	16	17	18	58	122
Mean ± SD	63.5 ± 24.00	61.1 ± 24.86	64.5 ± 24.56	57.3 ± 29.68	67.3 ± 27.13	59.0 ± 29.50	66.7 ± 31.30	71.8 ± 31.58
Median (min, max)	73.3 (15, 95)	57.4 (27, 112)	63.1 (27, 105)	59.6 (13, 112)	60.4 (25, 124)	60.0 (8, 112)	60.8 (11, 168)	70.2 (12, 176)
Time since diagnosis, months[a]								
Mean ± SD	44.4 ± 21.61	44.6 ± 27.69	47.8 ± 26.48	45.5 ± 29.70	47.1 ± 26.35	46.5 ± 26.76	54.2 ± 32.84	58.0 ± 35.16
Median (min, max)	35.5 (12, 82)	41.4 (3, 96)	47.0 (3, 105)	44.5 (9, 111)	38.3 (13, 108)	46.2 (7, 96)	49.8 (6, 148)	54.5 (6, 163)
Time since first corticosteroid taken, months[a]								
Mean ± SD	24.2 ± 14.02	26.0 ± 21.20	32.6 ± 17.04	37.1 ± 24.31	33.3 ± 15.98	26.8 ± 22.51	29.1 ± 25.77	35.6 ± 28.99
Median (min, max)	22.5 (7, 60)	13.7 (7, 69)	33.8 (7, 63)	38.9 (7, 85)	28.0 (8, 58)	18.5 (6, 81)	18.9 (7, 135)	26.6 (6, 146)
Corticosteroid regimen, n (%)[b]								
Continuous	11 (61)	12 (67)	9 (53)	15 (94)	15 (88)	18 (100)	52 (85)	108 (86)
Intermittent	7 (39)	6 (33)	8 (47)	1 (6)	2 (12)	0	9 (15)	17 (14)
Baseline 6MWD, meters								
Mean ± SD	403.18 ± 45.13	427.61 ± 70.05	394.57 ± 66.95	416.41 ± 56.99	415.21 ± 58.05	396.18 ± 60.66	348.00 ± 92.15	337.46 ± 95.59
Median (min, max)	400.00 (322.0, 489.3)	425.00 (323.0, 561.0)	381.00 (237.8, 540.5)	420.00 (298.0, 525.0)	403.00 (314.0, 514.0)	396.00 (301.0, 532.0)	354.00 (108.0, 566.0)	349.00 (107.0, 525.0)
Baseline rise from floor time, seconds								
n	18	18	17	16	17	18	55[d]	106[d]
Mean ± SD	4.67 ± 1.018	4.83 ± 1.627	5.79 ± 2.917	4.49 ± 1.617	4.96 ± 2.214	5.19 ± 2.465	13.41 ± 15.882	12.34 ± 14.984
Median (min, max)	4.55(3.0, 7.0)	4.40 (3.2, 8.6)	5.70 (2.8, 15.9)	3.90 (2.6, 7.5)	4.70 (2.6, 9.7)	4.60 (2.9, 12.5)	6.80 (0.5, 63.0)	6.60 (2.7, 105.0)
Method of diagnosis, n (%)[c]								
Clinical symptoms	8 (44)	11 (61)	9 (53)	8 (50)	10 (59)	11 (61)	56 (92)	110 (88)
Muscle biopsy	4 (22)	5 (28)	4 (24)	0	1 (6)	3 (17)	21 (34)	47 (38)
Genetic testing	18 (100)	18 (100)	17 (100)	16 (100)	17 (100)	18 (100)	61 (100)	125 (100)
Comparative genomic hybridization	0	0	0	1 (6)	3 (18)	2 (11)	0	7 (6)
Multiplex ligation-dependent probe amplification	17 (94)	16 (89)	12 (71)	14 (88)	10 (59)	13 (72)	59 (97)	117 (94)

	Phase II Study 117			Phase II Study 876			Phase III Study 044	
	Placebo (Combined) (n=18)	**Drisapersen 6 mg/kg/wk (n=18)**	**Drisapersen 6 mg/kg Intermittent (n=17)**	**Placebo (Combined) (n=16)**	**Drisapersen 3 mg/kg/wk (n=17)**	**Drisapersen 6 mg/kg/wk (n=18)**	**Placebo (n=61)**	**Drisapersen 6 mg/kg/wk (n=125)**
Single condition amplification/ internal primer	0	1 (6)	1 (6)	1 (6)	4 (24)	3 (17)	1 (2)	1 (<1)
Other	1 (6)	1 (6)	4 (24)	0	0	0	1 (2)	0
Exon mutation, n (%)								
DMD 43–50 deletion	0	0	0	0	0	1 (6)	0	0
DMD 45–50 deletion	7 (39)	6 (33)	5 (29)	9 (56)	4 (24)	4 (22)	16 (26)	40 (32)
DMD 47–50 deletion	0	0	0	1 (6)	0	0	1 (2)	0
DMD 48–50 deletion	3 (17)	6 (33)	6 (35)	4 (25)	5 (29)	3 (17)	7 (11)	26 (21)
DMD 49–50 deletion	1 (6)	4 (22)	3 (18)	1 (6)	5 (29)	6 (33)	20 (33)	31 (25)
DMD 50 deletion	4 (22)	1 (6)	3 (18)	1 (6)	2 (12)	1 (6)	5 (8)	11 (9)
DMD 52 deletion	3 (17)	1 (6)	0	0	1 (6)	3 (17)	10 (16)	16 (13)
Other	0	0	0	0	0	0	2 (3)	1 (<1)

6MWD, 6-minute walk distance in meters; DMD, Duchenne muscular dystrophy; SD, standard deviation.

[a] Date of first dose used to calculate number of months for each patient.

[b] Corticosteroid regimen identified by clinical review (for Studies 117 and 876, during first 24 weeks of the study).

[c] Patients could have more than 1 method of diagnosis and, therefore, numbers may not add up to the treatment total.

[d] Rise-from-the-floor test in Study 044 only included patients who were physically able to perform the test.

4.5 Efficacy Endpoints

The primary and secondary endpoints for the placebo-controlled trials are shown in Table 4.5.1.

Table 4.5.1: Primary and Secondary Efficacy Endpoints Assessed in Placebo-Controlled Studies

	Phase II Study 117	Phase II Study 876	Phase III Study 044
Primary efficacy endpoint			
Change from baseline at Wk 24 in the 6MWD[a]	X	X	X[b]
Change from baseline at Wk 48 in the 6MWD	X[b]		X
Secondary efficacy endpoints			
Change from baseline in rise-from-the-floor time[c]	X	X	X
Change from baseline in 10 meter walk/run time[c]	X	X	X
Change from baseline in 4-stair climb/ascent time[c]	X	X	X
Change from baseline in 4-stair climb/descent time[c]	X	X	X
Change from baseline in the North Star Ambulatory Assessment total score[d]	X	X	X
Change from baseline in muscle strength total score[e]	X	X	X
Change from baseline in pulmonary function parameters[f]	X	X	X
Change from baseline in serum creatine kinase concentrations	X	X	X
Frequency of accidental falls during 6MWD	X	X	X
Time to loss of ambulation	X	X	X
PedsQL™ Neuromuscular Module	X[g]		X
Clinician Global Impression of Improvement		X	X
Health Utilities Index			X
Functional Outcomes Survey		X	
Dystrophin expression/Exon 51 skipping (muscle biopsies)[h]	X	X	X

6MWD, 6-minute walk distance in meters; PedsQL™, Pediatric Quality of Life.

The primary endpoint is bolded for each study.

[a] The primary time points of interest were Wk 48 in Study 044 and Wk 24 in Studies 117 and 876. Note that Week 24 and Week 25 represent the same duration of treatment (ie, after 24 weeks of treatment), because the naming conventions were different across studies.

[b] Changes from baseline in 6MWD at Wk 48 in Study 117 and at Wk 24 in Study 044 were also evaluated, but not specified as a primary or secondary endpoint.

[c] Timed function tests and grading were performed for all 3 studies; times in Study 044 (for all timed function tests except rise from floor) were converted to velocities.

[d] North Star Ambulatory Assessment (NSAA) total scores were transformed to a linearized scale in Study 044.

[e] Knee flexors, knee extensors, elbow flexors, elbow extensors, shoulder abductors, and hip flexors, as determined by handheld myometry using a microFET2 myometer.

[f] Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), peak cough flow (PCF), peak flow (PF); in Study 117, also maximum inspiratory pressure (MIP) and maximum expiratory pressure (MEP).

[g] PedsQL™ Neuromuscular Module was an exploratory endpoint in Study 117.

[h] No baseline biopsies were taken in Study 044.

4.5.1 6MWD as the Primary Endpoint

Given the heterogeneity of further disease progression and lack of sensitive endpoints to measure treatment benefit, the primary focus of the development program was based on 6MWD tests. The efficacy of drisapersen was examined in the ambulatory Duchenne muscular dystrophy population using mean change from baseline 6MWD as the primary endpoint assessment. The 6MWD is a measure of integrated function that is dependent on respiratory, cardiovascular, and nutritional status, as well as skeletal muscle function. A modified version of the 6-minute walk test is used specifically for younger children with Duchenne muscular dystrophy (McDonald 2010b, Henricson 2012). Patients were asked to walk, as quickly and safely as possible, back and forth across a fixed distance until told to stop after 6 minutes. The patients were warned periodically of the time and could stop earlier if necessary. The total distance walked within 6 minutes (or until the patient stopped in case of early termination of the test) was recorded in meters; any falls while walking were also recorded.

Baseline 6MWD is an important predictor of subsequent ambulatory status in patients with Duchenne muscular dystrophy; incremental decreases in baseline 6MWD are correlated with an increased likelihood for future loss of ambulation (Mazzone 2013). 6MWD has been shown to correlate with patient reported outcomes and also shows that smaller levels of change are associated with meaningful patient benefits as walking impairment progresses (Henricson 2013b). Thus, the 6MWD test respresents a functional benefit that is tangibly meaningful to patients, over a wide range of ambulatory capacity. McDonald demonstrated that 6MWD is more sensitive to detect change in functional status in patients with Duchenne muscular dystrophy compared with other commonly used timed function assessments (McDonald 2010b).

Even small improvements in the 6MWD are relevant for patients affected with Duchenne muscular dystrophy. The minimal clinically important difference (MCID) for 6MWD has been defined as 30 meters or around 8% improvement over baseline (McDonald 2013a); however, this is only based on statistical calculations using a broad cohort of patients. Improvements of less than 30 meters are clinically meaningful and relevant for patients with poor baseline functioning. Inclusion criteria for all 3 placebo-controlled trials allowed enrollment of patients with baseline 6MWD of as low as 75 meters. When combined distribution- and anchor-based approaches to determine minimally important differences are used, smaller increases or changes due to treatment in achievable walking distance are likely to result in meaningful changes in health-related quality of life (Henricson 2015). Recently, the 6MWD test was used to evaluate muscle function and endurance in other neuromuscular disorders and was successfully used as the primary endpoint for regulatory approval of therapies for neuromuscular and pulmonary disorders, such as Pompe disease (Wokke 2008, van der Ploeg 2010), mucopolysaccharidosis I (Wraith 2004, Clarke 2009), Hunter syndrome (Muenzer 2006), mucopolysaccharidosis IV type A (Hendriksz 2014), and pulmonary arterial hypertension (Rubin 2002, Suleman 2004).

Multiple published studies have recently documented the changes in the 6MWD in boys with Duchenne muscular dystrophy from clinical trial placebo populations (Mendell 2013,

McDonald 2013c) and natural history cohorts (McDonald 2010a, Mazzone 2011, Mazzone 2013, Goemans 2013, Henricson 2013a, Pane 2014) for periods of 24–156 weeks. Based on these data, a patient with Duchenne muscular dystrophy is expected to lose on average 40−60 meters of performance on the 6MWD in 1 year.

However, this decline is not consistent throughout a child's life. Growing boys with Duchenne muscular dystrophy maintain a stable or even improving 6MWD up to about 7 years of age. After age 7, these boys experience a significant decline in walking ability compared with healthy boys of the same age (Pane 2014). This pattern accords with the progressive replacement of healthy muscle with fat and fibrous tissue as boys with Duchenne muscular dystrophy age (Mazzone 2013, Pane 2014). As walking ability deteriorates, the 6MWD loses value as an appropriate endpoint due to its dependence on muscle tissue; other endpoints may provide more appropriate measures of therapeutic effect in these patients.

Natural history data of 6MWD in 96 ambulant boys aged 5–12 years over a 3-year period showed progressive deterioration in distance walked in meters that increased with each additional year and a corresponding effect of both age and baseline walking ability on disease outcomes over time (Pane 2014). Boys younger than 7 years showed some improvement in 6MWD for the first 2 years, which was not maintained in the third year (mean change from baseline 6MWD: +18.5 meters at 1 year, +34.11 meters at 2 years, and -2.9 meters at 3 years). In contrast, boys older than 7 years demonstrated progressive deterioration (mean change from baseline in 6MWD: -29.9 meters at 1 year, -97.3 meters at 2 years, and -146.0 meters at 3 years).

The 6MWD also showed a variable decrease according to the baseline value (Pane 2014). Boys with a baseline 6MWD <350 meters had a mean 3-year decrease of 160 meters, whereas boys with a baseline 6MWD ≥350 meters had a 3-year decrease of 74 meters.

When these prognostic factors are combined, patients can be classified into 4 groups depending on age and 6MWD at baseline: age < 7 years and 6MWD >350 meters; age < 7 years and 6MWD < 350 meters; age > 7 years and 6MWD > 350 meters; and age > 7 years and 6MWD <350 meters (Pane 2014). Changes in 6MWD were significantly different among the 4 groups at 3 years: an increase of 19.1 meters in patients with baseline age < 7 and 6MWD > 350, a decrease of 49.3 meters in patients with baseline age < 7 and 6MWD < 350 meters, a decrease of 115.0 meters in patients with baseline age > 7 and 6MWD > 350, and a decrease of 199.2 meters in patients with baseline age > 7 and 6MWD < 350. In the worst performing subgroup (baseline age > 7 and 6MWD < 350), 16 of the 25 patients lost ambulation by 3 years compared with a combined total of 8 of the 71 patients in the other 3 groups.

Sources of 6MWD Variability in Clinical Trials

In clinical trials in boys with Duchenne muscular dystrophy, the variability observed in 6MWD may reflect heterogeneity in ambulatory capacity and in rate of disease progression, both characteristic of patients in the age range typically studied as well as in studies with small sample sizes. In an observational study of 6MWD in boys aged 5–15 years with Duchenne muscular dystrophy (n=65), 50 random samples of 10 patients with data over 52

weeks (± 12 weeks) were analyzed to estimate variability in small samples (Goemans 2013). The mean change in 6MWD at 52 weeks in these 50 samples ranged from +2 meters to -78 meters (medians ranged from +18 meters to -62 meters; SD from 46 meters to 126 meters). Such variability must be taken into account in the design and interpretation of clinical trials.

Variability increases with disease progression. McDonald found that once ambulatory patients with Duchenne muscular dystrophy have progressed beyond a threshold 6MWD (<325 meters, or <55% predicted 6MWD), a high percentage will decline ≥10% in 6MWD performance or even lose ambulation in the next year (McDonald 2013c). The authors noted that increasing variability over time can be mitigated in clinical studies by choosing inclusion criteria that produce a more homogeneous population.

Inclusion of Patients Who Lose Ambulation in the Calculation of Change in 6MWD

An important consideration in analysis of change in 6MWD data is whether patients who lose ambulation are included, particularly in intent-to-treat (ITT) analyses and in comparisons with natural history controls. In natural history findings, analyses of change in 6MWD that exclude loss of ambulation data differ substantially from those that impute a value of 0 meters after ambulation is lost (personal communication, Dr. Eugenio Mercuri, April 2014). When patients with loss of ambulation are included, natural history data show greater decrements in 6MWD over time. If excluded, the change in 6MWD is notably less and disease progression appears to be slower. Unless otherwise indicated, patients with evidence of lost ambulation are included in the drisapersen analyses with imputed 6MWD values of 0 meters once ambulation is lost.

4.5.2 Secondary Endpoints

A range of secondary efficacy variables was assessed in the placebo-controlled Phase II and Phase III studies. These tests are commonly used for clinical evaluation and reflect the varying manifestations of the disorder, both through time and in the context of supportive therapy. Nevertheless, heterogeneity of disease progression, along with variations in corticosteroid and physical therapy regimens, make secondary endpoint measurement a challenge. The secondary measures included:

- Percent-predicted 6MWD
- Timed function tests (rise-from-the-floor, 10-meter walk/run, 4-stair ascent/descent)
- North Star Ambulatory Assessment (NSAA)
- Muscle strength testing
- Pulmonary function testing (forced vital capacity [FVC], percent-predicted FVC, etc.)
- Quality of life/functional outcomes testing (done using different instruments in different studies)

Descriptions of Secondary Endpoints

The 6MWD is related to stride length, influenced by skeletal maturation, and cadence. To correct for this growth effect, Henricson and colleagues have compared 6MWD from patients with Duchenne muscular dystrophy versus healthy controls to calculate the percent-predicted

6MWD using an age- and height-based equation fit to data (Henricson 2012). This measure is an estimate of performance relative to a healthy control population; an increase in the percent-predicted 6MWD is consistent with functional improvement. The percent-predicted 6MWD accounts for normal growth and development, and has shown that Duchenne muscular dystrophy patients aged 4 to 7 years maintain a stable 6MWD approximately 80% of that of typically developing peers, with a variable decline at later ages. Across all age groups, the expected 1-year decline in percent-predicted 6MWD is approximately 14% in patients with Duchenne muscular dystrophy compared with healthy controls (Henricson 2012). The normal control population used for the percent-predicted analysis was comprised of 280 males aged 3 to 18 years (Geiger 2007).

Timed function tests are adjunct tests of muscle function. Rise-from-the-floor is the time from initiation of movement in a standardized supine position to upright standing. The 10-meter walk/run test is the time to traverse 10 meters unaided in bare feet. The 4-stair climb is the time to ascend and descend 4 steps. The times to perform the 10-meter walk/run test and 4-stair climb can be converted to velocities in order to include all patients, even those who became nonambulant (Bushby 2011).

The NSAA, derived from the Hammersmith Functional Motor Scale, grades patients on a series of 17 physical activities generally required for ambulatory activity and includes items that are rarely achieved in untreated patients with Duchenne muscular dystrophy (eg, jump, hop, raise head), as well as items that are known to progressively deteriorate over time (eg, stand from a chair, walk). The total score ranges from 0 to 34, with a score of 34 implying normal function. The NSAA is specifically used in clinical studies of ambulant children with Duchenne muscular dystrophy (Mazzone 2009, Scott 2012). As with 6MWD, patients with Duchenne muscular dystrophy aged <7 years show smaller and less rapid decline in NSAA scores compared with patients aged ≥7 years. The NSAA also declines more rapidly in boys with a lower (<350 meters) baseline 6MWD. The NSAA data were Rasch-transformed to a linearized measurement to ensure that a 1-point change has the same meaning across the scale (Mayhew 2011, Mayhew 2013).

Quantitative measurement of muscle strength is important in the management of Duchenne muscular dystrophy. However, the ability to accurately and reliably identify early muscle weakness is problematic, because approximately 50% of a muscle's power may be lost before detectable difficulties are seen in activities of daily living. Quantitative measurement of isometric muscle strength using handheld myometers (dynamometers) has been used in early studies of children with Duchenne muscular dystrophy (Bohannon 1986, Agre 1987, Stuberg 1988), but more recent data suggest that myometry may not be sensitive to change in short-term studies of younger patients (Lerario 2012).

Although pulmonary function has a predictable decline in later-stage Duchenne muscular dystrophy patients, these changes are less evident in younger ambulatory patients. Changes in pulmonary function in patients with the disorder have significant prognostic value. In patients who had FVC values less than 1 liter, the population median survival was 3.1 years with a 5-year survival of 8%. However, these values occur later in the course of the disorder, with a median age of 17 years to reach a FVC of 1 liter (Phillips 2001). Relatively less is

known about the course and modifying covariates of more direct measures of respiratory muscle strength such as maximal inspiratory pressure or maximal expiratory pressure.

The Pediatric Quality of Life™ Version 3.0 Neuromuscular Module (PedsQL™ 3.0 NMM) specifically measures pediatric quality of life in children with neuromuscular disorders. The 25-item PedsQL™ 3.0 NMM has 3 scales, consisting of parallel child self-report and parent proxy-report formats for children aged 5 to 18 years:

- About my child's neuromuscular disease: 17 items related to the disease process and associated symptomatology
- Communication: 3 items related to the patient's ability to communicate with health care providers and others about their illness
- About our family resources: 5 items related to family financial and social support systems

Although initial findings suggested that the PedsQL™ 3.0 NMM may have utility in Duchenne muscular dystrophy (Davis 2010), more recent publications indicate that this is not the case (personal communication). Studies have shown that although quality of life is reduced about 30% in patients with Duchenne muscular dystrophy compared with healthy peers, there appears to be little or no apparent change in quality of life over the course of the disorder, as measured by the PedsQL™ (Henricson 2013b), 36-item short-form health survey (SF-36) (Kohler 2005), or Duchenne muscular dystrophy-specific quality-of-life scales (Bendixen 2012). Static quality of life in chronic progressive disorders with little pain or discomfort has been described previously (Hendriksen 2009, Simon 2011, Uzark 2012). More specific and sensitive patient-reported functional outcome measures such as the Pediatric Outcomes Data Collection Instrument (PODCI) and Neuro-QOL (Quality of Life in Neurological Disorders) physical function and health Section are currently being investigated as tools to measure changes over the progression of the disorder (Henricson 2013b, Han 2015, Henricson 2015).

The Clinical Global Impression of Improvement (CGI-I) is a single question designed to provide a brief, stand-alone assessment of the clinician's view of the patient's global functioning after initiating study drug compared with their global functioning just prior to initiating treatment. The CGI-I scale was measured on a 7-point Likert scale with ratings of very much improved, much improved, minimally improved, no change, minimally worse, much worse, and very much worse (Guy, 1976).

4.6 Statistical Methods

4.6.1 Efficacy Studies of Drisapersen in Duchenne Muscular Dystrophy

In Studies 117, 876, and 044, efficacy evaluation was based on the ITT population, defined as all randomized patients who received ≥ 1 dose of study medication and had ≥ 1 post-baseline efficacy assessment. The per-protocol (PP) population was defined as all ITT patients who had no major protocol deviations; this population was assessed as a sensitivity analysis.

Study 117 included 2 treatment regimens and the type 1 error rate was preserved by utilizing the Bonferroni-Holm adjustment. The p-values from the 2 primary analyses (6 mg/kg drisapersen continuous vs. placebo, and 6 mg/kg drisapersen intermittent vs. placebo), were ordered smallest to largest. The smallest p-value was compared to a significance level of $\alpha/2$ (0.025). If the result was statistically significant at this level ($p < 0.025$), the second p-value was then compared to a significance level of α (0.05). If the initial comparison did not reach statistical significance, the second comparison was automatically considered not to have reached statistical significance.

Similarly for Study 876 with 2 drisapersen doses, the type 1 error rate was preserved by utilizing a hierarchical approach. The difference in 6MWD between the 6 mg/kg dose of drisapersen and placebo was assessed first and if a statistically significant difference was observed, the significance of the 3 mg/kg dose versus placebo could be tested. If no statistically significant difference was observed between the 6 mg/kg dose and placebo, further analyses of the 3 mg/kg dose were considered exploratory, and no conclusions regarding the statistical significance of the treatment difference could be made.

For Study 044, statistical testing was performed for the primary endpoint of mean change from baseline 6MWD. For key secondary endpoints included in a hierarchical testing set, conclusions regarding statistical significance were made for each test only if the preceding test gave a statistically significant result at the 5% level. Therefore, no adjustments were required for multiplicity. The endpoints tested sequentially were: (1) change from baseline in the NSAA linearized score; (2) change from baseline in the 4-stair climb (ascent) velocity; and (3) change from baseline in the 10-meter walk/run velocity. The results from analyses of other secondary endpoints were considered supportive.

A mixed-effect model repeated measure (MMRM) analysis was the primary analysis conducted for all of the placebo-controlled studies. The model included treatment, visit, treatment by visit interaction, country/country grouping (center grouping in Study 876), baseline 6MWD, and baseline 6MWD by visit as fixed effects.

In the long-term Study 673, efficacy was evaluated using the ITT population, defined as all patients who received at least 1 dose of study medication and had at least 1 post-baseline efficacy parameter (where baseline is Visit 13, start of the extension study).

For the long-term extension Study 349, efficacy was evaluated using 2 different populations:

- The modified ITT population, defined as all patients enrolled in the study who received ≥1 dose of study medication, or entered the natural history arm at the start of the study and as such did not take any study medication, and had ≥1 post-baseline efficacy assessment. The modified ITT was the primary population for evaluation of efficacy parameters that were not restricted to the ambulant population.

- The modified ambulant ITT population, defined as all patients in the study who were ambulant at the baseline visit, received ≥1 dose of study medication, or entered the natural history arm at the start of the study and as such did not take any study medication and had ≥1 post-baseline efficacy assessment. This was the primary population for evaluation of efficacy parameters relevant only to the ambulant population.

In the long-term Studies 673 and 349, the primary means of analysis was via descriptive statistics. For Study 673, an additional analysis was performed by comparing study patients with natural history patients from a single cohort at a single treatment site (Data on file, BioMarin Pharmaceutical Inc., May 2014).

4.6.2 Integrated Analyses

Integrated analyses of efficacy data were conducted to further characterize the efficacy of drisapersen when administered for up to 1 year and for >1 year. Data from Study 117, the first 24 weeks of Study 876, and Study 044 were analyzed to assess efficacy up to 1 year. Extension Study 349 and parent Studies 117 and 044 characterize the efficacy of drisapersen for >1 year. Phase II placebo-controlled Studies 117 and 876 characterize the efficacy of drisapersen after 24 weeks in similar populations. All integrated efficacy summaries are based on the ITT population, including all patients who received at least 1 dose of study medication regardless of whether post-baseline assessment were available. No primary or secondary efficacy analyses or hypotheses were defined for the integrated data, no adjustments for multiplicity were required, and all analyses are considered supportive. The MMRM model described above was used to analyze the change from baseline in 6MWD in the integrated analyses.

4.6.3 Missing Data Handling Conventions

For 6MWD in all studies, a value of 0 was imputed when evidence indicated that a test was not completed because the patient was reported as nonambulatory in the study milestone dataset, which captures major disease events in the progression of Duchenne muscular dystrophy. For other timed test parameters, if a subject was unable to complete an activity their time was missing which can cause bias in analysis. In order to address this the times to perform each of these activities were converted to velocities (Bushby 2011). For timed test velocities, 0's have been imputed in case the subject did not perform the test with incapability of the subject given as a reason.

4.7 Results

The primary efficacy endpoint for all placebo-controlled studies was change from baseline 6MWD. The treatment effect is the difference between drisapersen treatment and placebo treatment in the mean change from baseline in 6MWD. Although the primary comparison evaluated in all 3 placebo-controlled trials was continuous drisapersen 6 mg/kg/wk compared with placebo, data for the intermittent drisapersen regimen from Study 117 and the 3 mg/kg/wk dose from Study 876 are also presented for some analyses. Adjusted mean change from baseline 6MWD in the placebo-controlled studies is shown in Table 4.7.1.

Table 4.7.1: Adjusted Mean Change from Baseline in 6MWD in Placebo-Controlled Studies (ITT Populations)

	Phase II Study 117			Phase II Study 876			Phase III Study 044	
	Placebo (Combined) (n=18)	Drisapersen 6 mg/kg/wk (n=18)	Drisapersen 6 mg/kg Intermittent (n=17)	Placebo (Combined) (n=16)	Drisapersen 6 mg/kg/wk (n=18)	Drisapersen 3 mg/kg/wk (n=17)	Placebo (n=61)	Drisapersen 6 mg/kg/wk (n=125)
Baseline 6MWD, n	18	18	17	16	18	17	61	125
Mean ± SD, meters	403.2 ± 45.1	427.6 ± 70.1	394.6 ± 67.0	416.4 ± 57.0	396.2 ± 60.7	415.2 ± 58.1	348.0 ± 92.1	337.5 ± 95.6
Week 24, n	16	16	15	16	18	17	59	122
Mean change ± SE, meters	-3.6 ± 9.73	31.5 ± 9.75	-0.1 ± 10.34	-10.98 ± 10.67	16.12 ± 9.94	-19.93 ± 9.96	-29.11 ± 8.27	-24.34 ± 5.82
Mean difference vs. placebo, meters	–	35.09	3.51	–	27.099	-8.946	–	4.767
(95% CI)	–	(7.59, 62.60)	(-24.34, 31.35)	–	(-2.21, 56.41)	(-39.12, 21.23)	–	(-14.90, 24.43)
p-value	–	0.014	0.801	–	0.069	0.554	–	0.633
Week 48, n	17	18	15	15	18	17	59	117
Mean change ± SE, meters	-24.7 ± 12.75	11.2 ± 12.64	2.4 ± 13.63	-13.17 ± 14.843	14.69 ± 13.89	-37.92 ± 14.06	-52.65 ± 10.42	-42.32 ± 7.38
Mean difference vs. placebo, meters	–	35.84	27.08	–	27.866	-24.750	–	10.33
(95% CI)	–	(-0.11, 71.78)	(-9.83, 63.99)	–	(-13.04, 68.78)	(-66.37, 16.87)	–	(-14.65, 35.31)
p-value	–	0.051	0.147	–	0.177	0.238	–	0.42

6MWD, 6-minute walking distance in meters; CI, confidence interval; MMRM, mixed model repeated measures; ITT, intent-to-treat; SD, standard deviation; SE, standard error.

The primary efficacy endpoint for each study is indicated by bold font. Patients in Study 876 received study treatment for 24 weeks, followed by a 24-week post-treatment period during which patients did not receive drisapersen (shaded cells).

All mean changes are adjusted.

MMRM model included terms for treatment, visit, treatment by visit, country grouping (center grouping in DMD114876), baseline value, and baseline value by visit.

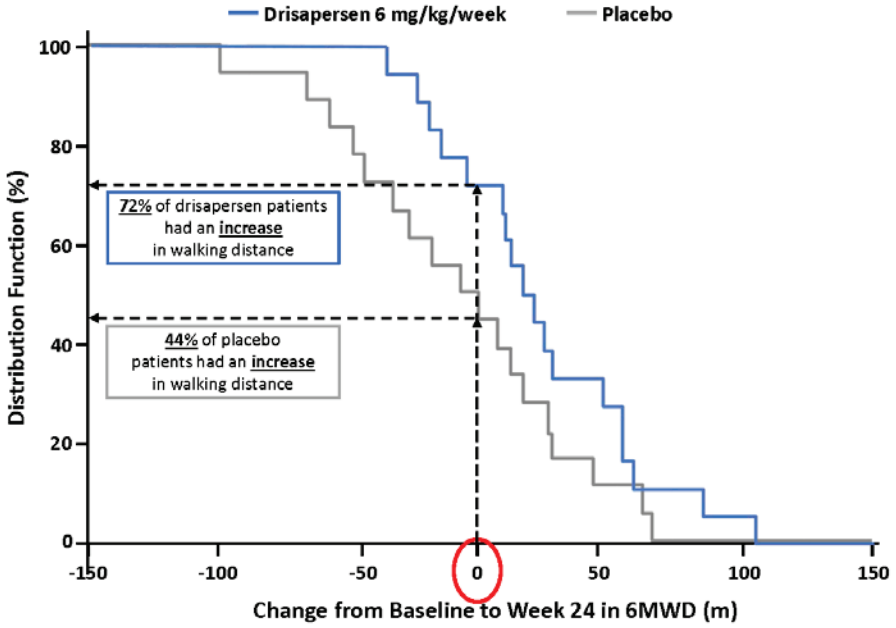
4.7.1 Phase II Studies – Primary Endpoint

Study 117

In Study 117 for the primary endpoint at Week 24, the 6MWD improved 31.5 meters from baseline in patients treated with continuous drisapersen 6 mg/kg/wk, a statistically significant treatment difference compared with placebo (35.09 meters, p=0.014) (Table 4.7.1). A treatment effect was also observed for the continuous 6 mg/kg/wk group at Week 48 (35.8 meters; p=0.051). In the intermittent 6 mg/kg group, only a small treatment difference versus placebo was seen at Week 24 (3.5 meters), which increased to 27.1 meters (p=0.147) by Week 48. The different results for continuous versus intermittent treatment may reflect the more advanced disease of patients in the intermittent group (see Table 4.4.2), based on time since diagnosis and duration of steroid treatment, and differences in patient ages: the intermittent group (mean age 7.7 years) was on average older than the combined placebo (6.9 years) and continuous 6 mg/kg drisapersen (7.2 years) groups, and had more patients aged >7 years (n = 10 [58.8%]) compared with the combined placebo (5 [27.8%]) and continuous 6 mg/kg drisapersen (7 [38.9%]) groups.

Figure 4.7.1.1 shows the clear separation between drisapersen-treated patients and placebo-treated patients in the cumulative distribution of change from baseline in 6MWD at Week 24. Overall, 72% of drisapersen patients in Study 117 had an increase in 6MWD (> 0 change from baseline 6MWD) and 50% had an increase ≥ 20 meters. In contrast, 44% of placebo patients had an increase in 6MWD and 28% of placebo patients had an increase ≥ 20 meters.

Figure 4.7.1.1: Cumulative Distribution Function at Week 24 in Study 117 (ITT Population)



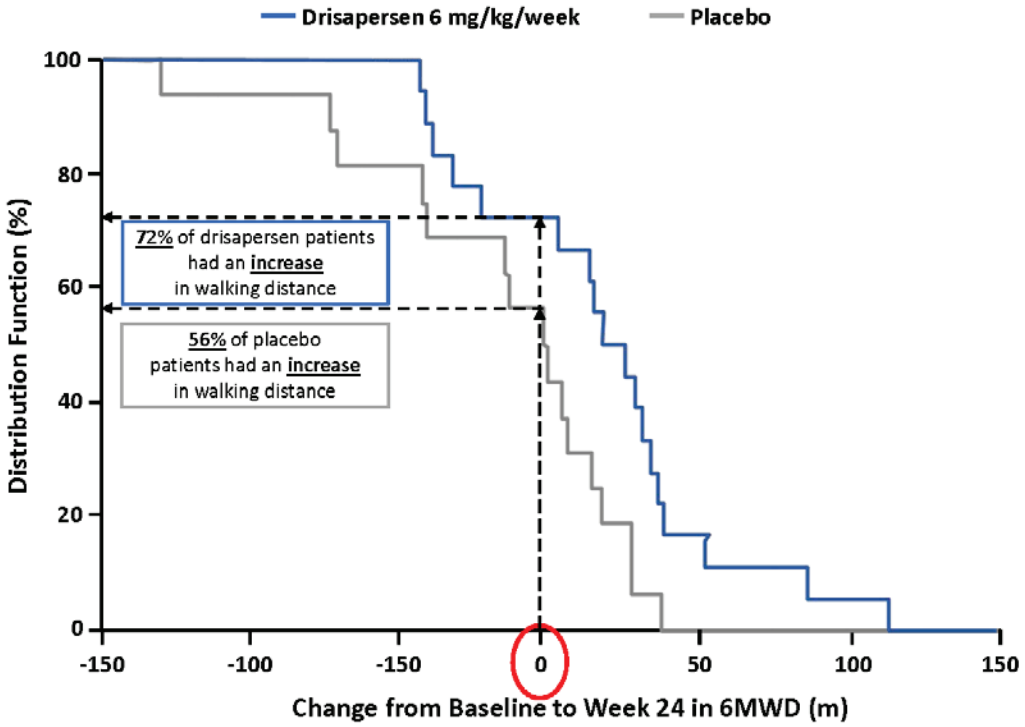
6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population.
Patients in Study 117 received treatment for 48 weeks.

Study 876

For the primary endpoint analysis in Study 876 (Table 4.7.1), the 6MWD improved 16.1 meters from baseline at Week 24, although the treatment difference of 27.1 meters between the drisapersen 6 mg/kg/wk and placebo groups was not statistically significant (p=0.069). No statistically significant difference was found between the drisapersen 3 mg/kg/wk and placebo treatment groups. The increase in 6MWD seen at Week 24 in patients treated with drisapersen 6 mg/kg/wk was maintained to Week 48 (27.9 meters; p=0.177), suggesting a long-term post-treatment effect in this study. Patients treated with drisapersen 3 mg/kg/wk and placebo showed a continued decline in 6MWD during the post-treatment period.

Similar to Study 117, a clear separation between the treatment groups in the cumulative distribution of change from baseline in 6MWD at Week 24 is evident in Study 876 (Figure 4.7.1.2). Likewise, more patients treated with drisapersen had increases in 6MWD from baseline than with placebo.

Figure 4.7.1.2: Cumulative Distribution at Week 24 in Study 876 (ITT Population)



6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population.
Patients received study treatment for 24 weeks, followed by a 24-week post-treatment period.

In the 3 mg/kg drisapersen group, the 6MWD results were numerically lower compared with placebo at Week 24 (treatment effect of -8.9 meters) and showed additional decline following 24 weeks off treatment. One patient in the 3-mg/kg drisapersen group had a strong decline in 6MWD, which had a disproportionate impact on the group average due to the relatively low numbers of patients per group. In addition, differences in clinical responses with the 3 mg/kg

and 6 mg/kg dose levels may be explained by low exposure to the 3 mg/kg dose in a 24-week treatment period. The drisapersen exposure levels between the 2 dose groups were well separated; the ranges (first and third quartile values) of drisapersen tissue levels were 6.3 to 13.4 µg/g for patients treated with drisapersen 6 mg/kg compared with 1.4 to 3.1 µg/g with drisapersen 3 mg/kg in muscle biopsies at Week 24.

Integrated analysis of the 6MWD results of the Phase II placebo-controlled studies (n=70) showed that 6MWD statistically significantly improved in patients treated with drisapersen 6 mg/kg/wk (19.92 meters), but decreased in those treated with placebo (-11.20 meters) at Week 24 for a treatment difference at of 31.11 meters (p=0.0025). This strongly positive result in favor of drisapersen highlights the benefits of treating a younger, more functional population.

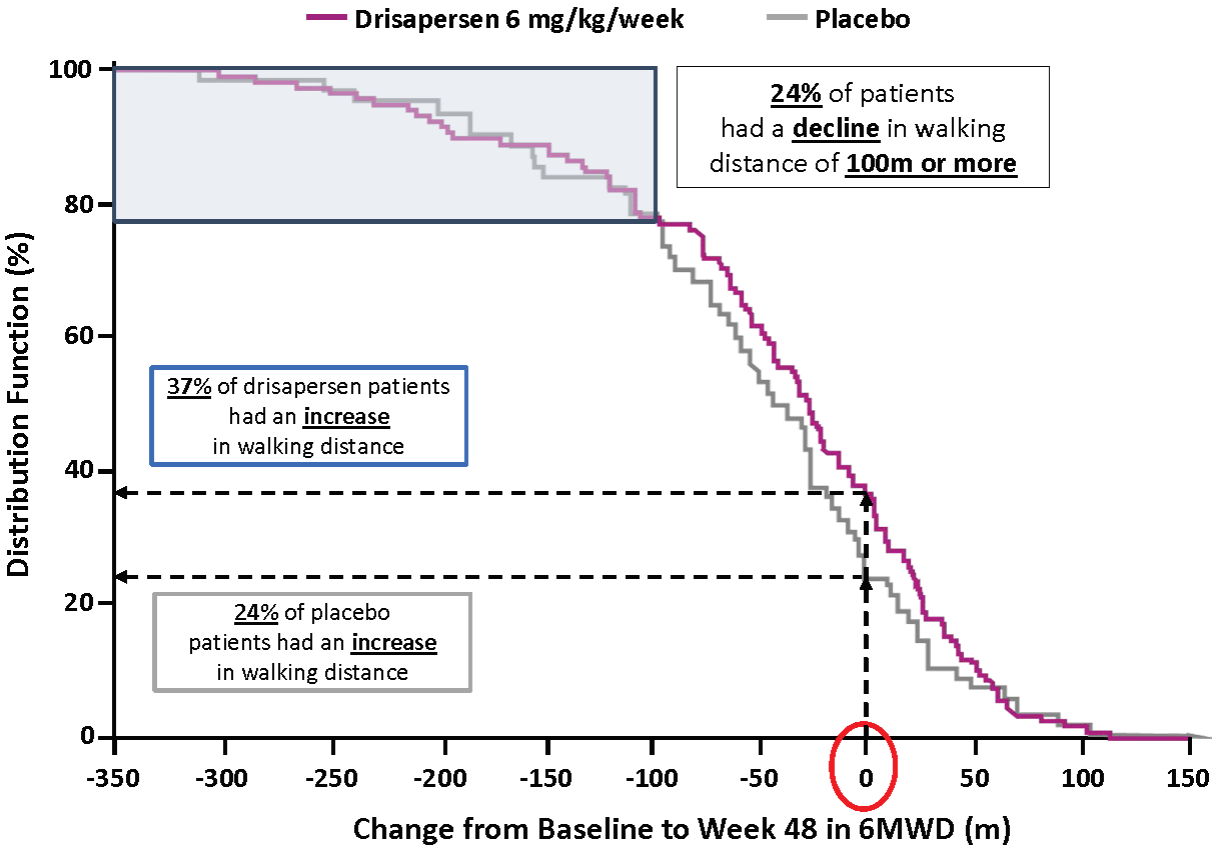
4.7.2 Phase III Study 044

4.7.2.1 Primary Endpoint

In the Study 044 (Table 4.7.1), the primary endpoint was change in 6MWD from baseline at Week 48. The treatment effect for drisapersen 6 mg/kg/wk was 10.3 meters, a difference that was not statistically significant. Based on disease trajectory measured by the 6MWD over time, some patients in Study 044 were on a steep progression curve; 21 patients lost ambulation (6 [10%] for placebo, 15 [12%] for drisapersen) during the 48 weeks of the study. No patient in Studies 117 or 876 lost ambulation. The lesser improvement in 6MWD seen in Study 044 compared with the other placebo-controlled studies may reflect the greater functional impairment at baseline in Study 044. The 6MWD may not be an appropriate measure of drug effect in more rapidly progressing patients who have lost substantial muscle tissue.

In Study 044, 24% of patients had a decline from baseline in 6MWD of ≥100 meters and 7% of patients had a decline in 6MWD of ≥200 meters (Figure 4.7.2.1.1), suggesting a large number of patients in this study were in a stage of accelerated ambulatory decline. By contrast, natural history data indicate that the annual decline is 40–60 meters on average. A treatment effect is most evident in patients with declines of <100 meters, with a consistent separation from placebo in favor of drisapersen.

Figure 4.7.2.1.1: Cumulative Distribution at Week 48 in Study 044 (ITT Population)



6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population.
In Study 044, patients received study treatment for 48 weeks.

It is plainly evident that Study 044 evaluated a more impaired population as evidenced by the proportion of placebo-treated patients who experienced improvement in the 6MWD test result. Nonetheless, the absolute difference in proportion of patients who improve is similar between Study 044 and Study 876, albeit taking longer for that difference to emerge in Study 044. The best results in terms of absolute proportion of patients who improved was observed in Study 117, the only study in which a loading dose of drisapersen was incorporated.

4.7.2.2 Further Evaluation of Study 044 Results

To understand this result, it is helpful to consider four factors which influenced the response:

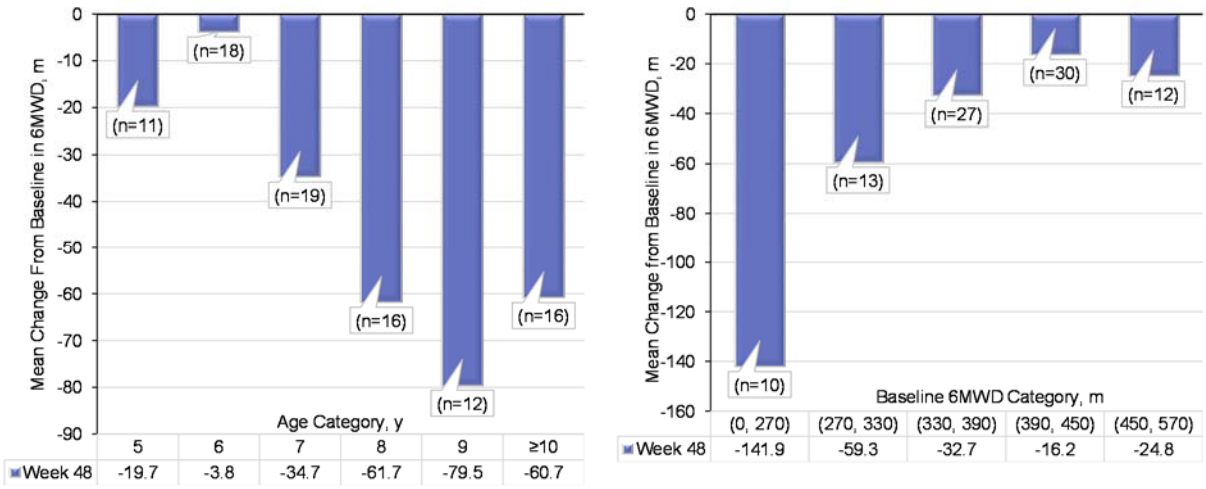
1. An imbalance between the placebo and drisapersen-treated groups in certain key prognostic factors
2. Dilution of treatment effect by inclusion of an older, more progressed patient population at imminent risk of losing ambulation

3. Inclusion of a broad range of study sites with varying expertise in treatment patients with Duchenne muscular dystrophy
4. The short duration at which patients being assessed at Week 48 in Study 044 had likely been exposed to steady-state concentrations of drisapersen (in part because of lack of a loading dose)

Prognostic Factor Imbalance

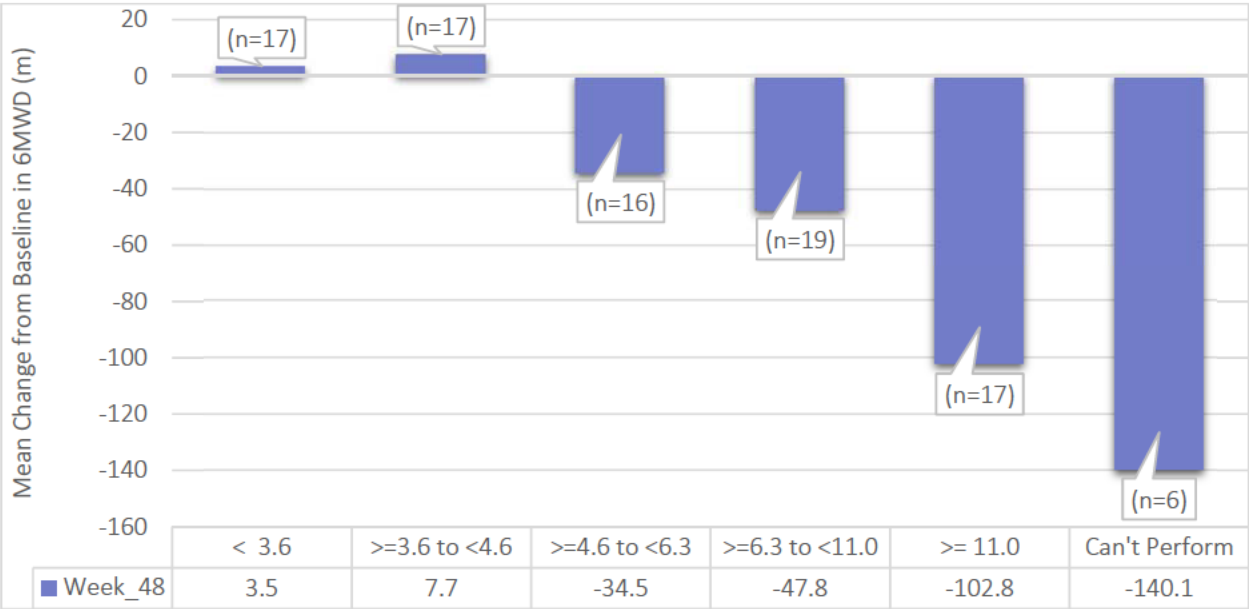
Natural history data that emerged only after Study 044 was well underway indicated that age, baseline walking ability, and baseline rise-from-the-floor time are all prognostic variables. Unfortunately, the well-motivated inclusion of a broadly eligible population resulted in 24% of patients losing at least 100 meters of ambulation (Figure 4.7.2.1.1), a far greater fraction than in the other randomized placebo-controlled trials (Figure 4.7.1.1 and Figure 4.7.1.2). Several natural history studies have described the relationship between age and level of function as measured by the 6-minute walk test or time to rise-from-the-floor and the loss of ambulation. Baseline 6MWD predicts both future 6MWD and time to loss of ambulation; once a patient's 6MWD falls below a threshold of around 330 meters, a rapid and precipitous decline in 6MWD is observed over the following 12–24 months. A similar observation is made based on the rise-from-the-floor time, with increasing times predictive for increased risk of losing ambulation, and higher times correlating with greater decrease in 6MWD over time. (Mazzone 2013, Goemans 2013, McDonald 2013a). Older patients also fare worse over time; patients < 7 years of age have preserved or increasing 6MWD, whereas patients > 7 years of age exhibit more heterogeneous trajectories, with a slow and persistent decline or more rapid decrease over time (Mazzone 2013, Goemans 2013, McDonald 2013a).These relationships are confirmed in the data from the placebo arms in the drisapersen efficacy trials, as shown in Figure 4.7.2.2.1 and Figure 4.7.2.2.2.

Figure 4.7.2.2.1: Change from Baseline in 6MWD at Week 48 vs. Baseline Age and vs. Baseline 6MWD in Studies 117, 876, and 044 (Placebo ITT Population)



6MWD, 6 minute walking distance in meters.

