APPENDICES

Exon-Skipping Pharmaceutical Treatments for Duchenne Muscular Dystrophy

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The Medicaid Evidence and Review of Cost Initiative (MERCI) describes policy considerations for drugs approved by the US Food and Drug Administration (FDA) through the accelerated approval pathway. This document is the appendix of a brief titled *Exon-Skipping Pharmaceutical Treatments for Duchenne Muscular Dystrophy*. The brief and the associated appendix provide information on the estimated prevalence of target diagnoses (the accelerated approval drug's indication[s]) among Medicaid members; the clinical trial population used to support FDA approval, and how similar it is to Medicaid members overall; and projected drug costs for state Medicaid programs, including a breakdown of state and federal funds using the Federal Medical Assistance Percentage (FMAP).

APPENDIX A

SUMMARY OF STUDIES USED TO SUPPORT EFFICACY OF EXON-SKIPPING DRUGS

EXHIBIT A1

Summary characteristics of studies used to support efficacy of eteplirsen[a]

Trial results used for accelerated FDA approval highlighted in green.

	Study 1[1-3]	Study 2[3-5]	Study 3[3]
Official title	A randomized, double-blind, placebo-controlled, multiple dose efficacy, safety, tolerability, and pharmacokinetics study of AVI-4658 (eteplirsen) in the treatment of ambulant subjects with Duchenne muscular dystrophy	Open-label, multiple-dose, efficacy, safety, and tolerability study of eteplirsen in subjects with Duchenne muscular dystrophy who participated in Study 4658-US-201 (*Study 1)*	Open-label study of eteplirsen in people with DMD
ClinicalTrials.gov ID	NCT01396239	NCT01540409	Not known
Clinical trial phase	Phase 2	Phase 2	Not known
Study population description	12 boys with DMD (aged 7 to 13 years)	12 boys with DMD who completed 28 weeks of treatment in Study 1	13 people with DMD (with a mean age of 8.9 years)
DMD genetic mutation eligibility requirements	Participants needed to have a confirmed genetic mutation amenable to exon 51 skipping	NA	Not known
Corticosteroid treatment eligibility requirements	Participants needed to be receiving oral corticosteroids and on a stable dose for at least 24 weeks before study entry	NA	Participants needed to be receiving corticosteroids and have been on a stable dose for at least 24 weeks before study entry
Walking independently eligibility requirements	Participants had to achieve an average distance within 10% of 200 m and 400 m (i.e., within 180 m and 440 m) while walking independently over 6 minutes	NA	Not known
Intervention	Eteplirsen 30 mg/kg per weekly IV infusion Eteplirsen 50 mg/kg per weekly IV infusion	Eteplirsen 30 mg/kg per weekly IV infusion Eteplirsen 50 mg/kg per weekly IV infusion	Eteplirsen 30 mg/kg per weekly IV infusion
Control	Placebo: phosphate-buffered saline weekly IV infusion	No comparator group	No comparator group

	Study 1[1-3]	Study 2[3-5]	Study 3[3]
Primary outcome used for accelerated approval	Dystrophin production	Dystrophin production	Dystrophin production
Study duration	24 weeks	Up to 240 weeks	48 weeks
Trial funding	Sarepta Therapeutics	Sarepta Therapeutics	Not known

Notes. [a] FDA prescribing label also cited Study 3; however, we were unable to identify any further information about this study.
Sources. Information is taken from trial publications and ClinicalTrials.gov trial registry records and may vary from information reported in prescribing label.
Abbreviations. DMD: Duchenne muscular dystrophy; IV; intravenous; NA; not applicable; NR; not reported.

EXHIBIT A2

Summary characteristics of study used to support efficacy of golodirsen

Trial results used for accelerated FDA approval highlighted in green.