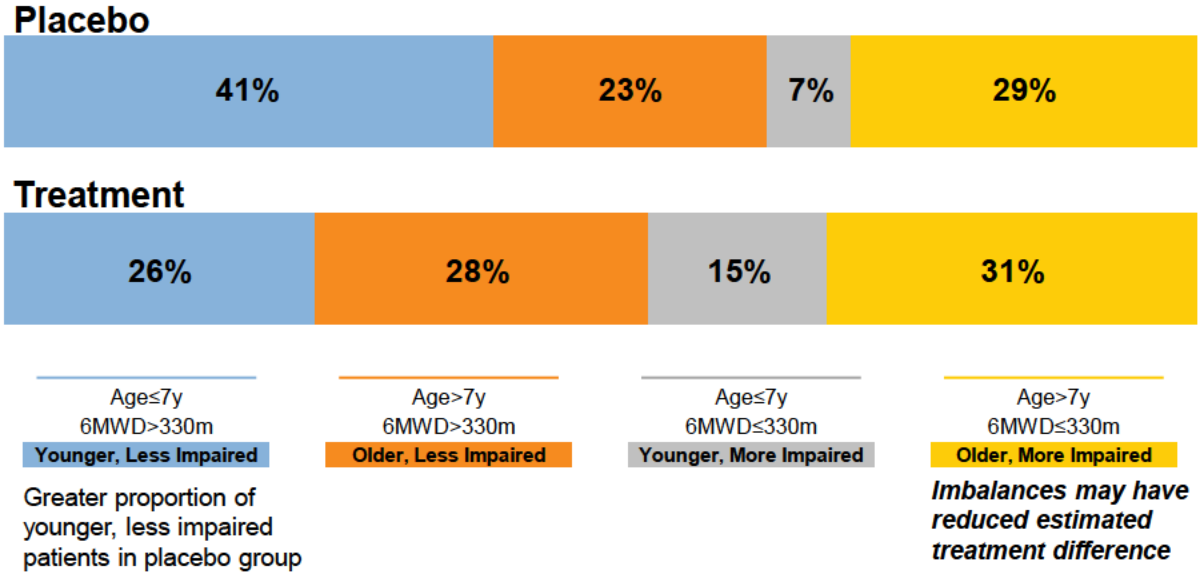
Figure 4.7.2.2.2: Change from Baseline in 6MWD at Week 48 vs. Baseline Rise-From-the-Floor Time in Studies 117, 876, and 044 (Placebo ITT Population)



6MWD, 6 minute walking distance in meters.

Additionally, prognostic factors are typically incorporated into the randomization scheme in an effort to produce comparable study arms. However, in this case, stratification was not used because these prognostic factors were not known at the time the studies were designed. This lack in stratification resulted in an imbalance as described in Figure 4.7.2.2.3 (showing imbalance in baseline age and 6MWD).

Figure 4.7.2.2.3: Proportion of Patients in Categories of Baseline Age and 6MWD by Treatment Group in Study 044 (ITT Population)



A standard method to address these imbalances is to add these variables as covariates in the mixed model repeat measures (MMRM) analysis of the primary efficacy endpoint. An MMRM analysis of 6MWD taking these imbalances into account produced an estimated treatment difference in favor of drisapersen at Week 48 of 15.6 meters (95% CI -8.4 to 39.7) (Table 4.7.2.2.1), a nearly 60% increase in the magnitude of treatment effect compared with that seen using the original analysis without adjustment of these covariates (Table 4.7.1).

Table 4.7.2.2.1: Adjusted Mean Change from Baseline in 6MWD at Week 48 Adjusted for Age, Baseline 6MWD, and Baseline Rise-from-the-Floor Velocity in Study 044 (ITT Population)

	Placebo (n=61)	Drisapersen 6 mg/kg/wk (n=125)
Baseline 6MWD, n	61	125
Mean ± SD, meters	348.0 ± 92.2	337.5 ± 95.6
Week 48, n	**59**	**117**
Mean change ± SE, meters	**-56.5 ± 10.0**	**-40.9 ± 7.1**
Mean difference vs. placebo, meters	–	**15.6**
(95% CI)	–	**(-8.4, 39.7)**
p-value	–	**0.20**

6MWD, 6-minute walking distance in meters; CI, confidence interval; MMRM, mixed model repeated measures; ITT, intent-to-treat; SD, standard deviation; SE, standard error.

All mean changes are adjusted.

MMRM model included terms for treatment, visit, treatment by visit, age, age by visit, baseline 6MWD, baseline 6MWD by visit, baseline rise-from-the-floor velocity, and baseline rise-from-the-floor velocity by visit.

Older, More Progressed Population

The treatment effect in Study 044 was diluted by inclusion of an older, more progressed patient population at imminent risk of losing ambulation and ability to complete the 6-minute-walk test. A standard way to address this characteristic is to analyze the subgroup of patients with baseline rise-from-the-floor time ≤7 seconds, reflecting the additional inclusion criterion in Studies 117 and 876 that was absent in Study 044. Repeating the primary analysis in this subgroup yields an estimated treatment difference of 5 meters. However, this result was also significantly affected by imbalances in age and baseline 6MWD (refer to Figure 4.7.2.2.4), and baseline rise-from-the-floor time (refer to Figure 4.7.2.2.5).

Figure 4.7.2.2.4: Proportion of Patients in Categories of Baseline Age and 6MWD by Treatment Group in Study 044 Patients with Rise-From-the-Floor Times ≤ 7 seconds

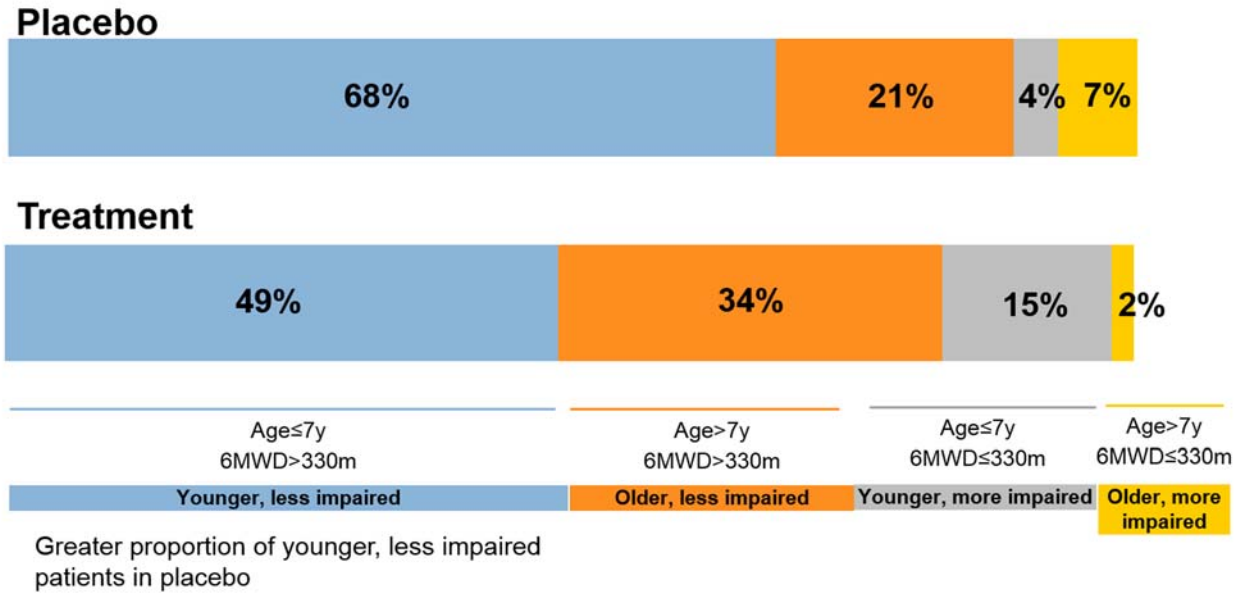
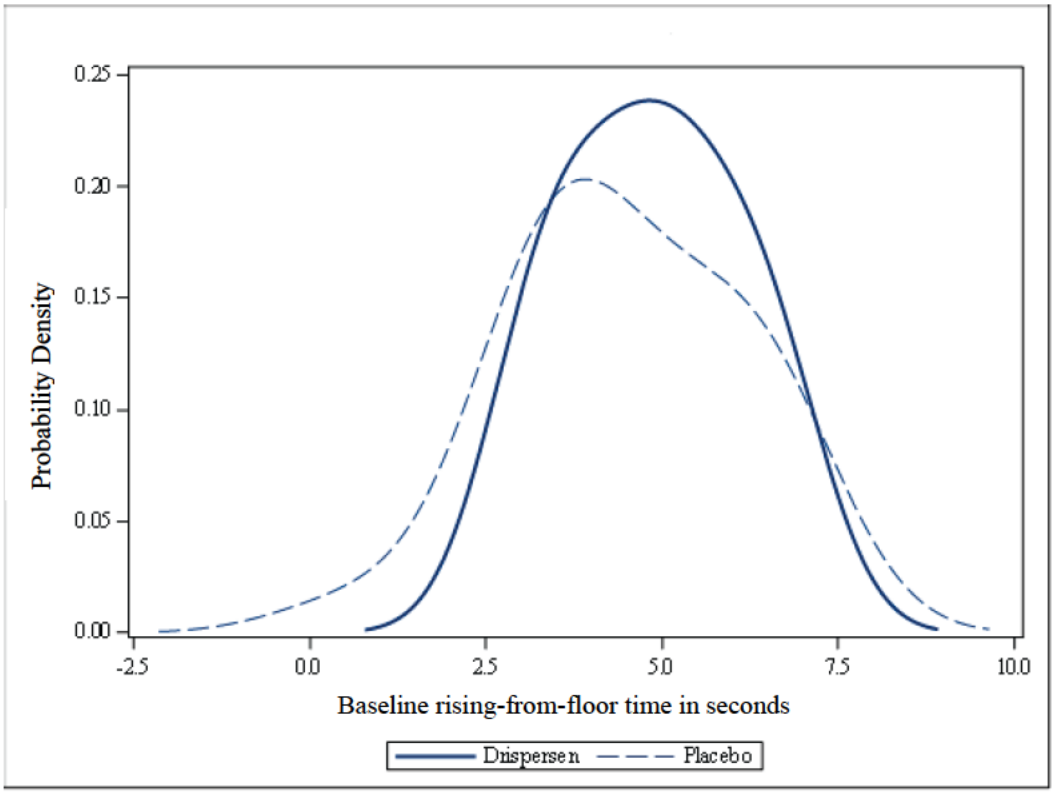
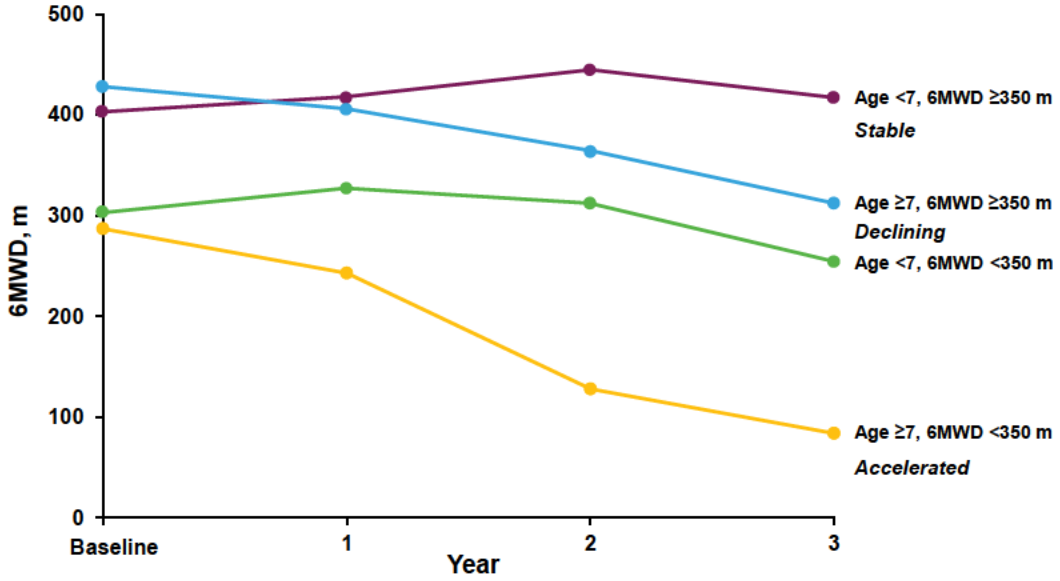


Figure 4.7.2.2.5: Density Plot of Baseline Rise from Floor (RFF) Time (in Seconds) – (Study 044 – All Subjects with RFF ≤ 7 Seconds)



At the time of Study 044 initiation, it was not understood that the combination of age and 6MWD has greater influence on ambulatory function than either variable alone (Pane 2014). Specifically, older boys with poor baseline function from a natural history cohort had the greatest rate of decline in 6MWD. These characteristics of disease progression are shown in Figure 4.7.2.2.6 (Pane 2014).

Figure 4.7.2.2.6: 6MWD over Time by Baseline Age and 6MWD in a Natural History Cohort

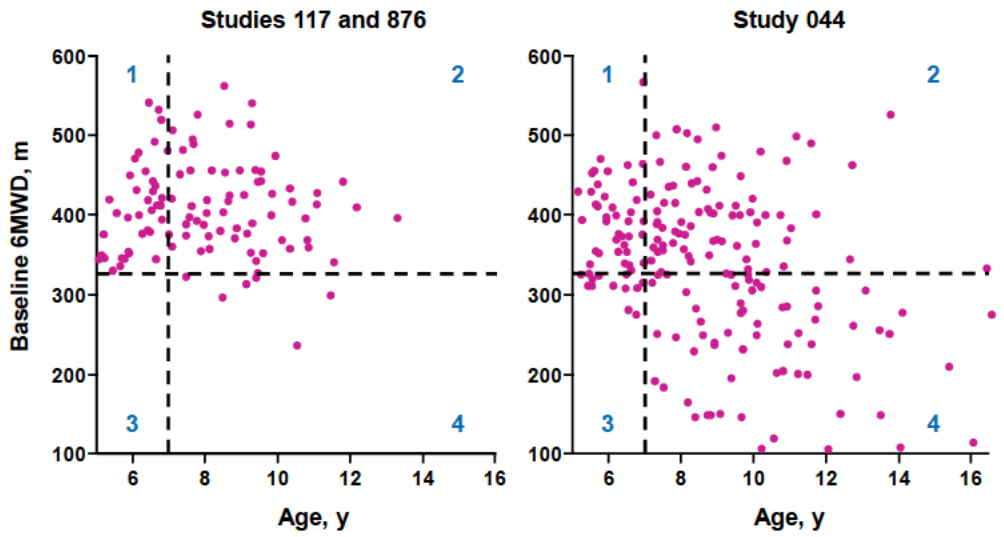


6MWD, 6 minute walking distance in meters.
Adapted from Pane M, et al. PLoS One. 2014;9(10):e108205.

With the understanding that patients with poor performance in the functional walk test, as measured by the 6MWD, have poorer prognoses in regards to their future walk ability, several studies have tried to define the cut point for this baseline 6MWD. Values of 350 meters (Pane 2014, McDonald 2013a), 330 meters (Goemans 2013, Mazzone 2013), and 300 meters (Mazzone 2013) have all been used to show this relationship between baseline function and future precipitous decline in 6MWD. Mazzone et al looked at multiple cut-points and determined that 330 meters was the optimal cut-point for predicting loss of ambulation (Mazzone 2013). When considering the various natural history studies exploring this relationship, a cut-point of 330 meters appears to be the most appropriate baseline 6MWD to allow additional analysis for the data presented here.

Considering these 2 critical variables, baseline age and walk, it is evident that many more severely affected patients were enrolled in Study 044 compared to Studies 117 and 876. As shown in Figure 4.7.2.2.7, fewer younger patients with longer baseline 6MWDs are represented in quadrant 1 and a greater number of older patients with shorter baseline 6MWDs are shown in quadrant 4 in Study 044 compared with Studies 117 and 876. Overall, Studies 117 and 876 enrolled a relatively homogeneous, early ambulant population seen in quadrants 1 and 2 in Figure 4.7.2.2.7.

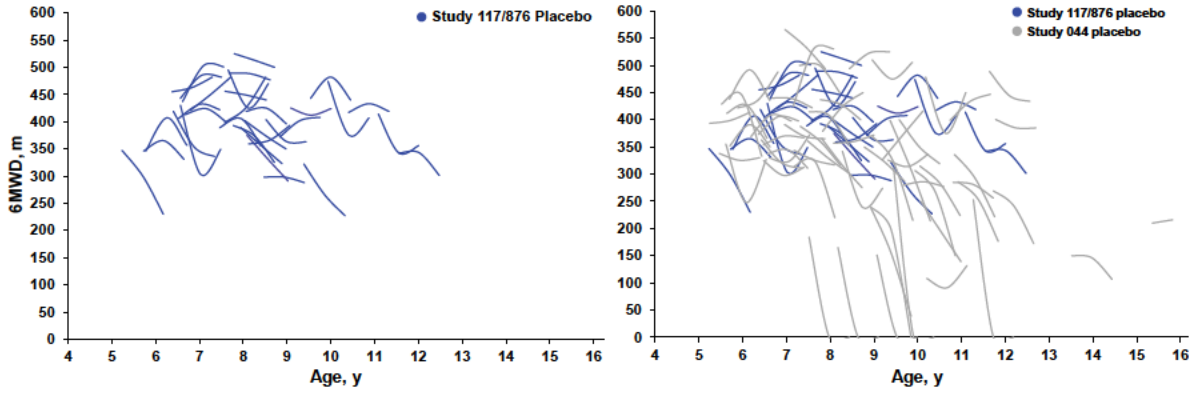
Figure 4.7.2.2.7: Patients by Age and 6MWD at Baseline in the Placebo-Controlled Studies



6MWD, 6-minute walking distance in meters. Quadrant 1 shows patients aged ≤7 years with baseline 6MWD >330 meters, quadrant 2 shows patients aged >7 years with baseline 6MWD >330 meters, quadrant 3 shows patients aged ≤7 years with baseline 6MWD ≤330 meters, and quadrant 4 shows patients aged >7 years with baseline 6MWD ≤330 meters.

The Study 044 population is very different from the other placebo-controlled studies due to inclusion of more patients in the decline phase of their ambulatory capacity. As the natural history data would predict, the difference in patient populations resulted in a difference in outcome, with more Study 044 patients experiencing precipitous declines in their 6MWD. The 6MWD trajectories in Figure 4.7.2.2.8 show the different outcomes for placebo patients in Study 044 compared with Study 117, and are consistent with the natural history data predicting poorer outcome for patients who are older and/or have greater functional deficit at baseline.

Figure 4.7.2.2.8: Comparison of Individual Trajectories of Placebo-Treated Patients in Studies 117, 876 and 044



6MWD, 6-minute walking distance in meters.

The correlation of ambulatory function with the combination of age and 6MWD accords physiologically with the observed progressive replacement of healthy muscle with fat and fibrous tissue with increasing age, as shown in the MRI data from a natural history cohort (Bonati 2015), see Figure 3.2.1.1 in Section 3.2.1). Therefore, the potential for therapeutic effect of drisapersen is directly related to walking ability, because less target tissue is available as ambulation declines.

Taking these issues into consideration, an analysis excluding patients aged >7 years and with baseline 6MWD ≤ 330 meters is appropriate. In this large subgroup of younger, less advanced patients, an MMRM analysis including covariates for age, baseline 6MWD, and baseline rise-from-floor velocity produced an estimated treatment difference in favor of drisapersen at Week 48 of 23.5 meters (Table 4.7.2.2.2).

Table 4.7.2.2.2: Adjusted Mean Change from Baseline in 6MWD at Week 48 Adjusted for Age, Baseline 6MWD, and Baseline Rise-from-the-Floor Velocity in Study 044 (ITT Populations Excluding Subjects with Age > 7 and Baseline 6MWD ≤ 330 meters)

	Placebo (n=61)	**Drisapersen 6 mg/kg/wk (n=125)**
Baseline 6MWD, n	43	86
Mean ± SD, meters	389.7 ± 65.5	385.5 ± 62.5
Week 48, n	**42**	**84**
Mean change ± SE, meters	**-35.1 ± 9.7**	**-11.6 ± 6.7**
Mean difference vs. placebo, meters	–	**23.5**
(95% CI)	–	**(0.7, 46.4)**
p-value	–	**0.044**

6MWD, 6-minute walking distance in meters; CI, confidence interval; MMRM, mixed model repeated measures; ITT, intent-to-treat; SD, standard deviation; SE, standard error.

All mean changes are adjusted.

MMRM model included terms for treatment, visit, treatment by visit, age, age by visit, baseline 6MWD, baseline 6MWD by visit, baseline rise-from-the-floor velocity, and baseline rise-from-the-floor velocity by visit.

If different cutpoints in baseline 6MWD are used, the results vary (meters improved and confidence intervals), but the essential finding that advanced patients meaningfully diluted the estimated treatment effect in Study 044 remains constant.

Variability of Study Site Expertise

Study 044 included a broad range of sites of varying expertise in treating patients with Duchenne muscular dystrophy. Centers of excellence in treating Duchenne muscular dystrophy have expertise in participating in clinical trials, as well as in optimizing the use of physiotherapy, corticosteroid use, and other aspects of patient care that may not be available at other study sites. An MMRM analysis conducted in the subgroup of patients from centers

that also participated in Study 117 produced an estimated treatment difference in favor of drisapersen at Week 48 of 62 meters (95% CI -2, 126) (Table 4.7.2.2.3).

Table 4.7.2.2.3: Adjusted Mean Change from Baseline in 6MWD at Week 48 Adjusted for Age, Baseline 6MWD, and Baseline Rise-from-the-Floor Time in Study 044 (ITT Populations)

	Placebo (n=61)	Drisapersen 6 mg/kg/wk (n=125)
Baseline 6MWD, n	9	17
Mean ± SD, meters	361.8 ± 85.4	363.0 ± 114.3
Week 48, n	**9**	**16**
Mean change ± SE, meters	**-108. 6 ± 24.8**	**-46.9 ± 18.4**
Mean difference vs. placebo, meters	–	**61.7**
(95% CI)	–	**(-2.2, 125.6)**
p-value	–	**0.058**

6MWD, 6-minute walking distance in meters; CI, confidence interval; MMRM, mixed model repeated measures; ITT, intent-to-treat; SD, standard deviation; SE, standard error.

All mean changes are adjusted.

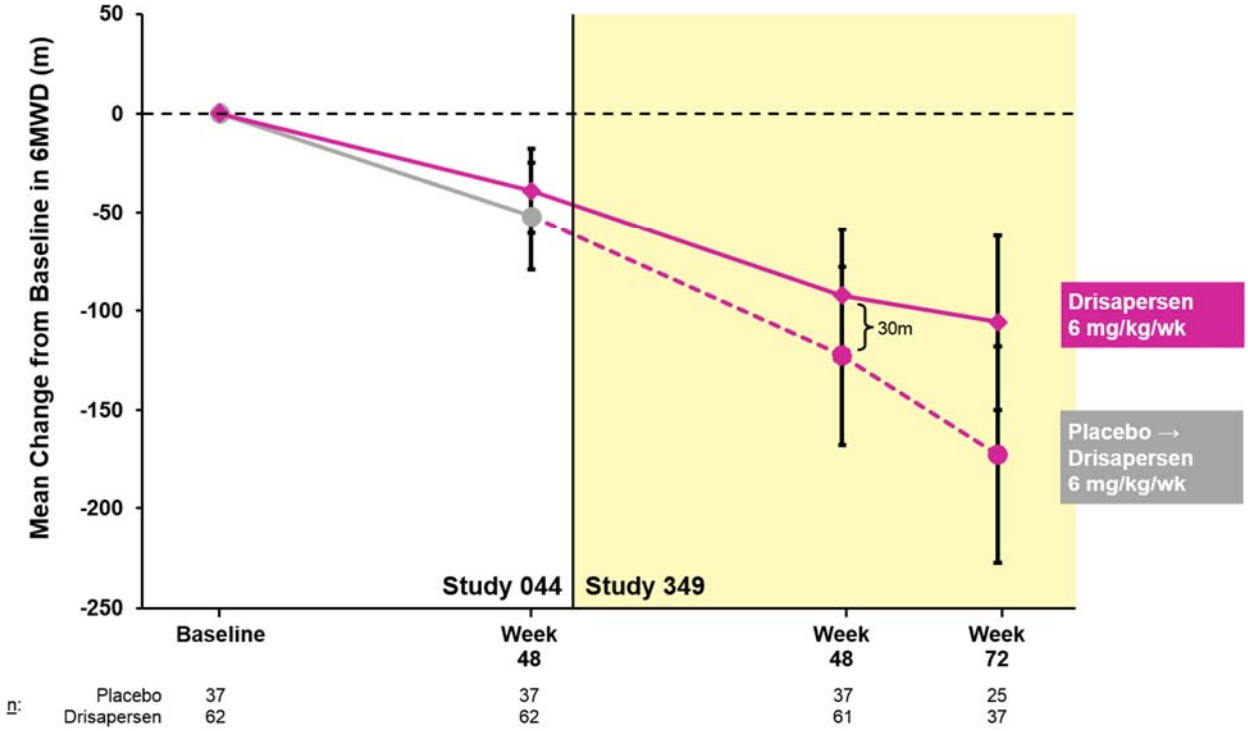
MMRM model included terms for treatment, visit, treatment by visit, age, age by visit, country grouping, baseline 6MWD, and baseline 6MWD by visit.

Short Duration of Steady-State Concentration of Drisapersen

Because steady state tissue concentrations of drisapersen are not reached until after approximately 36 weeks of administration, patients in Study 044 (a 48-week trial without a loading dose) have been at a steady-state tissue concentration for only a short duration when the Week 48 assessments are performed (see Section 3.1.1). This is especially important in light of data demonstrating a relationship between tissue concentration and dystrophin expression in a parallel randomized, placebo-controlled clinical trial (see Section 4.7.1). Moreover, this long time to steady-state tissue concentration is exaggerated in the more impaired patient population of Study 044, in which advanced fat and fibrous tissue infiltration reduced the amount of muscle tissue that drisapersen could target.

These issues likely caused underestimation of the benefit of drisapersen in patients with preserved ambulatory capacity in Study 044. Nevertheless, with longer-term treatment and follow-up, a greater effect emerges, in that the treatment difference at 96 weeks is 30 meters comparing two years of continuous treatment versus one year placebo followed by one year of treatment (Figure 4.7.2.2.9).

Figure 4.7.2.2.9: Change from Baseline in 6MWD at Week 48 in Study 044 and Long-Term Follow-Up (Week 48 Completer Analysis)



To summarize, key variables (age, baseline 6MWD, baseline rise-from-the-floor time), subsequently shown to be prognostic, were not stratified in the randomization scheme for Study 044, resulting in substantial imbalances in these variables between treatment groups in favor of placebo. Moreover, the broad eligibility criteria in Study 044 resulted in inclusion of patients unlikely to benefit from drisapersen treatment, due to advanced fat and fibrous infiltration into the muscles of patients at imminent risk of losing ambulation and ability to perform the 6-minute-walk test, with a corresponding dilution of treatment effect.

Appropriately addressing these issues to estimate the magnitude of benefit in Study 044 is a challenging endeavor. In attempt to understand these issues, a number of sensitivity analyses were performed. Nearly all of these analyses directionally favored drisapersen, the most informative of which are reported above. While these post hoc analyses should be interpreted with caution, they provide valuable insight to the results of Study 044 and show that drisapersen improves 6MWD in an ambulatory population in Study 044. Additional important considerations in evaluating these results include the rarity of Duchenne muscular dystrophy, the limited information and understanding of natural history available when the trials were designed, and the urgent unmet medical need for therapies for this disorder.

Taking these considerations into account for Study 044, a consistently positive treatment effect as measured by 6MWD has been observed across 3 independent studies conducted contemporaneously providing an unbiased characterization of the magnitude of benefit.

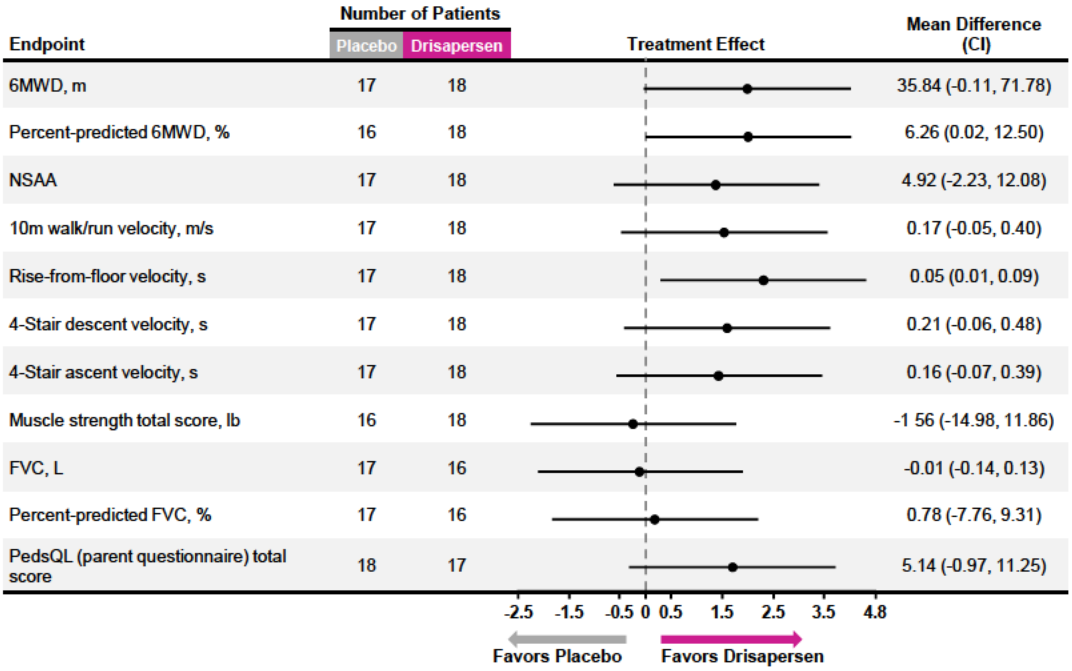
4.7.3 Secondary Endpoints

The secondary endpoints assessed in different trials as part of the drisapersen clinical development program used different scales and units of measurement; therefore, the estimates were standardized to a common scale of measurement by dividing the estimate and CI bounds for each endpoint by the SD of that estimate for presentation in forest plots. The calculations were based on all ITT patients without data imputation, with the exception of those who did not perform and complete the timed function tests; velocities of 0 were imputed for these patients.

4.7.3.1 Studies 117 and 876

In Study 117 at Week 24, changes directionally favored drisapersen treatment compared with placebo for the majority of secondary endpoints, and these treatment effects were largely sustained or improved at Week 48 (Figure 4.7.3.1.1).

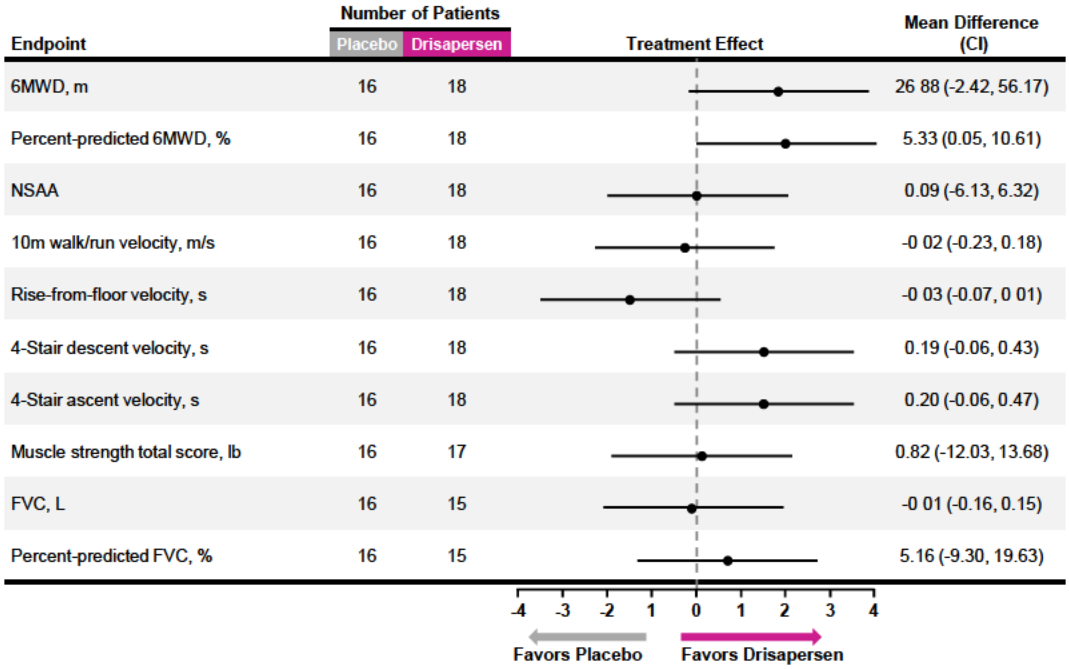
Figure 4.7.3.1.1: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints at Week 48 in Study 117



6MWD, 6-minute walking distance in meters; CI, confidence interval; FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment; PedsQL™, Pediatric Quality of Life™; SD, standard deviation. Numbers on x-axis of forest plot represent the standardized mean difference which is the difference in mean outcome between treatment groups divided by the SD of outcome among patients.

In Study 876 at Week 24, patients treated with drisapersen 6 mg/kg/wk group had more positive responses compared with placebo for most of the standardized endpoints (Figure 4.7.3.1.2).

Figure 4.7.3.1.2: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints at Week 24 in Study 876



6MWD, 6-minute walking distance in meters; CI, confidence interval; FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment; PedsQL™, Pediatric Quality of Life™; SD, standard deviation.
Numbers on x-axis represent the standardized mean difference which is the difference in mean outcome between treatment groups divided by the SD of outcome among patients.

Results for the majority of secondary endpoints favored drisapersen treatment versus placebo in the Phase II placebo-controlled studies; however, some differences between studies were seen. For example, patients in Study 117 had more NSAA improvement and a stronger treatment effect overall in the timed function tests compared with Study 876. The variability of these findings was not unexpected given the differences in study design and conduct, including the slightly older population in Study 876, use of a loading dose in Study 117, and treatment duration of 24 versus 48 weeks in the 2 studies, respectively.

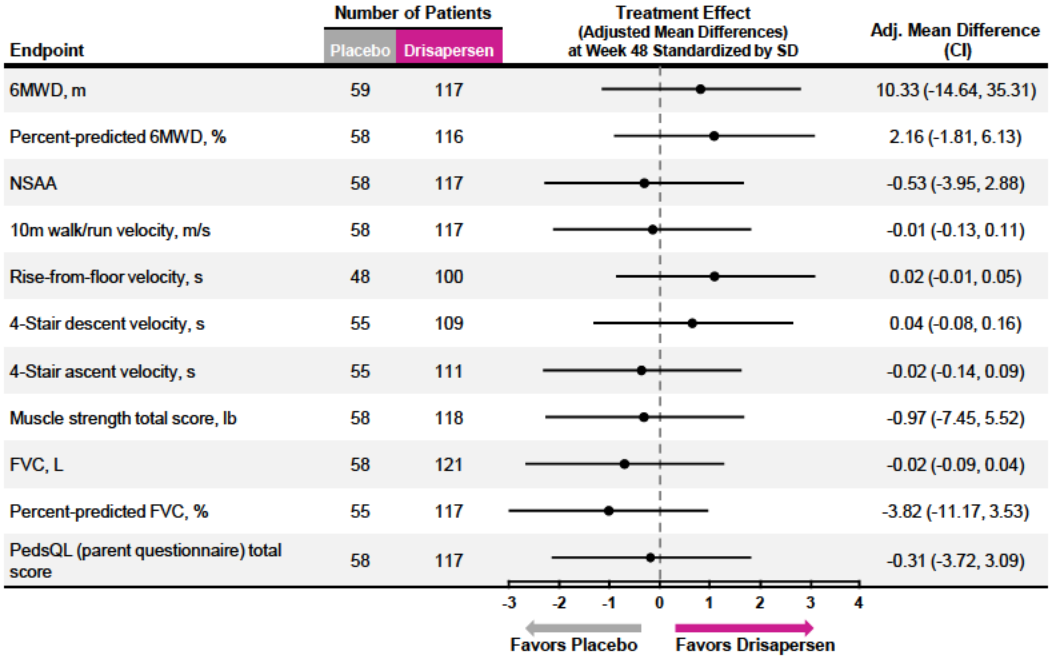
Normalizing 6MWD data through conversion to a percent-predicted 6MWD helps to distinguish normal growth and development from disease-related progression and treatment effects (Henricson 2012). As with change in 6MWD, a treatment benefit for percent-predicted 6MWD was observed in both Studies 117 and 876. In Study 117, the difference in percent-predicted 6MWD favored continuous drisapersen 6 mg/kg/wk over placebo at both Week 24 (6.40% difference; p=0.010) and Week 48 (6.26%; p=0.049). Although the difference from placebo for the intermittent 6 mg/kg group was smaller, the value was

numerically greater than placebo (0.71% at Week 24, p=0.776; 4.91% at Week 48, p=0.139). In Study 876, the treatment difference at Week 24 (5.25%, p=0.051) favored drisapersen 6 mg/kg/wk over placebo treatment. The treatment effect was also observed at the end of the post-treatment period (Week 48), albeit slightly reduced (4.85%). No treatment benefit was observed in the drisapersen 3 mg/kg/wk group.

4.7.3.2 Study 044

As with the primary endpoint (6MWD), the treatment effect for the secondary endpoints tended to be smaller in Study 044 than in the Phase II studies, with fewer secondary endpoint results favoring drisapersen treatment over placebo at Week 48 overall (Figure 4.7.3.2.1).

Figure 4.7.3.2.1: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints at Week 48 in Study 044



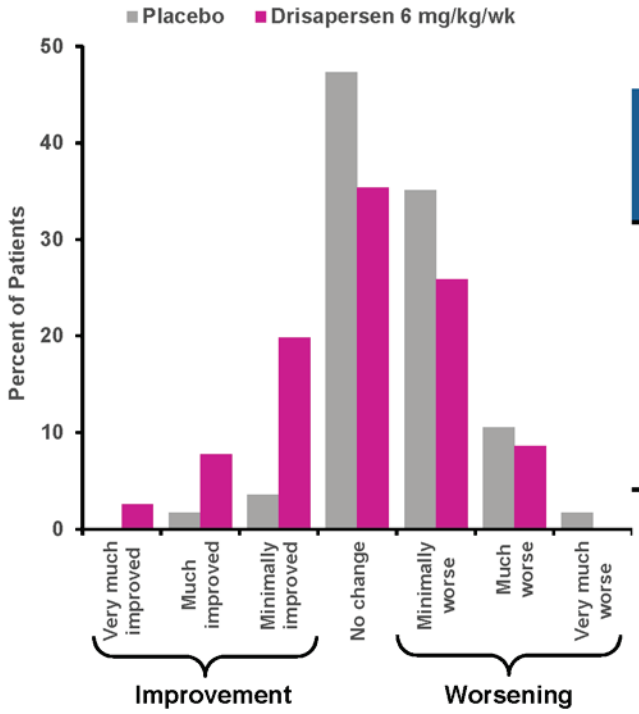
6MWD, 6-minute walking distance in meters; CI, confidence interval; FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment; PedsQL™, Pediatric Quality of Life™; SD, standard deviation.

Numbers on x-axis represent the standardized mean difference which is the difference in mean outcome between treatment groups divided by the SD of outcome among patients.

In Study 044, percent-predicted 6MWD decreased in both treatment groups, with a smaller decrease at Week 48 in patients treated with drisapersen 6 mg/kg/wk than placebo (treatment difference: 2.01%, p=0.32). Similar to the values for baseline 6MWD, baseline percent-predicted 6MWD was lower in this study than in the Phase II studies.

A significant effect in favor of drisapersen was seen in the clinician assessment of how treatment affected the patients in Study 044 as measured by the Clinical Global Impression of Improvement (CGI-I) (Figure 4.7.3.2.2).

Figure 4.7.3.2.2: Clinical Global Impression of Improvement in Study 044 at Week 48



	Placebo N=57 %	Drisapersen 6 mg/kg/wk N=116 %
Any improvement	5	30
Much or very improved	2	10
Any worsening	47	35
Much or very much worse	12	9

Expressing the CGI-I data for Study 044 categorically, only 5% of placebo-treated patients showed any improvement compared with 30% of drisapersen-treated patients. Drisapersen treatment also resulted in more patients assessed as much improved by clinicians (10%) than placebo (2%) (Table 4.7.3.2.1).

Table 4.7.3.2.1: Clinical Global Impression of Improvement by Category in Study 044 at Week 48

CGI-I Category, n (%)	Placebo n=57	Drisapersen 6 mg/kg/wk n=116
Any improvement	3 (5.3)	35 (30.1)
Much improved	1 (1.8)	12 (10.3)
Any worsening	27 (47.4)	40 (34.5)
Much worsened	7 (12.3)	10 (8.6)

CGI-I, Clinical Global Impression of Improvement.

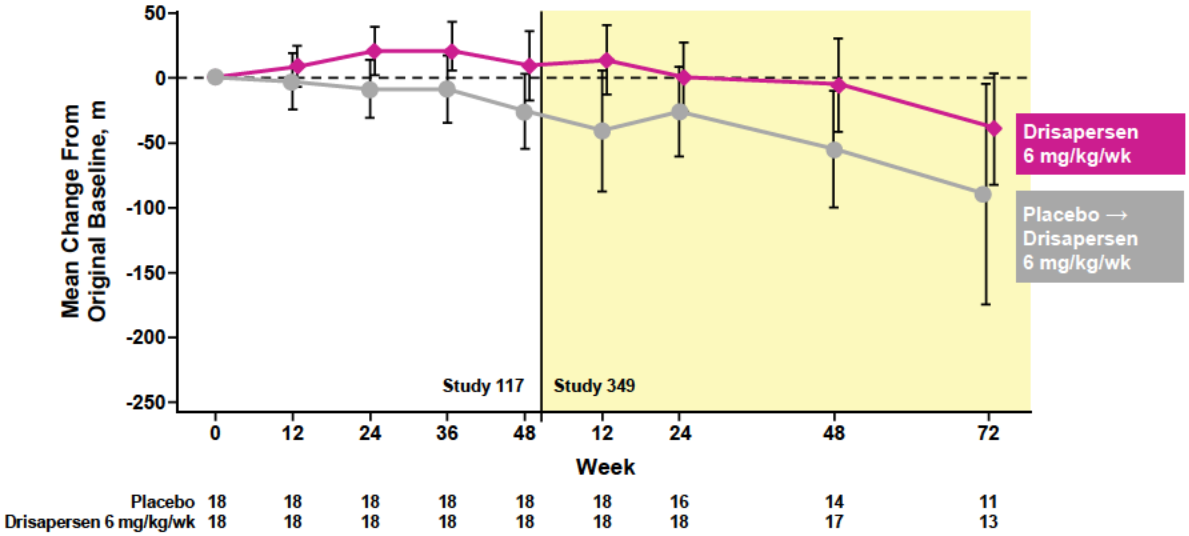
4.7.4 Long-Term Studies

4.7.4.1 Study 349

Study 349 was designed as a long-term, open-label extension study for patients who participated in Study 117 and Study 044. Patients with tolerability issues had the option to enter the intermittent arm of 6 mg/kg/wk for 8 weeks followed by 4 weeks off dose. Patients who did not wish to receive drisapersen or who had to withdraw from both active arms during the study had the option to go into a natural history observation arm. At study initiation, 228 patients were enrolled in the continuous treatment arm (6 mg/kg/wk), 4 in the intermittent arm, and 1 in the natural history arm. In addition, original study data for 6 patients who participated in Study 044 but did not enroll in or receive treatment in Study 349 were added to this long-term efficacy and safety population. Prior to entry into Study 349, 79 of the 239 patients had been treated with placebo, 143 with drisapersen 6 mg/kg/wk, and 17 with drisapersen 6 mg/kg intermittently. At time of study termination (20 September 2013), treatment duration ranged from 5 to 101 weeks.

Long-term data from Study 349 for patients initially enrolled in Study 117 showed the effect of drisapersen treatment on maintenance of functional capacity (Figure 4.7.4.1.1). After a total of 96 weeks of treatment (Study 349 Week 48), there was an ~50-meter treatment difference for change in 6MWD from the parent study baseline 6MWD value in patients who had received drisapersen 6 mg/kg/wk in the parent study (-5.06 meters) compared with patients who had received placebo in the parent study (-54.7 meters). These patients had a maximum treatment duration of 101 weeks. After the end of treatment, a decline in 6MWD was seen in both treatment groups. A treatment difference was still evident after 120 weeks, with a mean change in 6MWD of 39.2 meters in the drisapersen 6 mg/kg/wk group compared with 89.4 meters in the placebo group. These findings reinforce that patients who are treated with drisapersen at a younger age (and presumably prior to onset of more serious functional impairment) will benefit more in the long term.

Figure 4.7.4.1.1: Mean Change from Original Baseline in 6MWD in Long-Term Study 349 for Patients from Parent Study 117 (ITT Population)

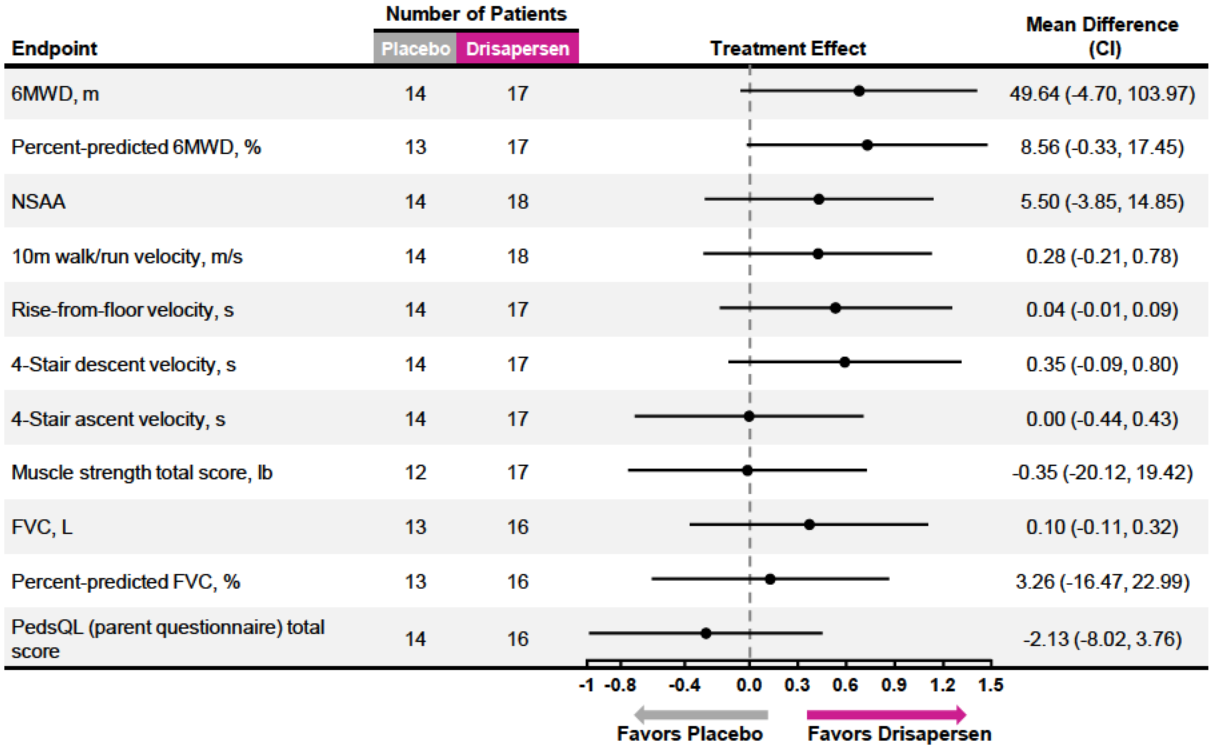


6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population.

In the long-tern extension Study 349, patients who received placebo in Study 117 switched to drisapersen 6 mg/kg/wk and patients who received drisapersen 6 mg/kg/wk continued to receive drisapersen; the vertical line on the graph delineates the transition from placebo to treatment.

After a total of 96 weeks of treatment (Study 349 Week 48), patients treated with drisapersen 6 mg/kg/wk in parent Study 117 continued to show a favorable directional change in the majority of secondary endpoints compared with those who received placebo in the parent study and drisapersen in the extension study (Figure 4.7.4.1.2).

Figure 4.7.4.1.2: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints at Week 96 in Long-Term Study 349 in Patients from Parent Study 117

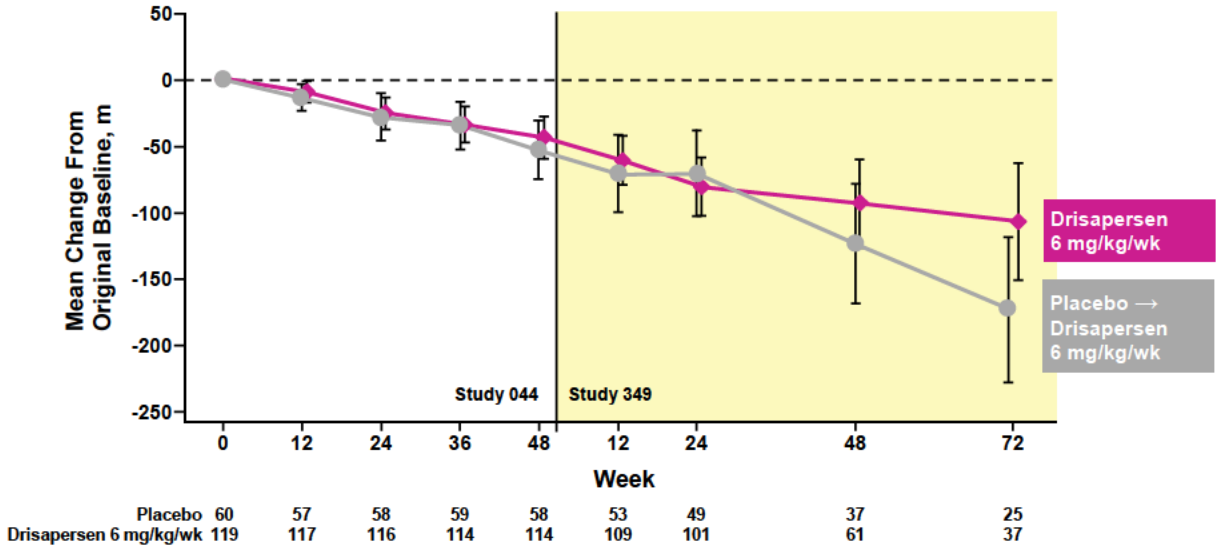


6MWD, 6-minute walking distance in meters; CI, confidence interval; FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment; PedsQL™, Pediatric Quality of Life™; SD, standard deviation.

Numbers on x-axis represent the standardized mean difference which is the difference in mean outcome between treatment groups divided by the SD of outcome among patients.