	Study 1[6-8]
Official title	A 2-part, randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and pharmacokinetics study (part 1) followed by an open-label efficacy and safety evaluation (part 2) of SRP-4053 in patients with Duchenne muscular dystrophy amenable to exon 53 skipping
ClinicalTrials.gov ID	NCT02310906
Clinical trial phase	Phase 1 and Phase 2
Study population description	25 boys with DMD (aged 6 to 15 years)
DMD genetic mutation eligibility requirements	Participants needed to have a confirmed genetic mutation amenable to exon 53 skipping
Corticosteroid treatment eligibility requirements	Participants needed to be receiving oral corticosteroids and on a stable dose for at least 6 months before study entry
Walking independently eligibility requirements	Participants had to achieve an average distance of 250 m or greater while walking independently over 6 minutes
Intervention	Part 1: Golodirsen titrated to 30 mg/kg per weekly IV infusion Part 2: Golodirsen titrated to 30 mg/kg per weekly IV infusion
Control	Part 1: Placebo weekly IV infusion
Primary outcome used for accelerated approval	Dystrophin production
Study duration	12 weeks (part 1) 168 weeks (part 2)
Trial funding	Sarepta Therapeutics and European Union Framework Project 7 SKIP-NMD

Sources. Information is taken from trial publications and ClinicalTrials.gov trial registry records and may vary from information reported in prescribing label.
Abbreviations. DMD: Duchenne muscular dystrophy; IV; intravenous; NA; not applicable; NR: not reported.

EXHIBIT A3

Summary characteristics of study used to support efficacy of viltolarsen

Trial results used for accelerated FDA approval highlighted in green.

	Study 1[9-11]
Official title	A phase II, dose-finding study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of NS-065/NCNP-01 in boys with Duchenne muscular dystrophy (DMD)
ClinicalTrials.gov ID	NCT02740972
Clinical trial phase	Phase 2
Study population description	16 boys with DMD (aged 4 to 9 years)
DMD genetic mutation eligibility requirements	Participants needed to have a confirmed genetic mutation amenable to exon 53 skipping
Corticosteroid treatment eligibility requirements	Participants needed to be receiving oral corticosteroids and on a stable dose for at least 3 months before study entry
Walking independently eligibility requirements	Participants had to be ambulatory, and able to complete time to stand from supine, time to run or walk 10 m, and time to climb 4 stairs assessments at screening
Intervention	Viltolarsen 40 mg/kg per weekly IV infusion Viltolarsen 80 mg/kg per weekly IV infusion
Control	Placebo weekly IV infusion, for 4 weeks
Primary outcome used for accelerated approval	Dystrophin production
Study duration	4 weeks, followed by a 20-week period with all participants receiving viltolarsen (40 mg or 80 mg)
Trial funding	NS Pharma

Sources. Information is taken from trial publications and ClinicalTrials.gov trial registry records and may vary to that reported in the prescribing label.

Abbreviations. DMD: Duchenne muscular dystrophy; IV; intravenous; NA; not applicable; NR: not reported.

TABLE A4

Summary characteristics of study used to support efficacy of casimersen

Trial results used for accelerated FDA approval highlighted in green.

	Study 1[12,13]
Official title	A double-blind, placebo-controlled, multicenter study with an open-label extension to evaluate the efficacy and safety of SRP-4045 and SRP-4053 in patients with Duchenne muscular dystrophy (ESSENCE)
ClinicalTrials.gov ID	NCT02500381
Clinical trial phase	Phase 1 and phase 2
Study population description	229 boys[a] with DMD (aged 6 to 13 years)
DMD genetic mutation eligibility requirements	Participants needed to have a confirmed genetic mutation amenable to exon 45 or exon 53 skipping
Corticosteroid treatment eligibility requirements	Participants needed to be receiving oral corticosteroids and on a stable dose for at least 24 weeks before study entry
Walking independently eligibility requirements	Participants had to achieve a minimum of 300 m, but no more than 450 m, on the 6-minute walk test
Intervention	Casimersen 30 mg/ kg per weekly IV infusion Golodirsen 30 mg/ kg per weekly IV infusion
Control	Placebo weekly IV infusion
Primary outcome used for accelerated approval	Dystrophin production
Study duration	Up to 96 weeks, followed by a 48-week period with all participants receiving casimersen or golodirsen
Trial funding	Sarepta Therapeutics

Note. [a] At the time of approval, data were available for 43 participants assigned to casimersen or placebo for 48 weeks.
Sources. This information is taken from trial publications and ClinicalTrials.gov trial registry records and may vary from that reported in prescribing label.
Abbreviations. DMD: Duchenne muscular dystrophy; IV; intravenous; NA; not applicable.

APPENDIX B

STUDIES REQUESTED TO SUPPORT FULL APPROVAL OF EXON-SKIPPING DRUGS

EXHIBIT B1

Summary characteristics of study requested to support full approval of eteplirsen

	PMR 3095-1[14,15]
Official title	A randomized, double-blind, dose finding and comparison study of the safety and efficacy of a high dose of eteplirsen, preceded by an open-label dose escalation, in patients with Duchenne muscular dystrophy with deletion mutations amenable to exon 51 skipping
ClinicalTrials.gov ID	NCT03992430
Study name	MIS51ON
Study design	Part 1: Open-label, dose escalation trial Part 2: Randomized, quadruple-blind, placebo-controlled trial
Clinical trial phase	Phase 3
Study population description	Boys with DMD and a confirmed genetic mutation amenable to exon 51 skipping
Age of participants	4 to 13 years
Study arms	2 study arms
Intervention	Part 1: Eteplirsen 100 mg/kg *or* 200 mg/kg by weekly IV infusion Part 2: Eteplirsen 100 mg/kg *or* 200 mg/kg by weekly IV infusion
Control	Part 1: No comparator group Part 2: Eteplirsen 30 mg/kg by weekly IV infusion
Study duration	Part 1: Up to 8 weeks Part 2: Up to 144 weeks
Study sites	58 study sites, including in the US
Trial funding	Sarepta Therapeutics
Primary outcome	Part 1: Adverse events up to 148 weeks Part 2: North Star Ambulatory Assessment score at 144 weeks
Outcomes requested by the FDA	North Star Ambulatory Assessment score
Estimated date of final report submission at the time of FDA approval	May 2021
Status of requested study	Active, not recruiting
Primary completion date	November 2024 (estimated)

Sources. This information is taken from the trial publications and ClinicalTrials.gov trial registry records and may vary from information reported in accelerated approval record.

Abbreviations. DMD: Duchenne muscular dystrophy; FDA: US Food and Drug Administration; PMR: postmarketing requirement.

EXHIBIT B2

Summary characteristics of studies requested to support full approval of golodirsen and casimersen

	PMR 3609-1 and PMR 4005-1[12,15]
Official title	A double-blind, placebo-controlled, multicenter study with an open-label extension to evaluate the efficacy and safety of SRP-4045 and SRP-4053 in patients with Duchenne muscular dystrophy
ClinicalTrials.gov ID	NCT02500381
Study name	ESSENCE
Study design	Part 1: Randomized, quadruple-blind, placebo-controlled trial Part 2: Open-label (nonrandomized, unblinded) trial
Clinical trial phase	Phase 1 and Phase 2
Study population description	Boys with DMD and a confirmed genetic mutation amenable to exon 45 or exon 53 skipping
Age of participants	6 to 13 years
Study arms	3 study arms
Intervention	Casimersen: 30 mg/kg by weekly IV infusion Golodirsen: 30 mg/kg by weekly IV infusion
Control	Placebo weekly IV infusion
Study duration	Up to 96 weeks, followed by a 48-week period with all participants receiving casimersen or golodirsen
Study sites	75 study sites, including in the US
Trial funding	Sarepta Therapeutics
Primary outcome	6-minute walk test at 96 weeks
Outcomes requested by the FDA	6-minute walk test
Estimated date of final report submission at the time of FDA approval	October 2024
Status of requested study	Active, not recruiting
Primary completion date	October 2025

Sources. This information is taken from the trial publications and ClinicalTrials.gov trial registry records and may vary from information reported in accelerated approval record.

Abbreviations. DMD: Duchenne muscular dystrophy; FDA: US Food and Drug Administration; PMR: postmarketing requirement.