Long-term data from Study 349 for patients initially enrolled in Study 044 showed an improved treatment effect in patients who received longer-term drisapersen treatment compared with those who received drisapersen from Week 48 onward. After 96 weeks (Study 349 Week 48), a treatment difference of ~30 meters was observed for change in 6MWD from the original parent study baseline (-92.3 meters for drisapersen 6 mg/kg/wk patients vs -124.6 meters in placebo patients now receiving drisapersen 6 mg/kg in the extension study) (Figure 4.7.4.1.3, Table 4.7.4.1.1). After 120 weeks (Study 349 Week 72), the treatment difference had increased further (~58 meters), suggesting that more progressed patients can still receive a treatment benefit with drisapersen with a longer course of treatment. Although the drop-out rate complicates interpretation of these long-term data, the loss of patients was mostly due to termination of parent study, rather than patient outcomes.

Figure 4.7.4.1.3: Mean Change From Original Baseline in 6MWD for Patients in Long-Term Study 349 From Parent Study 044 (ITT Population)



6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population.

In the long-tern extension Study 349, patients who received placebo in Study 044 switched to drisapersen 6 mg/kg/wk and patients who received drisapersen 6 mg/kg/wk continued to receive drisapersen; the vertical line on the graph delineates the transition from placebo to treatment.

Table 4.7.4.1.1: Change From Original Baseline in 6MWD in Long-Term Study 349 by Parent Study 044 (ITT Populations)

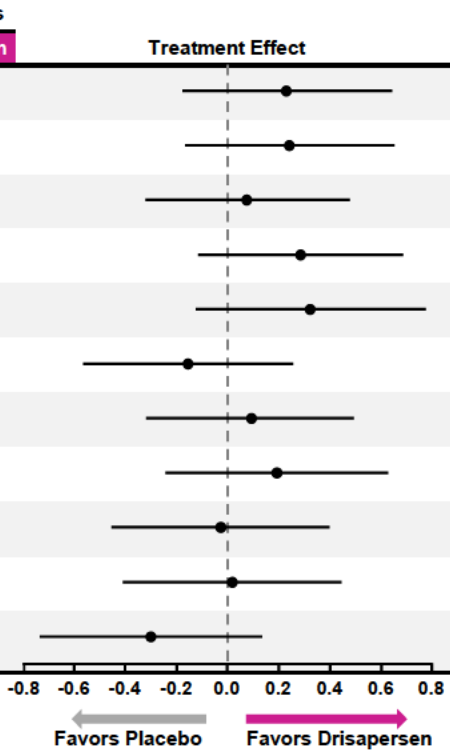
Treatment in Parent Study 044	**Placebo**	**Drisapersen 6 mg/kg/wk**
Treatment in Study 349	**Drisapersen 6 mg/kg/wk**	**Drisapersen 6 mg/kg/wk**
Original baseline, n	60	116
Mean 6MWD ± SD, meters	348.26 ± 92.91	345.90 ± 92.18
Median 6MWD, meters	354.50	360.00
Change to Study 349 Week 48, n	36	61
Mean 6MWD ± SD, meters	-124.64 ± 136.06	-92.29 ± 130.45
Median 6MWD, meters	-94.50	-65.00
Change to Study 349 Week 72, n	24	35
Mean ± SD	-165.78 ± 130.73	-107.86 ± 133.86
Median 6MWD, meters	-171.25	-83.60

6MWD, 6-minute walking distance in meters; ITT, intent-to-treat population; SD, standard deviation.

Although the effects of drisapersen for the secondary endpoints in Study 044 were smaller than those of the other placebo-controlled studies at Week 48, the treatment effect improved in patients who received an additional 48 weeks of treatment with drisapersen 6 mg/kg/wk in extension Study 349 (Figure 4.7.4.1.4). At Week 96 (Study 349 Week 48), the treatment effect was similar in patients who participated in parent Study 044 compared with Study 117. As with the 6MWD, the more severely progressed patients in Study 044 had treatment benefits for the majority of secondary endpoints with a longer duration of treatment.

Figure 4.7.4.1.4: Treatment Effect of Drisapersen 6 mg/kg/wk on Efficacy Endpoints in Long-Term Study 349 in Patients from Parent Study 044 at Week 96

Endpoint	Number of Patients: Placebo	Number of Patients: Drisapersen	Mean Difference (CI)
6MWD, m	37	61	30.34 (-24.29, 84.96)
Percent-predicted 6MWD, %	37	61	4.64 (-3.33, 12.61)
NSAA	38	65	1.10 (-4.95, 7.15)
10m walk/run velocity, m/s	38	64	0.15 (-0.06, 0.37)
Rise-from-floor velocity, s	30	53	0.07 (-0.03, 0.16)
4-Stair descent velocity, s	36	61	-0.08 (-0.29, 0.13)
4-Stair ascent velocity, s	37	62	0.04 (-0.14, 0.22)
Muscle strength total score, lb	31	58	5.55 (-7.15, 18.25)
FVC, L	33	59	-0.01 (-0.18, 0.16)
Percent-predicted FVC, %	33	59	0.50 (-13.13, 14.14)
PedsQL (parent questionnaire) total score	32	56	-3.31 (-8.13, 1.52)



6MWD, 6-minute walking distance in meters; CI, confidence interval; FVC, forced vital capacity; NSAA, North Star Ambulatory Assessment; PedsQL™, Pediatric Quality of Life™; SD, standard deviation.

Numbers on x-axis represent the standardized mean difference which is the difference in mean outcome between treatment groups divided by the SD of outcome among patients.

In the overall ITT population of Study 349, patients who received drisapersen in both the parent study and the extension study had a notably smaller decline in 6MWD and percent-predicted 6MWD than those who received placebo in the parent study followed by drisapersen in the extension study.

After 96 weeks of drisapersen 6 mg/kg/wk (Study 349 Week 48), the mean change in percent-predicted 6MWD was -16.0% compared with -21.2% in patients who received placebo in the parent study and drisapersen 6 mg/kg/wk in the extension study, a difference

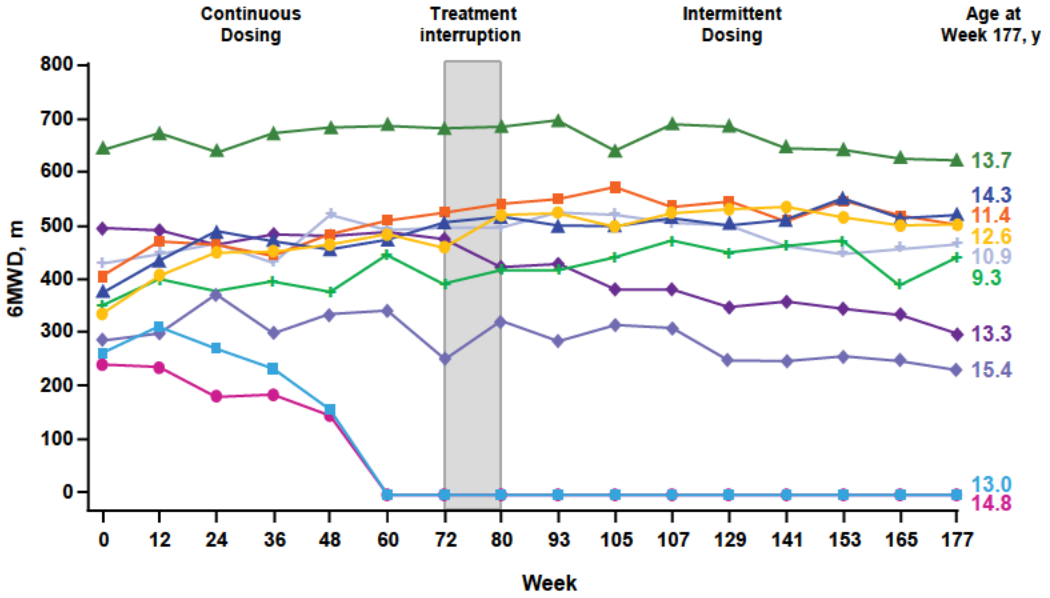
of approximately 5%. After 120 weeks (Study 349 Week 72), the difference in the change in mean percent-predicted 6MWD between these 2 groups had increased to approximately 9.4% (-18.5% vs -27.9%).

Due to the relative sizes of the parent study populations, the overall results from Study 349 mirror the results seen for the subset of patients from parent Study 044 (53/239 patients from parent Study 117). At Week 48 in extension Study 349, the mean change in 6MWD was -73.3 meters for drisapersen 6 mg/kg/wk (96 weeks of drisapersen treatment) compared with -104.0 meters in patients who received placebo in the parent study and drisapersen 6 mg/kg/wk in the extension study, for a difference of approximately 31 meters. At Week 72 in Study 349, the difference between these 2 patient groups in the change in mean 6MWD had increased to about 59 meters (-88.5 meters with 120 weeks of drisapersen treatment vs -147.2 meters with 72 weeks of drisapersen treatment).

4.7.4.2 Study 673

Study 673 is a Phase I/II open-label extension of study PRO051-02, a Phase I/II open-label, rising-dose study of 12 ambulant and nonambulant patients with Duchenne muscular dystrophy, and is the longest running study in the drisapersen clinical program. Given the need for chronic treatment in Duchenne muscular dystrophy, Study 673 provides key data to support the long-term benefit of drisapersen on the natural course of disease progression. In Study 673, the 12 patients had been treated for approximately three and a half years, and in the 11 patients who attempted the 6MWD (10 of whom were able to complete the assessment), median change from baseline at Week 177 was -22.0 meters (range, -263 to 163 meters) as shown in Figure 4.7.4.2.1 much less than would be expected in this time period in patients treated with the current standard of care. Those patients who were considered “stable” at baseline (7/12) and able to complete the 6MWD showed a median improvement of 91 meters (range, -198 to 163 meters). Stable patients were able to complete the timed function tests with a similar performance as their baseline value. In contrast, the “declining” patients (5/12) had decreases in their timed function tests compared with their baseline values. Overall, patients in Study 673, particularly those identified as having “stable” disease at baseline, showed stable performance on secondary endpoints over more than 3 years of treatment as shown in Figure 4.7.4.2.2 for rise-from-the-floor time. These results represent an improvement over the expected decline trajectory seen in natural history studies for this progressive disorder.

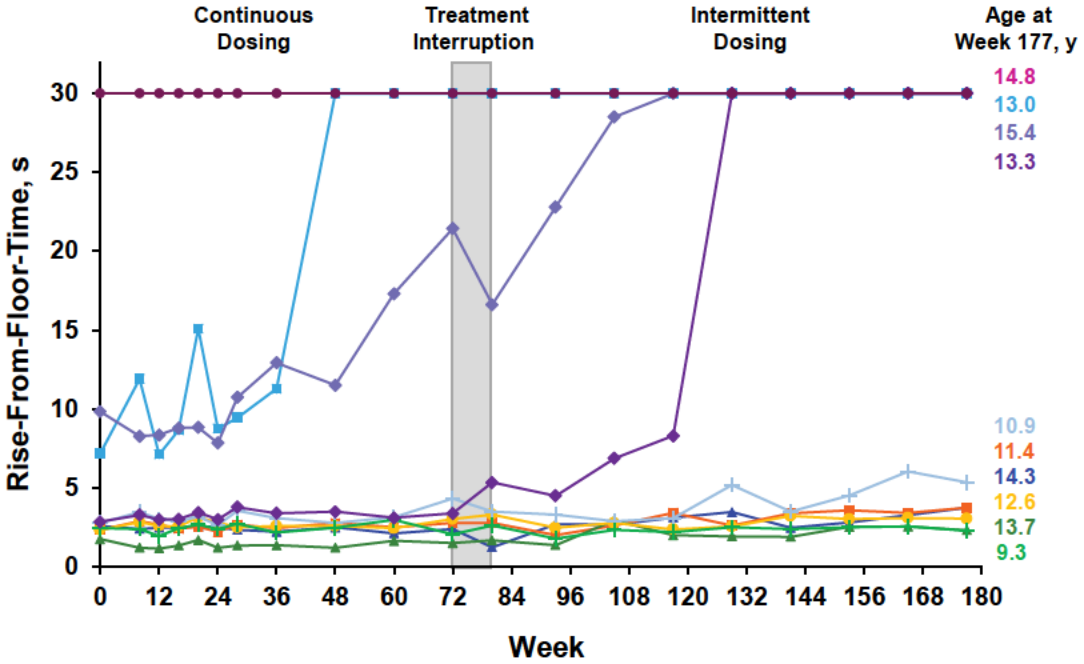
Figure 4.7.4.2.1: Long-Term 6MWD Results in Study 673



6MWD, distance walked in 6 minutes in meters.

Data shown are for all patients who completed the test at extension study baseline. One patient (Patient 201) was nonambulant at study entry and did not participate in any 6MWD tests; another patient (Patient 103) was unable to complete the 6MWD test at extension study baseline. Data for both of these patients are not included here.

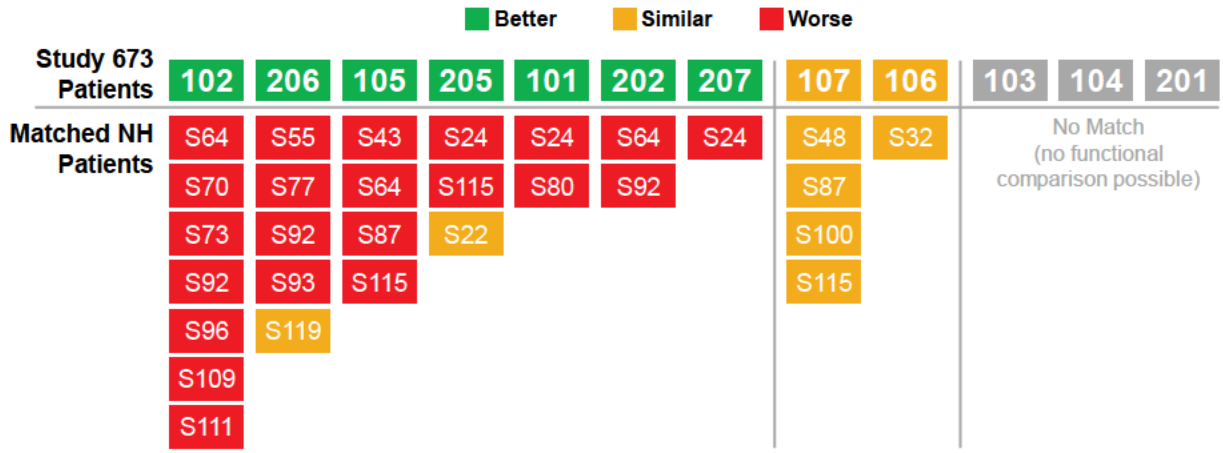
Figure 4.7.4.2.2: Long-Term Rise-From-the-Floor Results in Study 673



Data shown are for all patients who completed the test at extension study baseline. Rise-from-the-floor time is imputed as 30 seconds when patients were unable to perform the test.

Long-term data from this study demonstrate a durable treatment effect over more than 3 years of treatment when compared with control patients with Duchenne muscular dystrophy in a matched natural history (NH) cohort (data on file, BioMarin Pharmaceutical Inc., May 2014). Patients in Study 673 were matched to 1 or more patients receiving continuous steroid treatment in a NH cohort from 1 investigative site in Study 673 (n=89) using age and baseline 6MWD. Matching was possible for 9 of the 12 drisapersen-treated patients; each was matched to at least 1 and up to 7 NH patients (n=29), as shown in Figure 4.7.4.2.3. The 3 unmatched patients are in grey in the figure below. Overall, of the 9 drisapersen-treated patients with NH matches, 7 had a better functional trajectory compared with their matched NH patients (green), and 2 (both of whom lost ambulation) had similar functional ability as their NH matches (yellow). None of the drisapersen-treated patients were considered to be functionally worse than their NH matches. Patient trajectories from this matching exercise are found in Appendix A.

Figure 4.7.4.2.3: Comparison of Individually Matched Drisapersen and Natural History Cohort Patients in Study 673



NH, natural history cohort.

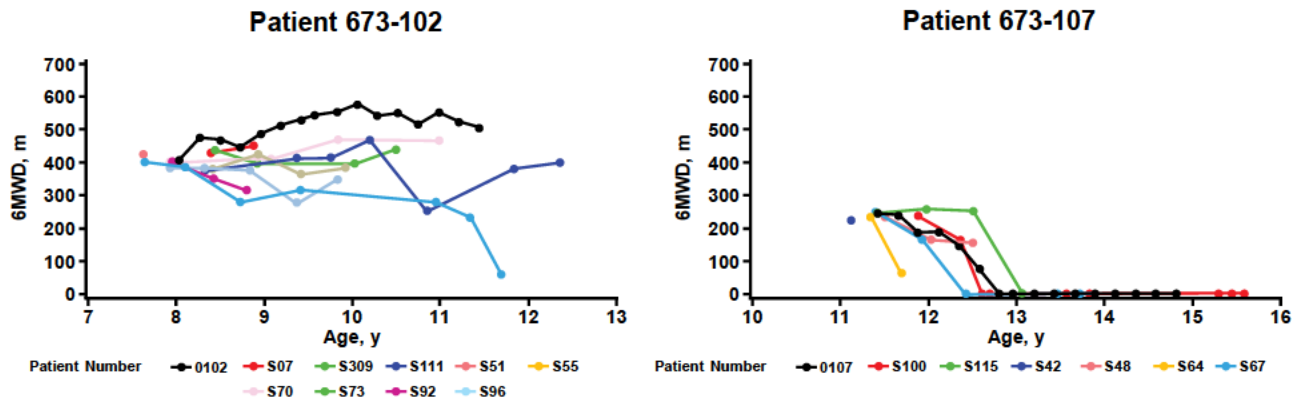
The 9 matched drisapersen patients were divided into 2 categories based on baseline ambulatory ability; 6 patients had stable function at baseline (6MWD ≥ 300 meters) and 3 patients had declined function at baseline (6MWD < 300 meters).

In the 6 matched drisapersen patients with stable function at baseline, a clear difference in ambulatory ability, measured by 6MWD, was evident compared with their NH matches. None of these drisapersen patients lost ambulation, and substantial gains from baseline of up to 192 meters were reported. Increases of this magnitude were not seen in patients in the NH control population. In contrast, 25% of the unique matched NH patients lost ambulation during the period of observation and 1 additional NH match lost approximately 85% of their ambulatory capacity.

In the 3 matched drisapersen patients with declined function at baseline, a difference between drisapersen and NH patients was less apparent; 2 of the 3 drisapersen patients lost ambulation (67%) compared with 6 of the 8 (75%) NH unique matches.

Measurements of 6MWD over time (6MWD trajectories) for 2 representative patients and their matched control subjects are shown in Figure 4.7.4.2.4. Patient 673-102, representing stable ambulatory status, had stable function over time, while patient 673-107, representing patients with declining ambulatory status, had declining function over time as measured by 6MWD. See Appendix A for the remaining patient trajectories.

Figure 4.7.4.2.4: Example Patient Trajectories From Study 673 With Matched Natural History Subjects



Black dotted line represents the patient from Study 673. Other lines are contemporaneous control data. Control data presented from the first record that matched with the Study 673 patient at baseline. Single data points are subjects that match, but have no additional follow-up data.

Despite limitations to this exercise, this analysis shows a divergence between drisapersen patients and the anticipated natural history of Duchenne muscular dystrophy over a three and a half year period, highly relevant in a rare disease setting.

4.8 Efficacy Conclusions

Overall, drisapersen demonstrated a substantial beneficial effect in 3 placebo-controlled and 2 open-label extension studies. In all studies conducted to date, a treatment difference in favor of drisapersen was observed on the 6MWD assessment. Secondary endpoint analyses also supported the positive treatment effect of drisapersen as summarized in Figure 4.8.1.

Figure 4.8.1: Summary of Primary and Key Secondary Endpoint Results

Endpoint	Study 117 Week 48	Study 876 Week 24	Study 044 Week 48	349 from Study 117 Week 96	349 from Study 044 Week 96
6MWD (m)	●	●	●	●	●
Percent-predicted 6MWD (%)	●	●	●	●	●
NSAA	●	●	●	●	●
10m walk/run velocity (m/s)	●	●	●	●	●
Rise from floor velocity (rises/s)	●	●	●	●	●
4-stair descent velocity (stairs/s)	●	●	●	●	●
4-stair ascent velocity (stairs/s)	●	●	●	●	●
Muscle strength total score (lbs)	●	●	●	●	●
Forced vital capacity (L)	●	●	●	●	●
Percent predicted FVC (%)	●	●	●	●	●

6MWD, distance walked in 6 minutes in meters; FVC, forced vital capacity; NSAA, North Star Ambulatory assessment; PedsQL, Pediatric Quality of Life Inventory.
Green circles indicate endpoint result favored drisapersen; red circles indicate endpoint result favored placebo.

Two studies (Studies 117 and 876) demonstrated improvement in 6MWD after 24 weeks of treatment, compared with placebo. This improvement was statistically significant in Study 117 and was sustained through an additional 24 weeks of treatment. The primary endpoint findings in Study 117 were supported by improvement at 48 weeks in percent-predicted 6MWD (nominal $p = 0.049$), a measure that corrects for maturation. In Study 876, a pronounced but not statistically significant ($p < 0.07$) improvement trend was seen at 24 weeks in the drisapersen-treated group, which persisted though an additional 24 weeks of observation off-treatment.

An important difference in design between the 2 Phase II studies was the use of a loading dose in Study 117 and its absence in Study 876. Pharmacokinetic data indicate that steady state with weekly dosing may not be reached until after 36 weeks of treatment. In Study 117, the loading dose increased initial exposure of muscle to drisapersen and maximized the time at steady state. Lack of a loading dose in Study 876 may have influenced the difference in the results of the 2 studies. A post hoc integrated analysis of the Studies 117 and 876 confirmed the beneficial treatment effect of drisapersen at 24 weeks, with a nominal p value of 0.0025.

The Phase III Study 044 demonstrated a smaller but positive trend (non-statistically significant) toward improvement in 6MWD compared with placebo. In this study, the key variables of baseline rise-from-the-floor time, age, and 6MWD, subsequently shown to be

prognostic, were not stratified in the randomization scheme for Study 044, resulting in substantial imbalances in these variables between treatment groups. Moreover, the broad eligibility criteria in Study 044 resulted in inclusion of patients unlikely to benefit from drisapersen treatment, due to advanced fat and fibrous infiltration into the muscles of patients at imminent risk of losing ambulation, with a corresponding dilution of treatment effect. Study 044 enrolled an older and more progressed patient population that was not represented in Studies 117 and 876; 31% of patients were aged 7 years or older and had a baseline 6MWD of ≤ 330 meters at baseline.

Removal of the older and more progressed subgroup, which is less sensitive to improvement in ambulatory function, revealed that the treatment effect in Study 044 in younger, less progressed patients – those with well-preserved muscle – was similar in magnitude to that seen in Studies 117 and 876. A similar treatment effect was also seen in older but more functional patients (baseline 6MWD > 330 meters) in Study 044.

However, appropriately addressing these issues to estimate the magnitude of benefit in Study 044 is a challenging endeavor. Post hoc analyses should be interpreted with caution; yet the rarity of Duchenne muscular dystrophy, the limited information and understanding of natural history available when the trials were designed, and the urgent unmet medical need for therapies for this disorder are important considerations in evaluating the results. These analyses show that drisapersen improves 6MWD in an ambulatory population in Study 044. This finding is corroborated by the results of the 2 other randomized placebo-controlled trials, which can be used to characterize the magnitude of benefit in an unbiased fashion.

Long-term data from extension Study 349 for patients initially treated with drisapersen in Study 117 showed a durable treatment effect in 6MWD through 120 weeks of treatment. The treatment benefit in favor of continuous drisapersen treatment compared with delayed treatment (patients who received placebo in the controlled phase of the study) reinforces the need to treat early to maintain functional capacity.

Patients initially treated with drisapersen in Study 044 showed a treatment benefit in 6MWD compared with those initially treated with placebo after 96 weeks that was similar to the other placebo-controlled results at Week 48. This treatment effect continued to increase in magnitude through Week 120 and was supported by directional trends in secondary endpoint analyses. These long-term findings suggest more severely affected patients with Duchenne muscular dystrophy may still benefit from treatment with drisapersen over an extended period of time.

Long-term data from the open-label Study 673 demonstrated a durable treatment effect over three and a half years of treatment. Drisapersen-treated patients with stable ambulatory function at baseline preserved their walking ability over the course of the study, whereas 25% of the matched cohort of non-treated patients lost ambulation.

The totality of data from the development program demonstrates that drisapersen, at the recommended dose of 6 mg/kg/wk administered by SC injection, provides meaningful and potentially life-changing benefits for patients with an immediate, urgent, unmet medical need.

5 OVERVIEW OF SAFETY

The safety of drisapersen has been evaluated in the largest database of patients with Duchenne muscular dystrophy assembled to date, which includes 326 patients with the disorder. The safety profile has been examined in as much detail as possible given the rarity of Duchenne muscular dystrophy, and shown to be acceptable at the recommended dose of 6 mg/kg/wk based on extensive, long-term exposure of up to 3.5 years.

The majority of drisapersen-related AEs were mild or moderate in intensity. The most clinically significant side effects were thrombocytopenia, proteinuria (primarily nonprogressive subclinical events), and injection site reactions. The observed AEs were consistent with the class-related effects identified for phosphorothioate oligonucleotides (Kwoh 2008, Levin 2001, Levin 2008, Henry 2008).

Most of the adverse drug reactions observed to date are considered manageable through close monitoring and risk minimization measures that will be described in the proposed prescribing information.

5.1 Clinical Studies with Drisapersen

Nine studies, 2 of which are ongoing, provide information to characterize the safety of drisapersen (see Table 1.3.1.1). A total of 312 patients have received at least 1 dose of the drug (safety population). The primary focus of the safety summary is the integrated safety dataset, comprising 302 patients treated in 6 repeat-dose studies (Studies PRO051-02, 117, 876, 044, 673, and 349); 285 of these patients received drisapersen, 267 patients with the 6 mg/kg/wk regimen.

Table 5.1.1 shows key eligibility criteria for enrollment in the short-term repeat-dose and placebo-controlled repeat-dose studies that are relevant to safety considerations.

Table 5.1.1: Key Eligibility Criteria Important for Safety Considerations for PRO051-02 and Placebo-Controlled Repeat-Dose Studies 117, 876, and 044

PRO051-02 (Short-term, repeat-dose, open-label)	• Aged 5–16 years • Life expectancy of ≥6 months • Ambulant and nonambulant • Not ventilator dependent • No serum AST or ALT concentrations suggesting hepatic impairment • Creatinine concentration not >1.5 x ULN • No history of liver or renal disease or severe mental retardation or cardiac myopathy deemed by the investigator to prohibit study participation

Studies 117, 876, and 044 (Repeat-dose, placebo-controlled, Phase II and III studies)	• Aged ≥5 years • Life expectancy of ≥1 year • Ambulant (able to complete 6MWD of ≥75 meters) • QT interval corrected for heart rate (QTc), either by Bazett's formula (QTcB) or Fridericia's formula (QTcF), of <450 msec (or <480 msec for patients with bundle branch block in Studies 044 and 876) • No history of liver or renal disease/impairment and no symptomatic cardiomyopathy • Corticosteroid treatment for ≥6 months prior to screening (stable dose for ≥3 months) • In Study 876 only, aPTT < the ULN and platelets > the LLN

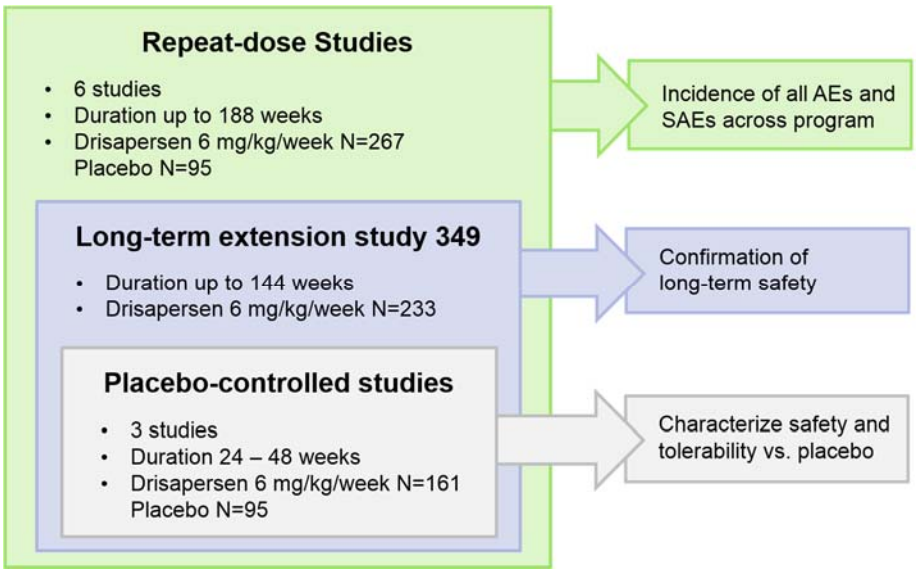
aPTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; LLN, lower limit of normal; ULN, upper limit of normal.

Patients who completed short-term, repeat-dose Study PRO051-02 were eligible to participate in Study 673, the uncontrolled open-label extension study, if the patient and/or parents, the investigator, and sponsor all agreed that treatment appeared to improve the patient's clinical status. Patients in Studies 117 and 044 were eligible to enter the long-term extension Study 349 if they had successfully completed the parent study, or withdrawn due to safety issues or did not wish to continue drisapersen treatment but were willing to participate in the natural history observation arm. Ambulant patients who became nonambulant during the parent study were permitted in the extension study.

5.2 Overall Safety Analysis Plan

Figure 5.2.1 shows the key study groupings for safety analyses.

Figure 5.2.1: Study Groupings for Safety Analyses



AE, adverse event; SAE, serious adverse event.

A comprehensive safety monitoring plan was followed in all drisapersen clinical studies. Clinical trial safety assessments included recording of AEs and SAEs; monitoring of hematology, blood chemistry and urinary parameters; and physical examination, blood pressure, and ECG assessments. Table 5.2.1 lists the safety assessments in each study.

In addition, adverse events of special interest (AESI) were identified based on the nonclinical experience with drisapersen and published safety data of other phosphorothioate oligonucleotides (Levin 2001, Levin 2008, Henry 2008). These include thrombocytopenia, renal abnormalities, injection site reactions, inflammation events, coagulation abnormalities, and hepatic abnormalities.

Table 5.2.1: Safety Assessments in Drisapersen Studies

	Repeat-Dose Placebo-Controlled Studies			Short-Term Repeat-Dose	Open-Label Extensions		Single-Dose Studies	
Safety Variable	Study 117	Study 876	Study 044	PRO051 -02	Study 673	Study 349	PRO051 -01	Study 118
AEs/SAEs	X	X	X	X	X	X	X	X
Physical examinations[a]	X	X	X	X	X	X	X	X
Hematology and biochemistry[b]	X	X	X	X	X	X	X	X
Urinalysis[c]	X	X	X	X	X	X	X	X
24-hour urinalysis[d]	X	X	X		X	X		X
Vital signs	X	X	X	X	X	X	X	X
ECG parameters	X	X	X	X	X	X	X	X
Echocardiogram	X	X	X		X	X		
Renal ultrasound		X						

AE, adverse event; ECG, electrocardiogram; SAE, serious adverse event.

a Included measurement of weight at regular intervals throughout the studies.

b Including nonstandard parameters such as coagulation parameters (in particular, activated partial thromboplastin time [aPTT]), cystatin C, α1-microglobulin, kidney injury molecule-1 (KIM-1), complement factor C3, haptoglobin, fibrinogen, high sensitivity C-reactive protein (CRP) in most studies

c In addition to urinalysis (which included microscopy in all studies except PRO051-02), urine cystatin C was assessed (not done in Study 118).

d Included creatinine concentrations for creatinine clearance assessment, total protein, and protein electrophoresis.

5.3 Exposure

A total of 312 patients have received at least 1 dose of drisapersen. In the placebo-controlled studies group (n=290), similar proportions of patients in the placebo (92.6%) and drisapersen 6 mg/kg/wk (95.7%) groups were treated for at least 24 weeks; slightly more patients in the placebo than drisapersen 6 mg/kg/wk group were treated for at least 48 weeks (Table 5.3.1). In the 48-week placebo-controlled studies (Studies 117 and 044), most patients in both treatment groups were treated for at least 24 weeks (78/79 [98.7%] with placebo and

142/143 [99.3%] with drisapersen 6 mg/kg/wk), and slightly more with placebo (64/79 [81.0%]) than drisapersen (95/143 [66.4%]) were treated for at least 48 weeks.

Table 5.3.1: Overall Cumulative Exposure Duration (Placebo-Controlled Studies)

Exposure (Weeks)	Placebo n=95 n (%)	Drisapersen 3 mg/kg/wk n=17 n (%)	Drisapersen 6 mg/kg/wk n=161 n (%)	Drisapersen 6 mg/kg Intermittent [a] N=17 n (%)	Drisapersen All Regimens N=195 n (%)
≥ 1	99 (104.2)[b]	17 (100)	162 (100.6)[b]	17 (100)	196 (100.5)[b]
≥ 4	95 (100)	17 (100)	161 (100)	17 (100)	195 (100)
≥ 12	94 (98.9)	17 (100)	160 (99.4)	17 (100)	194 (99.5)
≥ 24	88 (92.6)	13 (76.5)	154 (95.7)	17 (100)	184 (94.4)
≥ 48	64 (67.4)	0	95 (59.0)	17 (100)	112 (57.4)

[a] Intermittent dosing was 9 doses in 10-week cycle (6 mg/kg twice weekly in Weeks 1, 3, and 5; 6 mg/kg once weekly in Weeks 2, 4, and 6; no dosing in Weeks 7 to 10.

[b] Four patients in Study 044 randomized to drisapersen 6 mg/kg/wk received a single dose of placebo, and 1 patient in Study 117 randomized to placebo received a single dose of drisapersen 6 mg/kg/wk; these patients are counted in both treatment groups for the actual exposure to each treatment received and thus the number (%) of patients exposed can be greater than the number randomized to each treatment.

Note: Table includes data from Studies 117, 044, and 876.

Of 285 patients treated with drisapersen (any regimen) in the repeat dose studies grouping, 95.1% were treated for at least 24 weeks, 78.2% for at least 48 weeks, and 42.8% for at least 96 weeks. The maximum exposure was ≥192 weeks (3 patients [1.1%]). In the drisapersen 6 mg/kg/wk group, 82.0% (219/267) of patients were treated for at least 48 weeks and 36.7% (98/267) for at least 96 weeks (Table 5.3.2).

The total drisapersen exposure was 490.1 patient-years. In the repeat-dose studies, exposure to drisapersen 6 mg/kg/wk was 432.7 patient-years compared with 79.4 patient-years for placebo. These exposure differences should be considered when reviewing safety data for the repeat-dose studies.

Table 5.3.2: Overall Cumulative Exposure Duration (Repeat-Dose Studies)

Exposure (Weeks)	Placebo n=95 n (%)	Drisapersen 3 mg/kg/wk n=17 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen 6 mg/kg Intermittent[a] n=17 n (%)	Drisapersen 6 mg/kg Intermittent[b] n=24 n (%)	Drisapersen All Regimens[c] n=285 n (%)
≥ 1	99 (104.2)[d]	17 (100)	267 (100)	17 (100)	24 (100)	285 (100)
≥ 4	95 (100)	17 (100)	267 (100)	17 (100)	24 (100)	285 (100)
≥ 12	94 (98.9)	17 (100)	266 (99.6)	17 (100)	23 (95.8)	284 (99.6)
≥ 24	88 (92.6)	13 (76.5)	257 (96.3)	17 (100)	20 (83.3)	271 (95.1)
≥ 48	64 (67.4)	0	219 (82.0)	17 (100)	15 (62.5)	223 (78.2)
≥ 72	0	0	180 (67.4)	0	15 (62.5)	192 (67.4)
≥ 96	0	0	98 (36.7)	0	11 (45.8)	122 (42.8)
≥ 120	0	0	57 (21.3)	0	0	84 (29.5)
≥ 144	0	0	15 (5.6)	0	0	32 (11.2)
≥ 168	0	0	0	0	0	12 (4.2)
≥ 192	0	0	0	0	0	3 (1.1)

[a] Intermittent dosing with 9 doses in 10-week cycle: 6 mg/kg twice weekly in Weeks 1, 3, and 5; 6 mg/kg once weekly in Weeks 2 and 4; and no dosing in Weeks 7–10.

[b] Intermittent dosing with 8 doses in 12-week cycle: 6 mg/kg/wk for 8 weeks then 4 weeks with no dosing.

[c] Patients treated with >1 drisapersen regimen are only counted once in this group; group also includes data from 3 patients treated with 0.5 mg/kg/wk, 3 with 2 mg/kg/wk, and 3 with 4 mg/kg/wk, each for ≥4 weeks; the data for each individual treatment group are not shown in table.

[d] Four patients randomized to drisapersen 6 mg/kg/wk received a single dose of placebo, and 1 patient randomized to placebo received a single dose of drisapersen 6 mg/kg/wk; these patients are counted in both treatment groups for the actual exposure to each treatment received and thus the number (%) of patients exposed can be greater than the number randomized to each treatment.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673. Since patients could have used >1 drisapersen regimen, the exposure duration to drisapersen all regimens is longer than for any individual regimen.

In addition, safety data have been evaluated for the 120-day safety update. As of the cut-off date for this update (April 2015), 297 patients had been treated with drisapersen (all regimens) in the repeat-dose studies. Among these patients, 133 (45%) had been exposed to drisapersen for at least 96 weeks, and the total exposure was 542 patient-years. No new safety findings were identified.

5.4 Patient Disposition

In the placebo-controlled studies group, 99% (160/161) of patients treated with drisapersen 6 mg/kg/wk and 99% (94/95) with placebo were treated for at least 24 weeks, and 86% (139/161) and 82% (78/95), respectively, for at least 48 weeks. Five patients withdrew from

the studies, including 1 of 95 patients (1%) treated with placebo and 4 of 161 (2%) with drisapersen 6 mg/kg/wk. The placebo patient withdrew for a protocol violation; 2 (1%) drisapersen-treated patients withdrew consent, and 2 (1%) withdrew for adverse events. More details about patients withdrawing for AEs can be found in Section 5.10.

In the repeat-dose studies group, 93.3% of patients were treated with drisapersen (any regimen) for at least 24 weeks and 75.1% for at least 48 weeks. Excluding 220 patients who withdrew early because of study closure/termination, a total of 16 patients withdrew prematurely (Table 5.4.1). The most common reason was consent withdrawn (11 patients). Of the 11 patients who withdrew consent, 5 did not specify a reason, 3 cited the burden of trial visits, 2 noted uncertainty regarding the effect of the drug or the side effects, and for 1 patient the investigator noted that "parents did not want the patient to become aware of his gradually declining muscle strength."

Three patients withdrew for an AE (see Section 5.10). Patients withdrawing from treatment for AEs could have continued participating in the intermittent or natural history arms of extension Study 349, and were therefore not counted as discontinuations from the study.

Table 5.4.1: Patient Disposition (Repeat-Dose Studies)

	Placebo n=95 n (%)	Drisapersen 3 mg/kg/wk n=17 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen Intermittent[a] n=17 n (%)	Drisapersen 6 mg/kg Intermittent[b] n=24 n (%)	Drisapersen All Regimens[c] n=285 n (%)
Completed Week 24	94 (98.9)	17 (100)	248 (92.9)	17 (100)	22 (91.7)	266 (93.3)
Completed Week 48[d]	78 (82.1)	0	211 (79.0)	17 (100)	20 (83.3)	214 (75.1)
Withdrawn	1 (1.1)	0	224 (83.9)	0	12 (50.0)	236 (82.8)
Primary reason[e] for study withdrawal						
Adverse events	0	0	3 (1.1)	0	0	3 (1.1)
Lack of efficacy	0		2 (0.7)	0	0	2 (0.7)
Protocol deviation	1 (1.1)	0	0	0	0	0
Study closed/terminated	0	0	208 (77.9)	0	12 (50.0)	220 (77.2)
Withdrew consent	0	0	11 (4.1)	0	0	11 (3.9)

a Intermittent dosing with 9 doses in 10-week cycle (6 mg/kg twice weekly in Weeks 1, 3, and 5; 6 mg/kg once weekly in Weeks 2, 4, and 6; no dosing in Weeks 7–10).

b Intermittent dosing with 8 doses in 12-week cycle (6 mg/kg/wk for 8 weeks then 4 weeks with no dosing).

c Patients treated with >1 drisapersen regimen are only counted once in this group. Group includes data from 3 patients treated with 0.5 mg/kg/wk, 3 with 2 mg/kg/wk, and 3 with 4 mg/kg/wk; the data for each of these treatment groups are not shown; no patient was withdrawn during treatment with these doses.

d Patients in Study 876 received study medication for 24 weeks only, and are therefore not included in the number of patients completing 48 weeks of treatment.

e Patients may have only 1 primary reason for withdrawal.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673.

'Completed Week 24' and 'Completed Week 48' means that the patient had nominally reached these time points in the study but if some treatment doses were missed they may not have completed 24 and 48 weeks, respectively, of exposure to study treatment. Also in Study 117, the baseline visit was labelled 'Week 1 Day 1', and 'Week 25' occurred at the end of 24 weeks of treatment and 'Week 49' occurred at the end of 48 weeks of treatment, so Week 25 and Week 49 correspond to Week 24 and Week 48 in other studies.

5.5 Concomitant Medications

There was no integrated analysis of concomitant medication use. Use of concomitant medications, including corticosteroids, was similar across treatment groups in each of the placebo-controlled studies. The majority of patients were treated with continuous rather than intermittent corticosteroids: 86% continuous versus 14% intermittent, respectively, in Study 044; 60% versus 40% in Study117; and 94% versus 6% in Study 876.

In extension Study 349, inclusion criteria included being on a stable corticosteroid regimen. The most common corticosteroids used by the 233 enrolled patients were deflazacort (45%), prednisolone (32%), or prednisone (27%). Many patients received oral analgesics, local

anesthetics, or dermatologic creams to minimize discomfort of the SC injection. Other commonly used medications were for pediatric standard of care (eg, immunization, nutritional supplements, and antibiotics) or other standard-of-care medications for respiratory and cardiac management of children with Duchenne muscular dystrophy.

5.6 Adverse Events Overview

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version that was used for each individual study (MedDRA version [v] 12.1 for Studies PRO051-02 and 673, v15 for Study 117, v16 for Studies 044 and 349, and v16.1 for Study 876). For the integrated safety analyses, all AEs were recoded using the MedDRA v16.1. Treatment-emergent AEs included on-treatment AEs (occurred within 28 days of the last dose of study treatment) and follow-up AEs (occurred from Day 29 after the last dose).

A serious AE was defined as an AE that resulted in death, disability, or incapacity; was life-threatening; required/or prolonged hospitalization; was a congenital anomaly or birth defect; was an important medical event requiring medical intervention to prevent any of the above outcomes; and all events of possible drug-induced liver injury (the latter not included in SAE definition in PRO051-02 or PRO051-01).

In the following tables, data are shown for the placebo, drisapersen 6 mg/kg/wk, and drisapersen all-regimens groups. For the placebo-controlled studies, data are not explicitly shown in the tables for the 3 mg/kg/wk (n=17) and 6 mg/kg intermittent (n=17) dose groups due to their small sample sizes, but are included in the drisapersen all regimens column. For the repeat-dose studies, data are not explicitly shown for the drisapersen 0.5 mg/kg/wk (n=3), 2 mg/kg/wk (n=3), 3 mg/kg/wk (n=17), 4 mg/kg/wk (n=3), or 6 mg/kg intermittent (n=38) dose groups; those data are included in the drisapersen all regimens column.

5.6.1 Placebo-Controlled Studies

Almost all patients in the drisapersen and placebo treatment groups reported AEs in the placebo-controlled studies (Table 5.6.1.1). Most events (~90%) were mild or moderate, with similar distribution by intensity in both treatment groups. The investigators considered more AEs to be study drug–related with drisapersen 6 mg/kg/wk compared with placebo treatment.

Similar proportions of patients had SAEs in the placebo (9.5%), drisapersen 6 mg/kg/wk (9.3%), and drisapersen all regimens (8.7%) treatment groups. Two patients, both treated with drisapersen 6 mg/kg/wk, had study drug discontinued or were withdrawn due to AEs (Section 5.10).

More patients treated with drisapersen than placebo experienced AESIs. Rates of injection site reactions and renal abnormalities were higher with drisapersen compared with placebo, and hepatic abnormality rates were slightly higher with drisapersen. Rates of inflammation events were similar in the 2 treatment groups, and coagulation abnormalities were reported more frequently with placebo (AESIs are described in more detail in Section 5.11).

Table 5.6.1.1: Overview of Adverse Events (Placebo-Controlled Studies)

	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=161 n (%)	Drisapersen All Regimens n=195 n (%)
Any AE (on treatment or during follow-up)	90 (94.7)	158 (98.1)	192 (98.5)
Any on-treatment AE	89 (93.7)	158 (98.1)	191 (97.9)
Any AE during follow-up period	10 (10.5)	18 (11.2)	27 (13.8)
Any mild AE	37 (38.9)	65 (40.4)	78 (40.0)
Any moderate AE	49 (51.6)	82 (50.9)	102 (52.3)
Any severe AE	4 (4.2)	11 (6.8)	12 (6.2)
Any drug-related AE[a]	46 (48.4)	142 (88.2)	167 (85.6)
Any death	0	0	0
Any nonfatal SAE	9 (9.5)	15 (9.3)	17 (8.7)
Any drug-related SAE[a]	0	2 (1.2)	3 (1.5)
Study drug discontinued or study withdrawal due to on-treatment AE[b]	0	2 (1.2)	2 (1.0)
Any AESI	58 (61.1)	147 (91.3)	173 (88.7)

AE, adverse event; AESI, adverse event of special interest; SAE, serious adverse event.

a Investigator judgement of causality.

b Includes patients who had on-treatment AE with action taken recorded as study drug discontinued.

Note: Table includes data from Studies 117, 044, and 876. Patients were counted once in each treatment group they were dosed in and once in the 'all regimens' group. The all regimens group includes 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups. Only AEs recorded as part of the included studies are presented for this study grouping. There may be some differences compared with tables for the repeat-dose study grouping where AEs recorded between the end of treatment in the parent studies (Studies 117 and 044) and the beginning of extension Study 349 were also included and allocated to the treatment group within the parent study as on-treatment AEs if the onset was within 28 days of the last dose in parent study, or as AEs during follow-up if AE onset was >28 days. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received a single dose of placebo, and 1 patient from Study 044 randomized to placebo received a single dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

5.6.2 Repeat-Dose Studies

The differences in exposure durations between the placebo (79.4 patient-years) and the drisapersen 6 mg/kg/wk (432.7 patient-years) and drisapersen all regimens (490.1 patient-years) groups should be considered when evaluating AE data in the repeat-dose studies.

Almost all patients receiving placebo and drisapersen reported an on-treatment AE in the repeat-dose studies (Table 5.6.2.1). The AEs were considered study drug–related by the investigator in more patients treated with drisapersen than placebo.

Most of the AEs were mild or moderate in intensity. Serious AEs were reported in 9.5% of patients treated with placebo, 16.5% with drisapersen 6 mg/kg/wk, and 16.1% with drisapersen all regimens. Twelve patients (4.2%), all treated with drisapersen 6 mg/kg/wk, experienced AEs leading to study drug discontinuation (Section 5.10).

More patients treated with drisapersen than placebo reported AEs within the AESI categories, with the exception of coagulation abnormalities (AESIs are described in more detail in Section 5.11).

There were no major differences between each of the repeat-dose studies in rates of AEs or SAEs. There were no important AE differences in subgroups defined by race or age, or in AE reporting in different countries.

All patients in the repeat-dose studies were required to be on stable corticosteroid treatment. Analyses showed no important differences in the overview of AEs between those taking corticosteroids continuously versus intermittently in the repeat-dose studies grouping.

Table 5.6.2.1: Overview of Adverse Events (Repeat-Dose Studies)

	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens n=285 n (%)
Any AE (on-treatment or during follow-up)	90 (94.7)	263 (98.5)	281 (98.6)
Any on-treatment AE	89 (93.7)	262 (98.1)	279 (97.9)
Any AE during follow-up period[b]	16 (16.8)	142 (53.2)	160 (56.1)
Any mild AE	37 (38.9)	85 (31.8)	93 (32.6)
Any moderate AE	49 (51.6)	134 (50.2)	143 (50.2)
Any severe AE	4 (4.2)	44 (16.5)	45 (15.8)
Any drug-related AE[c]	46 (48.4)	247 (92.5)	259 (90.9)
Any death	0	0	0
Any nonfatal SAE[d]	9 (9.5)	44 (16.5)	46 (16.1)
Any drug-related SAE[c,d]	0	15 (5.6)	16 (5.6)
Study drug discontinued or study withdrawal due to on-treatment AE[e]	0	12 (4.5)	12 (4.2)
Any AESI	58 (61.1)	252 (94.4)	265 (93.0)

AE, adverse events; AESI, adverse event of special interest; SAEs, serious adverse events.

[a] In addition to drisapersen 6 mg/kg/wk, the all regimens group include patients treated with 0.5 mg/kg/wk (n=3), 2 mg/kg/wk (n=3), 3 mg/kg/wk (n=17), 4 mg/kg/wk (n=3), and 6 mg/kg intermittently (n=38). Patients treated with >1 drisapersen regimen are only counted once in this group.

[b] Study 876 had a defined 24-week follow-up period; in other studies no follow-up period was defined for all patients.

[c] Investigator judgment of causality.

[d] Both on-treatment and follow-up SAEs are included.

[e] Includes patients who had on-treatment AE with action taken recorded as study drug discontinued; includes patients who discontinued the study and those who moved to another treatment arm if permitted.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673. Patients were counted once in each treatment group they were dosed in and once in the 'all regimens' group. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received 1 dose of placebo, and 1 patient from Study 044 randomized to placebo received 1 dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the 'n' for the placebo group only.

5.7 Common Adverse Events

5.7.1 Placebo-Controlled Studies

Table 5.7.1.1 shows the common AEs in patients treated with drisapersen 6 mg/kg/wk or placebo in the placebo-controlled studies, by System Organ Class (SOC) and preferred term. Adverse events occurring in more patients (>5%) treated with drisapersen 6 mg/kg/wk than placebo were injection-site reactions and renal abnormalities. Other AEs reported more commonly with drisapersen 6 mg/kg/wk were gastroenteritis, diarrhea, headache, and arthralgia.