EXHIBIT B3

Summary characteristics of study requested to support full approval of viltolarsen

	PMR 3895-1[15,16]
Official title	A Phase 3 randomized, double-blind, placebo-controlled, multicenter study to assess the efficacy and safety of viltolarsen in ambulant boys with Duchenne muscular dystrophy
ClinicalTrials.gov ID	NCT04060199
Study name	RACER53
Study design	Randomized, quadruple-blind, placebo-controlled trial
Clinical trial phase	Phase 3
Study population description	Boys with DMD and a confirmed genetic mutation amenable to exon 53 skipping
Age of participants	4 to 7 years
Study arms	2 study arms
Intervention	Viltolarsen 80 mg/kg by weekly IV infusion
Control	Placebo weekly IV infusion
Study duration	Up to 48 weeks
Study sites	40 study sites, including in the US
Trial funding	NS Pharma
Primary outcome	Time to stand at 48 weeks
Outcomes requested by the FDA	Time to stand
Estimated date of final report submission at the time of FDA approval	December 2024
Status of requested study	Completed No publications identified at the time of writing this brief
Primary completion date	October 2023

Sources. This information is taken from the trial publications and ClinicalTrials.gov trial registry records and may vary from information reported in accelerated approval record.

Abbreviations. DMD: Duchenne muscular dystrophy; FDA: US Food and Drug Administration; PMR: postmarketing requirement.

APPENDIX C

METHODS

Data Sources

Researchers from the Center for Evidence-based Policy (Center) used the Transformed Medicaid Statistical Information System (T-MSIS) Analytic Files (TAF) as the primary data source for drug indication cohort identification, prevalence estimates, and medication uptake. The TAF are a research-optimized version of state-submitted T-MSIS data, which include information on Medicaid and Children's Health Insurance Program (CHIP) enrollment, demographics, health care service use, and payments, based on enrollment and claims records. State-submitted T-MSIS data are processed by the University of Minnesota Research Data Center, and then compiled for use as national data files.

We obtained TAF demographic and enrollment data, with inpatient, other service, and pharmacy claims data for years 2019 through 2021 for all Medicaid and CHIP members aged 0 to 64, excluding those with any months of dual enrollment in Medicaid and Medicare. Using these criteria, we were not able to obtain data from Utah or Alabama, as these states do not submit claim information related to dual enrollment status using this method. Cohorts for analysis were anchored in the most recent year of data available (2021), with preceding years used to maintain internal validity for diagnosis and service-use identification, based on established methods specific to the indication of interest. Other sources used to inform cohort definitions, drug indication, and drug identification included peer-reviewed literature, grey literature sources, and publicly available databases.

The TAF data are subject to quality concerns. To identify data quality or usability issues affecting internal analytical validity, the Medicaid Data Quality (DQ) Atlas was used as a reference.[17] In general, if the DQ Atlas identified a state's data as "unusable" for a topic, variable, or year, that state was eliminated from analysis. If a state's data were of "high concern," we investigated further to determine the reason behind the rating and made a topic-specific or variable-specific judgment about inclusion or exclusion for analysis; we made decisions to include, with a bias towards underreporting (as opposed to overreporting). We used 3 distinct methods to address large-scale data quality issues during initial data processing, as described below.

Member Demographic Identification and State Assignment

Members have 2 identifiers in the TAF: a primary identifier assigned during processing at the University of Minnesota Research Data Center that compiles claims across states for individual members, and a member-specific identifier (MSIS ID) assigned by the state (plus the identifying state). Ninety-seven percent of members had primary identifiers. For the remaining 3%, we used the combination of MSIS ID and state code. A very small proportion of members with primary identifiers had multiple enrollment records, sometimes with differing state codes and demographic information. Those members were assigned a state code based on the highest frequency and consistency of the

following attributes and in this order: state of residence, state with the highest proportion of claims, and state with the longest period of enrollment. If there were ties among states for a member, we randomly assigned them to one of the states within which they had claims.

Differences in demographic information for members with multiple enrollment records were similarly reconciled. In the case of multiple records with missing demographic information, missing values were imputed from records assigned to the member in other states, or the most frequently reported characteristic was assigned. Race and ethnicity were the most common missing characteristics; age and sex were rarely missing in this dataset.