Table 5.7.1.1: On-Treatment Adverse Events (≥5%) (Placebo-Controlled Studies)

System Organ Class Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=161 n (%)
Any adverse event	**89 (93.7)**	**158 (98.1)**
General disorders and administration site conditions	**44 (46.3)**	**138 (85.7)**
Injection site erythema	8 (8.4)	85 (52.8)
Injection site discoloration	5 (5.3)	56 (34.8)
Pyrexia	22 (23.2)	41 (25.5)
Injection site reaction	2 (2.1)	29 (18.0)
Injection site pain	5 (5.3)	26 (16.1)
Injection site pruritus	1 (1.1)	26 (16.1)
Injection site bruising	9 (9.5)	19 (11.8)
Injection site hematoma	6 (6.3)	14 (8.7)
Injection site induration	1 (1.1)	17 (10.6)
Injection site swelling	0	11 (6.8)
Injection site atrophy	0	9 (5.6)
Injection site urticaria	0	10 (6.2)
Chest pain	5 (5.3)	2 (1.2)
Infections and infestations	**70 (73.7)**	**110 (68.3)**
Nasopharyngitis	30 (31.6)	51 (31.7)
Upper respiratory tract infection	18 (18.9)	20 (12.4)
Gastroenteritis	6 (6.3)	19 (11.8)
Rhinitis	9 (9.5)	15 (9.3)
Influenza	5 (5.3)	10 (6.2)
Pharyngitis	5 (5.3)	6 (3.7)
Ear infection	6 (6.3)	6 (3.7)
Gastrointestinal disorders	**48 (50.5)**	**85 (52.8)**
Vomiting	23 (24.2)	38 (23.6)
Diarrhea	15 (15.8)	35 (21.7)
Abdominal pain	10 (10.5)	21 (13.0)
Abdominal pain upper	4 (4.2)	12 (7.5)
Constipation	6 (6.3)	10 (6.2)
Nausea	7 (7.4)	8 (5.0)
Investigations	**28 (29.5)**	**76 (47.2)**
Protein urine present	6 (6.3)	20 (12.4)
Cystatin C increased	4 (4.2)	17 (10.6)
Urine protein/creatinine ratio increased	4 (4.2)	14 (8.7)
Red blood cells urine positive	5 (5.3)	15 (9.3)
Red blood cells urine	5 (5.3)	13 (8.1)
Protein urine	0	8 (5.0)
Blood fibrinogen decreased	7 (7.4)	6 (3.7)

System Organ Class Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=161 n (%)
Injury, poisoning and procedural complications	**47 (49.5)**	**71 (44.1)**
Fall	19 (20.0)	35 (21.7)
Procedural pain	7 (7.4)	9 (5.6)
Contusion	10 (10.5)	12 (7.5)
Excoriation	7 (7.4)	8 (5.0)
Ligament sprain	6 (6.3)	8 (5.0)
Renal and urinary disorders	**26 (27.4)**	**66 (41.0)**
Proteinuria	16 (16.8)	47 (29.2)
Hematuria	5 (5.3)	24 (14.9)
Respiratory, thoracic and mediastinal disorders	**32 (33.7)**	**52 (32.3)**
Cough	22 (23.2)	29 (18.0)
Epistaxis	6 (6.3)	12 (7.5)
Nasal congestion	3 (3.2)	9 (5.6)
Rhinorrhea	3 (3.2)	9 (5.6)
Oropharyngeal pain	7 (7.4)	6 (3.7)
Nervous system disorders	**26 (27.4)**	**49 (30.4)**
Headache	20 (21.1)	43 (26.7)
Dizziness	5 (5.3)	1 (0.6)
Musculoskeletal and connective tissue disorders	**28 (29.5)**	**38 (23.6)**
Pain in extremity	15 (15.8)	13 (8.1)
Arthralgia	1 (1.1)	11 (6.8)
Back pain	9 (9.5)	9 (5.6)
Muscle spasms	5 (5.3)	6 (3.7)
Skin and subcutaneous tissue disorders	**25 (26.3)**	**35 (21.7)**
Rash	13 (13.7)	5 (3.1)
Vascular disorders	**7 (7.4)**	**7 (4.3)**
Hematoma	5 (5.3)	2 (1.2)
Eye disorders	**6 (6.3)**	**9 (5.6)**
Psychiatric disorders	**8 (8.4)**	**6 (3.7)**
Metabolism and nutrition disorders	**6 (6.3)**	**8 (5.0)**
Ear and labyrinth disorders	**7 (7.4)**	**7 (4.3)**
Ear pain	5 (5.3)	6 (3.7)

Note: Table includes data from Studies 117, 044, and 876.

Only AEs recorded as part of the included studies are presented for this study grouping. There may therefore be some differences compared with the repeat-dose study grouping where AEs recorded between the end of treatment in the parent studies (Studies 117 and 044) and the beginning of Study 349 have also been included and have been allocated to the treatment group within in the parent study as on-treatment AEs if the onset was within 28 days of the last dose in the parent study, or as AEs during follow-up if the onset is >28 days. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received 1 dose of placebo, and 1 patient from Study 044 randomized to placebo received 1 dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

5.7.1.1 Time to Occurrence of Adverse Events

Most of the AEs within the general disorders and administrative site conditions SOC, including injection-site reactions, occurred in more than 2% of patients within 4 weeks of drisapersen treatment and were more frequent compared with placebo in the placebo-controlled studies (Table 5.7.1.1.1). In contrast, in the investigations and renal and urinary disorders SOCs, fewer than 2% of drisapersen-treated patients had AEs in the first 4 weeks. While proteinuria was rare in the first 4 weeks of treatment, this AE was more common in patients treated with drisapersen compared with placebo over the first year. (Patients were defined as having "proteinuria" as determined by the investigator.)

At 1 year after treatment initiation, AEs observed in at least 20% of patients treated with drisapersen 6 mg/kg/wk were injection site erythema, injection site discoloration, nasopharyngitis, proteinuria, headache, pyrexia, vomiting, fall, and diarrhea (Table 5.7.1.1.1). These AEs were observed in more patients after 52 weeks than after 24 weeks of treatment.

The pattern of incidence over 1 year of nasopharyngitis, headache, pyrexia, vomiting, fall, and diarrhea was similar for the drisapersen 6 mg/kg/wk and placebo treatment groups.

Table 5.7.1.1.1: Cumulative Incidence of Most Frequent (≥5%) On-Treatment Adverse Events by Time to First Occurrence up to 1 Year of Treatment (Placebo-Controlled Studies)

Adverse Event SOC and Preferred Term	Placebo (n=95)				Drisapersen 6 mg/kg/wk (n=161)			
	Time Since Start of Study Medication							
	≤1 wk n (%)	≤4 wk n (%)	≤24 wk n (%)	≤52 wk n (%)	≤1 wk n (%)	≤4 wk n (%)	≤24 wk n (%)	≤52 wk n (%)
Any adverse event	17 (17.9)	43 (45.3)	80 (84.2)	87 (91.6)	64 (39.8)	106 (65.8)	142 (88.2)	154 (95.7)
General disorders and administration site conditions								
Injection site erythema	1 (1.1)	3 (3.2)	7 (7.4)	8 (8.4)	28 (17.4)	52 (32.3)	78 (48.4)	85 (52.8)
Injection site discoloration	0	0	4 (4.2)	5 (5.3)	6 (3.7)	18 (11.2)	40 (24.8)	56 (34.8)
Pyrexia	1 (1.1)	4 (4.2)	12 (12.6)	22 (23.2)	7 (4.3)	12 (7.5)	30 (18.6)	41 (25.5)
Injection site pruritus	NR	NR	NR	NR	2 (1.2)	10 (6.2)	24 (14.9)	26 (16.1)
Injection site reaction	0	1 (1.1)	1 (1.1)	NR	0	4 (2.5)	21 (13.0)	29 (18.0)
Injection site pain	0	0	3 (3.2)	5 (5.3)	7 (4.3)	8 (5.0)	17 (10.6)	26 (16.1)
Injection site bruising	1 (1.1)	2 (2.1)	7 (7.4)	9 (9.5)	8 (5.0)	10 (6.2)	18 (11.2)	19 (11.8)
Injection site hematoma	0	2 (2.1)	5 (5.3)	6 (6.3)	4 (2.5)	7 (4.3)	11 (6.8)	14 (8.7)
Injections site induration	NR	NR	NR	NR	1 (0.6)	5 (3.1)	10 (6.2)	17 (10.6)
Injection site swelling	NR	NR	NR	NR	1 (0.6)	3 (1.9)	10 (6.2)	11 (6.8)
Injection site urticaria	NR	NR	NR	NR	1 (0.6)	5 (3.1)	7 (4.3)	10 (6.2)
Injection site atrophy	NR	NR	NR	NR	0	0	2 (1.2)	9 (5.6)
Chest pain	1 (1.1)	1 (1.1)	4 (4.2)	5 (5.3)	NR	NR	NR	NR
Infections and infestations								
Nasopharyngitis	0	4 (4.2)	22 (23.2)	30 (31.6)	0	6 (3.7)	41 (25.5)	51 (31.7)
Gastroenteritis	0	0	4 (4.2)	6 (6.3)	1 (0.6)	3 (1.9)	11 (6.8)	19 (11.8)
Upper respiratory tract infection	2 (2.1)	6 (6.3)	14 (14.7)	18 (18.9)	1 (0.6)	4 (2.5)	10 (6.2)	20 (12.4)
Rhinitis	0	1 (1.1)	8 (8.4)	9 (9.5)	0	2 (1.2)	13 (8.1)	15 (9.3)
Influenza	0	0	4 (4.2)	5 (5.3)	1 (0.6)	2 (1.2)	6 (3.7)	10 (6.2)
Ear infection	1 (1.1)	1 (1.1)	4 (4.2)	6 (6.3)	0	0	4 (2.5)	6 (3.7)
Pharyngitis	0	2 (2.1)	3 (3.2)	5 (5.3)	0	0	2 (1.2)	6 (3.7)

Adverse Event SOC and Preferred Term	Placebo (n=95)				Drisapersen 6 mg/kg/wk (n=161)			
	Time Since Start of Study Medication							
	≤1 wk n (%)	≤4 wk n (%)	≤24 wk n (%)	≤52 wk n (%)	≤1 wk n (%)	≤4 wk n (%)	≤24 wk n (%)	≤52 wk n (%)
Gastrointestinal disorders								
Vomiting	1 (1.1)	2 (2.1)	12 (12.6)	23 (24.2)	3 (1.9)	8 (5.0)	28 (17.4)	38 (23.6)
Diarrhea	1 (1.1)	2 (2.1)	11 (11.6)	15 (15.8)	4 (2.5)	9 (5.6)	24 (14.9)	35 (21.7)
Abdominal pain	0	2 (2.1)	8 (8.4)	10 (10.5)	1 (0.6)	6 (3.7)	16 (9.9)	21 (13.0)
Abdominal pain upper	0	0	4 (4.2)	4 (4.2)	1 (0.6)	2 (1.2)	8 (5.0)	12 (7.5)
Constipation	0	1 (1.1)	4 (4.2)	6 (6.3)	1 (0.6)	3 (1.9)	6 (3.7)	10 (6.2)
Nausea	1 (1.1)	1 (1.1)	3 (3.2)	7 (7.4)	2 (1.2)	2 (1.2)	4 (2.5)	8 (5.0)
Injury, poisoning and procedural complications								
Fall	0	1 (1.1)	10 (10.5)	19 (20.0)	1 (0.6)	8 (5.0)	20 (12.4)	35 (21.7)
Procedural pain	1 (1.1)	2 (2.1)	5 (5.3)	7 (7.4)	5 (3.1)	5 (3.1)	7 (4.3)	9 (5.6)
Contusion	0	1 (1.1)	6 (6.3)	10 (10.5)	2 (1.2)	3 (1.9)	7 (4.3)	12 (7.5)
Excoriation	1 (1.1)	2 (2.1)	4 (4.2)	7 (7.4)	0	0	4 (2.5)	8 (5.0)
Ligament sprain	0	2 (2.1)	5 (5.3)	6 (6.3)	0	1 (0.6)	5 (3.1)	8 (5.0)
Investigations								
Protein urine present	0	1 (1.1)	5 (5.3)	6 (6.3)	0	1 (0.6)	9 (5.6)	20 (12.4)
Red blood cells urine positive	0	0	4 (4.2)	5 (5.3)	0	1 (0.6)	8 (5.0)	15 (9.3)
Red blood cells urine	0	0	3 (3.2)	5 (5.3)	0	2 (1.2)	9 (5.6)	13 (8.1)
Urine protein/creatinine ratio increased	0	1 (1.1)	4 (4.2)	4 (4.2)	0	2 (1.2)	4 (2.5)	14 (8.7)
Cystatin C increased	0	0	2 (2.1)	4 (4.2)	0	1 (0.6)	5 (3.1)	17 (10.6)
Protein urine	NR	NR	NR	NR	0	1 (0.6)	6 (3.7)	8 (5.0)
Blood fibrinogen decreased	0	2 (2.1)	5 (5.3)	7 (7.4)	1 (0.6)	2 (1.2)	6 (3.7)	6 (3.7)
Renal and urinary disorders								
Proteinuria	0	1 (1.1)	8 (8.4)	16 (16.8)	0	1 (0.6)	29 (18.0)	47 (29.2)
Hematuria	0	0	3 (3.2)	5 (5.3)	0	2 (1.2)	14 (8.7)	24 (14.9)
Respiratory, mediastinal and thoracic disorders								
Cough	1 (1.1)	3 (3.2)	14 (4.7)	22 (23.2)	1 (0.6)	5 (3.1)	14 (8.7)	29 (18.0)
Epistaxis	0	1 (1.1)	2 (2.1)	6 (6.3)	2 (1.2)	4 (2.5)	9 (5.6)	12 (7.5)
Nasal congestion	0	0	3 (3.2)	3 (3.2)	0	1 (0.6)	7 (4.3)	9 (5.6)
Rhinorrhea	0	0	0	3 (3.2)	0	2 (1.2)	5 (3.1)	9 (5.6)
Oropharyngeal pain	0	1 (1.1)	6 (6.3)	7 (7.4)	0	2 (1.2)	6 (3.7)	6 (3.7)
Nervous system disorders								
Headache	3 (3.2)	8 (8.4)	16 (16.8)	20 (21.1)	6 (3.7)	10 (6.2)	32 (19.9)	43 (26.7)
Dizziness	1 (1.1)	1 (1.1)	4 (4.2)	5 (5.3)	NR	NR	NR	NR
Musculoskeletal and connective tissue disorders								
Pain in extremity	2 (2.1)	2 (2.1)	12 (12.6)	15 (15.8)	1 (0.6)	2 (1.2)	9 (5.6)	13 (8.1)
Back pain	0	0	3 (3.2)	9 (9.5)	0	1 (0.6)	5 (3.1)	9 (5.6)

Adverse Event SOC and Preferred Term	Placebo (n=95)				Drisapersen 6 mg/kg/wk (n=161)			
	Time Since Start of Study Medication							
	≤1 wk n (%)	≤4 wk n (%)	≤24 wk n (%)	≤52 wk n (%)	≤1 wk n (%)	≤4 wk n (%)	≤24 wk n (%)	≤52 wk n (%)
Arthralgia	NR	NR	NR	NR	0	0	3 (1.9)	11 (6.8)
Skin and subcutaneous tissue disorders								
Rash	1 (1.1)	2 (2.1)	6 (6.3)	13 (13.7)	0	0	4 (2.5)	5 (3.1)
Ear and labyrinth disorders								
Ear pain	0	1 (1.1)	2 (2.1)	5 (5.3)	0	0	2 (1.2)	6 (3.7)
Vascular disorders								
Hematoma	0	0	2 (2.1)	5 (5.3)	NR	NR	NR	NR

NR, not reported in at least 2% of patients in this treatment group; SOC, system organ class.

Notes: Table includes data from Studies 117, 044, and 876. Most frequent defined as AEs occurring in ≥5% in either treatment group. Events are ordered by SOC and by descending cumulative frequency of preferred term in the drisapersen group within each SOC. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received 1 dose of placebo, and 1 patient from Study 044 randomized to placebo received 1 dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

5.7.2 Repeat-Dose Studies

Based on exposure-adjusted incidence rates, more on-treatment AEs occurred in patients who received placebo (112.09/100 patient-years) than drisapersen 6 mg/kg/wk (60.55/100 patient-years) or drisapersen all regimens (56.93/100 patient-years).

By this analysis, the only AEs (occurring in ≥5% of patients) reported more frequently with drisapersen 6 mg/kg/wk than placebo were injection-site events (such as injection site erythema, discoloration, induration, pain, reaction, pruritus, atrophy, and swelling), renal abnormalities (such as proteinuria, hematuria, albuminuria, protein urine present, red blood cells urine positive, cystatin C increased, urine protein/creatinine ratio increased, protein urine), thrombocytopenia, complement factor C3 decreased, glutamate dehydrogenase increased, arthralgia, gastroenteritis, and abdominal pain upper (Table 5.7.2.1). Some of these AEs by preferred term are within the AESI categories (see Section 5.11).

For AEs reported in ≥2% but <5% of drisapersen-treated patients, exposure-adjusted incidence rates were higher with drisapersen 6 mg/kg/wk than placebo for injection site reactions, renal abnormalities, inflammation events (C-reactive protein increased), hepatic abnormalities (gamma glutamyl transferase increased), alopecia, asthenia, paronychia, femur fracture, arthropod sting, muscle contracture, foot fracture, neck pain, hypersensitivity, and urinary tract infection.

Table 5.7.2.1: Incidence Rates/100 Patient-Years of On-Treatment Adverse Events (≥5%) (Repeat-Dose Studies)

Adverse Event System Organ Class and Preferred Term	Placebo n=95 Exposure: 79.4 Patient-years Rate per 100 Patient-years	Drisapersen 6 mg/kg/wk n=267 Exposure: 432.7 Patient-years Rate per 100 Patient-years	Drisapersen All Regimens[a] n=285 Exposure: 490.1 Patient-years Rate per 100 Patient-years
General disorders and administration site conditions			
Injection site erythema	10.08	32.82	32.65
Injection site discoloration	6.30	29.12	27.14
Pyrexia	27.71	20.11	18.77
Injection site induration	1.26	18.26	16.53
Injection site pain	6.30	12.02	11.83
Injection site reaction	2.52	12.25	11.43
Injection site pruritus	1.26	10.86	11.43
Injection site bruising	11.34	8.09	8.37
Injection site hematoma	7.56	7.86	8.37
Injection site atrophy	0	7.63	8.77
Injection site swelling	0	6.24	6.33
Fatigue	3.78	4.39	4.49
Infections and infestations			
Nasopharyngitis	39.04	22.19	21.22
Upper respiratory tract infection	22.67	9.94	10.41
Gastroenteritis	7.56	9.94	9.79
Rhinitis	11.34	8.55	7.75
Influenza	6.30	5.08	4.90
Ear infection	7.56	3.47	3.06
Pharyngitis	6.30	3.24	3.26
Bronchitis	5.04	3.00	3.06
Gastrointestinal disorders			
Vomiting	28.97	20.11	19.18
Diarrhea	18.89	16.87	15.92
Abdominal pain	13.85	10.86	10.41
Abdominal pain upper	5.04	6.70	6.73
Nausea	8.82	5.08	5.31
Constipation	7.56	4.85	4.90
Investigations			
Protein urine present	7.56	9.71	9.59
Red blood cells urine positive	6.30	8.55	8.16
Cystatin C increased	5.04	7.63	8.16
Urine protein/creatinine ratio increased	5.04	6.93	7.35
Red blood cells urine	6.30	5.55	5.51
Complement factor C3 decreased	0	3.93	3.67
Glutamate dehydrogenase increased	0	3.00	3.26

Adverse Event System Organ Class and Preferred Term	Placebo n=95 Exposure: 79.4 Patient-years Rate per 100 Patient-years	Drisapersen 6 mg/kg/wk n=267 Exposure: 432.7 Patient-years Rate per 100 Patient-years	Drisapersen All Regimens[a] n=285 Exposure: 490.1 Patient-years Rate per 100 Patient-years
Protein urine	0	3.00	3.06
Injury, poisoning and procedural complications			
Fall	23.93	15.95	14.08
Contusion	12.59	7.16	6.53
Ligament sprain	7.56	4.85	4.90
Excoriation	8.82	3.24	3.26
Procedural pain	8.82	2.08	3.06
Renal and urinary disorders			
Proteinuria	20.15	26.58	24.08
Hematuria	6.30	9.94	8.98
Albuminuria	0	2.08	3.26
Respiratory, thoracic and mediastinal disorders			
Cough	27.71	13.40	13.06
Epistaxis	7.56	8.09	7.96
Oropharyngeal pain	8.82	5.78	5.51
Rhinorrhea	3.78	3.70	3.67
Nasal congestion	3.78	3.00	3.06
Nervous system disorders			
Headache	25.19	21.96	20.40
Musculoskeletal and connective tissue disorders			
Pain in extremity	18.89	9.71	9.59
Back pain	11.34	6.70	6.53
Arthralgia	1.26	4.62	5.10
Muscle spasms	6.30	3.93	3.88
Myalgia	5.04	3.24	3.06
Skin and subcutaneous tissue disorders			
Rash	16.37	3.93	3.88
Blood and lymphatic disorders			
Thrombocytopenia	0	3.47	3.26
Ear and labyrinth disorders			
Ear pain	6.30	4.16	3.67

[a] Patients treated with >1 drisapersen regimen are only counted once in this group.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673. Rate is the number of patients per 100 patient-years adjusted for exposure. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received 1 dose of placebo, and 1 patient from Study 044 randomized to placebo received 1 dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

Table 5.7.2.2 shows the most common AEs in the repeat-dose studies, without adjustment for exposure. In the 6 mg/kg/wk arm, injection site erythema and discoloration, proteinuria,

nasopharyngitis, headache, vomiting, and pyrexia were most common and, except for nasopharyngitis, were reported in more patients treated with drisapersen than placebo. Some AEs in ≥5% (but <10%) of patients treated with drisapersen all regimens did not occur with placebo treatment. These included complement factor C3 decreased, albuminuria, glutamate dehydrogenase increased, protein urine, and thrombocytopenia. These AEs were considered within the categories of AESIs (see Section 5.11).

Other common events (>10% of drisapersen-treated patients) included diarrhea, fall, cough, upper respiratory tract infection, abdominal pain, pain in extremity, gastroenteritis, epistaxis, rhinitis, back pain, and upper abdominal pain.

Table 5.7.2.2: On-Treatment Adverse Events by System Organ Class and Preferred Term in ≥ 5% of Patients in Drisapersen All Regimen Group (Repeat-Dose Studies)

Adverse Event System Organ Class and Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
General disorders and administration site conditions			
Injection site erythema	8 (8.4)	142 (53.2)	160 (56.1)
Injection site discoloration	5 (5.3)	126 (47.2)	133 (46.7)
Pyrexia	22 (23.2)	87 (32.6)	92 (32.3)
Injection site induration	1 (1.1)	79 (29.6)	81 (28.4)
Injection site pain	5 (5.3)	52 (19.5)	58 (20.4)
Injection site reaction	2 (2.1)	53 (19.9)	56 (19.6)
Injection site pruritus	1 (1.1)	47 (17.6)	56 (19.6)
Injection site bruising	9 (9.5)	35 (13.1)	41 (14.4)
Injection site hematoma	6 (6.3)	34 (12.7)	41 (14.4)
Injection site atrophy	0	33 (12.4)	43 (15.1)
Injection site swelling	0	27 (10.1)	31 (10.9)
Fatigue	3 (3.2)	19 (7.1)	22 (7.7)
Infections and infestations			
Nasopharyngitis	31 (32.6)	96 (36.0)	104 (36.5)
Upper respiratory tract infection	18 (18.9)	43 (16.1)	51 (17.9)
Gastroenteritis	6 (6.3)	43 (16.1)	48 (16.8)
Rhinitis	9 (9.5)	37 (13.9)	38 (13.3)
Influenza	5 (5.3)	22 (8.2)	24 (8.4)
Ear infection	6 (6.3)	15 (5.6)	15 (5.3)
Bronchitis	4 (4.2)	13 (4.9)	15 (5.3)
Pharyngitis	5 (5.3)	14 (5.2)	16 (5.6)

Adverse Event System Organ Class and Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Gastrointestinal disorders			
Vomiting	23 (24.2)	87 (32.6)	94 (33.0)
Diarrhea	15 (15.8)	73 (27.3)	78 (27.4)
Abdominal pain	11 (11.6)	47 (17.6)	51 (17.9)
Abdominal pain upper	4 (4.2)	29 (10.9)	33 (11.6)
Nausea	7 (7.4)	22 (8.2)	26 (9.1)
Constipation	6 (6.3)	21 (7.9)	24 (8.4)
Investigations			
Protein urine present	6 (6.3)	42 (15.7)	47 (16.5)
Red blood cells urine positive	5 (5.3)	37 (13.9)	40 (14.0)
Cystatin C increased	4 (4.2)	33 (12.4)	40 (14.0)
Urine protein/creatinine ratio increased	4 (4.2)	30 (11.2)	36 (12.6)
Red blood cells urine	5 (5.3)	24 (9.0)	27 (9.5)
Complement factor C3 decreased	0	17 (6.4)	18 (6.3)
Glutamate dehydrogenase increased	0	13 (4.9)	16 (5.6)
Protein urine	0	13 (4.9)	15 (5.3)
Injury, poisoning, and procedural complications			
Fall	19 (20.0)	69 (25.8)	69 (24.2)
Contusion	10 (10.5)	31 (11.6)	32 (11.2)
Ligament sprain	6 (6.3)	21 (7.9)	24 (8.4)
Excoriation	7 (7.4)	14 (5.2)	16 (5.6)
Procedural pain	7 (7.4)	9 (3.4)	15 (5.3)
Renal and urinary disorders			
Proteinuria	16 (16.8)	115 (43.1)	118 (41.4)
Hematuria	5 (5.3)	43 (16.1)	44 (15.4)
Albuminuria	0	9 (3.4)	16 (5.6)
Nervous system disorders			
Headache	20 (21.1)	95 (35.6)	100 (35.1)
Respiratory, thoracic, and mediastinal disorders			
Cough	22 (23.2)	58 (21.7)	64 (22.5)
Epistaxis	6 (6.3)	35 (13.1)	39 (13.7)
Oropharyngeal pain	7 (7.4)	25 (9.4)	27 (9.5)
Rhinorrhea	3 (3.2)	16 (6.0)	18 (6.3)
Nasal congestion	3 (3.2)	13 (4.9)	15 (5.3)

Adverse Event System Organ Class and Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Skin and subcutaneous tissue disorders			
Rash	13 (13.7)	17 (6.4)	19 (6.7)
Musculoskeletal and connective tissue disorders			
Pain in extremity	15 (15.8)	42 (15.7)	47 (16.5)
Back pain	9 (9.5)	29 (10.9)	32 (11.2)
Arthralgia	1 (1.1)	20 (7.5)	25 (8.8)
Muscle spasms	5 (5.3)	17 (6.4)	19 (6.7)
Myalgia	4 (4.2)	14 (5.2)	15 (5.3)
Blood and lymphatic disorders			
Thrombocytopenia	0	15 (5.6)	16 (5.6)
Ear and labyrinth disorders			
Ear pain	5 (5.3)	18 (6.7)	18 (6.3)

[a] Patients treated with >1 drisapersen regimen are only counted once in this group.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received a single dose of placebo, and 1 patient from Study 044 randomized to placebo received a single dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

Most AEs were reported as mild or moderate in intensity. In the repeat-dose studies group, AEs were categorized as mild, moderate, or severe, respectively, in 31.8%, 49.1%, and 16.1% of patients treated with drisapersen 6 mg/kg/wk, 31.9%, 49.5%, and 15.4% with drisapersen all regimens, and 37.9%, 50.5%, and 4.2% with placebo. The pattern of AEs was generally similar in patients aged ≤7 or >7 years.

Thrombocytopenia was the most commonly reported severe AE (n=7 [2.5%]). Ten patients (3.7%) treated with drisapersen 6 mg/kg/wk experienced Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or 4 thrombocytopenia with platelet counts decreasing to <50 x 10^9/L. One of the patients had the Grade 4 thrombocytopenia at baseline (prior to receiving treatment), and the other had only a single unconfirmed platelet count less than the lower limit of normal (LLN); 7 of the remaining 8 events were reported as severe thrombocytopenia and all were also considered SAEs. The severe thrombocytopenia events all occurred during extension Study 349, with the earliest onset >9 months after starting drisapersen treatment (see Section 5.11.1, and narratives in Appendix B).

Other on-treatment severe AEs occurring in >1 patient were injection site atrophy (n=3 [1.1%]); injection site pain (n=3 [1.1%]); injection site induration (n=2 [0.7%]); injection site discoloration (n=2 [0.7%]), injection site edema (n=2 [0.7%]), femur fracture (n=3 [1.1%]), tibia fracture (n=2 [0.7%]), lower limb fracture (n=2 [0.7%]), protein urine present, (n=2 [0.7%]), and headache, (n=2 [0.7%]). The severe AEs reported in >1 patient were all in the

drisapersen 6 mg/kg/wk arm with the exception of 1 femur fracture with drisapersen 6 mg/kg intermittently and 1 injection site pain with drisapersen 4 mg/kg/wk.

Serious AEs are described in Section 5.9.

In addition, there was a single report of Henoch-Schönlein purpura in a patient who, on several occasions, had experienced symptoms including fatigue, extreme weakness, pale skin, feeling cold, bright eyes, or rash, within hours of receiving drisapersen (6 mg/kg/wk in Study 349). Most of the events were considered treatment-related by the investigator. During one of these events, the patient's pediatrician reported a Henoch-Schönlein purpura–like rash on the lower limbs, categorized as non-serious and moderate in intensity, as well as mild pharyngitis and conjunctivitis. The pediatrician also concluded the rash was possibly of viral origin. Tests of anti-drisapersen antibodies were positive for this patient on several study visits. Treatment was interrupted multiple times because of the rash and was eventually permanently discontinued because of suspension of all study dosing in September 2013. Further details on this patient can be found in narrative in Appendix B.

5.7.3 Long-Term Safety

In the long-term safety Study 349, most patients (180/238 [75.6%]) were treated with drisapersen for at least 72 weeks, and 30.3% (72/238) for more than 120 weeks. Almost all patients reported on-treatment AEs (96.2% with placebo; 98.3% with drisapersen 6 mg/kg/wk). The AEs that occurred in ≥20% of drisapersen-treated patients by 24 months were AESIs such as injection site reactions, renal abnormalities, or inflammation events (pyrexia), and nasopharyngitis, headache, vomiting, diarrhea, fall, cough, and abdominal pain. The incidences of these and other AEs at 24 months was only marginally greater than at 12 months.

In extension Study 673, 12 patients were treated with drisapersen for up to 188 weeks. While AEs were generally similar to those seen in the placebo-controlled studies, clinically significant injection site reactions were reported, including events of injection site induration. All 12 patients had one or more injection site reactions described as sclerotic or fibrotic.

5.7.4 Adverse Events During Follow-Up Period

On-treatment AEs were compared with AEs that occurred during the follow-up phase of the repeat-dose studies group. Results for the placebo, drisapersen 6 mg/kg/wk, and drisapersen all regimens groups for the most common AEs (≥2% of patients in any of these groups) indicated a lower incidence in the follow-up than the on-treatment period. There was no evidence of an increased frequency of any AE during follow-up.

During the follow-up phases of repeat-dose studies, AEs were reported by 53.2% (142/267) of patients treated with drisapersen 6 mg/kg/wk, 56.1% (160/285) with drisapersen all regimens, and 16.8% (16/95) with placebo. The most common events (>5% of drisapersen treatment group) were nasopharyngitis (reported by 7.9%, 8.4%, and 3.2% of patients in the drisapersen 6 mg/kg/wk, drisapersen all regimens, and placebo groups, respectively), vomiting (5.6%, 5.6%, 0), headache (4.9%, 5.3%, 3.2%), and pyrexia (5.2%, 4.9%, 1.1%).

The AEs were considered to be treatment related in 45 patients (16.9%) treated with drisapersen 6 mg/kg/wk, 49 (17.2%) with drisapersen all regimens, and 3 (3.2%) with placebo. Injection site induration (3.5%) and injection site discoloration (2.8%) were the only treatment-related AEs reported by ≥2% of patients in the drisapersen all regimens group during follow-up. Four patients had SAEs during the follow-up period that were not considered treatment-related and resolved (described in Section 5.9).

The placebo-controlled Study 876 included a formally defined 24-week follow-up period, during which AE incidence was similar in all treatment groups (placebo, drisapersen 3 mg/kg/wk, and drisapersen 6 mg/kg/wk).

5.8 Deaths

No deaths were reported across the drisapersen clinical program.

5.9 Other Serious Adverse Events

A total of 58 patients reported 76 SAEs; 55 of these patients participated in the repeat-dose studies. In addition, 1 patient in single-dose Study PRO051-01 underwent scoliosis surgery, which had been planned prior to study enrollment; and 1 patient in the IV substudy of Study 673 had gastritis. Both of these events were reported as SAEs, not related to study treatment. In the ongoing Study 501, 1 patient had an SAE of appendicitis requiring appendectomy, not considered treatment-related.

The exposure-adjusted incidence rates for SAEs were similar in placebo- and drisapersen-treated patients (11.66 and 11.29 per 100 patient-years, respectively).

Among drisapersen-treated patients in repeat-dose studies (all regimens), 46 patients (16.1%) experienced 66 SAEs (Table 5.9.1). Of these SAEs, 16 patients experienced 18 SAEs reported as possibly related to study treatment by the investigator. Thrombocytopenia was the most common treatment-related SAE, reported in 8 patients (2.8%) receiving drisapersen 6 mg/kg wk in extension Study 349 (also see Section 5.11.1; and narratives in Appendix B). Two patients had injection site edema, reported as possibly treatment-related. Other SAEs considered possibly treatment-related, each reported in 1 patient, were pyrexia, biopsy-proven membranous glomerulonephritis, severe nephrotic-level proteinuria, intracranial venous sinus thrombosis, spinal pain, hepatotoxicity, and small intestinal obstruction (drisapersen 6 mg/kg/wk group), and hematuria (drisapersen 6 mg/kg intermittent group). Two patients experienced 2 SAEs (injection site edema and pyrexia in 1 patient; and intracranial venous sinus thrombosis and spinal pain in the other). (Appendix B includes narrative for patient with intracranial venous sinus thrombosis and spinal pain.) Femur fractures, not unexpected in patients with Duchenne muscular dystrophy, were not considered treatment-related.

Table 5.9.1: On-Treatment Serious Adverse Events in >1 Patient (Repeat-Dose Studies)

Serious Adverse Event Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Any SAE	9 (9.5)	44 (16.5)	46 (16.1)
Any on-treatment SAE	8 (8.4)	42 (15.7)	44 (15.4)
Thrombocytopenia	0	8 (3.0)	8 (2.8)
Femur fracture[b]	0	4 (1.5)	5 (1.8)
Alanine aminotransferase increased	0	2 (0.7)	2 (0.7)
Appendicitis	0	2 (0.7)	2 (0.7)
Cyanosis	0	2 (0.7)	2 (0.7)
Dehydration	0	2 (0.7)	2 (0.7)
Injection site edema	0	2 (0.7)	2 (0.7)
International normalized ratio increased	0	2 (0.7)	2 (0.7)
Tibia fracture	0	2 (0.7)	2 (0.7)
Head injury	1 (1.1%)	1 (0.4)	1 (0.4)

SAE, serious adverse event.

[a] Patients treated with >1 drisapersen regimen are only counted once in this group This group also includes data from patients treated with drisapersen 0.5 mg/kg/wk (n=3), 2 mg/kg/wk (n=3), 3 mg/kg/wk (n=17), 4 mg/kg/wk (n=3), and 6 mg/kg intermittently (n=38). Among patients in these groups, 4 of 38 patients (10.5%) in the 6 mg/kg intermittent group had any on-treatment SAE; no SAEs occurred in >1 patient in this group. No patients in the other dosing groups experienced an SAE while being treated with these drisapersen doses.

[b] 1 of 38 patients (2.6%) treated with drisapersen 6 mg/kg intermittently had femur fracture SAE.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673.

Only 1 SAE (glomerulonephritis) was not resolved/resolving at the end of the study; however, further follow-up noted it was resolving. This patient, who received drisapersen 6 mg/kg/wk in Study 044, reportedly developed lower limb edema in association with proteinuria and hypoalbuminemia approximately 6 months after treatment initiation. Computed tomography scans taken approximately 2 weeks later revealed pulmonary emboli and partial thrombosis of the right renal vein with prominent thrombus in the inferior vena cava. Drisapersen treatment was discontinued and antithrombotic therapy initiated. Renal biopsy showed evidence of Stage 1 membranous glomerulonephritis. The patient received periodic therapy with warfarin and perindopril in the following months. Approximately 3 months after the initial event of proteinuria, the patient experienced right renal vein thrombosis, inferior vena cava thrombosis, and bilateral pulmonary emboli, and had lower limb edema. The 24-hour urine protein result indicated the patient had proteinuria. The perindopril dose was increased. Approximately 2 weeks later, the patient was noted to be well and 24-hour protein value had improved. Additional follow-up showed normal urine protein value, although the patient had evidence of lower limb edema (see patient narrative in Appendix B).

Evaluation of SAEs during the follow-up period of repeat-dose studies showed that 2 patients had femur fracture and 1 had tibia fracture (drisapersen 6 mg/kg/wk group), and 1 patient had atypical pneumonia (placebo group). These SAEs were not considered treatment-related and all resolved.

5.10 Adverse Events That Led to Discontinuation

In the repeat-dose studies with up to 188 weeks of treatment, 12 patients, all treated with drisapersen 6 mg/kg/wk, had AEs that led to permanent treatment discontinuation (Table 5.10.1). Two of the discontinuations occurred during the placebo-controlled studies up to 1 year of treatment (1 patient for biopsy-proven glomerulonephritis, and 1 patient for intracranial venous sinus thrombosis with associated spinal pain). Ten of the discontinuations occurred in extension Study 349. Thrombocytopenia was the only AE that led to treatment discontinuation in more than 1 patient. All AEs that led to discontinuation were considered treatment-related, and all were SAEs with the exception of asthenia (narratives for these 12 patients are available in Appendix B). Three of the 12 patients also permanently withdrew from the study (1 patient each with glomerulonephritis, intracranial venous sinus thrombosis/spinal pain, and thrombocytopenia).

Table 5.10.1: Adverse Events That Led to Permanent Treatment Discontinuation (Repeat-Dose Studies)

Adverse Event Preferred Term	Drisapersen 6 mg/kg/wk n=267 n (%)
Any AE leading to treatment discontinuation[a]	**12 (4.5)**
Thrombocytopenia	7 (2.6)
Asthenia	1 (0.4)
Glomerulonephritis	1 (0.4)
Injection site edema	1 (0.4)
Intracranial venous sinus thrombosis[b]	1 (0.4)
Proteinuria	1 (0.4)

[a] All were SAEs except the event of asthenia.
[b] This patient also experienced an SAE of spinal pain.

5.11 Adverse Events of Special Interest

Thrombocytopenia, renal abnormalities, injection site reactions, hepatic abnormalities, inflammation events, and coagulation abnormalities were identified as AESIs, based on the nonclinical experience with drisapersen and published safety data of other phosphorothioate oligonucleotides (Levin 2001, Levin 2008, Henry 2008).

Table 5.11.1 shows rates of AESIs in the placebo-controlled studies. Up to 1 year of treatment, patients treated with drisapersen 6 mg/kg/wk had a significantly greater calculated relative risk of experiencing the AESIs injection site reaction and renal abnormality, compared with placebo (the 95% CI for the relative risk excluded 1). Hepatic abnormality rates were low but slightly higher with drisapersen (95% CI included 1), suggesting no

significant difference. Rates of inflammation events were similar in the 2 treatment groups. For coagulation abnormalities, the relative risk was significantly higher with placebo than with drisapersen 6 mg/kg/wk (95% CI excluded 1). The relative risk for thrombocytopenia could not be calculated because no patient experienced thrombocytopenia for up to 1 year of treatment in the placebo-controlled studies.

Table 5.11.1: On-Treatment Adverse Events of Special Interest (Placebo-Controlled Studies)

Adverse Event Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=161 n (%)	Drisapersen All Regimens[a] n=195 n (%)	Relative Risk (95% CI) Drisapersen 6 mg/kg/wk vs Placebo
Injection site reaction	21 (22.1)	124 (77.0)	150 (76.9)	3.48 (2.37, 5.13)
Renal abnormality	32 (33.7)	98 (60.9)	112 (57.4)	1.81 (1.33, 2.46)
Inflammation event	26 (27.4)	48 (29.8)	55 (28.2)	1.09 (0.73, 1.63)
Coagulation abnormality	14 (14.7)	13 (8.1)	13 (6.7)	0.47 (0.23, 0.97)
Hepatic abnormality	2 (2.1)	10 (6.2)	10 (5.1)	2.95 (0.66, 13.18)
Thrombocytopenia	0	0	0	–

CI, confidence interval.

[a] This group includes data from drisapersen 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups.

Note: Table includes data from Studies 117, 044, and 876. Total number of patients in each AESI category per preferred terms within the category. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received 1 dose of placebo, and 1 patient from Study 044 randomized to placebo received 1 dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

The AESIs in the repeat-dose studies population are shown in Table 5.11.2. The different durations of exposures to placebo and drisapersen should be considered when reviewing AESI data for the repeat-dose studies group.

Table 5.11.2: On-Treatment Adverse Events of Special Interest (Repeat-Dose Studies)

Adverse Event Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Injection site reaction	21 (22.1)	210 (78.7)	224 (78.6)
Renal abnormality	32 (33.7)	191 (71.5)	194 (68.1)
Inflammation events	26 (27.4)	102 (38.2)	111 (38.9)
Coagulation abnormality	14 (14.7)	32 (12.0)	33 (11.6)
Hepatic abnormality	2 (2.1)	28 (10.5)	31 (10.9)
Thrombocytopenia	0	19 (7.1)	20 (7.0)

[a] This group also includes data from patients treated with drisapersen 0.5 mg/kg/wk (n=3), 2 mg/kg/wk (n=3), 3 mg/kg/wk (n=17), 4 mg/kg/wk (n=3), and 6 mg/kg intermittently (n=38). Patients treated with >1 drisapersen regimen are only counted once in this group.

Note: Table includes data from Studies 117, 044, and 876 and shows total number of patients in each AESI category per preferred term within the category. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received 1 dose of placebo, and 1 patient from Study 044 randomized to placebo received 1 dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

5.11.1 Thrombocytopenia

Thrombocytopenia AESIs include AEs of "thrombocytopenia" and the preferred terms platelet disorder, platelet count decreased, and rectal hemorrhage. Thrombocytopenia was only reported during long-term extension studies, not in the placebo-controlled studies.

In the repeat-dose studies group, 20 patients (7.0%) treated with drisapersen experienced 40 thrombocytopenia events (Table 5.11.1.1); most (32/40 events; 80%) were mild to moderate, asymptomatic decreases in platelet count that were self-limiting or resolved with treatment interruption. Outcome was reported for 38 AEs, which either resolved (37 AEs) or resolved with sequelae (1 AE). There were no serious bleeding events associated with thrombocytopenia.

Table 5.11.1.1: On-Treatment Thrombocytopenia Adverse Events by Preferred Term (Repeat-Dose Studies)

Adverse event, preferred term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Any thrombocytopenia AE[b]	0	19 (7.1)	20 (7.0)[b]
Any thrombocytopenia SAE	0	8 (3.0)	8 (2.8)
Any severe thrombocytopenia AE	0	7 (2.6)	7 (2.5)
Any thrombocytopenia AE leading to study drug discontinuation	0	7 (2.6)	7 (2.5)
Preferred Term			
Thrombocytopenia[b]	0	15 (5.6)	16 (5.6)[b]
Platelet disorder	0	1 (0.4)	1 (0.4)
Platelet count decreased	0	5 (1.9)	5 (1.8)
Rectal hemorrhage	0	1 (0.4)	1 (0.4)

AE, adverse event; SAE, serious adverse event.

[a] This group also includes data from patients treated with drisapersen 0.5 mg/kg/wk (n=3), 2 mg/kg/wk (n=3), mg/kg/wk (n=17), 4 mg/kg/wk (n=3), and 6 mg/kg intermittently (n=38). Patients treated with >1 drisapersen regimen are only counted once in this group.

[b] In the drisapersen 6 mg/kg intermittent group, 2/38 (5.3%) patients had any thrombocytopenia AE; preferred term was thrombocytopenia for both events.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673.

Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received 1 dose of placebo, and 1 patient from Study 044 randomized to placebo received 1 dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

Eight patients (3.0%), all in the drisapersen 6 mg/kg/wk group, experienced confirmed thrombocytopenia SAEs with platelet counts decreasing to <50 x 10^9/L (range: 5–48 x 10^9/L) (Table 5.11.1.1). Two of the 8 events were CTCAE Grade 3 (<50 x 10^9/L) and 6 were Grade 4 (<25 x 10^9/L). The median time to onset of these events was 74.3 weeks (range 43.1–125.0 weeks). These patients experienced a rapid decline in platelet counts from the lower limit of normal (see narratives with graphs in Appendix B). Five patients with platelet counts ≤15 x 10^9/L had clinical symptoms including one or more of ecchymosis, bleeding gums, bruises on arms or legs; petechiae, or epistaxis.

Seven of the patients with severe thrombocytopenia (2.6%) permanently discontinued treatment. Treatment was interrupted in the 8th patient and never resumed due to study termination. The median time for platelet count recovery to >75 x 10^9/L was 3 weeks (range 1–9 weeks) after discontinuation of drisapersen, and 6 of the 8 patients were treated with one or more of tranexamic acid, intravenous immunoglobulin, platelets, or steroids. All 8 SAEs

resolved and no patient. Of 5 patients with thrombocytopenia SAEs tested for anti-platelet antibodies, 4 (80%) had a positive result at ≥1 time point.

In addition to the patients with thrombocytopenia SAEs, 6 patients had ≥1 platelet count <75 x 10^9/L and only 1 had repeated low values; drisapersen dosing was interrupted and platelet counts increased in these patients.

Thrombocytopenia is a recognized class effect of antisense oligonucleotides, although the precise mechanism is not fully understood. In addition, risk factors for the delayed onset of severe thrombocytopenia observed in the drisapersen studies have not been identified. Severe thrombocytopenia was observed in Mauritian monkeys; treatment interruption led to recovery, but upon re-dosing, platelet counts declined again after 2 to 4 weekly doses.

5.11.1.1 Laboratory Data Relevant to Thrombocytopenia

In the placebo-controlled studies, all patients except 1 had normal platelet counts at baseline; 1 patient in the drisapersen 6 mg/kg intermittent group had a Grade 4 platelet count at baseline with normal counts at Weeks 12, 24, 36, and 48. Mean decreases in platelet counts were greater with drisapersen than placebo at Weeks 24 and 48 (Table 5.11.1.1.1). Shifts in platelet counts from normal to a Grade 1 decrease occurred in 1 patient (0.5%) at Week 12, 0 at Week 24, 5 (3.2%) at Week 36, and 5 (3.3%) at Week 48. No shifts to Grade 2–4 in any treatment group occurred in the placebo-controlled studies. In long-term Study 349, low platelet counts were observed for 11 of 228 (5%) patients treated with drisapersen 6 mg/kg/wk.

Table 5.11.1.1.1: Mean Changes in Platelets From Baseline at Weeks 24 and 48 (Placebo-Controlled Studies)

	Placebo n=95		Drisapersen 6 mg/kg/wk n=161		Drisapersen All Regimens[a] n=195	
Platelet count, GI/L						
Baseline mean ± SD	n=95	306.4 ± 64.8	n=161	309.5 ± 68.8	n=195	306.9 ± 71.2
Week 24 mean ± SD change	n=92	-1.3 ± 49.6	n=157	-49.8 ± 52.9	n=190	-47.4 ± 60.4
Week 48 mean ± SD change	n=73	-8.7 ± 37.6	n=136	-67.1 ± 54.6	n=150	-62.7 ± 61.4

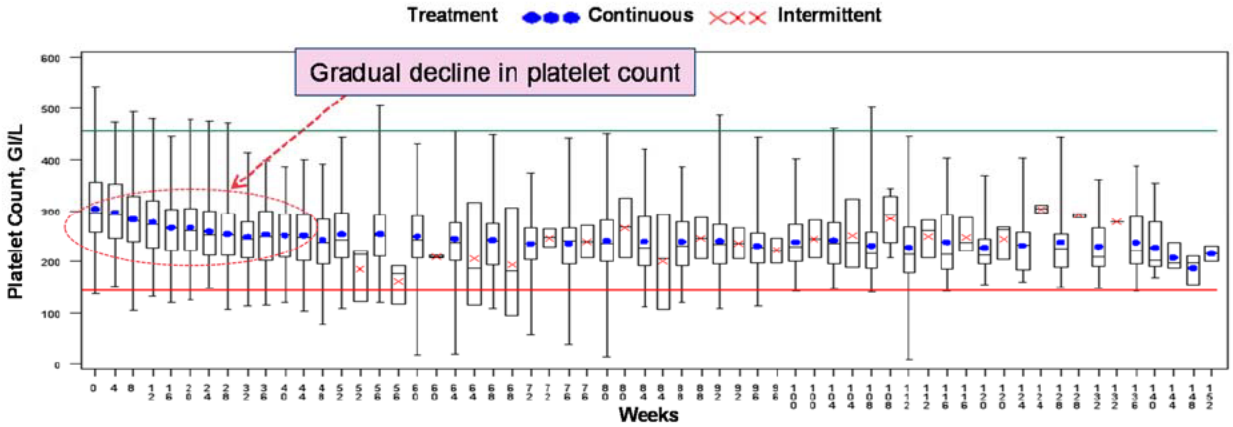
GI, giga; SD, standard deviation.

[a] The all regimens group includes 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups.

Note: Table includes data from Studies 117, 044, and 876 (first 24 weeks only).

The effects of drisapersen 6 mg/kg/wk treatment on platelets were characterized by an initial gradual reduction in mean platelet counts in the first 12 to 24 weeks, which appeared to stabilize by Week 32 (Figure 5.11.1.1.1). Thereafter, mean platelet counts remained relatively stable and within normal limits, but with high variability; some patients experienced lower values.

Figure 5.11.1.1.1: Platelet Levels by Visit in Patients Treated with Drisapersen 6 mg/kg/wk in Their Parent Study (Long-Term Safety)



Note: The green and red lines indicate the upper limit of normal and lower limit of normal values, respectively. Figure includes data from Studies 117, 044, and 349.

The potential for severe thrombocytopenia can be managed by close patient monitoring, including recognition of characteristic signs and symptoms, periodic platelet count measurement, and rapid intervention. The proposed prescribing information will include recommendations for platelet monitoring and management guidance for severe thrombocytopenia (see Proposed Risk Management Plan in Section 7).

See Section 5.11.6, Table 5.11.6.1 for rates of coagulation abnormality-related events, including blood fibrinogen decreased, fibrin D-dimer increased, and fibrinogen degradation products, which in general had a similar or higher frequency in patients treated with placebo than with drisapersen.

5.11.2 Renal Abnormalities

Renal abnormalities were the second most commonly reported AEs in the clinical program and occurred more frequently with drisapersen than placebo treatment. Most renal abnormalities were reversible, subclinical laboratory findings such as mild proteinuria, microscopic hematuria, and mild increases in cystatin C concentration.

In the placebo-controlled studies, 98 of 161 patients (60.9%) treated with drisapersen 6 mg/kg/wk and 32 of 95 patients (33.7%) with placebo experienced any renal abnormality. Adverse events reported in ≥2% of patients treated with drisapersen 6 mg/kg/wk versus placebo were proteinuria (29.2% vs 16.8%), hematuria (14.9% vs 5.3%), protein urine present (12.4% vs 6.3%), cystatin C increased (10.6% vs 4.2%), red blood cells urine positive (9.3% vs 4.2%), urine protein/creatinine ratio increased (8.7% vs 4.2%), red blood cells urine (8.1% vs 5.3%), and protein urine (5.0% vs 0).

In the repeat-dose studies group: 191 of 267 patients (71.5%) treated with drisapersen 6 mg/kg/wk reported renal abnormalities, most commonly (≥10%) proteinuria (43.1%), protein urine present (15.7%), hematuria (16.1%), cystatin C increased (12.4%), red blood cells urine positive (13.5%), and urine protein/creatinine ratio increased (11.2%). These laboratory abnormalities were not associated with severe or progressive renal function deterioration.

Clinically, the proteinuria that patients experienced was primarily mild proteinuria comprising low-molecular-weight species such as α1-microglobulin, which was nonprogressive and reversible. Features of more general tubular dysfunction (such as Fanconi's syndrome) were not apparent. As serum creatinine is influenced by muscle mass, serum cystatin C was used as a measure of glomerular filtration rate. Although some variability was seen with this measure, progressive or irreversible decrease in glomerular filtration rate was not observed. Subclinical proteinuria was not associated with thrombotic events.

The mild and transient elevations in urinary low-molecular-weight proteins are considered to reflect interference with the tubular reabsorption of proteins from the glomerular filtrate rather than indications of overt renal toxicity.

Four of 285 patients (1.4%) in the drisapersen all regimens group experienced renal abnormality SAEs, 3 treated with drisapersen 6 mg/kg/wk and 1 with 6 mg/kg intermittently in the repeat-dose studies. Two of these patients had severe proteinuria: 1 as asymptomatic severe proteinuria (no biopsy taken), and the other associated with Stage 1 membranous glomerulonephritis diagnosed by renal biopsy. These events were considered possibly treatment related although the cause had not been established, and were the only renal AEs that led to treatment withdrawal (see narratives in Appendix B). In both of these patients, the severe proteinuria normalized with discontinuation of drisapersen treatment. The other 2 SAEs were moderate renal impairment and severe hematuria; both events resolved.

Of 1,183 renal abnormalities reported in the drisapersen all regimens group, 36 (3.2%) were unresolved at the end of the study (compared with 1 of 78 [1.3%] in the placebo group). The mean durations of resolved renal abnormalities were 40.1 days and 40.9 days, respectively, in the drisapersen all regimens and 6 mg/kg/wk groups (maximum of 1,002 days for both groups).

The proposed prescribing information will provide recommendations for monitoring of urinary protein, cystatin C, and creatinine, and management guidance for potentially clinically significant renal effects.

5.11.2.1 Laboratory Data Relevant to Renal Abnormalities

Urinalysis

In the placebo-controlled studies, mean and median increases from baseline in urine protein and urine α1-microglobulin were greater with drisapersen 6 mg/kg/wk compared with placebo. After 48 weeks of treatment, the mean increase (± SD) from baseline in urine protein level in patients receiving drisapersen 6 mg/kg/wk was 63.9 mg/L (± 144.2), compared with an increase of 5.6 mg/L (± 62.0) in patients receiving placebo. Similarly, urine α1-microglobulin increased by 23.34 mg/L (± 26.25) at Week 48 in patients receiving drisapersen 6 mg/kg/wk, compared with an increase of 0.15 mg/K (± 1.29) with placebo. Changes in urine albumin levels were generally similar in both treatment groups.

Shift analyses were performed using the CTCAE version 4.03 (see Appendix C for shift criteria definitions); for laboratory parameters for which no CTCAE grades were available, shift tables were produced showing shifts to above or below the laboratory normal range. More patients (76.5%) in the drisapersen 6 mg/kg/wk group had shifts from normal at baseline to high for urine α1-microglobulin compared with the placebo group (2.6%).

One patient in Study 349 had an SAE of severe proteinuria and was withdrawn from treatment (see Section 5.11.2).

Blood Urea Nitrogen, Creatinine, and Cystatin C

Greater mean increases in blood urea nitrogen (BUN) and creatinine were observed with drisapersen treatment compared with placebo in the placebo-controlled studies. Blood urea nitrogen values were normal at all time points in all patients, with the exception of 1 patient whose elevated BUN level was considered by the physician to be related to a viral infection/dehydration. Similar proportions of patients in the placebo and drisapersen treatment groups had shifts in creatinine from normal at baseline to abnormal values at Weeks 12 and 24 in the placebo-controlled studies. At Week 48, more patients treated with drisapersen had shifts to abnormal values (34.1% no shift, 61.5% shift to Grade 1, and 4.4% shift to Grade 2) compared with placebo (55.8%, 42.9%, and 1.3%, respectively).

Greater mean increases in cystatin C were observed with drisapersen treatment compared with placebo in the placebo-controlled studies; in addition, more patients treated with drisapersen than placebo had serum cystatin C shifts from normal at baseline to high values during treatment (Table 5.11.2.1.1). While the proportions with shifts in serum cystatin C increased with increasing exposure (17.3% at Week 12, versus 31.0% at Week 24 and 40.4% at Week 48), progressive loss of glomerular function was not observed. Based on case narratives of 15 patients with abnormal cystatin C measurements (defined as any measurement greater than the upper limit of normal and >75% increase from baseline), no patient had persistent cystatin C elevation. Two patients had low cystatin C values. All other patients had transient elevations that returned to normal values without treatment.

Table 5.11.2.1.1: Mean Changes and Shifts From Baseline in Cystatin C at Weeks 24 and 48 (Placebo-Controlled Studies)

	Placebo n=95		Drisapersen 6 mg/kg/wk n=161		Drisapersen All Regimens[a] n=195	
Cystatin C (mg/L)						
Baseline mean ± SD	n=95	0.67 ± 0.13	n=161	0.71 ± 0.12	n=195	0.70 ± 0.12
Week 24 mean ± SD change	n=94	0.05 ± 0.11	n=158	0.11 ± 0.13	n=190	0.10 ± 0.13
Week 48 mean ± SD change	n=75	0.04 ± 0.13	n=136	0.16 ± 0.15	n=151	0.17 ± 0.14
Cystatin C – shift from normal at baseline, n (%)	Low	High	Low	High	Low	High
Week 12	3 (3.4)	7 (8.0)	2 (1.3)	27 (17.3)	2 (1.1)	28 (15.1)
Week 24	0	6 (6.4)	1 (0.6)	49 (31.0)	2 (1.1)	54 (28.4)
Week 48	3 (4.0)	4 (5.3)	0	55 (40.4)	0	62 (41.1)

SD, standard deviation.

[a] The all regimens group includes 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups.

Note: Table includes data from Studies 117, 044, and 876 (first 24 weeks only).

Percentages calculated using number with an assessment as denominator and not the overall number of patients in each group.

5.11.3 Injection-Site Reactions

Injection-site reactions were the most common AEs reported in the clinical development program. Most injection site reactions were reported as mild or moderate in intensity and resolved. In the placebo-controlled studies, 124 of 161 patients (77.0%) treated with drisapersen 6 mg/kg/wk reported 1,614 injection site reactions, and 21 of 95 patients (22.1%) treated with placebo reported 64 injection site reactions. Rates of the most common (≥10%) injection site reactions in the drisapersen versus placebo groups were erythema (50.9% vs 8.4%), discoloration (34.8% vs 5.3%), pain (16.1% vs 5.3%), reaction (15.5% vs 1.1%), pruritus (14.9% vs 1.1%), bruising (11.8% vs 9.5%), and induration (10.6% vs 1.1%).

In the repeat-dose studies, 210 of 267 patients (78.7%) treated with drisapersen 6 mg/kg/wk reported injection site reactions, most commonly (≥10%) injection site erythema (52.1%), injection site discoloration (47.2%), injection site induration (29.6%), injection site pain (19.5%), injection site pruritus (16.9%), injection site reaction (18.4%), injection site atrophy (12%), injection site bruising (13.1%), injection site hematoma (12%), and injection site swelling (10.1%). The mean (± SD) duration of injection site reactions was 57.7 (± 129.8) days in the drisapersen all regimens group compared with 12.6 (± 9.2) days in the placebo group; 20.9% compared with 1.6% of events in the 2 groups, respectively, were reported as ongoing or not resolved at the end of the study.

A total of 10 patients (3.5%) had at least 1 severe injection site reaction in the drisapersen all regimens group (repeat-dose studies). These included injection site edema, injection site atrophy, injection site discoloration, injection site induration, injection site pain, injection site inflammation, injection site erythema, injection site warmth, and injection site nodule. There

were 2 injection site reaction SAEs in patients receiving drisapersen 6 mg/kg/wk; both were severe injection site edema. One of these patients discontinued treatment, and this was the only discontinuation due to an injection site reaction in repeat-dose studies (see narrative in Appendix B).

For drisapersen 6 mg/kg/wk, 50% of patients had injection site reactions within the first few weeks of treatment. The incidence continued to increase over time but at a slower rate.

The most common reactions, including benign, transient erythema and injection site discoloration (both hyperpigmentation and less commonly hypopigmentation), usually occurred within the first 6 months. More dermatologically significant reactions were observed with longer-term treatment but still occurred in a minority of patients (Table 5.11.3.1). Injection site induration, injection site atrophy, and injection site edema were reported mostly after 12 to 24 months of treatment. Injection site induration progressed to persistent sclerosis in 12 patients (4%), with associated microcalcification in 1 patient (0.4%). Injection site nodules developing in areas of sclerosis were reported infrequently after longer-term treatment. Three patients (1%) reported ulceration at the site of sclerotic skin due to scratching/mechanical abrasion, with no associated systemic infection. A disproportionate number of the dermatologically significant injection site reactions were reported in extension Study 673. The 12 patients in this study received treatment for up to 188 weeks, with relatively intense SC administration of drisapersen exclusively in the abdomen for the first 50 to 72 weeks of weekly treatment, prior to the institution of a requirement to rotate injection sites, which may have contributed to these more dermatologically severe reactions.

In all of the other repeat-dose studies, rotation of injection sites was recommended from the study outset. Initially, rotation was around 8 sites (right side abdomen, back left upper arm, front right thigh, right side upper arm, left side abdomen, back right upper arm, front left thigh, and left side upper arm); subsequently, 4 additional sites were added (left and right lower back and left and right buttocks).

Table 5.11.3.1: Overview of Chronic, Dermatologically Significant Injection Site Reactions (Repeat-Dose Studies)

Adverse event, preferred term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Injection site induration[b]	1 (1.1)	79 (29.6)	81 (28.4)
Injection site atrophy (lipodystrophy and lipoatrophy)	0	32 (12.0)	42 (14.7)
Injection site edema	0	11 (4.1)	11 (3.9)
Injection site nodule	0	3 (1.1)	3 (1.1)
Injection site ulcer	0	0	3 (1.1)
Injection site calcification	0	0	1 (0.4)

[a] The all regimens group includes 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups.
[b] 12 patients (~4%) developed injection site reactions described as sclerotic, which coded to the preferred term injection site induration.

To minimize the potential for injection site reactions, the proposed prescribing information will contain instructions for proper administration of subcutaneous injections and rotation of injection sites, and recommendation for dermatologic assessment.

5.11.4 Hepatic Abnormalities

Hepatocellular injury did not emerge as a safety issue. Hepatic abnormalities were reported at low rates, and were primarily mild to moderate, nonprogressive, and reversible increases in liver enzymes (including glutamate dehydrogenase [GLDH] and gamma-glutamyl transferase [GGT]). There was no report of Hy's Law (ie, alanine aminotransferase or aspartate aminotransferase increase to >3 times the upper limit of normal [ULN], associated with bilirubin increase ≥2 times the ULN, and no other cause for increase) or of other serious events suggesting meaningful hepatocellular injury. No patient was withdrawn for a hepatic abnormality.

In the placebo-controlled studies, 10 of 161 (6.2%) patients treated with drisapersen 6 mg/kg/wk and 2 of 95 (2.1%) with placebo reported hepatic abnormalities. The most common events were mild to moderate increases in GLDH and GGT, reported by 4 (2.5%) and 2 (1.2%) patients, respectively, in the drisapersen 6 mg/kg/wk group (and no placebo patients). The only other AE seen in >1 patient was ALT increased (2 [1.2%] with drisapersen 6 mg/kg/wk, and 2 [2.1%] with placebo). The relative risk of experiencing hepatic abnormalities up to 1 year of treatment was numerically higher with drisapersen 6 mg/kg/wk than placebo but the 95% CIs included 1.

In the repeat-dose studies, 10.5% of patients treated with drisapersen 6 mg/kg/wk had hepatic abnormalities (Table 5.11.4.1), and 6.4% (17/267) were considered treatment-related. Of the most common AEs, more patients treated with drisapersen 6 mg/kg/wk than placebo had reversible increases in GLDH and GGT, and similar proportions in each group experienced ALT increases.

Table 5.11.4.1: On-Treatment Hepatic Abnormalities by Preferred Term (Repeat-Dose Studies)

Adverse Event Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Any hepatic abnormality AE	2 (2.1)	28 (10.5)	31 (10.9)
Glutamate dehydrogenase increased	0	13 (4.9)	16 (5.6)
Alanine aminotransferase increased	2 (2.1)	7 (2.6)	7 (2.5)
Gamma-glutamyl transferase increased	0	7 (2.6)	7 (2.5)
Alanine aminotransferase	0	1 (0.4)	1 (0.4)
Aspartate aminotransferase increased	0	1 (0.4)	1 (0.4)
Transaminases increased	0	1 (0.4)	1 (0.4)
Ultrasound liver abnormal	0	1 (0.4)	1 (0.4)
Hepatic function abnormal	0	1 (0.4)	1 (0.4)
Hepatic steatosis	0	1 (0.4)	1 (0.4)
Hepatocellular injury	0	1 (0.4)	1 (0.4)
Hepatomegaly	0	1 (0.4)	1 (0.4)
Hepatotoxicity	0	1 (0.4)	1 (0.4)
Liver disorder	0	1 (0.4)	1 (0.4)
Hepatitis	1 (1.1)	0	0

AE, adverse event.

[a] Patients treated with >1 drisapersen regimen are only counted once in this group. This group also includes data from patients treated with drisapersen 0.5 mg/kg/wk (n=3), 2 mg/kg/wk (n=3), 3 mg/kg/wk (n=17), 4 mg/kg/wk (n=3), and 6 mg/kg intermittently (n=38). In the 6 mg/kg intermittent group, 5 of 38 patients (13.2%) experienced GLDH increased and 2 of 38 (5.3%) experienced GGT increased; no other patients experienced hepatic abnormalities while treated with these doses.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673.
Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received a single dose of placebo, and 1 patient from Study 044 randomized to placebo received a single dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

Four patients (1.5%) treated with drisapersen 6 mg/kg/wk had hepatic abnormality SAEs: 2 with ALT increased (both also had SAEs of International Normalized Ratio [INR] increase), 1 with hepatotoxicity of moderate intensity, and 1 with hepatocellular injury. Only the hepatocellular injury was reported as severe in intensity but was not considered treatment related. All SAEs resolved.

5.11.4.1 Laboratory Values Relevant to Hepatic Abnormities

Serum ALT and aspartate aminotransferase (AST) levels are often elevated in boys with Duchenne muscular dystrophy as a signal of occult muscle disease (McMillan 2011). In the drisapersen studies, baseline AST and ALT values were extremely high (compared with normal ranges in a healthy population for AST of ~10–36 IU/L and ALT ~10–40 IU/L),

complicating interpretation of changes in these parameters. Mean decreases from baseline were seen in all treatment groups (Table 5.11.4.1.1). Mean increases in GGT and GLDH were observed with drisapersen 6 mg/kg/wk compared with placebo and were greater at Week 48 than at Week 24. Small mean changes in alkaline phosphatase and bilirubin were of similar magnitude in both treatment groups.

Table 5.11.4.1.1: Changes in Liver Function Test Results From Baseline at Weeks 24 and 48 (Placebo-Controlled Studies)

	Placebo n=95		Drisapersen 6 mg/kg/wk n=161		Drisapersen All Regimens[a] n=195	
AST (IU/L)						
Baseline mean ± SD	n=95	259.0 ± 134.7	n=161	248.1 ± 160.3	n=195	265.4 ± 168.4
Week 24 mean ± SD change	n=94	-13.9 ± 148.0	n=159	-22.8 ± 122.4	n=191	-34.8 ± 131.9
Week 48 mean ± SD change	n=78	-17.4 ± 137.0	n=136	-26.3 ± 131.7	n=150	-30.9 ± 141.8
ALT (IU/L)						
Baseline mean ± SD	n=95	344.1 ±143.1	n=161	336.4 ± 156.5	n=195	356.6 ± 164.7
Week 24 mean ± SD change	n=94	-4.8 ±110.7	n=159	-12.2 ± 101.8	n=191	-22.5 ± 104.9
Week 48 mean ± SD change	n=78	-19.7 ±110.2	n=136	-28.1 ± 126.9	n=150	-28.4 ± 137.1
Alkaline phosphatase (IU/L)						
Baseline mean ± SD	n=95	110.0 ±31.7	n=161	108.0 ± 34.7	n=195	110.1 ± 57.2
Week 24 mean ± SD change	n=94	-1.9 ±15.6	n=159	-1.0 ± 17.2	n=191	-5.4 ± 53.7
Week 48 mean ± SD change	n=78	3.3 ±20.4	n=135	3.3 ± 21.9	n=149	-1.7 ± 62.1
GGT (IU/L)						
Baseline mean ± SD	n=95	11.7 ±3.5	n=161	12.8 ± 4.4	n=195	12.6 ± 4.3
Week 24 mean ± SD change	n=94	-0.2 ±2.5	n=159	8.2 ± 16.7	n=191	7.3 ± 15.6
Week 48 mean ± SD change	n=78	0.9 ±5.2	n=136	16.6 ± 34.0	n=150	16.5 ± 34.2
GLDH (U/L)						
Baseline mean ± SD	n=95	4.54 ±1.77	n=160	4.94 ± 2.20	n=194	5.22 ± 3.05
Week 24 mean ± SD change	n=94	0.09 ±1.69	n=158	2.14 ± 4.3	n=189	1.70 ± 4.27
Week 48 mean ± SD change	n=78	-0.04 ±2.12	n=137	3.59 ± 7.37	n=151	3.45 ± 7.11
Bilirubin, total (µmol/L)						
Baseline mean ± SD	n=95	6.3 ±3.7	n=161	6.0 ± 3.5	n=195	6.3 ± 3.9
Week 24 mean ± SD change	n=94	0.1 ±2.8	n=159	-0.4 ± 2.2	n=191	-0.6 ± 2.4
Week 48 mean ± SD change	n=78	0.1 ±2.1	n=136	-0.6 ± 2.7	n=150	-0.7 ± 2.8
Bilirubin direct (µmol/L)						
Baseline mean ± SD	n=95	1.3 ±0.9	n=161	1.4 ± 0.9	n=195	1.4 ± 1.0
Week 24 mean ± SD change	n=93	0.2 ±0.9	n=158	-0.1 ± 0.9	n=189	-0.1 ± 0.9
Week 48 mean ± SD change	n=78	0.2 ± 0.9	n=135	-0.2 ± 0.9	n=149	-0.2 ± 0.9

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; GLDH, glutamate dehydrogenase; NA, not applicable; SD, standard deviation.

[a] The all regimens group includes 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups.

Note: Table includes data from Studies 117, 044, and 876 (first 24 weeks only).

There were no shifts from CTCAE Grade 0 or 1 at baseline to Grade 2, 3, or 4 for bilirubin or alkaline phosphatase and few shifts for GGT: Grade 0 to Grade 2 in 3 patients (2.2%) in drisapersen 6 mg/kg/wk, and 1 patient (7.1%) in drisapersen 6 mg/kg intermittent group of placebo-controlled studies. More drisapersen-treated patients had GLDH shifts from normal at baseline to high during treatment compared with placebo (Table 5.11.4.1.2).

Table 5.11.4.1.2: Patients With Shifts in GLDH From Normal at Baseline to High or Low On Treatment (Placebo-Controlled Studies)

	Placebo n=95 n (%)		Drisapersen 6 mg/kg/wk n=161 n (%)		Drisapersen All Regimens[a] n=195 n (%)	
GLDH	**Low**	**High**	**Low**	**High**	**Low**	**High**
Week 12	0	7 (7.8)	0	25 (16.3)	0	29 (16.1)
Week 24	0	9 (9.6)	0	40 (25.3)	0	41 (21.7)
Week 48	0	5 (6.4)	0	45 (32.8)	0	50 (33.1)

GLDH, glutamate dehydrogenase; NA, not applicable.

[a] The all regimens group includes 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups.

Note: Table includes data from Studies 117, 044, and 876 (first 24 weeks only).

Percentages calculated using number with assessment as the denominator and not the overall number of patients in each group.

Phosphorothioate oligonucleotides are known to accumulate in the liver until steady state is achieved; hepatic effects, which have been minor for most compounds, are dose-dependent and would be expected to plateau (Muntoni 2010). Based on the drug class, assessment of hepatic enzyme levels every 6 months is considered prudent in patients treated with drisapersen. Recommendations will be included in the proposed prescribing information.

5.11.5 Inflammation Events

Inflammation events did not emerge as a safety issue. Rates of inflammation events were similar in the drisapersen and placebo groups. In placebo-controlled studies, 48 of 161 patients (29.8%) treated with drisapersen 6 mg/kg/wk and 26 of 95 (27.4%) with placebo experienced an inflammation AE. There was a similar mean duration of events (3.7 and 5.4 days, respectively) and a similar relative risk of experiencing an event up to 1 year of treatment in both treatment groups. Pyrexia was the most common AE, reported in 25.5% and 22.1% of the drisapersen 6 mg/kg/wk and placebo groups, respectively. Rates of other AEs were <2% in the drisapersen 6 mg/kg/wk group in the placebo-controlled studies.

In the repeat-dose studies, 38.2% of patients treated with drisapersen 6 mg/kg/wk and 27.4% with placebo reported an inflammation AE (Table 5.11.5.1). Pyrexia was most common; other AEs seen in at least 2% of the drisapersen 6 mg/kg/wk arm were complement factor C3 decreased, C-reactive protein increased, and influenza-like illness.

Table 5.11.5.1: On-Treatment Inflammation Events by Preferred Term (Repeat-Dose Studies)

Adverse Event Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Any inflammation AE	**26 (27.4)**	**102 (38.2)**	**111 (38.9)**
Pyrexia	21 (22.1)	79 (29.6)	83 (29.1)
Complement factor C3 decreased	0	17 (6.4)	18 (6.3)
C-reactive protein increased	0	9 (3.4)	12 (4.2)
Influenza like illness	2 (2.1)	7 (2.6)	8 (2.8)
Haptoglobin increased	3 (3.2)	1 (0.4)	4 (1.4)
Body temperature increased	0	1 (0.4)	1 (0.4)
Blood fibrinogen increased	1 (1.1)	2 (0.7)	3 (1.1)
Blood fibrinogen	0	0	1 (0.4)
Hyperthermia	0	0	1 (0.4)
Inflammation	0	1 (0.4)	1 (0.4)
Complement factor C3 increased	0	1 (0.4)	1 (0.4)
Complement factor decreased	0	1 (0.4)	1 (0.4)
Haptoglobin abnormal	0	1 (0.4)	1 (0.4)
Immunology test abnormal	0	1 (0.4)	1 (0.4)
Red blood cell sedimentation rate increased	0	1 (0.4)	1 (0.4)
Neutrophil toxic granulation present	1 (1.1)	0	0

AE, adverse event.

[a] This group also includes data from patients treated with drisapersen 0.5 mg/kg/wk (n=3), 2 mg/kg/wk (n=3), 3 mg/kg/wk (n=17), 4 mg/kg/wk (n=3), and 6 mg/kg intermittently (n=38). Patients treated with >1 drisapersen regimen are only counted once in this group.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received a single dose of placebo, and 1 patient from Study 044 randomized to placebo received a single dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

No inflammation AE was severe in intensity or led to withdrawal from treatment. One patient had an inflammation SAE (grade 2 pyrexia), which was assessed as treatment related.

The majority of inflammation AEs resolved; of 238 inflammation events reported by drisapersen-treated patients (all regimens) in the repeat-dose studies, 5 events (2.1%) had not resolved at the end of the study. The 5 unresolved events occurred in 3 patients receiving drisapersen 6 mg/kg/wk: complement factor C3 decreased (4 events) and blood fibrinogen increased (1 event).

5.11.5.1 Laboratory Values Relevant to Inflammation Events

Inflammation biomarkers (CRP, complement C3, MCP-1, fibrinogen, and haptoglobin) were within the normal range for the majority of patients receiving drisapersen 6 mg/kg/wk in the placebo-controlled studies, although at Week 48 small percentages of patients had abnormalities in 1 or more biomarkers: for complement C3, 16 (11.7%) patients treated with drisapersen 6 mg/kg/wk and 1 (1.3%) with placebo had a shift from normal to low values at Week 48; 10 (8.1%) and 1 (1.5%) in the 2 treatment groups, respectively, had a shift from normal to high for MCP-1; and 14 (10.4%) and 3 (3.8%), respectively, had a shift from normal to high for high-sensitivity CRP (hsCRP).

5.11.6 Coagulation Abnormalities

Coagulation disorders with associated signs and symptoms did not emerge as a safety issue. In the placebo-controlled studies, coagulation abnormalities were more frequent with placebo (14/95 [14.7%]) than drisapersen 6 mg/kg/wk (13/161 [8.1%]) treatment. Almost all individual coagulation abnormality preferred terms that were measured were reported by a similar or higher percentage of patients treated with placebo compared with drisapersen 6 mg/kg/wk. The mean duration of coagulation AEs was shorter for drisapersen 6 mg/kg/wk (17.1 days) than placebo (25.9 days).

In the repeat-dose studies (Table 5.11.6.1), 12.0% of drisapersen-treated patients (6 mg/kg/wk arm) had a total of 77 coagulation events; only 7 events (9.1%) had not resolved at the end of the study. No significant prolongation of aPTT was detected in drisapersen-treated patients in the repeat-dose or placebo-controlled studies.

Table 5.11.6.1: On-Treatment Coagulation Abnormalities by Preferred Term (Repeat-Dose Studies)

Adverse Event Preferred Term	Placebo n=95 n (%)	Drisapersen 6 mg/kg/wk n=267 n (%)	Drisapersen All Regimens[a] n=285 n (%)
Any coagulation AE	**14 (14.7)**	**32 (12.0)**	**33 (11.6)**
International normalized ratio increased	4 (4.2)	11 (4.1)	12 (4.2)
Blood fibrinogen decreased	7 (7.4)	11 (4.1)	11 (3.9)
Prothrombin time prolonged	4 (4.2)	7 (2.6)	7 (2.5)
Activated partial thromboplastin time prolonged	3 (3.2)	6 (2.2)	7 (2.5)
Fibrin D dimer increased	2 (2.1)	6 (2.2)	6 (2.1)
Fibrin degradation products increased	0	2 (0.7)	2 (0.7)
Coagulation time prolonged	2 (2.1)	1 (0.4)	1 (0.4)
Activated partial thromboplastin time abnormal	1 (1.1)	1 (0.4)	1 (0.4)
Activated partial thromboplastin time	0	1 (0.4)	1 (0.4)
Bleeding time prolonged	0	1 (0.4)	1 (0.4)
Blood test abnormal	0	1 (0.4)	1 (0.4)
Coagulation test abnormal	0	1 (0.4)	1 (0.4)
Blood fibrinogen	1 (1.1)	0	0
Fibrin degradation products	1 (1.1)	0	0
Hypofibrinogenemia	0	1 (0.4)	1 (0.4)

AE, adverse event.

[a] This group also includes data from patients treated with drisapersen 0.5 mg/kg/wk (n=3), 2 mg/kg/wk (n=3), 3 mg/kg/wk (n=17), 4 mg/kg/wk (n=3), and 6 mg/kg intermittently (n=38). Patients treated with >1 drisapersen regimen are only counted once in this group.

Note: Table includes data from Studies 117, 044, 876, 349, PRO051-02, and 673. Four patients (3 from Study 044 and 1 from Study 117) randomized to drisapersen 6 mg/kg/wk received a single dose of placebo, and 1 patient from Study 044 randomized to placebo received a single dose of drisapersen 6 mg/kg/wk; all AEs for these patients were assigned to the drisapersen 6 mg/kg/wk group although the patient randomized to placebo is included in the n for the placebo group only.

There were no confirmed reports of disseminated intravascular coagulation (DIC), and no patient was withdrawn from treatment due to a coagulation abnormality. Two patients treated with drisapersen 6 mg/kg/wk had severe coagulation AEs and 2 patients had SAEs of INR increased (INR values of 6.2 and 2.2 in each patient [normal range 0.8-1.2]). Both patients with SAEs of INR increased also had SAEs of ALT increased. It was reported that the patient with INR value of 6.2 had no signs of a bleeding disorder. Neither patient with SAEs of INR increased experienced thrombocytopenia or a bleeding event. The SAEs were not considered treatment related and resolved.

Analyses of AEs coded to the MedDRA Embolic and Thrombotic Events Standardized MedDRA Queries (SMQ) and the Hemorrhages SMQ showed no evidence for an increased incidence of bleeding, non-injection site–related bruising, hemorrhaging, or any other clinical sign or symptom of a coagulation disorder in the placebo-controlled and repeat-dose studies.

5.11.6.1 Laboratory Values Relevant to Coagulation Abnormalities

Only small mean changes in aPTT and INR were seen (Table 5.11.6.1.1), which were generally similar for drisapersen and placebo in the placebo-controlled studies. Few shifts in aPTT or INR occurred in either treatment group.

Table 5.11.6.1.1: Mean Changes From Baseline in aPTT and INR at Weeks 24 and 48 (Placebo-Controlled Studies)

	Placebo n=95		Drisapersen 6 mg/kg/wk n=161		Drisapersen All Regimens[a] n=195	
aPTT, seconds						
Baseline mean ± SD	n=95	31.5 ± 11.5	n=161	30.4 ± 5.4	n=195	30.5 ± 5.6
Week 24 mean ± SD change	n=91	-1.0 ± 11.2	n=156	-1.7 ± 5.4	n=186	-1.7 ± 5.8
Week 48 mean ± SD change	n=78	0.3 ± 4. 9	n=127	-1.9 ± 5.4	n=142	-2.0 ± 5.8
PTT (INR), ratio						
Baseline mean ± SD	n=95	1.11 ± 0.12	n=161	1.15 ± 0.43	n=195	1.16 ± 0.43
Week 24 mean ± SD change	n=91	0.03 ± 0.23	n=156	-0.00 ± 0.35	n=186	-0.01 ± 0.36
Week 48 mean ± SD change	n=78	0.05 ± 0.28	n=130	0.01 0.51	n=145	-0.01 ± 0.53

aPTT, activated partial thromboplastin time; INR, International Normalized Ratio; NA, not applicable; PTT, partial thromboplastin time; SD, standard deviation.

[a] The all regimens group includes 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups.

Note: Table includes data from Studies 117, 044, and 876 (first 24 weeks only).

5.12 Other Laboratory Findings

Sodium, potassium, calcium, and phosphate values were similar for patients treated with drisapersen and placebo, and few shifts in electrolyte values occurred during treatment. For both LDH and CK, mean decreases from baseline were greater with drisapersen than placebo (Table 5.12.1). Only small mean changes from baseline were seen in any treatment group for total protein, albumin and globulin, and glucose.

Table 5.12.1: Change in Clinical Chemistry Parameters from Baseline at Weeks 24 and 48 (Placebo-Controlled Studies)

	Placebo n=95		Drisapersen 6 mg/kg/wk n=161		Drisapersen All Regimens[a] n=195	
LDH (IU/L)						
Baseline mean ± SD	n=95	987.6 ± 414.0	n=161	951.0 (397.1	n=195	978.9 ± 402.3
Week 24 mean ± SD change	n=94	-64.4 ± 344.8	n=159	-278.5 ± 248.2	n=191	-288.0 ± 250.3
Week 48 mean ± SD change	n=78	-101.4 ± 283.3	n=136	-362.6 ± 257.0	n=150	-361.0 ± 272.5
CK (IU/L)						
Baseline mean ± SD	n=95	11588.1 ± 6625.3	n=161	11338.1 ± 7317.0	n=195	11921.0 ± 7503.1
Week 24 mean ± SD change	n=91	-876.5 ± 7204.0	n=157	-3490.4 ± 5866.0	n=188	-3778.4 ± 6139.7
Week 48 mean ± SD change	n=78	-1169.8 ± 5848.6	n=133	-5007.1 ± 6038.8	n=146	-5177.8 ± 6417.8

CK, creatine kinase; LDH, lactate dehydrogenase; NA, not applicable; SD, standard deviation.

[a] The all regimens group includes 3 mg/kg/wk (n=17), 6 mg/kg/wk (n=161), and 6 mg/kg intermittent (n=17) dose groups. Note: Table includes data from Studies 117, 044, and 876 (first 24 weeks only).

5.13 Electrocardiography

No evidence was found for a drisapersen-treatment effect on the QT interval corrected for heart rate (QTc).

In the placebo-controlled studies, most patients treated with placebo or drisapersen 6 mg/kg/wk had values ≤450 msec at baseline for QT interval corrected for heart rate using Bazett's formula (QTcB) and had similar on-treatment results. Similar proportions of patients in both treatment groups had maximum on-treatment changes (up to 1 year) in QTcB >60 msec (9.5% and 11.2%, respectively, for drisapersen 6 mg/kg/wk and placebo) or >30 to ≤60 msec (16.8% and 18.6%, respectively). No patient had a maximum on-treatment value >500 msec. Results for QT interval corrected according to Fridericia's formula (QTcF) were similar for placebo and drisapersen 6 mg/kg/wk.

In the repeat-dose studies, only 1 patient (treated with drisapersen 6 mg/kg/wk) had a QTcB value >500 msec at any time after starting treatment. This patient's QTcB value was 404 msec at baseline. At Week 12, just before study termination, QTcB measured 520 msec; heart rate measured 66 bpm at this time, and there was no reported syncope. Follow-up QTcB measurements approximately 3 and 6 months after study termination were 430 and 450 msec, respectively. This patient's heart rate ranged from 63 to 114 overall during the study and follow-up. The patient was reported to have had a pericardial effusion 2 months prior to the QTcB measurement of 520 msec.

Across the drisapersen clinical program, only 2 patients had presyncope and 1 patient had syncope AEs.

5.14 Echocardiography

Few patients showed a decrease in ejection fraction (EF) of ≥ 10% in the placebo-controlled studies. In Study 044, further examination showed that these results were not of clinical concern.

Only small mean changes in EF from baseline to the end of treatment were seen in any treatment group in the placebo-controlled studies. The pattern of changes was similar for drisapersen and placebo.

In long-term Study 349, mean and median EF at baseline were 63% and 64%, respectively, with a range of 36% to 78%, for 161 patients treated with drisapersen 6 mg/kg/wk. Median changes in EF from baseline were -0.53% at Week 24 and -1.28% at Week 48. Potentially clinically important EF decreases from baseline of ≥ 10% were observed in 6 patients (4%) at Week 24, 3 (2%) at Week 48, none at Weeks 72 and 104, and 10 (6%) at any post-baseline visit.

5.15 Vital Signs and Other Observations

No clinically important effects on vital signs were observed. Review of body measurement data, echocardiography, and renal ultrasound data did not indicate any issues of clinical concern.

5.16 Adverse Drug Reactions

Adverse drug reaction (ADRs), ie, undesirable effects reasonably associated with the use of drisapersen based on evidence to suggest a causal relationship, were identified by review of AEs from the repeat-dose studies and SAEs from all drisapersen clinical studies (regardless of investigator judgement about causality). The assessment of AEs as drug-related considered the known pharmacology of drisapersen, class effects, biologic plausibility, statistical evaluations (≥5% incidence and double the placebo rate), reversibility upon drug withdrawal, and rarity of the event in the Duchenne muscular dystrophy population.

The ADRs reported most commonly in drisapersen-treated patients in placebo-controlled studies were injection site reactions, subclinical renal laboratory abnormalities, and arthralgia (Table 5.16.1). Proteinuria was reported by >5% in patients treated with drisapersen 6 mg/kg/wk (29.2%) but at slightly less than double the placebo rate (16.8%) in placebo-controlled studies. Less common ADRs (incidence <5%) reported in repeat-dose studies were hepatic enzyme elevations (GLDH, GGT) and alopecia.

In both of the long-term extension studies (and no placebo-controlled study), thrombocytopenia was identified as an ADR. A total of 20 patients (7%) experienced thrombocytopenia events, the most common ADR leading to drisapersen treatment discontinuation across repeat-dose studies.

Table 5.16.1: Most Common Adverse Drug Reactions: ≥5% Incidence and ≥ Twice Placebo Rate (Placebo-Controlled Studies)

Adverse Event Preferred Term	Placebo n=95 N (%)	Drisapersen 6 mg/kg/wk n=161 n (%)
General disorders and administration site conditions		
Injection site reactions[a]	14 (14.7)	121 (75.2)
Renal and urinary disorders		
Proteinuria	15 (14.8)	47 (29.2)
Hematuria	5 (5.3)	24 (14.9)
Cystatin C increased	4 (4.2)	17 (10.6)
Urine protein/creatinine ratio increased	4 (4.2)	14 (8.7)
Musculoskeletal disorders		
Arthralgia	2 (2.1)	10 (6.2)

[a] Includes the preferred terms injection site erythema, injection site discoloration, injection site pain, injection site pruritus, injection site reaction, injection site induration, injection site swelling, injection site atrophy, injection site urticaria.

5.17 Immunogenicity

Anti-drisapersen antibodies (ADA) were evaluated in the 48-week placebo-controlled Study 044 using a hybridization-ligation enzyme-linked immunosorbent assay. A total of 32 of 109 patients (29.4%) treated with drisapersen 6 mg/kg/wk had ADAs detected in plasma samples with a general onset of antibody generation between 3 to 6 months of treatment; 30 of 107 patients (29.1%) in the drisapersen 6 mg/kg/wk group were confirmed positive for ADAs (median titer=800) at Week 48; 2 patients had a positive sample earlier in the study but no Week 48 sample was available. In the placebo group, 1 of 50 patients (2%) had a positive result at Week 0 (titer=200), and all subsequent samples were negative. Overall, median titers were low and increased with prolonged treatment (ranging from 50–300 at Weeks 8 to 24, and 1000 and 800 at Weeks 36 and 48, respectively). ADA positivity was associated with higher trough (pre-dose plasma) levels of drisapersen; however, no correlation was detected between ADA and muscle concentrations of drisapersen, indicating that ADAs do not inhibit distribution of drisapersen to muscle tissue.

No relevant differences were observed between ADA-positive and ADA-negative patients with regard to efficacy (6MWD) or safety (AEs that occurred in ≥5% of patients, SAEs, and AESIs) and laboratory parameters (platelet count, hsCRP, urine protein excretion, serum cystatin C, urine cystatin C, ALT, GLDH, and total bilirubin).

Anti-dystrophin antibody signals were detected in a limited number of serum samples from both drisapersen- and placebo-treated patients (n=3/186 [1.6%]).

Anti-drug antibody formation will be further monitored post-authorization.

5.18 Conclusions

The clinical safety database includes safety results from 9 clinical trials in 312 patients with Duchenne muscular dystrophy aged 5 to 16 years who were exposed to drisapersen, and is the most extensive database of patients with Duchenne muscular dystrophy assembled to date. The total exposure to drisapersen (all regimens) was 490.1 patient-years. In the repeat-dose studies, 42.8% of patients received at least 96 weeks of treatment; the exposure for drisapersen 6 mg/kg/wk was 432.7 patient-years compared with 79.4 patient-years for placebo. A total of 93.3% of patients were treated for at least 24 weeks and 75.1% for at least 48 weeks. Across all studies, 12 patients permanently withdrew from treatment due to an AE. There were no deaths.

Drisapersen was generally well tolerated. The majority of AEs were reported as mild to moderate in intensity. The most clinically significant identified risks associated with treatment were thrombocytopenia, renal abnormalities, and injection site reactions, all of which are considered manageable through close monitoring and risk minimization measures that will be described in the proposed prescribing information.

The majority of injection site reactions were reported as mild or moderate in intensity and resolved. Among the most common events, benign, transient injection site erythema generally occurred within the first month and injection site discoloration within the first 6 months of treatment. Dermatologically significant injection site reactions accumulated with longer-term treatment but still occurred in a minority of patients; injection site induration, injection site atrophy, and injection site edema were reported, mostly after 12 to 24 months of treatment. Injection site reactions including sclerosis, microcalcification, nodules, or ulceration were observed infrequently with longer-term treatment in patients with limited rotation of injection sites. A proportion of the injection site reactions were ongoing at the end of study. To minimize the potential for injection site reactions, the proposed prescribing information will contain instructions for proper administration of subcutaneous injections and rotation of injection sites.

Renal abnormalities (primarily proteinuria) were generally subclinical laboratory findings and tended to normalize when drisapersen treatment was paused or discontinued. There were 2 SAE reports of severe proteinuria: 1 was asymptomatic proteinuria (no biopsy taken), and the other was associated with stage 1 membranous glomerulonephritis, diagnosed by renal biopsy. Recommendations for monthly monitoring of urinary protein, cystatin C and creatinine, and management guidance for potentially clinically significant renal effects will be included in the proposed prescribing information.

Severe thrombocytopenia was reported for a low percentage of patients who were treated with drisapersen for at least 9 months. In these patients, platelet counts recovered after discontinuation of drisapersen treatment. Recommendations to measure the platelet count at regular intervals, or more frequently if signs or symptoms develop, and management guidance for thrombocytopenia will be included in the proposed prescribing information.

Adverse events of special interest observed in nonclinical studies that did not emerge as substantial safety issues in drisapersen-treated patients were hepatocellular damage,

coagulation abnormalities, inflammation events (except for injection site reactions), and complement activation with clinical sequelae. These events remain potential risks and will continue to be monitored post-authorization.

There were no clinically meaningful changes in laboratory findings, ECGs, or echocardiograms.

Anti-drisapersen antibodies were detected and confirmed for a sub-population of patients in Study 044; 29.4% of drisapersen-treated patients tested positive for ADAs. Safety results (AEs, SAEs, and AESIs) in patients who tested positive for anti-drisapersen antibodies were similar to patients who tested negative. Complement activation and immunogenicity, including antibody formation, are identified as potential risks in the proposed Risk Management Plan and will be monitored post-authorization.

In the context of treating a universally fatal disorder, drisapersen has an acceptable safety profile.

6 BENEFITS/RISKS

6.1 Benefits

The studies conducted to date have demonstrated evidence of a treatment difference favoring drisapersen on the 6MWD, the primary measure of ambulatory function. In particular, in two randomized, placebo-controlled studies primarily evaluating patients with preserved muscle strength (as evidence by rise from floor < 7 seconds), meaningful improvements in 6MWD were observed in as little as 24 weeks of therapy. The clinical course of Duchenne muscular dystrophy entails a progressive series of functional losses. Among these, losing the ability to walk represents a major impairment in patient well-being and function in patients with Duchenne muscular dystrophy and their families. It signifies loss of independence for the boys and heightened responsibility for the caregivers. It also heralds further deterioration in other body systems, including respiration and cardiac function, leading to early mortality. Delaying the loss of ambulation has been shown to delay these other disease manifestations (Biggar 2006, King 2007, Machado 2012, Markham 2008, Moxley 2010, Phelps 1995).

Positive trends in secondary endpoints of physical functioning (including timed function tests and the NSAA) were also observed in patients receiving drisapersen, providing supportive evidence of benefits considered meaningful and life changing to patients and their caregivers.

The randomized, double-blind, placebo-controlled Study 044 enrolled an older, more severely affected patient population compared to the randomized, placebo-controlled Studies 117 and 876, including individuals lacking well-preserved muscle and at imminent risk of losing ambulation. Key prognostic factors, which were not yet established at the time of the study design, were not considered in the randomization scheme, producing important imbalances in baseline characteristics between the treatment groups in favor of placebo and a consequently attenuated treatment effect. The overall results demonstrated a modest trend toward improvement in ambulation with drisapersen compared with placebo. However, re-analyses correcting for these baseline imbalances demonstrated a positive treatment effect with drisapersen in the large subgroup of patients with better preserved muscle and ambulatory capacity, consistent with the findings of Studies 117 and 876.

It is reasonable to expect that drisapersen might benefit even a more severely affected group. Evidence supporting this position includes improvement in ambulation in severely affected patients treated at experienced trial sites, improvement in clinical global impression, and consistent reductions in serum lactate dehydrogenase and creatine kinase. Research indicates that in individuals with severely affected ambulatory impairment patients perceive benefit from even relatively small improvements in 6MWD (Henricson 2013b).

The lasting, positive effect of drisapersen treatment on ambulation was shown in long-term extension studies. Patients initially treated in Study 117 showed a durable treatment effect in 6MWD through 120 weeks of treatment. Patients initially treated in Study 044 showed a treatment benefit in 6MWD after 96 weeks that was similar in magnitude to that seen in the Phase II studies at Week 48, suggesting that patients with Duchenne muscular dystrophy who have greater functional decline can still benefit from drisapersen treatment given over a longer period of time. Patients treated with drisapersen for up to 188 weeks in the long-term

Study 673 maintained more ambulatory capacity than their matched natural history comparators, with most of the drisapersen-treated patients performing better than the matched cohorts and none performing worse (see Figure 4.7.4.2.3).

The placebo-controlled study results also highlight the importance of treating patients early in their disease. Treating a younger patient population, when muscle function is still relatively well preserved, affords a better opportunity to stabilize or even improve function within a relatively short duration of treatment. The replacement of muscle with fat or fibrous tissue in older, more-progressed boys leaves less target tissue available for drisapersen to affect and therefore requires longer time for greater effect to accumulate. However benefits in those with more compromised tissue may occur with longer treatment and with optimized care.

The clinical program provides a large data set given the rarity of the disorder, demonstrating that eligible patients with Duchenne muscular dystrophy will see both near-term and long-term benefit with drisapersen treatment. The totality of data shows that treatment with drisapersen provides important benefits in patients with well-preserved muscle. The lasting, positive effect on 6MWD indicates that treatment with drisapersen helps to prolong the period of independent ambulation, which is relevant to patient well-being and function especially in the absence of alternative therapy.

6.2 Risks

The safety of drisapersen was thoroughly evaluated in clinical studies comprising 490 patient-years of exposure. The most clinically significant adverse events associated with drisapersen treatment were infrequent occurrences of severe thrombocytopenia, rare glomerulonephritis and more commonly injection site reactions.

Injection site reactions were the most common AEs associated with drisapersen treatment in the placebo-controlled studies. Injection site reactions were reported in the majority of drisapersen-treated patients. Most were mild or moderate in intensity and resolved. Dermatologically significant injection site reactions occurred in a minority of patients, but were potentially dose-limiting in some patients receiving long-term treatment. Only 1 patient in repeat-dose studies discontinued drisapersen treatment due to an injection site AE. To minimize the potential for injection site reactions, the proposed prescribing information will contain instructions for proper administration of SC injections and rotation of injection sites.

There were 2 occurrences of severe proteinuria: 1 was asymptomatic proteinuria (up to 11 grams protein excreted in 24 hours; no biopsy taken), and the other was associated with stage 1 membranous glomerulonephritis, diagnosed by renal biopsy. Other renal abnormalities were predominantly subclinical laboratory findings such as mild proteinuria, mainly comprising low-molecular-weight proteins such as α1-microglobulin, which normalized when drisapersen treatment was paused or discontinued. The proposed prescribing information will provide recommendations for monitoring of urinary protein, cystatin C and creatinine, and management guidance for potentially clinically significant renal effects.

Thrombocytopenia AEs were reported during the long-term extension studies. There was no report of thrombocytopenia in the placebo-controlled studies with up to 1 year of treatment. Most cases were mild to moderate, asymptomatic decreases in platelet count that were self-limiting or resolved with treatment interruption. Severe thrombocytopenia was infrequent: 8 patients experienced severe thrombocytopenia with platelet counts decreasing to $<50 \times 10^9$/L, with a time to onset from the first dose of drisapersen of at least 9 months. Five of these patients were tested for anti-platelet antibodies, and 4 had a positive result for at least 1 time point. Recommendations for measurement of platelet count and management guidance for thrombocytopenia will be included in the proposed prescribing information.

Adverse events of special interest observed in nonclinical studies that did not emerge as substantial safety issues in drisapersen-treated patients were hepatocellular damage, coagulation abnormalities, inflammation events (except for injection site reactions), and complement activation with clinical sequelae. These events remain potential risks and will continue to be monitored post-authorization.

In the context of treating a progressively debilitating and universally fatal disorder, in a patient population with a clear and urgent unmet medical need, the benefits afforded by drisapersen outweigh the known risks, which can be managed through active monitoring and the risk management plan summarized below.

7 PROPOSED RISK MANAGEMENT PLAN

Based on nonclinical studies, published class effects, and clinical findings to date, the safety specification for drisapersen is presented in Table 7.1.

Table 7.1: Safety Specification for Drisapersen

Important identified risks	• Injection site reactions • Thrombocytopenia • Renal toxicity
Important potential risks	• Hepatic toxicity • Prolongation of activated partial thromboplastin time (abnormal clotting) • Pro-inflammatory effects and complement activation • Immunogenicity (including anti-drug antibodies)
Missing information	• Extended long-term safety and tolerability • Use in females (including use in pregnancy and during lactation) • Use in boys <5 years of age • Use in patients with pre-existing renal impairment • Use in patients with pre-existing hepatic impairment • Use in patients without concomitant corticosteroids

Specifically, BioMarin proposes the following risk minimization and pharmacovigilance activities to ensure safe and effective use of drisapersen, and to gain more knowledge about the safety and long-term use of drisapersen in the post-authorization setting:

- *Evidence-based Prescribing Information and Medication Guide* that describes the risks, recommendations for minimizing them, and monitoring guidance
- *Continuous monitoring of the benefit-risk profile* of drisapersen, which includes assessment of aggregate safety data and taking appropriate actions in response, and communicating emerging safety concerns to applicable health authorities
- *Individual case safety report (ICSR) management*, which involves collection, collation, follow-up, assessment, and regulatory reporting of suspected AEs from any source
- *Signal management* to identify, evaluate, validate, and act upon previously unrecognized risks

- Periodic Safety Update Reports (PSUR)/Periodic Benefit-Risk Evaluation Reports (PBRER) to provide periodic benefit-risk evaluations of drisapersen during post-marketing use
- *Study management*, which includes active monitoring of adverse events and relevant laboratory test values in ongoing clinical studies, and planned post-marketing studies/registry.

Based on extensive safety evaluation, thrombocytopenia, renal abnormalities, and injection site reactions have been identified as the most clinically significant effects associated with drisapersen treatment. BioMarin has proposed the following risk minimization and management procedures for each of these events.

- Injection site reactions: Only health care professionals should administer drisapersen treatment. Prescribing and educational materials will include instructions for proper subcutaneous injection techniques and strict rotation of injection sites. Patients should receive periodic dermatologic assessments.
- Renal abnormalities: Urine protein by dipstick should be assessed at baseline and monthly, with 24-hour urine collection if the dipstick result is 3+ for protein. Serum cystatin C and serum creatinine levels should be measured at baseline and quarterly. Drisapersen treatment should be interrupted if urine protein measures >1 $g/m^2/24$ hours. Treatment may be resumed based on individual benefit-risk assessment if the urine protein is ≤500 $mg/m^2/24$ hours or after consultation with a pediatric nephrologist. Patients with persistent nephrotic level proteinuria should permanently discontinue drisapersen treatment. If cystatin C level increases to greater than the ULN and >75% of baseline, drisapersen treatment should be interrupted; treatment may be resumed when cystatin C level returns to normal values.
- Thrombocytopenia: Platelet count measurement is recommended at baseline and at regular intervals, and immediately if a patient develops signs or symptoms of thrombocytopenia. Platelet monitoring should be increased to monthly if any confirmed platelet count is less than the lower limit of normal. Anti-platelet antibody testing is recommended if any platelet count decreases to $<75 \times 10^9/L$. For patients with a confirmed platelet count $<75 \times 10^9/L$, drisapersen treatment should be interrupted. If platelet count recovers to $\geq 150 \times 10^9/L$, treatment may be resumed based on benefit-risk assessment for each patient. Drisapersen treatment should be permanently discontinued if the confirmed platelet count is $<50 \times 10^9/L$ and/or the anti-platelet antibody test result is positive. In addition, caregivers and health care providers will receive education about the signs and symptoms of thrombocytopenia to help facilitate early recognition of this event.

Collectively, the benefits of improved function and well-being exceed the potential for harm as evidenced by these trials. However, individual patients may experience variation in benefit or risk such that benefit-risk scenarios may be unfavorable for certain patients. These proposed risk management activities will help guide safe and appropriate use of drisapersen.

8 PROPOSED POSTMARKETING COMMITMENTS

BioMarin is experienced in partnering with regulatory agencies and patient groups to design and conduct appropriate postmarketing studies that strengthen the available data and evaluate long-term outcomes. In addition to the proposed risk management activities described in Section 7, BioMarin plans to conduct several studies as postmarketing commitments to further the understanding of drisapersen's effects. These commitments include: 1) a post-approval registry to holistically evaluate long-term outcomes; 2) a clinical study in younger patients (less than 5 years of age); 3) a clinical study in older, nonambulatory patients to further the understanding of drisapersen's effects in those important patient populations; and 4) a clinical study to examine intravenous dosing as an alternative to subcutaneous administration.

The design of the following studies is subject to further negotiation with global regulatory authorities.

8.1 Registry

The Registry will enroll and collect data on patients over a period of 6 years from the time of the first marketing approval globally, and data on individual patients will continue to be collected for 2 years from the time the last patient was enrolled or until the Registry is completed. Enrolled patients are required to have Duchenne muscular dystrophy treated by drisapersen and with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping, as determined by genetic testing.

Patients are not eligible to participate in the Registry if they are currently participating in a BioMarin-sponsored clinical study of drisapersen. The Registry will collect medical history and, if available, clinical assessment data on an annual basis at minimum. Safety data will be monitored and collected throughout the patients' participation in the Registry. Data will be collected as part of the usual care of the study patient as per local standard of medical practice. There is no diagnostic, therapeutic, or experimental intervention involved. Patients will receive clinical assessments and treatments as determined by their study physician.

Rationale and Background

This drug registry is being conducted to gather additional information relating to patient characteristics and the disease history of the Duchenne muscular dystrophy population treated by drisapersen, in addition to data on the long-term safety, effectiveness, and patterns of use of drisapersen in clinical practice.

Research Question and Objectives

The objectives of this Registry are: (1) to characterize and describe the Duchenne muscular dystrophy population with mutations in the dystrophin gene amenable to treatment with exon 51 skipping and drisapersen that is treated by drisapersen, including the variability, progression, and natural history of Duchenne muscular dystrophy; (2) to evaluate the long-term safety and effectiveness of drisapersen treatment in this specific population in clinical practice; and (3) to gather information on patterns of use of drisapersen in clinical practice.

Study Design

This is a voluntary multicenter, multinational, long-term observational Registry in patients diagnosed with Duchenne muscular dystrophy and treated with drisapersen. The registry is non interventional, and subjects will receive clinical assessments and treatments as determined by their study physician per local clinical practice. There is no diagnostic, therapeutic, or experimental intervention as specified by this Registry involved. The Registry will collect medical history, clinical and safety assessments at least annually according to the schedule of the usual care visits. The Registry will enroll and collect data on patients over a period of 6 years from the time of the first marketing approval globally, and data on individual patients will continue to be collected for 2 years from the time that the last patient was enrolled or until the Registry is completed. These assessments are designed to further characterize the spectrum of clinical signs and symptoms of the disease and the long-term outcomes of patients treated with drisapersen.

Investigators are encouraged to follow the Recommended Schedule of Events, which includes assessments that are currently used to monitor Duchenne muscular dystrophy-related clinical manifestations and to stage disease progression across the life-long course of the disorder. Data may be collected for all or some of the assessments as outlined in Table 8.1.1, depending upon the individual's standard care. The assessments listed in the schedule are consistent with the management and treatment guidelines published by Bushby (Bushby 2010, Bushby 2011).

Table 8.1.1: Recommended Schedule of Events

Registry Recommended Schedule of Events[a]	Registry Entry[b]	Annually	End of Study
Confirmed diagnosis of Duchenne muscular dystrophy with mutations in the dystrophin gene that are amenable to treatment with exon 51 skipping as determined by genetic testing	X		
Informed consent form (ICF)/patient information and authorization form (PIAF)	X		
Demographics	X		
Medical history[c]	X	X	X
Mechanical ventilation (continuous positive airway pressure [CPAP]/bi-level positive airway pressure [BiPAP]/other)[d]	X	X	X
Physical examination including vital signs and dermatologic exam	X	X	X
Electrocardiogram (ECG)	X	X	X
Echocardiogram	X	X	X
6MWT[e]	X	X	X
North Star Ambulatory Assessment (NSAA)	X	X	X
Pulmonary function tests	X	X	X
EQ-5D-5L test pediatric outcomes data collection instrument (PODCI)	X	X	X
Time to rise from floor	X	X	X
3-dimensional upper arm movement measurement	X	X	X
Urinary protein[g]	X	X	X
Platelet count[h]	X	X	X
Liver function tests[i]	X	X	X
Concomitant medications[f]	X	X	X
AEs[a]	X	X	X
DEXA scanning	X	X	X

[a] All recommended assessments should be collected until conclusion of the Registry, at intervals specified in the Recommended Schedule of Events, and may be performed at additional time points and as medically indicated at the discretion of the Investigator. Additional details are provided in the Study Reference Manual. AEs will be monitored and collected throughout the patients' participation in the Registry.

[b] The data to be collected at entry include current as well as historic data.

[c] Medical history may be collected at Registry entry and at least annually thereafter. Detailed medical history may be collected as described in Section 12.3 and will include additional information such as surgical

procedures; hospitalizations; any complications or sequelae related to surgeries and hospitalizations; and history of respiratory infections.

[d] Mechanical ventilation information may be collected on assisted breathing history for CPAP/BiPAP/other.

[e] In addition to the 6MWT findings, information pertaining to the use of wheelchairs, walking aids, and orthoses may be collected.

[f] Medications (i.e., prescription, over-the-counter [OTC], and herbal) and nutritional supplements taken at Registry entry should be recorded. At each subsequent visit, changes since the previous visit should be recorded.

[g] Monitoring of urinary protein is recommended during drisapersen treatment (see package label).

[h] Platelet counts should be monitored closely during drisapersen treatment (see package label).

[i] Periodic monitoring of liver function test once every 6 months is recommended during drisapersen treatment (see package label).

Population

All patients with a confirmed diagnosis of Duchenne muscular dystrophy with mutations in the dystrophin gene amenable to treatment with exon 51 skipping as determined by genetic testing and who are treated with drisapersen may be eligible to participate in this Registry.

Variables

The medical histories and clinical and safety assessments are designed to help further characterize the spectrum of clinical signs and symptoms of Duchenne muscular dystrophy and the effectiveness and safety profile of drisapersen in the real world setting. The assessments to be collected if and when available are listed in the Recommended Schedule of Events in the study design and Table 8.1.1.

Data Sources

Investigators treating Duchenne muscular dystrophy patients are encouraged to participate in the Registry by enrolling patients, following the Recommended Schedule of Events (Table 8.1.1), and entering all data from these assessments into the Registry database. Data may be collected for all or some of the assessments as outlined in the study design and Table 8.1.1, depending on the individual's standard care.

Study Size and Statistical Methods

All Duchenne muscular dystrophy patients treated by drisapersen will be invited to enroll in the Registry, assuming all regulatory requirements are met for sites that have agreed to participate, in countries where marketing authorization has been granted. Registry data will be analyzed as per the Registry's Statistical Analysis Plan (SAP) and reported. Safety data will be monitored and collected throughout the patients' participation in the Registry and reported annually.

All data collected from the Registry patients will be captured in the Registry database. Patient baseline information, including medical history, prior medications, and demographics, will be summarized using descriptive statistics. Safety data, including vital signs, findings from physical examinations, concomitant medications, and other safety assessments, will be described. Incidence rate calculations will be completed. Where

applicable, descriptive statistics will include the number of patients, means and standard deviations (SDs), medians with minimums and maximums, 95% confidence intervals (CIs) and/or inter-quartile ranges for continuous variables, and count and percent for categorical variables.

8.2 Additional Clinical Studies

In addition to the registry described above, additional clinical studies planned for drisapersen include:

- An open-label, Phase 3b study, designed to assess the safety, pharmacokinetics, and efficacy of drisapersen sodium for 48 weeks in non-ambulant boys compared to a population of matched untreated boys.
- An open-label, Phase 3b study, designed to assess the safety, tolerability, pharmacokinetics, and efficacy of drisapersen sodium for at least 30 weeks in boys less than 5 years of age compared to a population of matched untreated boys.
- A pharmacokinetic cross-over study to compare subcutaneous and intravenous administration of drisapersen in subjects with Duchenne muscular dystrophy

9 CONCLUSION

Duchenne muscular dystrophy is a rare, rapidly progressive, and highly heterogeneous disorder, which makes it challenging to study in both the laboratory and the clinical setting. There is an urgent unmet need for effective treatment for Duchenne muscular dystrophy, driven by the devastating nature and uniformly fatal outcome of the disorder. This urgency was reflected in the clinical development of drisapersen, a novel therapy that addresses the lack of functional dystrophin protein that causes Duchenne muscular dystrophy, specifically in patients with mutations amenable to skipping exon 51.

The efficacy and safety of drisapersen have been demonstrated in the largest and most comprehensive clinical program ever filed for approval with Duchenne muscular dystrophy. The 3 randomized, double-blind, placebo-controlled trials of drisapersen were all initiated within a span of a few months, at a time when limited data and precedent were available to guide the study designs.

Throughout the clinical program, a treatment effect favoring drisapersen was shown on the primary clinical endpoint, the 6MWD, in 3 randomized placebo controlled trials conducted contemporaneously. The 6MWD is widely used and widely accepted in studies of Duchenne muscular dystrophy and other progressive neuromuscular conditions, but has limitations in a heterogeneous patient population that includes individuals with reduced baseline ambulatory capacity. The primary endpoint results of the 3 placebo-controlled trials are impressive considering the long tissue distribution time of drisapersen. Supportive evidence for the efficacy of drisapersen was also demonstrated on secondary endpoints representing a range of other functional domains.

Study 117 demonstrated improvement in 6MWD after 24 weeks of drisapersen treatment versus placebo, which was statistically significant and sustained through an additional 24 weeks of treatment. The effect was maintained through 48 weeks of the double-blind phase and continued for a further 48 weeks in an open-label extension phase. In Study 117, an increase in dystrophin production was accompanied by reductions in biomarkers of muscle damage. An improvement in 6MWD after 24 weeks of treatment was nearly significant in spite of the absence of a loading dose in Study 876, and the effect was maintained during 24 weeks off drug. A post hoc integrated analysis of Studies 117 and 876 confirmed the beneficial treatment effect of drisapersen at 24 weeks, with a nominal p value of 0.0025. By themselves, these studies can be considered to provide substantial evidence of effectiveness.

Extensive analyses were conducted to understand and explain the attenuated treatment effect observed in Study 044, which enrolled a broader and less randomly distributed patient population than the other placebo-controlled studies, including more severely affected patients with less remaining muscle to support ambulation. These analyses demonstrate a consistent and important benefit with drisapersen in patients with well-preserved muscle across the 3 placebo-controlled trials. They also highlight the importance of early treatment with drisapersen in order to maximize the long-term benefits.

Long-term studies demonstrate a durable treatment effect in 6MWD of up to three and a half years, which compares favorably with data from natural history cohorts and indicates that drisapersen preserves the ability to walk independently.

The safety of drisapersen was evaluated in a comprehensive integrated safety database for a rare disorder which included >300 Duchenne muscular dystrophy patients treated up to three and a half years. Drisapersen was generally well tolerated. Injection site reactions were the most common AEs, but dermatologically significant events occurred in a minority of patients. Infrequent glomerulonephritis and severe thrombocytopenia were the most clinically significant AEs reported.

The identified and potential risks of drisapersen can be managed through close monitoring and the risk minimization measures that will be described in the proposed prescribing information. BioMarin has a robust post-marketing surveillance and ongoing clinical trial program planned to further quantify and characterize known and potential risks as well as to understand long-term benefits and further the knowledge of drisapersen's effects in a broad range of the patient population. The proposed indication is for all ages of patients and also for ambulatory and nonambulatory patients. This approach is in line with rare disease indications, where extrapolation beyond the primary population studied is warranted where patients are in desperate need, and where there is a plausible hypothesis that extrapolation is justified.

As with BioMarin's other rare disease programs, the proposed post-marketing program represents an ongoing, long-term commitment to the Duchenne muscular dystrophy community to systematically gather further information regarding the safety and effectiveness of drisapersen. These commitments include: 1) a post-approval registry to holistically evaluate long-term outcomes; 2) an enhanced risk management plan tailored to guide safe and appropriate use of drisapersen; 3) a clinical study in younger patients (less than 5 years of age); 4) a clinical study in older, nonambulatory patients to further the understanding of drisapersen's effects in those important patient populations; and 5) a clinical study to examine intravenous dosing as an alternative to subcutaneous administration.

The recently released FDA draft Guidance for Industry for developing drugs to treat Duchenne muscular dystrophy acknowledges that: "When making regulatory decisions regarding drugs for dystrophinopathies, FDA will consider patient and caregiver tolerance for risk, and the serious and life-threatening nature of these conditions" (FDA 2015). Parents of patients with Duchenne muscular dystrophy have clearly stated their urgent support for the development of therapies that may alter or delay the devastating consequences of disease progression (Muntoni 2010, Parent Project Muscular Dystrophy 2014).

The totality of data from the development program demonstrates that drisapersen, at the recommended dose of 6 mg/kg/wk administered by SC injection, provides meaningful and potentially life-changing benefits for patients with an immediate, urgent, unmet medical need.

10 REFERENCES

Aartsma-Rus A. Antisense-mediated modulation of splicing: therapeutic implications for Duchenne muscular dystrophy. RNA Biol. 2010;4:453-61. http://www.tandfonline.com/doi/pdf/10.4161/rna.7.4.12264

Aartsma-Rus A, Bremmer-Bout M, Janson AA, et al. Targeted exon skipping as a potential gene correction therapy for Duchenne muscular dystrophy. Neuromuscul Disord 2002;12(suppl 1); S71-7. http://www.researchgate.net/publication/11181677_Aartsma-Rus_A._et_al._Targeted_exon_skipping_as_a_potential_gene_correction_therapy_for_Duchenne_muscular_dystrophy._Neuromusc._Disorders_12_S71-S77

Aartsma-Rus A, Fokkema I, Verschuuren J, et al. Theoretic applicability of anti-sense mediated exon skipping for Duchenne muscular dystrophy mutations. Hum Mutat. 2009; 30(3): 293-9. http://www.researchgate.net/publication/11181677_Aartsma-Rus_A._et_al._Targeted_exon_skipping_as_a_potential_gene_correction_therapy_for_Duchenne_muscular_dystrophy._Neuromusc._Disorders_12_S71-S77

Aartsma-Rus A, Janson AA, Kaman WE, et al. Therapeutic antisense-induced exon skipping in cultured muscle cells from six different DMD patients. Hum Mol Genet. 2003;12(8);90714. http://hmg.oxfordjournals.org/content/12/8/907.full.pdf+html

Aartsma-Rus A, Janson AA, Kaman WE, Bremmer-Bout M, van Ommen GJ, den Dunnen JT, van Deutekom JC. Antisense-induced multiexon skipping for Duchenne muscular dystrophy makes more sense. Am J Hum Genet. 2004a;74:83-92. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1181915/

Aartsma-Rus A, Kaman WE, Bremmer-Bout M, et al. Comparative analysis of antisense oligonucleotide analogs for targeted DMD exon 46 skipping in muscle cells. Gene Ther. 2004b;11(18):1391-8. http://www.nature.com/gt/journal/v11/n18/pdf/3302313a.pdf

Aartsma-Rus A, Kaman WE, Weij R, et al. Exploring the Frontiers of therapeutic exon skipping for Duchenne muscular dystrophy by double targeting within one or multiple exons. Molec Ther. 2006;14(3):401-7. http://www.nature.com/mt/journal/v14/n3/full/mt20061311a.html

Agre JC, Magness JL, Hull SZ, et al. Strength testing with a portable dynamometer: reliability for upper and lower extremities. Arch Phys Med Rehabil. 1987;68(7):454-8.

Anderson JL. Head SI, Rae C, et al. Brain function in Duchenne muscular dystrophy. Brain. 2002;125:4-13. http://brain.oxfordjournals.org/content/125/1/4

Ando J, Kamiya A. Blood flow and vascular endothelial cell function. Front Med Biol Eng. 1993;5(4):245-64.

Aoki Y1, Nagata T, Yokota T, et al. Highly efficient in vivo delivery of PMO into regenerating myotubes and rescue in laminin-a2. Hum Mol Genet. 2013;22(24):4914-28. http://hmg.oxfordjournals.org/content/22/24/4914.full.pdf+html

Arechavala-Gomeza V, Graham IR, Popplewell LJ, et al. Comparative analysis of antisense oligonucleotide sequences for targeted skipping of exon 51 during dystrophin pre-mRNA splicing in human muscle. Hum Gene Ther. 2007;18(9):798-810.

Aston JP, Kingston HM, et al. Plasma pyruvate kinase and creatine kinase activity in Becker muscular dystrophy. J Neurol Sci. 1984;65(3):307-14.

Bendixen RM, Senesac C, Lott DJ, et al. Participation and quality of life in children with Duchenne muscular dystrophy using the International Classification of Functioning, Disability, and Health. Health Qual Life Outcomes. 2012;10:43. doi: 10.1186/1477-7525-10-43. http://www.biomedcentral.com/content/pdf/1477-7525-10-43.pdf

Biggar WD, Harris VA, Eliasoph L, Alman B. Long-term benefits of deflazacort treatment in boys with Duchenne muscular dystrophy in their second decade. Neuromuscul. Disord. 2006;16:249-55.

Bohannon RW. Test-retest reliability of hand-held dynamometry during a single session of strength assessment. Phys Ther. 1986;66:206-9. http://ptjournal.apta.org/content/66/2/206.full.pdf+html

Bonati U, Hafner P, Schädelin S, et al. Quantitative muscle MRI: A powerful surrogate outcome measure in Duchenne muscular dystrophy. Neuromuscul Disord. 2015;25:679-85. http://www.sciencedirect.com/science/article/pii/S0960896615001571

Bremmer-Bout M, Aartsma-Rus A, de Meijer EJ, et al. Targeted exon skipping in transgenic hDMD mice: A model for direct preclinical screening of human-specific antisense oligonucleotides. Mol Ther. 2004;10(2):232-40. http://www.nature.com/mt/journal/v10/n2/pdf/mt20041221a.pdf

Brenman JE, Chao DS, Aldape K, Bredt DS. Nitric oxide synthase complexed with dystrophin and absent from skeletal muscle sarcolemma in Duchenne muscular dystrophy. Cell. 1995;82(5):743-52. http://www.sciencedirect.com/science/article/pii/0092867495904719

Bresolin N, Castelli E, Comi GP, et al. Cognitive impairment in Duchenne muscular dystrophy. Neuromuscul Disord. 1994;4:359-69.

Bulfield G, Siller WG, Wight PA, Moore KJ. X chromosome-linked muscular dystrophy (mdx) in the mouse. Proc Natl Acad Sci USA. 1984;81(4):1189-92. V http://www.pnas.org/content/81/4/1189.full.pdf

Bushby K, Finkel R, Birndrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010;9(1):77-93. http://ac.els-cdn.com/S1474442209702716/1-s2.0-S1474442209702716-main.pdf?_tid=1439b750-7382-11e5-978b-00000aab0f01&acdnat=1444944002_b356336f0c08f4a1fce8f2d61c585395

Bushby K, Connor E. Clinical outcome measures for trials in Duchenne muscular dystrophy: report from international working group meetings. Clin Invest (London). 2011;1(9):1217-35. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3357954/

Chamanza, et al. Incidences and range of spontaneous findings in control cynomolgus monkeys (Macaca fascicularis) used in toxicity studies. Toxicol Pathol. 2010;38(4):642-57 http://tpx.sagepub.com/content/38/4/642.long

Ciafaloni E, Fox DJ, Pandya S, et al. Delayed diagnosis in Duchenne muscular dystrophy: data from the Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet). J Pediatr. 2009;155(3):380-5.

Clarke LA, Wraith KE, Beck M, et al. Long-term efficacy and safety of laronidase in the treatment of mucopolysaccharidosis I. Pediatrics. 2009;123(1):229-40.

Davis SE, Hynan LS, Limbers CA, et al. The PedsQL™ in pediatric patients with Duchenne muscular dystrophy: feasibility, reliability, and validity of the Pediatric Quality of Life Inventory Neuromuscular Module and Generic Core Scales. J Clin Neuromuscul Dis. 2010;11(3):97-109.

Eagle M, Baudouin SV, Chandler C, et al. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002;12(10):926-9. http://www.parentprojectmd.org/site/DocServer/filename?docID=175

Emery A, Muntoni F. Duchenne muscular dystrophy. 3rd Ed. Oxford University Press, New York. 2003.

Engelhardt JA, Fant P, Guionaud S, et al. Scientific and Regulatory Policy Committee Points-to-consider Paper*: Drug-induced Vascular Injury Associated with Nonsmall Molecule Therapeutics in Preclinical Development: Part 2. Antisense Oligonucleotides. Toxicol Pathol. 2015 Feb 24. pii: 0192623315570341.

Ennen JP, Verma M, Asakura A. Vascular-targeted therapies for Duchenne muscular dystrophy. Skelet Muscle 2013;3(1):9. http://www.skeletalmusclejournal.com/content/pdf/2044-5040-3-9.pdf

European Medicines Agency. Guideline on the clinical investigation of medicinal products for the treatment of Duchenne and Becker muscular dystrophy. Draft. 2013. European Medicines Agency website http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2013/03/WC500139508.pdf.

Fairclough RJ, Wood MJ, Davies KE. Therapy for Duchenne muscular dystrophy: renewed optimism from genetic approaches. Nat Rev Genet. 2013;14(6):373-8.

Flanigan KM, Dunn DM, von Niederhausern A, et al. Mutational spectrum of DMD mutations in dystrophinopathy patients: application of modern diagnostic techniques to a large cohort. Hum Mutat. 2009;30(12):1657-66. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3404892/

Food and Drug Administration. Duchenne Muscular Dystrophy and Related Dystrophinopathies: Developing Drugs for Treatment. Draft Guidance for Industry. 2015. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM450229.pdf.

Gaeta M, Messina S, Mileto A, et al. Muscle fat-fraction and mapping in Duchenne muscular dystrophy: evaluation of disease distribution and correlation with clinical assessments. Preliminary experience. Skeletal Radiol. 2012;41:955-61.

Geary RS. Antisense oligonucleotide pharmacokinetics and metabolism. Expert Opin Drug Metab Toxicol. 2009;5(4).381-91.

Geiger R1, Strasak A, Treml B, et al. Six-minute walk test in children and adolescents. J Pediatr. 2007;150(4):395-9.

Goemans NM, Tulinius M, van den Akker JT, et al. Systemic administration of PRO051 in Duchenne's muscular dystrophy. N Engl J Med. 2011;364(16);1513-22. http://www.nejm.org/doi/pdf/10.1056/NEJMoa1011367

Goemans N, van den Hauwe M, Wilson R, et al. Ambulatory capacity and disease progression as measured by the 6-minute-walk-distance in Duchenne muscular dystrophy subjects on daily corticosteroids. Neuromuscul Disord. 2013;23(8):618-23.

Goemans N, Tulinius M, Kroksmark A-K, et al. Drisapersen treatment for Duchenne muscular dystrophy (DMD): results of up to 188 weeks' follow-up of an open-label extension study. Poster presented at: 19th International Congress of the World Muscle Society (WMS); October 2014; Berlin, Germany; Poster G.P.113.

Griggs RC, Herr BE, Reha A et al. Corticosteroids in Duchenne muscular dystrophy: major variations in practice. Muscle Nerve 2013; 48(1):27-31.

Guy W. ECDEU Assessment Manual for Psychopharmacology. US Department of Health, Education and Welfare Public Health Service, Alcohol, Drug Abuse, and Mental Health Administration. Rockville MD: 1976.

Hammond SM, Wood MJ. PRO-051, an antisense oligonucleotide for the potential treatment of Duchenne muscular dystrophy. Curr Opin Mol Ther. 2010;12(4):478-86.

Han JJ, Kurillo G1, Abresch RT, et al. Upper extremity 3-dimensional reachable workspace analysis in dystrophinopathy using Kinect. Muscle Nerve. 2015;52(3):344-55. http://onlinelibrary.wiley.com/doi/10.1002/mus.24567/epdf

Hathout Y, Brody E, Clemens PR, et al. Large-scale serum protein biomarker discovery in Duchenne muscular dystrophy. Proc Natl Acad Sci USA. 2015;112(23):7153-8. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4466703/?report=reader

Heemskerk H, de Winter C, van Kuik P, et al. Preclinical PK and PD studies on 2'-O-methyl-phosphorothioate RNA antisense oligonucleotides in the mdx mouse model. Mol Ther. 2010;18(6):1210-7. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2889733/

Hendriksen JG, Poysky JT, Schrans DG, et al. Psychosocial adjustment in males with Duchenne muscular dystrophy: psychometric properties and clinical utility of a parent-report questionnaire. J Pediatr Psychol. 2009;34(1):69-78. http://jpepsy.oxfordjournals.org/content/34/1/69.full.pdf+html

Hendriksz CJ, Burton B, Fleming TR, et al. Efficacy and safety of enzyme replacement therapy with BMN 110 (elosulfase alfa) for Morquio A syndrome (mucopolysaccharidosis

IVA): a phase 3 randomised placebo-controlled study. J Inherit Metab Dis. 2014;37(6):979-90. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4206772/

Henricson E, Abresch R, Han JJ, et al. Percent predicted 6-minute walk distance in Duchenne muscular dystrophy to account for maturational influences. PLoS Curr. 2012;4:RRN1297. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3269886/

Henricson EK, Abresch T, Cnaan A, et al. The Cooperative International Neuromuscular Research Group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. Muscle Nerve. 2013a;48(1):55-67. http://onlinelibrary.wiley.com/doi/10.1002/mus.23808/pdf

Henricson E, Abresch R, Jay JJ, et al. The 6-minute walk test and person-reported outcomes in boys with Duchenne muscular dystrophy and typically developing controls: longitudinal comparisons and clinically-meaningful changes over one year. PLoS Curr. 2013b;5: ecurrents.md.9e17658b007eb79fcd6f723089f79e06. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3712467/

Henricson E, McDonald C, CINRG Investigators. G.P.392 – Five-year longitudinal UC Davis CINRG Duchenne Natural History Study (DNHS) data show mobility-focused POSNA PODCI items are sensitive to 12-month disease progression across all stages of DMD functional ability. Neuromuscul Disord. 2015;25 (Suppl 2):S303.

Henry SP, Kim T, Kramer-Stickland K, et al. Toxicologic properties of 2-o-methylethyl chimeric antisense inhibitors in animals and men. In: Crooke ST, ed. *Antisense Drug Technology: Principles, Strategies and Applications*. 2nd ed. New York, NY: CRC Press; 2008:327-64.

Henry SP, Jagels MA, Hugli TE, et al. Mechanism of alternative complement pathway dysregulation by a phosphorothioate oligonucleotide in monkey and human serum. Nucleic Acid Ther. 2014;24(5):326-35.

Hopf FW, Turner PR, Steinhardt RA. Calcium misregulation and the pathogenesis of muscular dystrophy. Subcell Biochem. 2007;45:429-64.

Jejurikar SS, Kuzon WM Jr. Satellite cell depletion in degenerative skeletal muscle. Apoptosis. 2003;8(6):573-8.

King WM, Ruttencutter R, Nagaraja HN, et al. Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. Neurology. 2007;68:1607-13.

Kohler M, Clarenbach CF, Böni L, et al. Quality of life, physical disability, and respiratory impairment in Duchenne muscular dystrophy. Am J Respir Crit Care Med. 2005;172(8):1032-6. Epub 2005 Jun 16. http://www.atsjournals.org/doi/pdf/10.1164/rccm.200503-322OC

Kwoh TJ. An overview of the clinical safety experience of first and second generation antisense oligonucleotides. In: *Antisense Drug Technology: Principles, Strategies and Applications.* 2nd ed. Boca Raton, FL: Taylor and Francis; 2008:365-400. Book.

Lerario A, Bonfiglio S, Sormani M, et al. Quantitative muscle strength assessment in Duchenne muscular dystrophy: longitudinal study and correlation with functional measures. BMC Neurol. 2012;12:91. http://www.biomedcentral.com/1471-2377/12/91

Levin AA, Henry SP, Monteith D, Templin MV. Toxicity of Antisense Oligonucleotides. In: Crooke ST, ed. *Antisense Drug Technology: Principles, Strategies and Applications*. New York, NY: Marcel Dekker, Inc, 2001:201-67.

Levin AA. Toxicity of oligonucleotide therapeutics and understanding the relevance of the toxicities. In: Cavagnaro JA, ed. *Preclinical Safety Evaluation of Biopharmaceuticals, A Science Based Approach to Facilitating Clinical Trials*. Hoboken, NJ: John Wiley and Sons Inc, 2008:545-74.

Lu QL, Mann CJ, Lou F, et al. Functional amounts of dystrophin produced by skipping the mutated exon in the mdx dystrophic mouse. Nat Med. 2003;9:1009-14.

Lu QL, Rabinowitz A, Chen YC, et al. Systemic delivery of antisense oligoribonucleotide restores dystrophin expression in body-wide skeletal muscles. Proc Natl Acad Sci FUSA. 2005;102(1):198-203. http://www.pnas.org/content/102/1/198.long

Machado DL, Silva EC, Resende MBD, et al. Lung function monitoring in patients with Duchenne muscular dystrophy on steroid therapy. BMC Res Notes. 2012;5:435-41. http://www.biomedcentral.com/1756-0500/5/435

Markham LW, Kinnett K, Wong BL, Woodrow Benson D, Cripe LH. Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy. Neuromuscul Disord. 2008; 18: 365–70.

Mayhew A, Cano S, Scott E, et al. Moving towards meaningful measurement: Rasch analysis of the North Star Ambulatory Assessment in Duchenne muscular dystrophy. Dev Med Child Neurol. 2011;53(6):535-42. http://onlinelibrary.wiley.com/doi/10.1111/j.1469-8749.2011.03939.x/full

Mayhew AG, Cano SJ, Scott E, et al. Detecting meaningful change using the North Star Ambulatory Assessment in Duchenne muscular dystrophy. Dev Med Child Neurol. 2013;55(11):1046-52. http://onlinelibrary.wiley.com/doi/10.1111/dmcn.12220/full

Mazzone E, Messina S, Vasco G, et al. Reliability of the North Star Ambulatory Assessment in a multicentric setting. Neuromuscul Disord. 2009;19(7):458-61.

Mazzone E, Vasco G, Sormani MP, et al. Functional changes in Duchenne muscular dystrophy: a 12-month longitudinal cohort study. Neurology. 2011;77(3):250-6.

Mazzone ES, Pane M, Sormani MP, et al. 24-month longitudinal data in ambulant boys with Duchenne muscular dystrophy. PLoS One. 2013;8(1):e52512. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0052512

McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test in Duchenne/Becker muscular dystrophy: longitudinal observations. Muscle Nerve. 2010a;42:966-74.

McDonald CM, Henricson EK, Han JJ, et al. The 6-minute walk test as a new outcome measure in Duchenne muscular dystrophy. Muscle Nerve. 2010b;41:500-10.

McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other clinical endpoints in Duchenne muscular dystrophy: reliability, concurrent validity, and minimal clinically important differences from a multicenter study. Muscle Nerve. 2013a;48(3):357-68. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3826053/

McDonald CM, Henricson EK, Abresch MS, et al. The cooperative International Neuromuscular Research Group Duchenne Natural History Study–A longitudinal investigation in the era of glucocorticoid therapy: Design of protocol and the methods used. Muscle Nerve. 2013b;48(1):32-54. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4147958/

McDonald CM, Henricson EK, Abresch RT, et al. The 6-minute walk test and other endpoints in Duchenne muscular dystrophy: Longitudinal natural history observations over 48 weeks from a multicenter study. Muscle Nerve. 2013c;48:343-56. http://onlinelibrary.wiley.com/doi/10.1002/mus.23902/full

McMillan HJ, Gregas M, Darras BT, et al. Serum transaminase levels in boys with Duchenne and Becker muscular dystrophy. Pediatrics. 2011;127:e132-6. http://pediatrics.aappublications.org/content/127/1/e132.long

McNeil DE, Davis C, Jillapalli D, et al. Duchenne Muscular Dystrophy: drug development and regulatory considerations. Muscle Nerve. 2010;41(6):740-5.

Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. Ann Neurol. 2013;74(5):637-47. http://onlinelibrary.wiley.com/doi/10.1002/ana.23982/full

Moxley RT 3rd, Pandya S, Ciafaloni E, et al. Change in natural history of Duchenne muscular dystrophy with long-term corticosteroid treatment: implications for management. J Child Neurol. 2010;25(9):1116-29.

Muenzer J, Wraith JE, Beck M, et al. A phase II/III clinical study of enzyme replacement therapy with idursulfase in mucopolysaccharidosis II (Hunter syndrome). Genet Med. 2006;8(8):465-73. http://www.nature.com/gim/journal/v8/n8/full/gim200682a.html

Muntoni F. The development of antisense oligonucleotide therapies for Duchenne muscular dystrophy: report on a TREAT-NMD workshop hosted by the European Medicines Agency (EMA), on September 25th 2009. Neuromuscul Discord. 2010;20(5):355-62. http://www.nmd-journal.com/article/S0960-8966(10)00110-0/pdf

Palladino M, Gatto I, Neri V, et al. Angiogenic impairment of the vascular endothelium: a novel mechanism and potential therapeutic target in muscular dystrophy. Arterioscler Thromb Vasc Biol. 2013;33(12):2867-76. http://atvb.ahajournals.org/content/33/12/2867.long

Pane M, Mazzone ES, Sivo S, et al. Long term natural history data in ambulant boys with Duchenne muscular dystrophy: 36-month changes. PLoS One. 2014;9(10):e108205. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0108205

Parent Project Muscular Dystrophy website. Guidance for Industry. Duchenne Muscular Dystrophy, Developing Drugs for Treatment over the Spectrum of Disease. 2014. http://www.parentprojectmd.org/site/DocServer/Guidance_Document_Submission_-_Duchenne_Muscular_Dystrop.pdf?docID=15283.

Pearce JM, Pennington RJ, Walton JN. Serum enzyme studies in muscle disease. II. Serum creatine kinase activity in muscular dystrophy and in other myopathic and neuropathic disorders. J Neurol Neurosurg Psychiatry. 1964;27:96-9. http://jnnp.bmj.com/content/27/2/96.long

Pearson CM, Kar NC, Peter JB, Munsat TL. Muscle lactate dehydrogenase patterns in two types of X-linked muscular dystrophy. Am J Med. 1965;39:91-7.

Phelps SF, Hauser MA, Cole NM, et al. Expression of full length and truncated dystrophin mini-genes in transgenic mdx mice. Hum Mol Genet. 1995;4:1251-58.

Phillips MF, Quinlivan RC, Edwards RH, Calverley PM. Changes in spirometry over time as a prognostic marker in patients with Duchenne muscular dystrophy. Am J Respir Crit Care Med. 2001;164(12):2191-4. http://www.atsjournals.org/doi/full/10.1164/ajrccm.164.12.2103052#.ViAcGo3luT8

Popplewell, LJ, Trollet C, Dickson G, Graham I R. Design of phosphorodiamidate morpholino oligomers (PMOs) for the induction of exon skipping of the human DMD gene. Mol Ther. 2009;17(3):554-61. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2835085/

Popplewell LJ, Adkin C, Arechavala-Gomeza V, et al. Comparative analysis of antisense oligonucleotide sequences targeting exon 53 of the human DMD gene: Implications for future clinical trials. Neuromuscul Disord. 2010;20(2):102-10.

Porter BF, et al. Polyarteritis nodosa in a cynomolgus macaque (Macaca fascicularis). Vet Pathol. 2003;40(5):570-3. http://vet.sagepub.com/content/40/5/570.long

Rall S, Grimm T. Survival in Duchenne muscular dystrophy. Acta Myol. 2012;31(2):117-20. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3476855/

Rubin LJ, Badesch DB, Barst RJ, et al. Bosentan therapy for pulmonary arterial hypertension. N Engl J Med. 2002;346:896-903. http://www.nejm.org/doi/pdf/10.1056/NEJMoa012212

Rybakova IN, Patel JR, Ervasti JM. The dystrophin complex forms a mechanically strong link between the sarcolemma and costameric actin. J Cell Biol. 2000;150(5):1209-14. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2175263/

Saito T. Coagulation and fibrinolysis in patients with muscular dystrophy, fibrinolysis, and thrombolysis. 2014. Dr Krasimir Kolev (Ed), ISBN 978-953-51-1265-5. InTech, DOI:10.5772/57411. http://www.intechopen.com/books/fibrinolysis-and-thrombolysis/coagulation-and-fibrinolysis-abnormalities-in-patients-with-muscular-dystrophy.

Sander M, Chavoshan B, Harris SA, et al. Functional muscle ischemia in neuronal nitric oxide synthase-deficient skeletal muscle of children with Duchenne muscular dystrophy. Proc Natl Acad Sci USA. 2000;97(25):13818-23. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC17659/

Sasinowski FJ. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Cataloguing FDA's Flexibility in Regulating Therapies for Persons with Rare Disorders. Drug Information Journal 238. Mar. 2012; Appendix 7. http://nordphysicianguides.org/wp-content/uploads/2012/02/NORD-study-of-FDA-approval-of-orphan-drugs.pdf.

Sasinowski FJ, Panico EB, Valentine JE. Quantum of Effectiveness Evidence in FDA's Approval of Orphan Drugs: Updated, July 2010 to June 2014. Therapeutic Innovation & Reg Sci. September 2015;49:680-697. http://www.fdalawblog.net/Quantum%20of%20Effectiveness%20-%20Update.pdf

Scott E, Eagle M, Mayhew A, et al and North Star Clinical Network for Paediatric Neuromuscular Disease. Development of a functional assessment scale for ambulatory boys with Duchenne muscular dystrophy. Physiother Res Int. 2012;17(2):101-9.

Shen L, Frazer-Abel A, Reynolds PR, et al. Mechanistic understanding for the greater sensitivity of monkeys to antisense oligonucleotide-mediated complement activation compared with humans. J Pharmacol Exp Ther. 2014;351(3):709-17. http://jpet.aspetjournals.org/content/early/2014/10/09/jpet.114.219378.full.pdf+html

Simon VA, Resende MB, Simon MA, et al. Duchenne muscular dystrophy: quality of life among 95 patients evaluated using the Life Satisfaction Index for Adolescents. Arq Neuropsiquiatr. 2011;69(1):19-22. http://www.scielo.br/scielo.php?script=sci_arttext&pid=S0004-282X2011000100005&lng=en&nrm=iso&tlng=en

Stuberg WA, Metcalf WK. Reliability of quantitative muscle testing in healthy children and in children with Duchenne muscular dystrophy using a hand-held dynamometer. Phys Ther. 1988;68(6): 977-82. http://ptjournal.apta.org/content/68/6/977.long

Suleman N, Frost AE. Transition from epoprostenol and treprostinil to the oral endothelin receptor antagonist bosentan in patients with pulmonary hypertension. Chest. 2004;126(3):808-15. http://journal.publications.chestnet.org/article.aspx?articleid=1082791

Somer H, Donner M, Murros J, Konttinen A. A serum isozyme study in muscular dystrophy. Particular reference to creatine kinase, aspartate aminotransferase, and lactic acid dehydrogenase isozymes. Arch Neurol. 1973;29(5):343-5.

Somer H, Dubowitz V, Donner M. Creatine kinase isoenzymes in neuromuscular diseases. J Neurol Sci. 1976;29(2-4):129-36.

Surono A1, Van Khanh T, Takeshima Y, et al. Chimeric RNA/ethylene-bridged nucleic acids promote dystrophin expression in myocytes of Duchenne muscular dystrophy by inducing skipping of the nonsense mutation-encoding exon. Hum Gene Ther. 2004;15(8):749-57. http://www.parentproject.cz/research/2004/vyzkum_2004_files/p749.pdf

Tanganyika-de Winter CL1, Heemskerk H, Karnaoukh TG, et al. Long-term exon skipping studies with 2′-O-methyl phosphorothioate antisense oligonucleotides in dystrophic mouse models. Mol Ther Nucleic Acids. 2012;1(9):e44. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3464881/

Takeshima Y1, Wada H, Yagi M, et al. Oligonucleotides against a splicing enhancer sequence led to dystrophin production in muscle cells from a Duchenne muscular dystrophy patient. Brain Dev. 2001;23(8):788-90.

Translarna [EPAR Product Information]. Dublin, Ireland: PTC Therapeutics International Limited; 2015. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/002720/human_med_001742.jsp&mid=WC0b01ac058001d124.

Uzark K, King E, Cripe L, et al. Health-related quality of life in children and adolescents with Duchenne muscular dystrophy. Pediatrics. 2012;130(6):e1559-66. http://pediatrics.aappublications.org/content/130/6/e1559.full

van den Bergen JC, Schade van Westrum SM, Dekker L, et al. Clinical characterisation of Becker Muscular Dystrophy patients predicts favourable outcome in exon-skipping therapy. J Neurol Neurosurg Psychiatry. 2014;85(1):92-8.

van der Ploeg AT, Clemens PR, Corzo D, et al. A randomized study of alglucosidase alfa in late-onset Pompe's disease. N Engl J Med. 2010;362:1396-406. http://www.nejm.org/doi/full/10.1056/NEJMoa0909859

van Deutekom JC, Bremmer-Bout M, Janson AA, et al. Antisense-induced exon skipping restores dystrophin expression in DMD subject derived muscle cells. Hum Mol Genet. 2001;10(15):1547-54. http://hmg.oxfordjournals.org/content/10/15/1547.full

van Deutekom JC, Janson AA, Ginjaar IB, et al. Local dystrophin restoration with antisense oligonucleotide PRO051. N Engl J Med. 2007;357(26):2677-86. http://www.nejm.org/doi/full/10.1056/NEJMoa073108

van Ommen GJ, van Deutekom J, Aartsma-Rus A. The therapeutic potential of antisense-mediated exon skipping. Curr Opin Mol Ther. 2008;10(2):140-9.

van Putten M, Hulsker M, Nadarajah VD, et al. The effects of low levels of dystrophin on mouse muscle function and pathology. PLoS One. 2012;7(2):e31937. http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0031937

van Putten M, Hulsker M, Young C, et al. Low dystrophin levels increase survival and improve muscle pathology and function in dystrophin/utrophin double-knockout mice. FASEB J. 2013;27(6):2484-95. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3659351/

Verhaart IE, Tanganyika-de Winter CL, Karnaoukh TG, et al. Dose-dependent pharmacokinetic profiles of 2'-O-methyl phosphorothioate antisense oligonucleotides in mdx mice. Nucleic Acid Ther. 2013;23(3):228-37.

Verhaart IE, van Vliet-van den Dool L, Sipkens JA, et al. The dynamics of compound, transcript, and protein effects after treatment with 2OMePS antisense oligonucleotides in

mdx mice. Mol Ther Nucleic Acids. 2014;3:e148.
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3950770/

Voit T, Topaloglu H, Straub V, et al. Safety and efficacy of drisapersen for the treatment of Duchenne muscular dystrophy (DEMAND II): an exploratory, randomised, placebo-controlled phase 2 study. Lancet Neurol. 2014;13(10):987-96.

Wagner KR, Lechtzin N, Judge DP. Current treatment of adult Duchenne muscular dystrophy. Biochim Biophys Acta. 2007;1772 (2):229-37.
http://www.sciencedirect.com/science/article/pii/S0925443906001232

Wilton SD1, Fall AM, Harding PL, et al. Antisense oligonucleotide-induced exon skipping across the human dystrophin gene transcript. Mol Ther. 2007;15(7):1288-96.
http://www.nature.com/mt/journal/v15/n7/full/6300095a.html

Wokke JH, Escolar DM, Pestronk A, et al. Clinical features of late-onset Pompe disease: a prospective cohort study. Muscle Nerve. 2008;38(4):1236-45.

Wraith JE, Clarke LA, Beck M, et al. Enzyme replacement therapy for mucopolysaccharidosis I: a randomized, double-blinded, placebo-controlled, multinational study of recombinant human alpha-L-iduronidase (laronidase). J Pediatr. 2004;144:581-8.

Wu B, Xiao B, Cloer C, et al. One-year treatment of morpholino antisense oligomer improves skeletal and cardiac muscle functions in dystrophic mdx mice. Mol Ther. 2011;19(3):576-83. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3048192/

Yasmineh WG, Ibrahim GA, Abbasnezhad M, Awad EA. Isoenzyme distribution of creatine kinase and lactate dehydrogenase in serum and skeletal muscle in Duchenne muscular dystrophy, collagen disease, and other muscular disorders. Clin Chem. 1978;24(11):1985-9.
http://www.clinchem.org/content/24/11/1985.long

Yokota T1, Lu QL, Partridge T, et al. Efficacy of systemic morpholino exon-skipping in Duchenne dystrophy dogs. Ann Neurol. 2009;65(6):667-76.

Zatz M, Rapaport D, Vainzof M, et al. Serum creatine-kinase (CK) and pyruvate-kinase (PK) activities in Duchenne (DMD) as compared with Becker (BMD) muscular dystrophy. J Neurol Sci. 1991,102(2):190-6.

Zhang 2012: Zhang Y, Huang JJ, Wang ZQ, Wang N, Wu ZY. Value of muscle enzyme measurement in evaluating different neuromuscular diseases. Clin Chim Acta. 2012;413(3-4):520-4.

Zhou S, Chen L. Neural integrity is maintained by dystrophin in *C. elegans*. J Cell Biol. 2011;349:349-63. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3172177/

11 APPENDICES

11.1 Appendix A: Natural History Matches with Patients in Study 673

A total of 75 natural history (NH) subject matches with the 12 Study 673 drisapersen-treated patients were available and included in the analysis of 6MWD. All matched NH subjects are included in the per subject plots. Only matched NH subjects with >2 assessments from the point of matching are including in the individual patient narratives.

There were no matches identified for 3 patients

Patient 673-104 had a high baseline 6MWD (>600 meters) comparable to the average 6MWD in healthy subjects of his age [Goemans 2013]. He maintained functional ability over the three and a half year observation period which is atypical and no matches were possible

Although a match was identified for patient 673-103; only 1 assessment was available from the point of matching and therefore this subject's data could not be interpreted. Patient 673-103 was unable to complete the 6MWD at baseline, therefore matching to natural history subjects in terms of 6MWD is unlikely to be informative

Patient 673-201 was nonambulant at baseline; a match was not possible based on 6MWD

Individual Patient Narratives

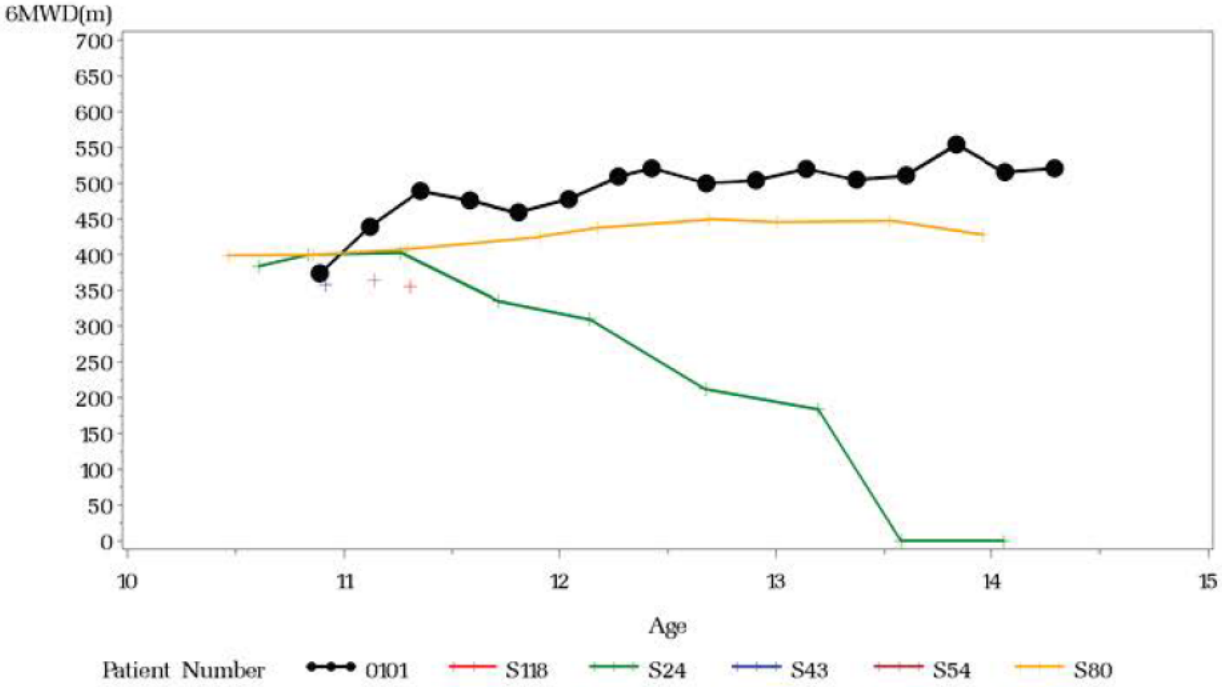
In all figures, the black dotted line represents the patient from Study 673. Other lines are contemporaneous control data. Control data presented from the first record that matched with the Study 673 patient at baseline. Single data points are subjects that match, but have no additional follow-up data.

Patients with Stable Baseline Function

Patient 673-101 (10.9 years)

Patient 101 had a baseline 6MWD of 674 meters and maintained a consistently good 6MWD over a three and a half year period. The overall change from baseline after 177 weeks of treatment with drisapersen was +147 meters. Achieving a 6MWD of 521 meters at the age of 14.3 years is not expected for a patient with Duchenne muscular dystrophy and is comparable to distance expected for healthy boys aged 7 to 8 years [McDonald 2010b]. Two natural history matches were identified with >2 assessments available, with an age range of 10.5–14.1 years and baseline 6MWD range of 356–399 meters. NH Subject S24 lost his ability to perform the 6MWD test at the age of 13.6 years. NH Subject S80 remained relatively stable with an improvement of 29 meters at 14 years. Comparison of this NH subject to Patient 101 at a similar age (14 years) indicates a substantial difference in the distance walked (428 meters and 515 meters, respectively). The rise-from-the-floor (RFF) results reveal that Patient 101 increased his time by 1.17 seconds compared with baseline; however, NH Subject S80 had a sharper decline with an increase of 2.59 seconds, confirming the 6MWD results.

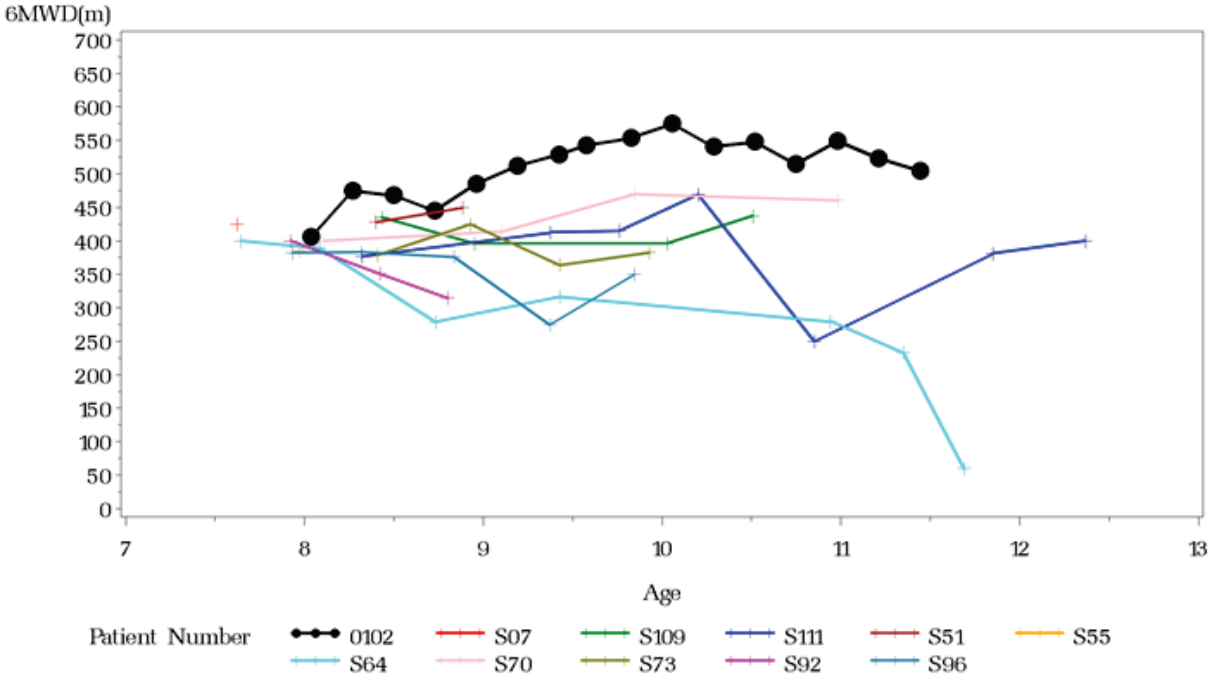
Figure 11.1.1: Patient 673-101 6MWD Trajectory per Matched Natural History Subject



Patient 673-102 (8.04 years)

Patient 102 had a baseline 6MWD of 406 meters and increased his distance by 99 meters over three and a half years. He was able to walk 505 meters at his last assessment (aged 11.4 years). Seven NH matches were identified with >2 assessments available, with an age range of 7.6–12.4 years and baseline 6MWD range of 377–435 meters. The NH subjects show variation in their functional abilities over time. Three NH subjects showed declines in their 6MWD compared with baseline (NH Subject S64, -340 meters at 11.7 years; NH Subject S92, -85 meters at 8.8 years; NH Subject S96, -32 meters at 9.9 years). NH Subject S64 had a sudden decline in his functional ability on the last recorded assessment of -167 meters. Two NH subjects remained relatively stable compared with their baseline 6MWD (NH Subjects S73, +4 meters at 9.9 years; S109, +2 meters at 10.5 years). Two NH subjects had an improvement in their 6MWD from baseline (NH Subject S70, +61 meters at 11.0 years; S111, +23 meters at 12.4 years). NH Subjects S70 and 102 follow a similar trajectory and the RFF indicates a small improvement of 0.3 seconds and an increase of 1.4 seconds over time for these subjects, respectively.

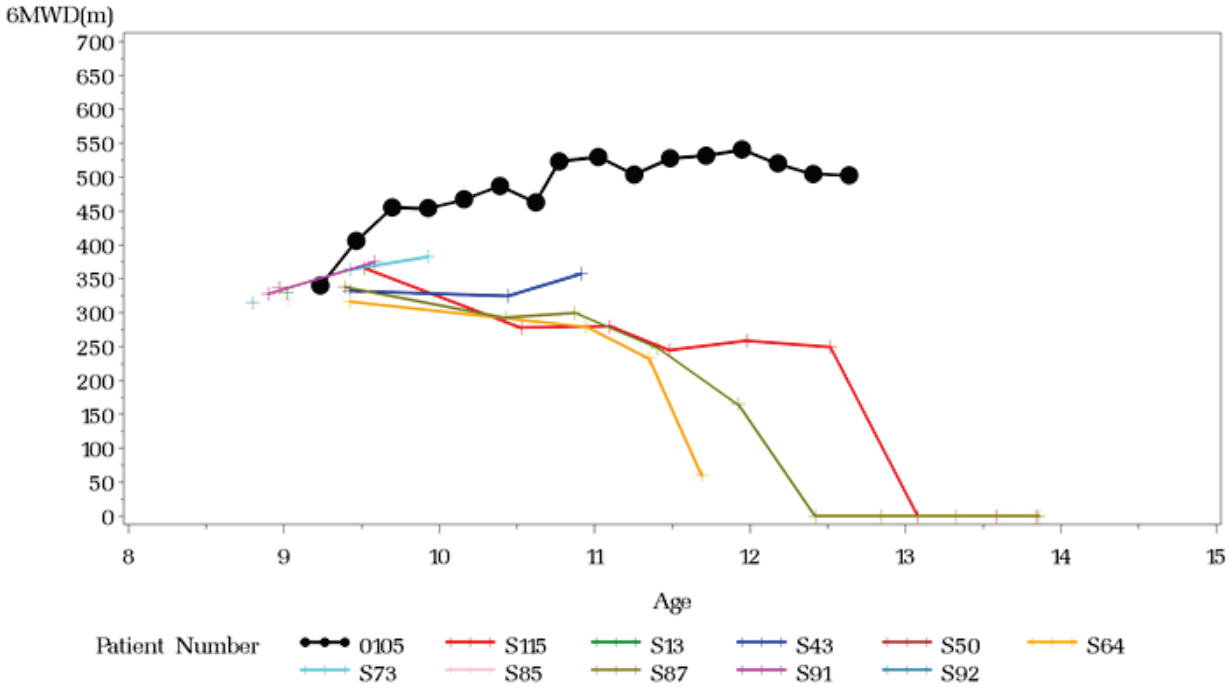
Figure 11.1.2: Patient 673-102 6MWD Trajectory per Matched Natural History Subject



Patient 673-105 (9.2 years)

Patient 105 had a baseline 6MWD of 340 meters and over time improved his 6MWD by 163 meters. At 12.6 years, he was able to walk 503 meters. Four NH matches were identified with >2 assessments available, with an age range of 8.8–13.9 years and baseline 6MWD range of 315–366 meters. Two of the NH subjects lost their ability to perform the 6MWD (NH Subjects S87 and S115 at 12.4 years and 13.1 years, respectively). NH Subject S64 had a significant decline in the distance recorded over time (256.8 meters) and was only able to walk 60 meters at the age of 11.7 years. At 10.9 years, he was unable to perform the RFF test. NH Subject S43 showed improvement from baseline of 26 meters at age 10.9 years; however, this covers a much shorter duration of observation (1.5 years). To put this into context, the 6MWD for NH Subject S43 at the last assessment was 358 meters (10.9 years) compared with 523 meters for Patient 105 at a similar time point (10.8 years); a substantial difference in 6MWD in favor of the drisapersen-treated child.

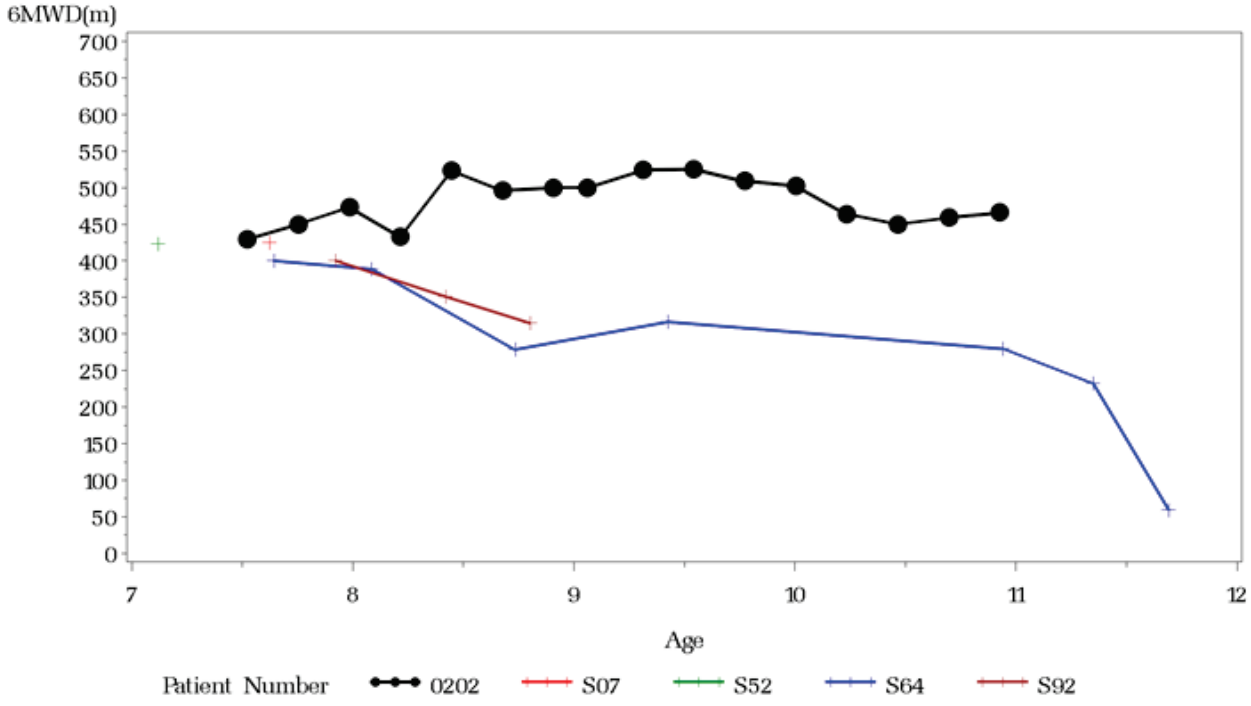
Figure 11.1.3: Patient 673-105 6MWD Trajectory per Matched Natural History Subject



Patient 673-202 (7.5 years)

Patient 202 had a baseline 6MWD of 429 meters and showed improvement of +37 meters. He was able to complete 466 meters in this timed test at 10.9 years. Two NH matches were identified with >2 assessments available with an age range of 7.1–11.7 years and baseline 6MWD range of 400–425 meters). Both NH subjects had a decline in functional ability; NH subject S64 6MWD declined by 340 meters at 11.7 years and NH Subject S92 6MWD declined by 85 meters at 8.80 years. The decline in 6MWD for NH Subject S64 was more severe in the last 6 months of the observation period. Comparison of the 6MWD tests for both NH Subject S64 (280 meters) and Patient 201 (466 meters) at the same age (10.9 years) indicates a substantial difference in functional ability in favor of Patient 202.

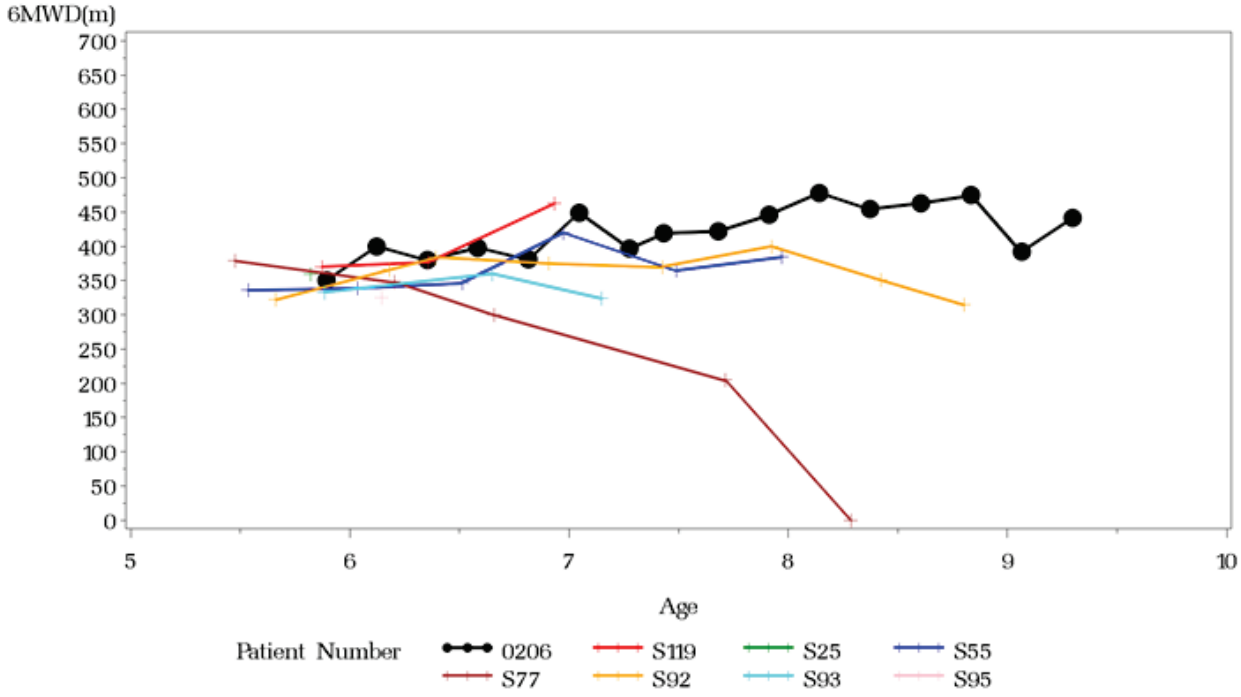
Figure 11.1.4: Patient 673-202 6MWD Trajectory per Matched Natural History Subject



Patient 673-206 (5.9 years)

Patient 206 had a baseline 6MWD of 350 meters with an improvement of +91 meters over time. He was able to walk 441 meters at 9.3 years. His RFF improved by 0.14 seconds. Five NH matches were identified with >2 assessments available with an age range of 5.5–8.8 years, which represents the youngest comparison group. The baseline 6MWD range for these NH subjects was 322–379 meters. One NH subject (S77) lost his ability to perform the 6MWD test at 8.3 years despite his baseline 6MWD of 379 meters. His treating physician confirmed that he developed severe contractures and suspected that this may be due to the lack of stretching within the physical therapy program. Two NH subjects (S92 and S93) had very small declines in their 6MWD. NH Subject S92 declined by 7.1 meters at 8.8 years and NH Subject S93 declined by 9 meters at 7.2 years. Their RFF results showed an increase of 2.02 seconds for NH Subject S92 and a decrease of 0.5 seconds for NH Subject S93. Two NH subjects (S55 and S119) improved their 6MWD. NH Subject S55 improved 49 meters at 8.0 years and NH Subject S119 improved 93 meters at 6.9 years. However, both subjects increased their RFF times (S55, +1.85 seconds; S119, +5.01 seconds). Due to the shorter follow-up for these 2 NH subjects, their functional trajectories based on 6MWD appear similar to Patient 206, but their RFF times indicate a decline in their functional ability.

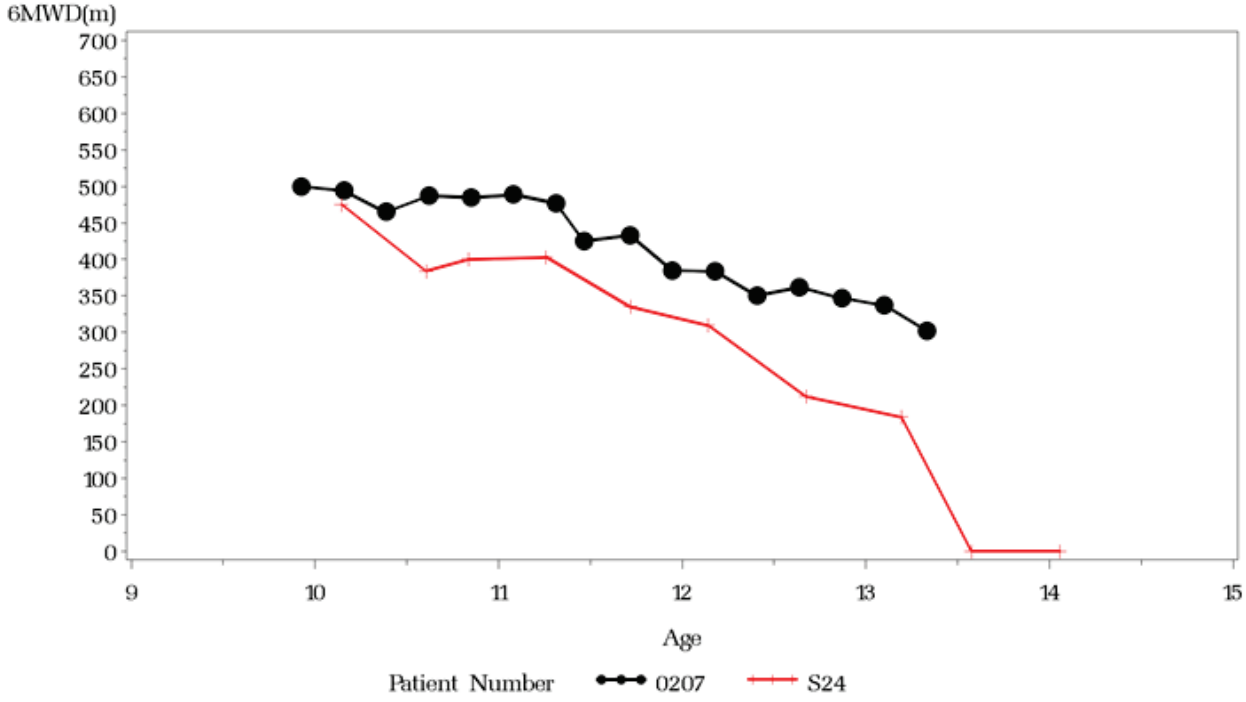
Figure 11.1.5: Patient 673-206 6MWD Trajectory per Matched Natural History Subject



Patient 673-207 (9.9 years)

Patient 207 had a baseline 6MWD of 500 meters with a steady decline of 198 meters over time. He was still able to walk 302 meters at the age of 13.3 years. This patient has been unable to perform the RFF test since the age of 12.4 years. His steroid regimen was changed in an attempt to address his short stature and he received intermittent corticosteroids for approximately 10 months (from Wk 60–105). One NH match was identified with >2 assessments available with an age range of 10.1– 14.1 years). The NH Subject S24 lost the ability to perform the 6MWD at 13.6 years. At the last reported assessment for Patient 207, he achieved a 6MWD of 302 meters at the age of 13.3 years compared with 184 meters at 13.2 years for NH Subject S24, indicating a substantial difference in physical ability between the 2 boys at the same age. Stable pulmonary function compared with baseline was seen in both Patient 207 (FVC +0.26 L, % predicted FVC -15%, peak flow [PF] +64.0 L/min, % predicted PF +2.77%) as well as NH Subject S24 (FVC +0.26 L, % predicted FVC -29%).

Figure 11.1.6: Patient 673-207 6MWD Trajectory per Matched Natural History Subject

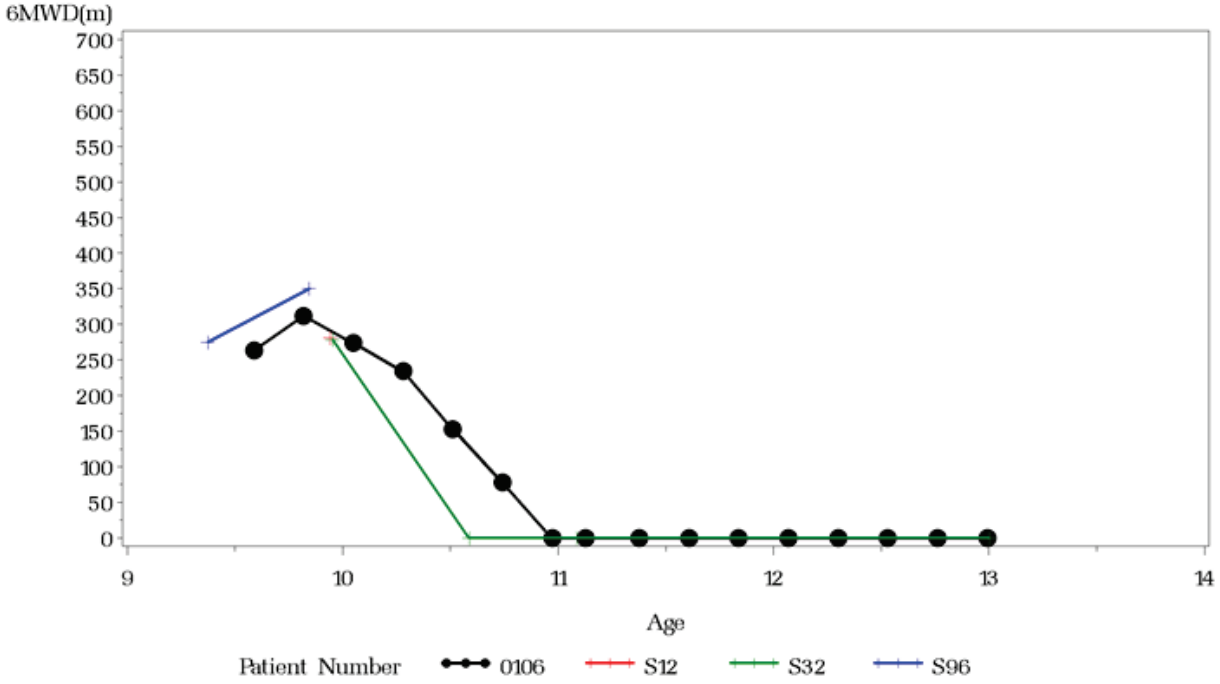


Patients With Declined Baseline Function

Patient 673-106 (9.6 years)

Patient 106 had a baseline 6MWD of 263 meters and was unable to perform since age 11 years. One NH match was identified with >2 assessments available, with an age range of 9.4-13.0 years. NH Subject S32 had a baseline 6MWD of 278 meters; but he also lost his ability to perform the test at 10.6 years. Thus, the functional ability of these boys cannot be compared and therefore, pulmonary function was reviewed across the matched observation period. The pulmonary function of both boys was comparable and showed no decline over the timeline observed. Patient 106 had FVC +0.13 L, % predicted FVC -10%, PF +50.0 L/min, and % predicted peak flow +6.25% compared with baseline; NH Subject S32 FVC +0.37 L, % predicted FVC -8%, and PF +48 L/min. The annualized decline in % predicted FVC for this observational period was comparable; 2.9% for Patient 106 and 2.6% for NH Subject S32.

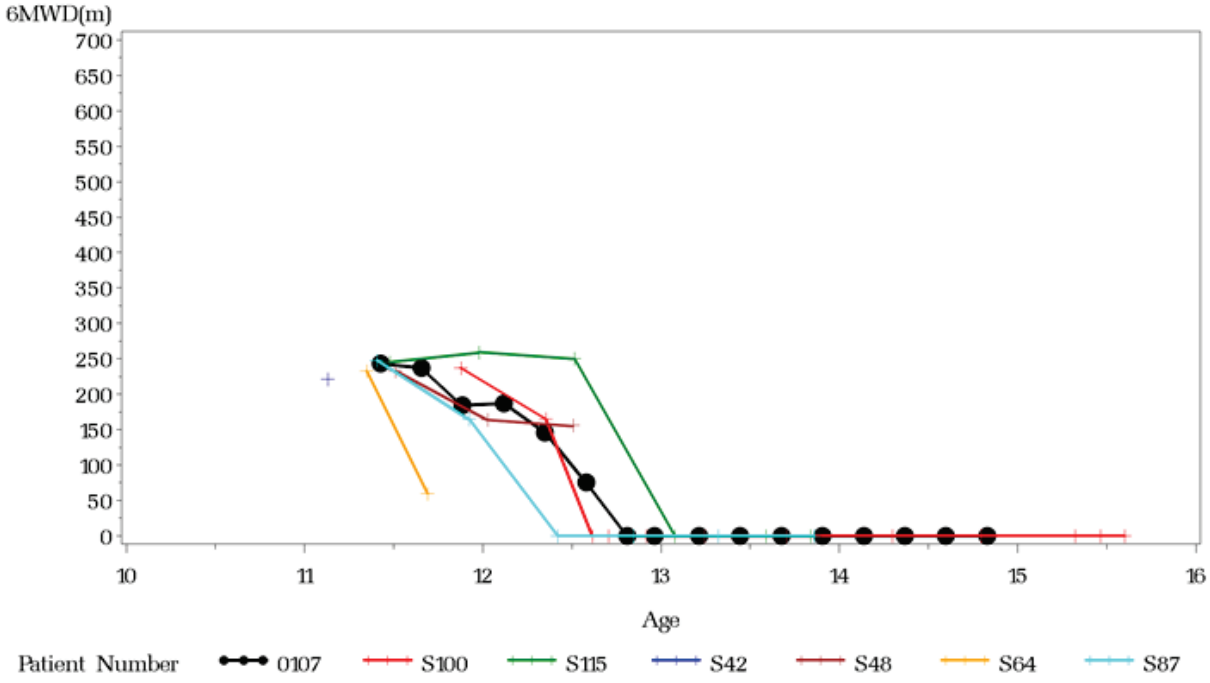
Figure 11.1.7: Patient 673-106 6MWD Trajectory per Matched Natural History Subject



Patient 673-107 (11.4 years)

Patient 107 had a baseline 6MWD of 243 meters and lost his ability to perform the test at 12.8 years. Four NH matches were identified with >2 assessments available with an age range of 11.1–15.6 years. Three NH Subjects (S87, S100 and S115) lost their ability to perform the 6MWD between 12.4–13.1 years. The baseline 6MWD range for these NH subjects was 221 to 248 meters. NH Subject S48 remained mobile at 12.5 years (156 meters), but was declining in functional ability (6MWD declined 77 meters compared with baseline and RFF increased by 4.35 seconds from a baseline RFF of 13.45 seconds). All boys appear to be following a similar trajectory in physical abilities and therefore pulmonary function was also reviewed.

Figure 11.1.8: Patient 673-107 6MWD Trajectory per Matched Natural History Subject

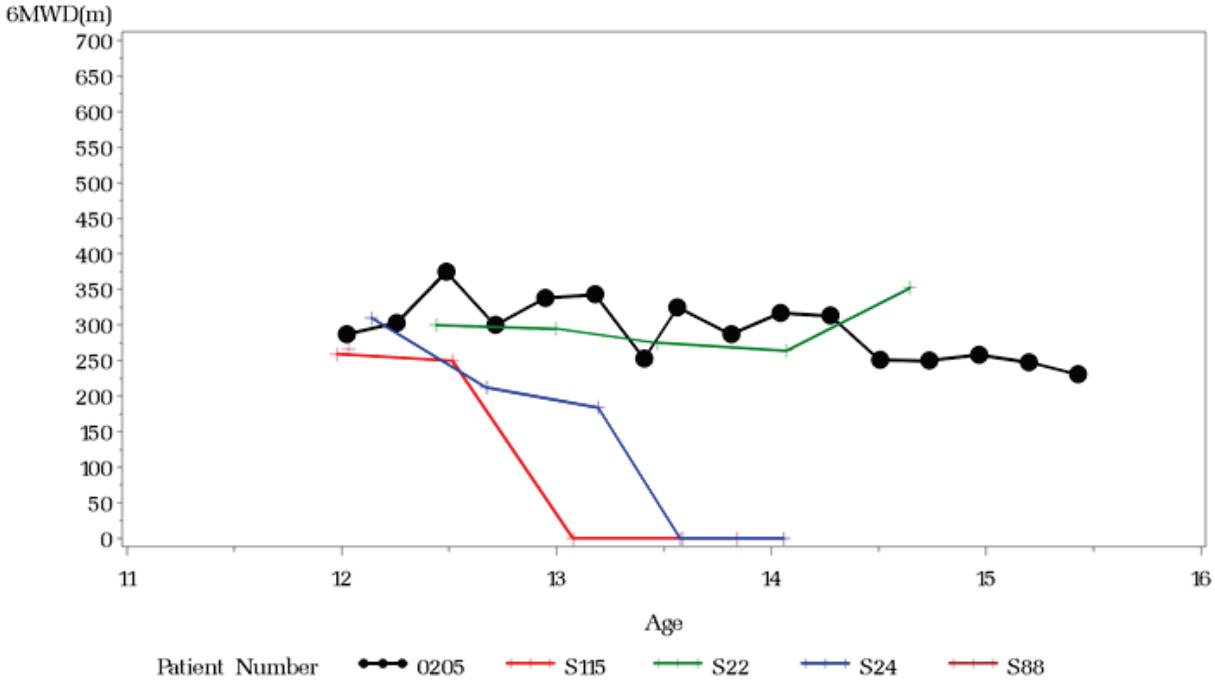


Pulmonary function (defined as FVC and PF): The NH subjects retained a positive FVC from baseline, however, their % predicted FVC was in decline. Patient 107 showed decline across both FVC and PF parameters. The annualized % predicted FVC had declined for all boys; Patient 107, -7.9%; NH S87, -6.4%; S100 -5%; S115, -3.3% (mean annualized % predicted FVC for these NH subjects was -4.9%).

Patient 673-205 (12.0 years)

Patient 205 had a baseline 6MWD of 287 meters, which declined by 56 meters over time. He was still able to walk 231 meters at 15.4 years, but lost the ability to perform the RFF test at 14.3 years. Three NH matches were identified with >2 assessments available with an age range of 12.0–14.6 years and baseline 6MWD range of 259–310 meters. Two NH Subjects (S24 and S115) lost their ability to perform the test at 13.6 and 13.1 years, respectively. NH Subject S22 had an improvement in 6MWD of 52.6 meters at 14.6 years. At baseline, this NH subject complained of back and foot pain, which resolved over time. His treating physician suspected the improvement showed resolution of pain and therefore this baseline may not be an accurate reflection of his ability. The RFF for NH Subject S22 increased by 1.74 seconds at last observed time point (14.6 years). All boys in this comparison had a baseline 6MWD of <300 meters with likely significant changes to their muscle composition.

Figure 11.1.9: Patient 673-205 6MWD Trajectory per Matched Natural History Subject

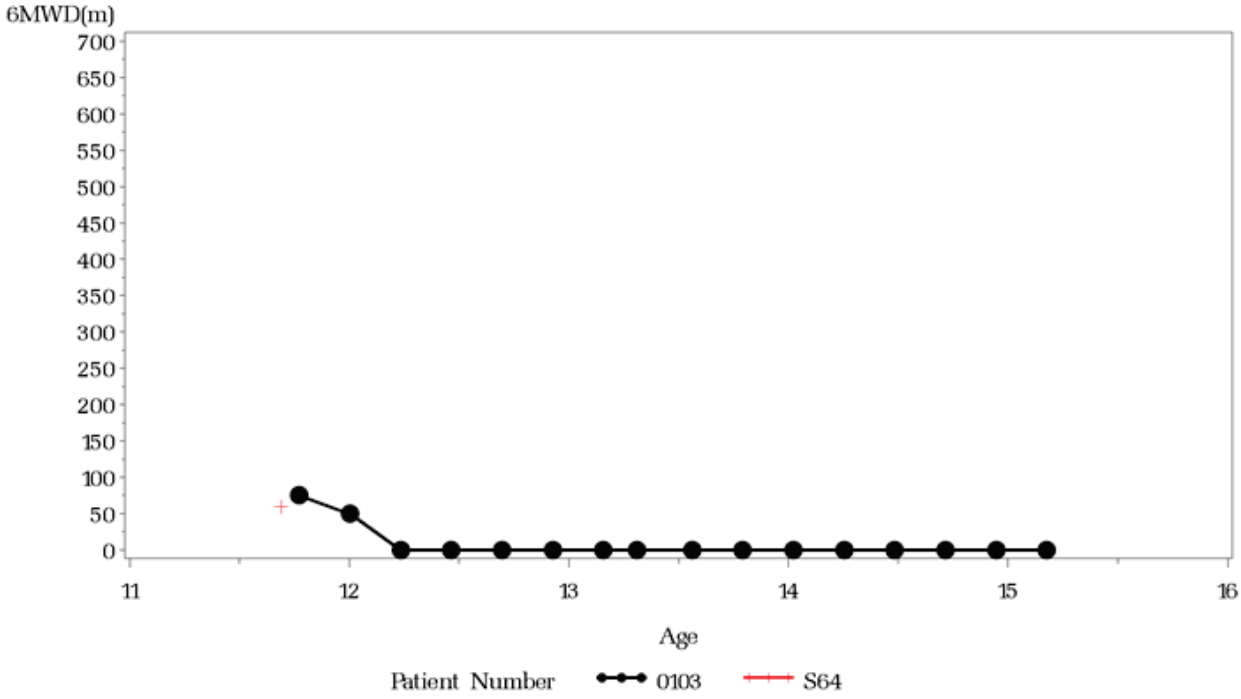


Patients With No Functional Matches

Patient 673-103 (11.8 years)

Patient 103 was clinically obese at enrolment and in functional decline. His baseline 6MWD was recorded as 75 meters, because he was unable to complete the test and attained this distance in 4 minutes and 5 seconds. Patient 103 was unable to attempt the 6MWD from the age of 12.2 years (less than 6 months from enrolment). Pulmonary function was reduced slightly over three and a half years; FVC -0.44 L (% predicted FVC -31.0%) and peak flow -50 L/min (% predicted peak flow -19.33%). No NH matches were identified with > 2 assessments available.

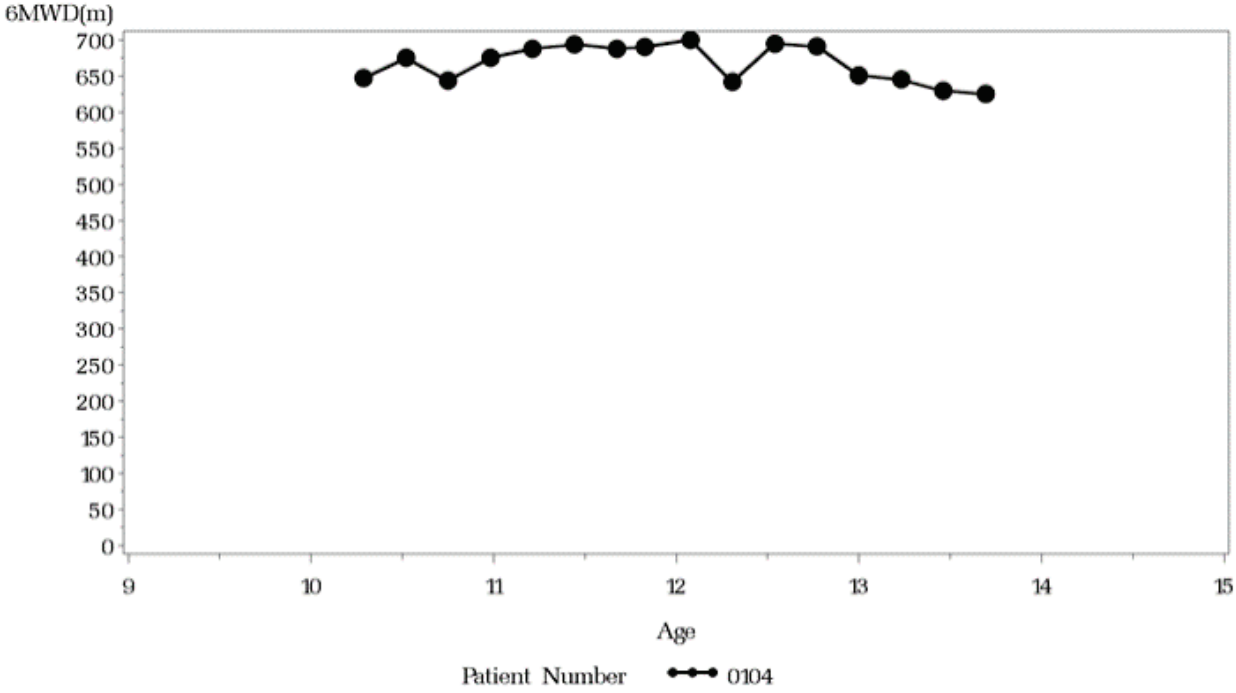
Figure 11.1.10: Patient 673-103 6MWD Trajectory per Matched Natural History Subject



Patient 673-104 (10.3 years)

Patient 104 achieved a baseline 6MWD of 647 meters and continued maintaining a 6MWD of >600 meters at the age of 13.7 years. Over time, the distance recorded for Patient 104 declined by 22 meters and his RFF time increased by 0.57 seconds compared with baseline. No NH matches were identified with >2 assessments available. This is not surprising as this patient has functionality akin to healthy peers of his age group (healthy boys aged ≥11 years achieve 6MWD of 646 ± 99 meters [Goemans 2013]).

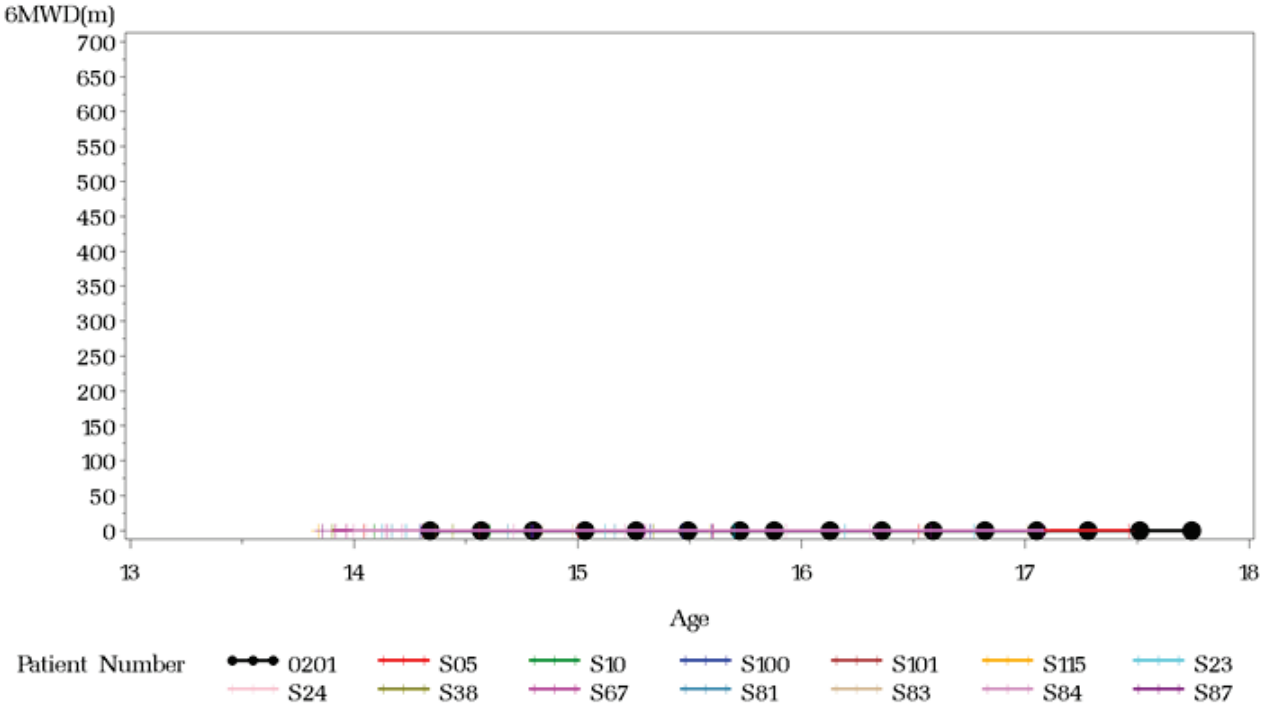
Figure 11.1.11: Patient 673-104 6MWD Trajectory per Matched Natural History Subject



Patient 673-201 (14.3 years)

Patient 201 was nonambulant at study entry and therefore no matches were identified using the 6MWD criteria. Nine NH subjects were identified as matches based on age only, with > 2 assessments available. The age range for the observation period was 13.8 to 17.5 years. As all boys were nonambulant, pulmonary function was reviewed.

Figure 11.1.12: Patient 673-201 6MWD Trajectory per Matched Natural History Subject



Pulmonary function remained stable for Patient 201, who was aged >17 years. The annualized % predicted FVC was -2.9% for Patient 201. FVC and % predicted FVC for the NH cohort appears comparable to Patient 201. For NH subjects with >2 years of FVC data, the annualized % predicted was -1.7% (S05), -4.4% (S23), and -11% (S84) for a mean annualized % predicted FVC of -5.68%. There was not enough data to summarize peak flow data for the NH cohort.

11.2 Appendix B: Patient Narratives: Thrombocytopenia Serious Adverse Events, Adverse Events that Led to Treatment Discontinuation, and Patient with Henoch-Schönlein Purpura

As outlined in the table below, this appendix includes narratives for 8 patients who experienced thrombocytopenia SAEs, 12 patients with AEs that led to discontinuation of drisapersen treatment (including 7 of the 8 patients with thrombocytopenia SAEs), and a single patient who experienced Henoch-Schönlein purpura.

Event	Patient ID	Study	Preferred Term(s)	Narrative
Thrombocytopenia SAE AE led to treatment discontinuation	000505	349	Thrombocytopenia	11.2.1
Thrombocytopenia SAE AE led to treatment discontinuation	000677	349	Thrombocytopenia	11.2.2
Thrombocytopenia SAE AE led to treatment discontinuation	000687	349	Thrombocytopenia	11.2.3
Thrombocytopenia SAE AE led to treatment discontinuation	001176	349	Thrombocytopenia	11.2.4
Thrombocytopenia SAE AE led to treatment discontinuation	001202	349	Thrombocytopenia	11.2.5
Thrombocytopenia SAE AE led to treatment discontinuation	002000	349	Thrombocytopenia	11.2.6
Thrombocytopenia SAE AE led to treatment discontinuation	003052	349	Thrombocytopenia	11.2.7
Thrombocytopenia SAE	001122	349	Thrombocytopenia	11.2.8
AE led to treatment discontinuation	000527	044	Glomerulonephritis	11.2.9
AE led to treatment discontinuation	001124	349	Proteinuria[b]	11.2.10
AE led to treatment discontinuation	001270	044	Intracranial venous sinus thrombosis; Spinal pain	11.2.11
AE led to treatment discontinuation	000511	349	Injection site edema	11.2.12
AE led to treatment discontinuation	000520	349	Asthenia	11.2.13
AE led to treatment interruption*	002026	349	Henoch-Schönlein purpura[c]	11.2.14

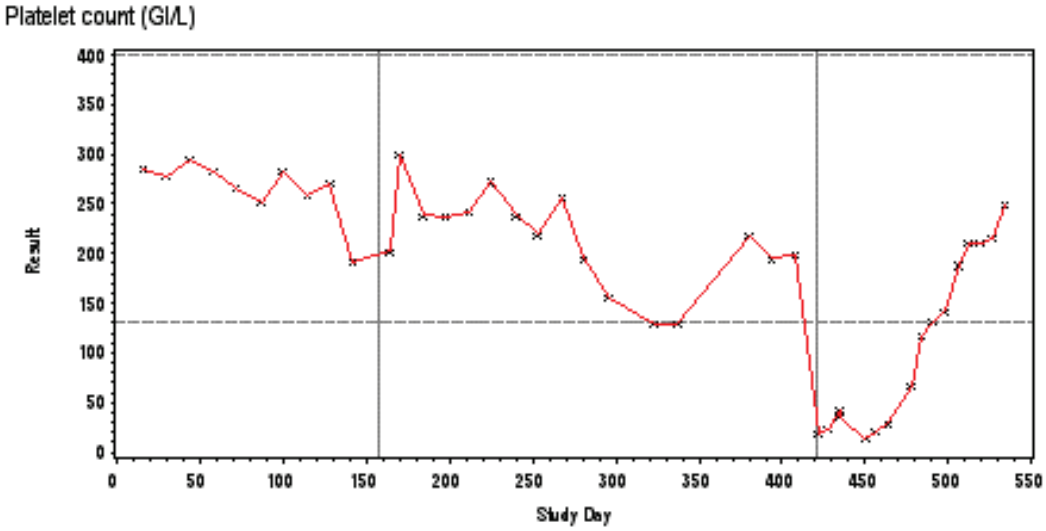
[a]Treatment was not resumed because all dosing was halted in Study 349 in September 2013.
[b]Proteinuria in this subject was nephrotic-level proteinuria
[c]Verbatim term for this AE was "Henoch-Schönlein rash-like event"

11.2.1 Patient 000505: SAE of moderate thrombocytopenia (CTCAE Grade 4) – AE led to treatment discontinuation

This 6-year-old patient of Asian heritage was treated with drisapersen 6 mg/kg/wk in Study 044 from 6 February 2012 to 2 January 2013. He received open-label drisapersen 6 mg/kg/wk starting 5 February 2013 in Study 349. The patient last received drisapersen on 2

April 2013. On 3 April 2013, 57 days after the start of open-label drisapersen, the patient developed thrombocytopenia that was reported by the investigator to be of moderate intensity. The platelet count on 2 April 2013 was 18 x 10^9/L (CTCAE Grade 4). There were no associated symptoms, such as gingival bleeding or hematoma. Tests revealed that antibodies against platelets were positive (against IIb and IIIb glycoproteins). Treatment with drisapersen was withdrawn. The event was reported as recovered on 25 June 2013. The investigator considered that there was a reasonable possibility that the thrombocytopenia may have been caused by drisapersen.

Figure 11.2.1.1: Patient 000505: Platelet Counts



SAE, serious adverse event. Vertical reference line is the first visit after the SAE, horizontal lines are upper/lower range. Patient was treated with drisapersen 6 mg/kg/wk from 6 February 2012 to 2 January 2013 in Study 044. He started treatment with open-label drisapersen 6 mg/kg/wk in Study 349 on 5 February, and remained on treatment until 2 April 2013.

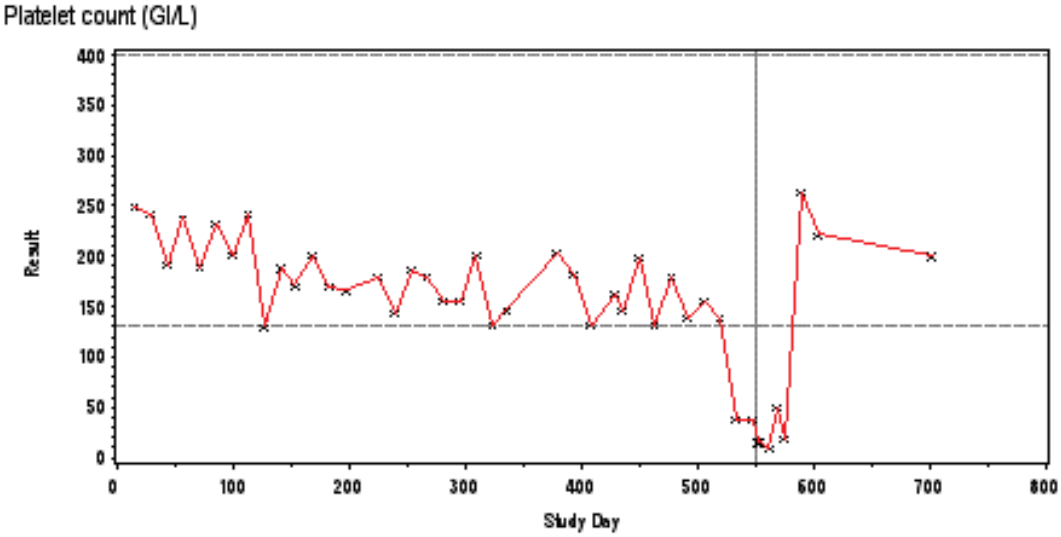
11.2.2 Patient 000677: SAE of severe thrombocytopenia (CTCAE Grade 3/4) – AE led to treatment discontinuation

This 10-year-old patient of white/Caucasian/European heritage was treated with drisapersen 6 mg/kg/wk in Study 044 from 8 July 2011 to 1 June 2012. He received open-label drisapersen 6 mg/kg/wk in Study 349 starting on 6 July 2012. The patient last received drisapersen on 4 January 2013. He developed Grade 3/severe thrombocytopenia on 21 December 2012, when the platelet count was 38 x 10^9/L. A repeat count on 4 January 2013 was 37 x 10^9/L. Treatment with drisapersen was stopped after the dose given on 4 January 2013. On 8 January 2013, he was treated with tranexamic acid, IV immunoglobulin, and prednisone. On 15 January 2013, the platelet count had decreased to 15 x 10^9/L. The patient was admitted on (b) (6) for a second IV immunoglobulin infusion (0.8 g/kg) and tranexamic acid was restarted. Before the second immunoglobulin infusion, anti-platelet antibodies showed an increased response (direct method: AB anti GPIIb/IIIa 5.7, anti

GPIa/IIa 2.8, anti GPIb/IX 2.2; while indirect Ab were persistently negative). Polymerase chain reaction for Epstein-Barr virus was increased in whole blood at 3488 copies/mL, while remaining negative in plasma. On (b) (6) while still an in-patient, the patient had an epistaxis which stopped with pressure to the vessels and local tranexamic acid. He was discharged on (b) (6). Platelet count at discharge was 105 x 10^9/L.

On 22 January 2013, the patient had a single episode of diarrhea, followed by epistaxis and vomiting with some blood clots in the vomit. The platelet count (measured at a local laboratory) on this date was 112 x 10^9/L. However, the central laboratory platelet count was 55 x 10^9/L on 25 January 2013. On 28 January 2013, hemoglobin was 10.7 g/dL with normal iron and ferritin and platelet count was 49 x 10^9/L. Epstein-Barr virus polymerase chain reaction was still positive in whole blood only with a decrease in the number of copies (367/mL). A bone marrow test was performed on 31 January 2013 (reported as normal). Blood count on 31 January 2013 showed red blood cells 3.64 x 10^6/µL (normal range 4.00–5.20), hemoglobin 10.6 g/dL (normal range 13.00–16.00), hematocrit 31.4% (normal range 36.00–49.00) and platelets 24 x 10^3/µL (normal range150–450). The patient was then restarted on prednisone 25 mg x 3/day and deflazacort was suspended. On 6 February 2013, the platelet count had recovered to 210 x 10^9/L.

Figure 11.2.2.1: Patient 000677: Platelet Counts



SAE, serious adverse event. Vertical reference line is the first visit after the SAE, horizontal lines are upper/lower range. Patient was treated with drisapersen 6 mg/kg/wk from 8 July 2011 to 1 June 2012 in Study 044. He started treatment with open-label drisapersen 6 mg/kg/wk in Study 349 on 6 July 2012 and remained on treatment until 4 January 2013.

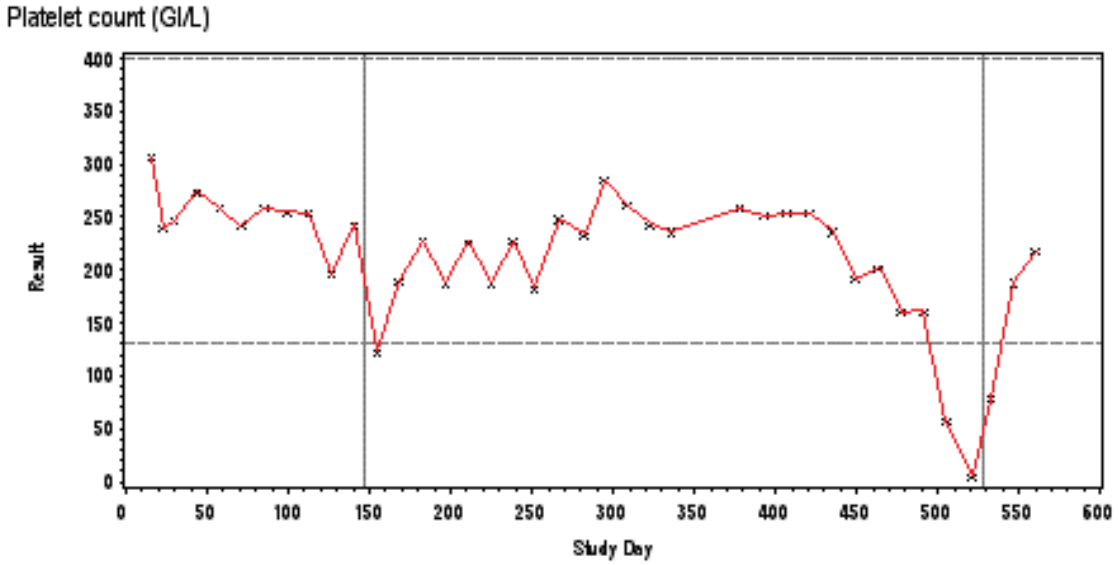
11.2.3 Patient 000687: SAE of severe thrombocytopenia (CTCAE Grade 3/4) – AE led to treatment discontinuation

This 11-year-old patient of white/Caucasian/European heritage was treated with drisapersen 6 mg/kg/wk from 26 July 2011 to 19 June 2012 in Study 044. He was treated with open-label drisapersen 6 mg/kg/wk starting on 23 July 2012 in Study 349. The patient last received

drisapersen on 11 December 2012. On 11 December 2012, the platelet count was 56 x 10^9/L, decreasing to 5 x 10^9/L on 27 December 2012. He was reported as having severe thrombocytopenia on 3 January 2013. The platelet count was 20 x 10^9/L on 3 January 2013 and 16 x 10^9/L on 4 January 2013.

The patient was admitted to hospital; it was reported that he was quite dehydrated and there was concern about recurrent protein in the urine. There was no sign of abnormal clotting with the exception of tendency to bruise easily. Treatment with tranexamic acid orally was started from 3 January 2013. Test for D-dimer performed on 3 January 2013 showed an abnormal value of 1.07 (normal value up to 0.50). Platelet antibodies were 'positive.' On 8 January 2013, the platelet count was 79 x 10^9/L and on 22 January 2013 it was 188 x 10^9/L.

Figure 11.2.3.1: Patient 000687: Platelet Counts



SAE, serious adverse event.

Vertical reference line is the first visit after the SAE, horizontal lines are upper/lower range.

Patient was treated with drisapersen 6 mg/kg/wk from 26 July 2011 to 19 June 2012 in Study 044. He was treated with open-label drisapersen 6 mg/kg/wk from 23 July 2012 to 11 December 2012.

11.2.4 Patient 001176: SAE of severe thrombocytopenia (CTCAE Grade 4) – AE led to treatment discontinuation

This 7-year-old patient of East Asian heritage (Korean) was treated with drisapersen 6 mg/kg/wk from 8 March 2011 to 1 February 2012 in Study 044. He was treated with open-label drisapersen 6 mg/kg/wk in Study 349 starting on 28 March 2012. The patient showed a gradual decrease in platelet counts over the course of the year in Study 044. The first low platelet counts were recorded toward the end of his treatment in Study 044, with a nadir count of 78 x 10^9/L on 7 February 2012.

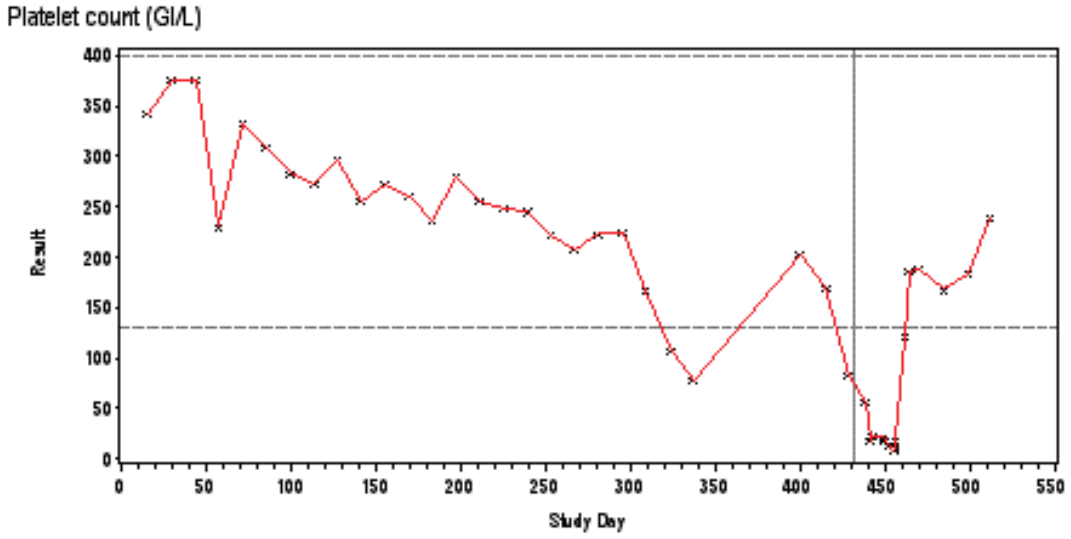
During the 8 weeks off treatment before entering Study 349, his platelet count recovered to 144 x 10^9/L and he continued with drisapersen treatment. After 7 weekly injections, his platelet count had fallen to 83 x 10^9/L on 8 May 2012, with petechiae noted 5 days later on 13 May 2012. There was no evidence of active bleeding. He was withdrawn from active treatment.

His platelet count decreased to 22 x 10^9/L on (b) (6) and decreased further to 17 x 10^9/L the following day. He was admitted to the hospital and treated with a platelet transfusion and immunoglobulin therapy (1 g/kg/day for 2 days). He was discharged on (b) (6) (b) (6). Repeat platelet count on 07 June 2012 was 18 x 10^9/L and in the local hematologist's opinion, this decrease to <20 x 10^9/L warranted further active treatment. The patient was given a second immunoglobulin infusion (1 g/kg for 2 days) on 7 June 2012 and steroid therapy (2 mg/kg) commenced the same day. His platelet count on 12 June 2012, after treatment, was 165 x 10^9/L.

A bone marrow examination performed on (b) (6) showed an "adequate number of megakaryocytes with normocellular marrow." Abdominal ultrasound showed mild enlargement of the spleen (10.6 cm). A follow-up abdominal ultrasound on 04 June 2012 showed "normal sized spleen (9.1 cm). No remarkable findings in the liver, gall bladder, pancreas, and both kidneys. No ascites."

The investigator considered that this SAE was related to study treatment.

Figure 11.2.4.1: Patient 001176: Platelet Counts



Vertical reference line is the first visit after the SAE, horizontal lines are upper/lower range.

Patient was treated with drisapersen 6 mg/kg/wk from 8 March 2011 to 1 February 2012 in Study 044. He was treated with open-label drisapersen 6 mg/kg/wk in Study 349 from 28 March 2012 until 13 May 2012.

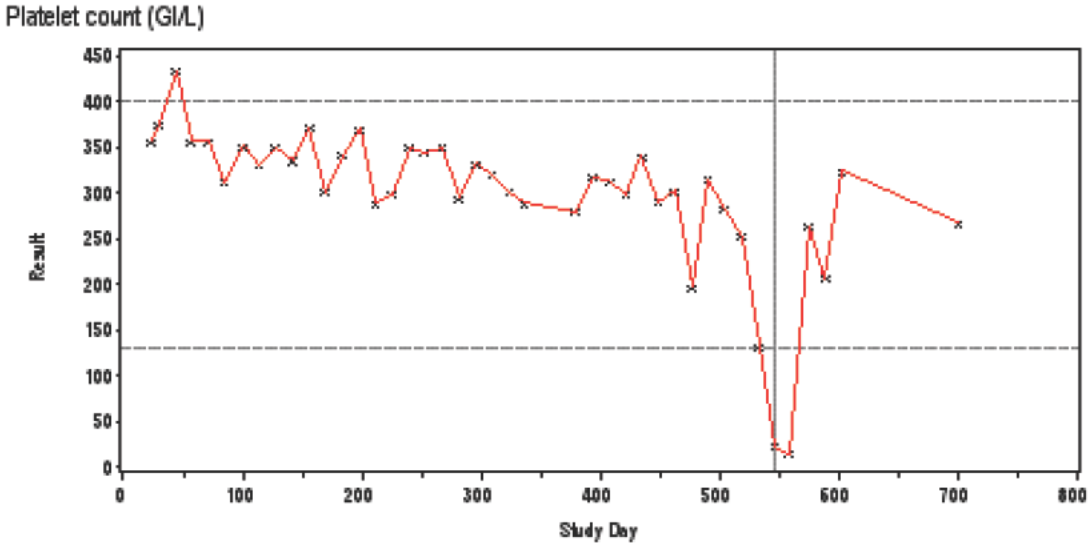
11.2.5 Patient 001202: SAE of severe thrombocytopenia (CTCAE Grade 4) – AE led to treatment discontinuation

This 6-year-old patient of East Asian heritage (Taiwan) was treated with drisapersen 6 mg/kg/wk from 1 July 2011 to 24 May 2012 in Study 044. He received open-label drisapersen 6 mg/kg/wk starting on 29 June 2012 in Study 349. The patient last received drisapersen on 28 December 2012. He developed "grade 3/severe thrombocytopenia" on 28 December 2012. It was noted that his platelet count had dropped from 132 x 10^9/L to 23 x 10^9/L on 28 December 2012. He was admitted to the hospital on (b) (6). Two weeks before admission ((b) (6)), a cough and mild rhinorrhea were reported, although he remained apyrexial. Two days before admission, bruising over both ankles was noted after a fall, and petechiae were found over his neck, thigh, back, and oral mucosa.

On the day of admission ((b) (6)), the platelet count decreased to 3 x 10^9/L and fibrinogen was <5 µg/mL (normal range, 2–4 µg/mL) and D-dimer 0.27 µg/mL. One unit of platelets was given. Intravenous immunoglobulin (500 mg/kg) was also given for 1 day and oral prednisolone at a dose of 1.5 mg/kg/day was prescribed. The platelet count increased to 32 x 10^9/L the next day ((b) (6)) and no new petechiae were found. Vital signs and consciousness level were normal. On (b) (6), the patient's anti-platelet antibody was reported as 'positive.' By (b) (6), the platelet count had returned to within the normal range.

The investigator considered that the SAE was related to study treatment.

Figure 11.2.5.1: Patient 001202: Platelet Counts



Vertical reference line is the first visit after the SAE, horizontal lines are upper/lower range.

Patient was treated with drisapersen 6 mg/kg/wk from 1 July 2011 to 24 May 2012 in Study 044. He received open-label drisapersen 6 mg/kg/wk from 29 June 2012 in Study 349 until 28 December 2012.

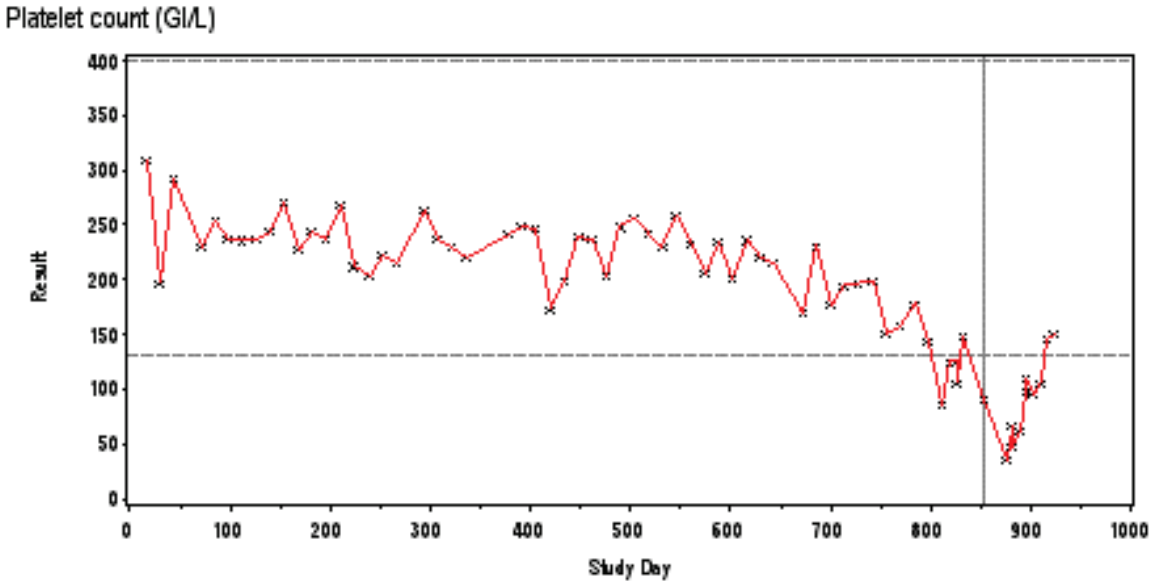
11.2.6 Patient 002000: SAE of severe thrombocytopenia (CTCAE Grade 3) – AE led to treatment discontinuation

This 9-year-old patient of white/Caucasian/European heritage was treated with drisapersen 6 mg/kg intermittently from 23 September 2010 to 22 August 2011 in Study 117. He received open-label drisapersen 6 mg/kg/wk starting on 21 September 2011 in Study 349. He was first reported to have decreased platelets on 12 December 2012. Treatment with drisapersen was interrupted for 1 week and treatment was restarted as the platelet count recovered.

However, the platelet count decreased again and on 14 February 2013 it was 35 x 10^9/L. This was reported as an SAE, and the patient was withdrawn from the study. The patient did not experience any signs or symptoms of bleeding. Anti-platelets antibodies test results were positive: broadly reactive platelet antibodies, mainly reactive with GPIIb/IIIa and GPIa/IIa. The SAE was noted as recovered on 29 March 2013.

The investigator considered that the SAE was related to study treatment.

Figure 11.2.6.1: Patient 002000: Platelet Counts



Vertical reference line is the first visit after the SAE, horizontal lines are upper/lower range.

Patient was treated with drisapersen 6 mg/kg intermittently from 23 September 2010 to 22 August 2011 in Study 117. He received open-label drisapersen 6 mg/kg/wk from 21 September 2011 in Study 349 until 14 February 2013.

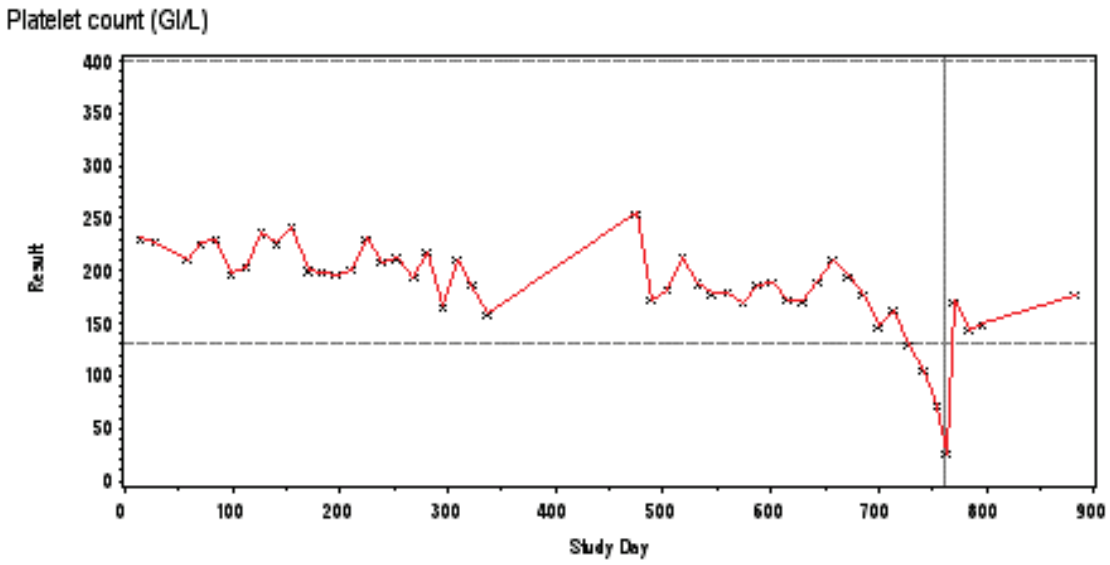
11.2.7 Patient 003052: SAE of severe thrombocytopenia (CTCAE Grade 3) – AE led to treatment discontinuation

This 6-year-old patient of white/Caucasian/European heritage was treated with placebo from 7 April 2011 to 5 March 2012 in Study 117. He started treatment with open-label drisapersen

6 mg/kg/wk in Study 349 on 10 July 2012. He developed "Grade 3 or severe thrombocytopenia" on (b) (6). On 30 April 2013, the platelet count was 71 x 10^9/L. The last injection of drisapersen was given this date. On (b) (6) the platelet count was 26 x 10^9/L, and investigations revealed increased megakaryocytes in bone marrow, compatible with thrombocytopenic purpura. The child was hospitalized to receive intravenous immunoglobulin. The patient's platelet count was 40 x 10^9/L on (b) (6) and on (b) (6) (b) (6) it was 171 x 10^9/L.

The investigator considered that there was a reasonable possibility that thrombocytopenia may have been caused by drisapersen.

Figure 11.2.7.1: Patient 003052: Platelet Counts



SAE, serious adverse event.

Vertical reference line is the first visit after the SAE, horizontal lines are upper/lower range.

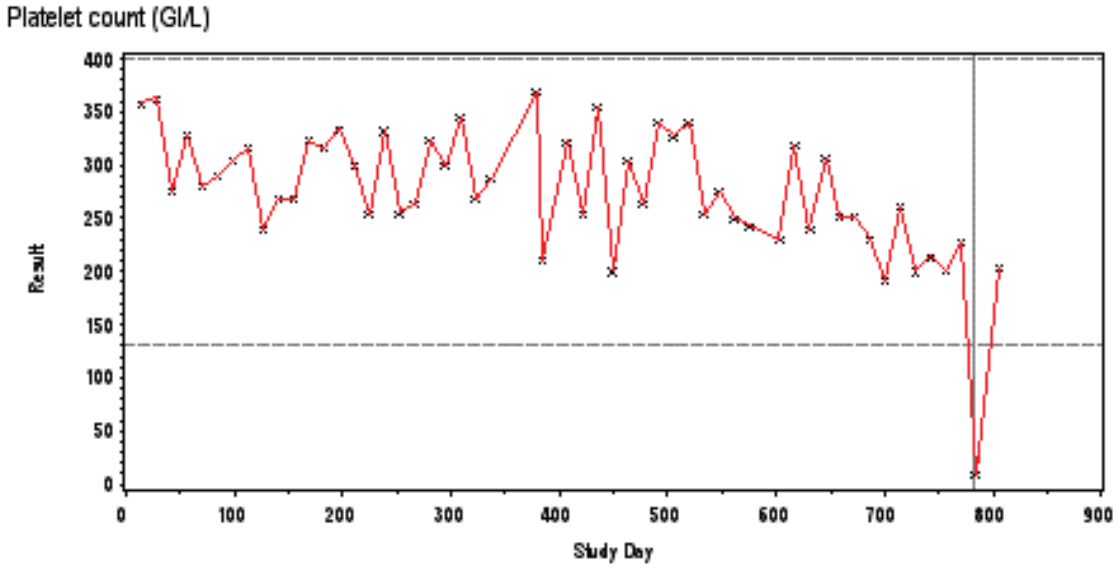
Patient was treated with placebo from 7 April 2011 to 5 March 2012 in Study 117. He started treatment with open-label drisapersen 6 mg/kg/wk in Study 349 from 10 July 2012 until 30 April 2013.

11.2.8 Patient 001122: SAE of severe thrombocytopenia (CTCAE Grade 4)

This 9-year-old patient of white/Caucasian/European heritage was treated with drisapersen 6 mg/kg/wk from 27 July 2011 to 20 June 2012 in Study 044. He received open-label drisapersen at 6 mg/kg/wk in Study 349 starting on 25 July 2012. He received his last drisapersen treatment on 17 September 2013. On that date, the patient developed severe thrombocytopenia (platelet count 9 x 10^9/L, normal range 130–400). Symptoms included gingival bleeding, epistaxis, and multiple ecchymosis. Study 349 was suspended by the sponsor (GSK) on 20 September 2013. The same day, the patient presented minor epistaxis and his mother noted bruising in the lower extremities. The platelet test was repeated on (b) (6) (b) (6) with result of 8 x 10^9/L. Because of the platelet count, it was decided to

hospitalize the patient where he received a platelet transfusion, which did not increase the platelet count. Therefore, immunoglobulin 2 g/kg was administered and the patient eventually recovered with a platelet count of 203 x 10^9/L on (b) (6). The investigator could not conclude whether the thrombocytopenia was caused by the investigative product or not.

Figure 11.2.8.1: Patient 001122: Platelet Counts



SAE, serious adverse event.

Vertical reference line is the first visit after the SAE, horizontal lines are upper/lower range.

Patient was treated with drisapersen 6 mg/kg/wk from 27 July 2011 to 20 June 2012 in Study 044. He received open-label drisapersen at 6 mg/kg/wk in Study 349 from 25 July 2013 to 17 September 2013.

11.2.9 Patient 000527: SAE of glomerulonephritis – AE led to treatment discontinuation

This 10-year-old patient of white/Caucasian/European heritage initiated treatment with drisapersen 6 mg/kg/wk on 6 April 2011 in Study 044. It was noted that the patient had no medical history of nephrotic syndrome or renal disease. Assay for anti-drug antibodies performed at Week 24 (21 September 2011) was reported as negative. As the patient discontinued treatment prematurely, no sample was available at Week 48 so the patient's overall anti-drug antibody status was reported as inconclusive.

On 26 October 2011, the patient developed proteinuria (measured as 5.8 g/24h). Repeat urine tests showed that the patient's urinary protein concentration was 8.05 g/L on 02 November 2011 and 8.96 g/L on 09 November 2011. At this time, it was reported that he had visible lower limb edema in 'association with proteinuria and hypoalbuminemia.' On (b) (6) (b) (6), the patient presented with back pain on his left side. A computerized tomography (CT) scan reportedly showed severe pulmonary embolism in the left lung and in the median lobe

of the right lung; anti-thrombotic treatment was initiated. Treatment with drisapersen was discontinued; the patient was hospitalized and withdrawn from the study. An abdominal and pelvic CT scan, performed on (b) (6), found partial thrombosis of the right renal vein with prominent thrombus in the inferior vena cava. A further scan also found bilateral pulmonary embolism and small left lower lobe infarctions; hospitalization was prolonged.

A renal biopsy, taken on (b) (6), after 24 h of anti-coagulation therapy, showed evidence of a stage 1 (stage 1 – least severe, stage 4 – most severe) membranous glomerulonephritis. The glomeruli showed no mesangial, extra- or endocapillary proliferation. Glomerular staining for immunoglobulin (IgG-intense and IgA-very low) and complement (C1q-trace) was present. The blood vessels showed no evidence of vasculitis. The patient was discharged on warfarin treatment on (b) (6). On 9 December 2011, the patient was noted to be clinically well. From this time on, the patient was treated periodically with warfarin and perindopril. On 24 January 2012, the patient continued to have right renal vein thrombosis, inferior vena cava thrombosis, and bilateral pulmonary emboli. There were no symptoms of hemorrhage, chest pain, lumbar pain, or macroscopic hematuria. Physical examination revealed lower limb edema (described as "stable") and no facial edema, and no palpable hepatosplenomegaly. The most recent 24-hour urine protein was 2.18 g/day (date not reported). The perindopril dose was increased from 5 mg/day to 7.5 mg/day.

On 10 February 2012, the patient was noted to be well. The most recent 24-h protein value was improved (0.3 g/day; date not reported). There was no edema. On 5 March 2012, the most recent 24-h protein measured 0.22 g/day (date not reported); the patient continued to be well although there was some evidence of lower limb edema. Additional follow-up on 25 June 2012 showed urine protein of 0.11 g/day (date not reported). Edema was not increasing and the patient had no other symptoms. Doppler ultrasound revealed no evidence of thrombus in the renal vein or inferior vena cava. The reporting investigator considered that there was a reasonable possibility that the events were related to treatment with drisapersen.

11.2.10 Patient 001124: SAE of proteinuria – AE led to treatment discontinuation

This 8-year-old patient of white/Caucasian/European heritage was treated with drisapersen 6 mg/kg/wk in Study 044 from 10 August 2011 to 04 July 2012. He received drisapersen open-label 6 mg/kg/wk starting on 8 August 2012 in Study 349. On 22 August 2012, the patient developed Grade 3 or severe proteinuria (urine protein measured 5.24 g/L). The patient remained asymptomatic. The event was reported as clinically significant (or requiring intervention). The patient was treated with enalapril. Treatment with drisapersen was discontinued on 5 September 2012. On this date the patient's urine protein levels were increased to 12.18 g/L on random urine protein and 11.02 g/24 hours with no signs or symptoms. On 10 October 2012, laboratory tests showed creatinine was 0.16 mg/dL, total protein was 6.2 g/dL, albumin was 3.1 g/dL, globulin was 3.1 g/dL, and 'uremia' was 21 mg/dL. Urine protein was 0.21 g/L on 31 October 2012, and the event was considered resolved on 7 November 2012. On 14 November 2012, 24-hour urine protein was within normal limits (0.07 g/24 h). The investigator considered that there was a reasonable possibility that the proteinuria may have been caused by drisapersen.

11.2.11 Patient 001270: SAEs of intracranial venous sinus thrombosis and spinal pain – AE led to treatment discontinuation

This 7-year-old white male patient started treatment with 6 mg/kg/wk drisapersen in Study 044 on 20 June 2012. No relevant medical history was reported. Concomitant medications included omeprazole and calcium/vitamin D. The last dose of drisapersen prior to the events of intracranial venous sinus thrombosis and spinal pain was administered on 11 December 2012, 174 days after the start of drisapersen treatment (cumulative dose of drisapersen: 5340 mg). This patient had no associated proteinuria or albuminuria.

On 11 December 2012, on the same date as the most recent dose, the patient experienced headache in the left temporal region which persisted despite unspecified pain killers. On 13 December 2012, the patient presented with seizures. A head CT scan was reported as normal. On 14 December 2012, the patient presented with "a frame of fall with stare – loss of visual contact." He was paralyzed for approximately 1 minute and when he recovered, he was confused and crying. He also had headache, strabismus, and serious, Grade 3 or severe thoracolumbar pain. On 16 December 2012, the patient showed mental confusion and worsening ambulation.

On (b) (6), the patient was hospitalized with a headache and associated vomiting without fever. A head CT showed hyperattenuating content partially filling the superior sagittal sinus and the straight sinus. There were also signs of engorgement of the rest of the superior sagittal sinus. The patient was diagnosed with a serious, grade 3 or severe cerebral venous sinus thrombosis. There was no evidence of infection, the paranasal sinuses were free, and otoscopic examination was normal. Treatment for the events included dipyrone, acetaminophen, and tramadol. The patient became more disoriented on (b) (6). Neurological assessment confirmed paralysis of cranial nerve VI (abducens) and signs of thrombosis of venous sinuses. Laboratory tests on that date included normal aPTT, normal platelet count, elevated D-dimer (2000 ng/mL; ULN 500), normal fibrinogen, and decreased platelet activity (61%; LLN 70%). Treatment with drisapersen was permanently withdrawn as a result of the events.

On (b) (6), the patient was more agitated and confused. An electroencephalogram (EEG) revealed diffuse disorganization of background activity predominantly in the areas 'to the left and above.' He was started on enoxaparin and acetazolamide. By the next day, the headache had improved but the back pain persisted, and the patient was described as being confused, angry, and tearful. An ophthalmologic examination showed reduction of abduction of both eyes; esotropia; deviation of the right eye fundus - optical nerve stained; papillae with blurry edges at 360 degree venous dilation and tortuosity; macula unchanged. On (b) (6), the headache and confusion were improving, but the convergent strabismus and thoracolumbar pain persisted, and worsened the following day ((b) (6)), although the 'double vision' was lessening. Additional treatment for the lumbar pain included gabapentin and ketorolac. The patient was reported to be pain free by (b) (6), but had 'nausea and isolated vomiting.' The pain had improved by the next day and the vomiting had stopped. On (b) (6), the

angiography CT scan showed an extensive failure to fill the superior sagittal, left transverse and sigmoid sinuses, with a slight filling irregularity of the straight sinus.

The patient's pain continued to improve, and he was discharged home on (b) (6). The event of spinal pain was considered resolved on 1 February 2013, and the event of intracranial venous sinus thrombosis was considered resolved with sequelae (paralysis of the VI cranial nerve) on that same date. The investigator assessed the events of intracranial venous sinus thrombosis and spinal pain as related to treatment.

11.2.12 Patient 000511: SAE of injection site edema – AE led to treatment discontinuation

This 9-year-old patient of white/Arabic/North African heritage was treated with drisapersen 6 mg/kg/wk in Study 044 from 24 March 2011 to 17 February 2012. He received open-label drisapersen at 6 mg/kg weekly starting on 22 March 2012 in Study 349. Concomitant medications included perindopril, ergocalciferol, calcium salt and prednisone. On (b) (6), the patient developed Grade 3 or severe injection site edema on the back of his upper arm. The patient was hospitalized and treated with paracetamol. Drisapersen treatment was discontinued on 19 August 2013. Ultrasound of the left arm showed edema and infiltration of subcutaneous tissues. The event resolved on (b) (6). The investigator considered that there was a reasonable possibility that the injection site edema may have been caused by drisapersen.

11.2.13 Patient 000520: Severe asthenia – AE led to treatment discontinuation

This 8-year-old white male received treatment with drisapersen 6 mg/kg/wk in Study 044. He then received open-label drisapersen 6 mg/kg/wk continuous initially in Study 349 and then transferred to the intermittent dosing arm and subsequently to the natural history arm of the study.

He received his first drisapersen dose in Study 349 on 9 May 2012 and his last dose of 6 mg/kg/wk on 14 November 2012 (Week 27) in the continuous phase of the study. Between the first and last injections in the continuous phase, there were 2 occasions when the visit/injection did not take place: Weeks 28 and 29 (21 and 28 November 2012, respectively; reason: diarrhea). A total of 28 doses were administered of 30 (93.3% compliance) in the continuous treatment phase

From 5 December 2012 (Week 30) through 9 January 2013 (Week 35), he was in the intermittent phase but did not receive any further study drug. The primary reason for the transfer to the intermittent dosing arm was diarrhea. He missed 2 doses (Weeks 30 and 31) in the intermittent phase (5 and 12 December 2012, respectively; reason: worsening of medical and social conditions). Thus, he received 0 of 2 doses (0% compliance) in the intermittent treatment phase.

The patient was then transferred to the natural history arm of the study on 16 January 2013 (Week 36), suspending study drug permanently. The primary reason for the transfer, in the Listing of Transitions Between Treatment Groups, was 'Other: fear of relapse, decrease

medical/social conditions.' Additional reasons given were 'asthenia, myalgia, abdominal pain, lack of efficacy.'

The AE that was reported as leading to permanent discontinuation of study drug was as follows: severe asthenia; onset: 1 August 2012, 9 days after the previous injection (85 days after starting treatment in the extension). The AE resolved after 153 days on 31 December 2012. No treatment was required for the AE, which was considered related to the study drug by the investigator.

Other AEs in the intermittent dosing phase reported as leading to suspension of study drug were moderate asthenia, moderate abdominal pain, moderate diarrhea, moderate disturbance in social behavior, and moderate myalgia; onset: 5 December 2012, 22 days after the previous injection (211 days after starting treatment in the extension). The AEs resolved after 27 days on 31 December 2012. Other than oral trimebutine once daily to treat abdominal pain (ongoing medication), no treatment was required for the other AEs. The AEs were considered related to the study drug by the investigator. The patient withdrew from the study on 3 March 2014 when the study was closed/terminated.

11.2.14 Patient 002026: Henoch-Schönlein Purpura

Feeder study	117
Treatment group	Placebo
Extension study	349
Treatment group	Drisapersen 6 mg/mg/wk continuous
Cumulative dose of drisapersen (extension study)	15,020 mg

This 6-year-old male (race not reported) received treatment with placebo in Study 117 from 19 October 2010 to 13 September 2011. The patient was anti-drisapersen antibody negative while in Study 117. He started treatment with 6 mg/kg/wk drisapersen in Study 349 on 2 November 2011. Starting on 2 October 2012 (Week 48), the patient tested positive for anti-drisapersen IgG; an additional positive test for IgG occurred on 22 January 2013 (Week 64).

On three consecutive dosing occasions, between 23 April 2013 and 7 May 2013, the patient developed symptoms approximately 1 hour after the injection which included fatigue, extreme weakness, pale skin, feeling cold, bright eyes, the need to "cover up," and an inability to get up. These episodes resolved spontaneously after about 1 hour. Each of these 3 injections was given at a local site rather than at the primary study center. Adverse events of non-serious severe fatigue were reported on 16 April 2013, 23 April 2013, and 30 April 2013. No treatment was reported for any of the events, and all 3 events were reported as resolved later the same day. An event of non-serious mild proteinuria was also reported, starting on 3 April 2013 (urine protein 308 mg/L) and lasting 13 days until 16 April 2013 (urine protein 50 mg/L). No albuminuria was reported (urine albumin 33 mg/L on 3 April 2013, falling to 4 mg/L on 16 April 2013). The patient had a positive anti-drisapersen IgG test on 16 April 2013 (Week 76).

On 14 May 2013, the patient was treated at the primary study center. Approximately 30 minutes after the injection, he developed extreme fatigue, involuntary tremor-like movements

of the upper limbs, the need to "cover up," and an inability to get up. His consciousness was intact and he was well-oriented, and vital signs were normal. The episode resolved spontaneously after 3 hours and the patient returned home. Adverse events of non-serious severe fatigue and non-serious mild hematuria (5-10 RBC noted on microscopy) and proteinuria (urine protein 208 mg/L; urine albumin 12 mg/L) were reported on 14 May 2013. No treatment was reported for the events. The event of fatigue was reported as resolved later that day; the events of proteinuria and hematuria were reported as resolved on 22 May 2013 (urine protein on that date not reported; on 28 May 2013 urine protein was 170 mg/L) and 28 May 2013 (urine microscopy negative for RBC), respectively. The investigator considered this event of fatigue, as well as the 3 events of fatigue reported in April 2013, to be related to study treatment.

Dosing on 21 May 2013 was skipped because of an elevation in cystatin C (0.9 mg/L on 14 May 2013). Dosing resumed on 28 May 2013, and the patient had no recurrence of symptoms with the injections on 28 May 2013 and 4 June 2013. Serum cystatin C remained between 0.8-0.9 mg/L from 14 May 2013 through the last measurement before the end of dosing on 3 September 2013.

On 11 June 2013, back at the study center, the patient had a reaction similar to those seen previously: 1 hour after the injection, he developed generalized fatigue, extreme weakness, pale skin, feeling cold, bright eyes, the need to "cover up," and an inability to get up. His blood pressure and temperature were normal, but his pulse was elevated (112 bpm). He complained of pain in the left thigh, above the injection site. The episode resolved after approximately 2 hours, and the patient returned home. An AE of non-serious severe fatigue was reported on 11 June 2013, along with non-serious events of generalized rash and tachycardia. Acetaminophen was given for the rash. The fatigue and tachycardia were reported as resolved later that day, and the event of generalized rash was reported as resolved on 12 June 2013. The investigator considered all 3 events to be related to study treatment.

Approximately 6 hours after the 11 June injection, while the patient was on his way home, his mother reported that the patient developed a skin reaction. He also complained of pain in his left thigh. When they arrived home and she examined him, she noted a rash on his legs, thighs, arms, and abdomen.

The reaction reportedly resolved within approximately 12 hours (although the resolution time was also described elsewhere as being 24 hours), and the patient's condition returned to normal. No skin biopsy of the rash was performed.

On 16 June 2013, the patient developed a rash of the lower limbs that was described as being slightly painful. The patient was sleeping quietly. He was seen by his local pediatrician the next day. The pediatrician reported a Henoch-Schönlein purpural rash on the lower limbs, along with mild pharyngitis and conjunctivitis. The patient's blood pressure was 104/68 mmHg. No urine protein was reported on this date; urine protein had been 161 mg/L on 11 June 2013, and was 101 mg/L on 26 June 2013; urine albumin was <10 mg/L on both dates. The patient was diagnosed with a non-serious moderate event of Henoch-Schönlein purpura, although the pediatrician also concluded that the rash could possibly be of viral origin. Treatment for the event included levocetirizine (taken as needed), starting on 17 June 2013.

The scheduled dose on 18 June 2013 was withheld because of the event. The event of Henoch-Schönlein purpura was considered resolved on 20 June 2013. No events of abdominal pain, arthritis, or arthralgia were reported in conjunction with the events of non-serious severe fatigue or the event of Henoch-Schönlein purpura. Subsequent doses scheduled for 26 June, 2 July, and 9 July 2013 were also withheld because of the Henoch-Schönlein purpura event. The patient had a positive anti-drisapersen IgG test on 9 July 2013 (Week 88). A decision was made not to restart dosing until (b) (6), when the patient would next be seen on an inpatient basis for overnight hospitalization, because of the repeated nature of the fatigue events and because the most recent event had shown signs of worsening (tachycardia at rest, purpural rash).

The next dose of drisapersen was given on (b) (6). No recurrence of the fatigue and other symptoms which had accompanied earlier injections was reported. On 22 August 2013, 3 days after dosing had restarted, the patient experienced non-serious mild rash (described as a "skin eruption" on the lower limbs).

No treatment for the event was reported, and it was considered resolved on 27 August 2013. Because of this event of rash, dosing was interrupted. Treatment was not resumed because all dosing in Study 349 was put on hold in September 2013. The patient again tested positive for anti-drisapersen IgG at the end of October 2013 (Week 104).

Laboratory results during the study are shown in Table 11.2.14.1.

Sponsor Assessment

The possibility that this event is an occurrence of drug induced cutaneous vasculitis has been considered. However, abdominal pain usually accompanies Henoch-Schönlein Purpura (HSP) so that diagnosis seems unlikely, as acknowledged by the reporting physician who termed the event "HSP-like". The patient was rechallenged once without recurrence, also suggestive that the event was not drug related. No other episodes of disseminated rash have been observed in drisapersen treated patients. Without specific biopsy evidence, definitive confirmation of the precise nature of this event cannot be confirmed.

Table 11.2.14.1: Laboratory Results in a Patient with Henoch-Schönlein Purpura

Date	Complement C3	C-Reactive Protein	Platelets	Cystatin C	Creatinine	Urine Protein	Urine RBC
	0.9-1.8 g/L	mg/L	130-400 GI/L	0.6-0.8 mg/L	33.6-64.5 µmol/L	mg/L	
2 November 2011 (Baseline)	1.41	0.3	371	0.6	14.7	83	None
20 March 2012	1.29	0.3	416	0.6	NR	99	None
2 October 2012	1.3	0.5	317	0.8	21.5	122	None
19 March 2013	1.44	0.6	338	0.9	20.4	52	None
14 May 2013	0.97	1.1	352	0.9	16.8	208	5-10
9 July 2013	0.93	1.2	231	0.9	18.5	51	None
3 September 2013	0.83	2.2	277	0.8	20.2	119	None
29 October 2013	1.21	0.4	293	0.8	17.5	50	None

RBC, red blood cells.

11.3 Appendix C: Shift Analysis

Analyses of routinely measured laboratory parameters using the placebo-controlled study grouping were performed. Summary statistics (mean, median, interquartile range and range) for each parameter within each treatment group were tabulated at baseline, as well as the post-treatment change from baseline at 12, 24, 36 and 48 weeks.

Shift analyses were also performed using the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 to determine shifts from baseline for Grade 1, Grade 2, Grade 3 or Grade 4 (mild, moderate, severe and very severe) post-baseline changes; the definitions of these criteria are shown in the table. Shifts from baseline to weeks 12, 24, 36 and 48 were tabulated. For other routinely measured laboratory parameters, not shown on the table below, for which no CTCAE grades were available, shift tables were produced showing shifts to above or below the laboratory normal range at weeks 12, 24, 36, and 48.

Table 11.3.1: CTCAE Criteria for Shifts in Laboratory Values

Laboratory Parameter	Criterion for Grade 1 shift	Criterion for Grade 2 shift	Criterion for Grade 3 shift	Criterion for Grade 4 shift
Hematology				
Hemoglobin (g/L) decreased (anemia)	<LLN–100	<100–80	<80	NA
Hemoglobin (g/L) increased	Increase >0–2 above ULN or above BL if BL is >ULN	Increase >2 – 4 above ULN or above BL if BL is >ULN	Increase >4 above ULN or above BL if BL is >ULN	NA
Leukocyte count (10^9/L) decreased	<LLN–3	<3–2	<2–1	<1
Lymphocytes (10^9/L) decreased	<LLN–0.8	<0.8–0.5	<0.5–0.2)	<0.2
Lymphocytes (10^9/L) increased	NA	>4–20	>20	NA
Neutrophils (10^9/L) decreased	<LLN–1.5	<1.5–1.0	<1.0–0.5	<0.5
Thrombocytes (10^9/L) decreased	<LLN–75	<75–50	<50–25	<25
Coagulation				
aPTT (sec) increased	>ULN–1.5 x ULN	>1.5–2.5 x ULN	>2.5 x ULN	NA
INR[a] increased	>1–1.5 x ULN or >1–1.5 x BL if on anticoagulation	>1.5–2.5 x ULN or >1.5–2 x BL if on anticoagulation	>2.5 x ULN or >2.5 x BL if on anticoagulation	NA
Clinical Chemistry				
Bilirubin (µmol/L) increased	>ULN–1.5 x ULN	>1.5–3 x ULN	>3–10 x ULN	>10 x ULN
Calcium (mmol/L) decreased	Serum calcium <LLN–2	Serum calcium <2–1.75	Serum calcium <1.75–1.5	Serum calcium <1.5
Calcium (mmol/L) increased	Corrected serum calcium >ULN–2.9	Corrected serum calcium >2.9–3.1	Corrected serum calcium >3.1–3.4	Corrected serum calcium >3.4

Laboratory Parameter	Criterion for Grade 1 shift	Criterion for Grade 2 shift	Criterion for Grade 3 shift	Criterion for Grade 4 shift
Glucose (mmol/L) decreased	<LLN–3.0	<3.0–2.2	<2.2–1.7	<1.7
Glucose (mmol/L) increased	>ULN–8.9	>8.9–13.9	13.9–27.8	>27.8
Potassium (mmol/L) decreased	NA	<LLN–3.0	<3.0–2.5	<2.5
Potassium (mmol/L) increased	>ULN–5.5	>5.5–6.0	>6.0–7.0	>7.0
Sodium (mmol/L) decreased	<LLN–130	NA	<130–120	<120
Sodium (mmol/L) increased	>ULN–150	>150–155	>155–60	>160
ALT (IU/L) increased	>ULN–3 X ULN	>3–5 x ULN	>5–20 x ULN	>20 x ULN
Alkaline phosphatase (IU/L) increased	>ULN–3 X ULN	>3–5 x ULN	>5–20 x ULN	>20 x ULN
AST (IU/L) increased	>ULN – 3 X ULN	>3 – 5 x ULN	>5 – 20 x ULN	>20 x ULN
GGT increased	>ULN – 2.5 x ULN	>2.5 - >5 x ULN	>5 – 20 x ULN	>20 x ULN
CK increased	>ULN – 2.5 x ULN	>2.5 - 5 x ULN	>5 – 10 x ULN	>10 x ULN
Creatinine (µmol/L) increased	>1–1.5 x BL, or >ULN –>1.5 x ULN	>1.5–3 x BL, or >1.5–3 x ULN	>3 x BL, or >3–6 x ULN	>6 x ULN
BUN increased	NA	>2.5–5 x ULN	>5–10 x ULN	>10 x ULN
Albumin (g/L) decreased	<LLN–30	<30–20	<20	NA
Phosphate (mmol/L) decreased	<LLN–0.8	<0.8–0.6	<0.6–0.3	<0.3
Fibrinogen (mg/dL) decreased	<1–0.75 x LLN or <25% decrease from BL	<0.75–0.5 x LLN or <50% decrease from BL	<0.5–0.25 x LLN or 50–75% decrease from BL	<0.25 x LLN or 75% decrease from BL or absolute value <50mg/dL
Haptoglobin (g/L) decreased	<LLN	NA	NA	NA

ALT, alanine aminotransferase; aPTT, activated partial thromboplastin time; AST, aspartate aminotransferase; BL, baseline; BUN, blood urea nitrogen; CK, creatine kinase; CTCAE, Common Terminology Criteria for Adverse Events; GGT, gamma glutamyl transferase; INR, International Normalized Ratio; LLN, lower limit of normal; NA, not applicable; ULN, upper limit of normal.

[a] Prothrombin time was used to calculate INR and so was not reported separately.