Mississippi Member Identification and Claims

Data linking of Mississippi claims records to member enrollment records was considered "unusable" by the DQ Atlas for 2019 to 2021. Any members with claims submitted in Mississippi were assigned to that state for drug indication prevalence reporting. Further, the only demographic information from submitted claims that we could identify for members from Mississippi was birth date. We could not use sex or race or ethnicity information in the enrollment files for these members. In the brief, only the following data are included from Mississippi:

- Number of people with drug indication, if no demographic information other than age is required for cohort inclusion
- A breakdown of members with a particular drug indication by age (sample size permitting)
- Comorbidities and health care service use for members with the drug indication, and matched comparisons where matching is based only on age
- Drug uptake, if applicable

In the case that other demographic characteristics are required for cohort inclusion (e.g., sex), members from Mississippi were not included.

Illinois Claims

Illinois claims data are known to be reported with multiple records per care episode, or "claim families," which would otherwise be aggregated into a single claim record in other states. Methods for including Illinois claims were applied according to TAF Technical Guidance resources and recommendations.[18]

Reporting of Data

Adhering to CMS reporting rules, we reported member counts in any subgroup only when the group size was at least 11. We reported rates and percentages when the group size on the numerator was at least 11 and the denominator group size was at least 50.If there were any race or ethnicity groups with 10 or fewer people, then only the largest group was reported when total of the unreported group sizes was greater than 10.

Prevalence Estimates

To identify members with Duchenne muscular dystrophy (DMD), we used a claims-based case-finding algorithm with a 3-year lookback period.[19] A member was classified as having DMD if at least 1 inpatient claim or 2 other service claims 30 days apart with ICD-10 (International Classification of Diseases, 10th revision) diagnosis code G71.01, or at least 1 claim for at least 1 of the exon-skipping treatments for DMD. To identify the treatment claims we searched prescription claims and other services claims (e.g., for infusions) containing National Drug Code (NDC) directory codes *60923-284-10*, *60923-363-02*, *60923-465-02*, *60923-227-02*, and *73292-011-01*, and then linked these by member identifier.[20] This algorithm has been used in other studies to identify DMD patients in claims data.[19,21]

Matched Comparison Group

We used a matched-comparison method to analyze health care service use and health states between members with the drug indication and the Medicaid population at large. We performed 1-to-3 exact matching between members with DMD and members without DMD, based on member state, sex, age in years, and race and ethnicity groups, when available. If we identified more than 3 exact matches for a member with DMD, 3 were chosen at random.

Comorbid Conditions

We used the Chronic Disability Payment System (CDPS) algorithm to identify prevalence of affected body systems and relevant comorbidities in the DMD cohort and matched comparisons.[22] The CDPS has a hierarchical method to classify members into risk groups by body system using ICD-10 diagnosis codes in medical claims. There are multiple risk groups per body system, and a member may only belong to 1 risk group per body system. Once categorized, we aggregated risk groups into whole-system categories (e.g., cardiovascular, pulmonary). We then identified and searched chronic conditions specific to the population with the drug indication in the data using value sets and algorithms gathered from the Chronic Conditions Warehouse,[23] CMS.gov billing and coding recommendations,[24] and input from clinical experts.

Health Care Service Use

We compared health care service use outcomes (hospitalizations, emergency department [ED] visits, outpatient physical therapy and occupational therapy claims, durable medical equipment), measured in both the drug indication and matched comparison groups, between January 1, 2021 and December 31, 2021. We identified hospitalizations in the inpatient files as episodes of care based on unique admission date. Unique discharge dates were used in the case of missing admission dates. We identified ED visits in both inpatient and outpatient files using revenue center codes 450 through 459 and 981, and service date. Accordingly, the ED visits we report include visits that resulted in an

admission. Outpatient physical and occupational therapy visits were calculated as the proportion of Medicaid members with at least 1 claim containing a CPT code for physical or occupational therapy evaluations, reevaluations, or services. Select durable medical equipment claims pertinent to the population of Medicaid members with DMD were reported as having at least 1 claim for the following devices: ventilation or respiratory assist devices, cough-assist devices, or wheeled mobility. To maximize inclusion, wheeled mobility claims included those for wheeled mobility devices and those for component parts.

Medication Adherence and Uptake

Medication uptake was calculated as the proportion of unique members with DMD with any identified claim in the prescription files for eteplirsen, golodirsen, viltolarsen, and casimersen (see NDC codes above). Medication adherence was calculated using the Medication Possession Ratio (MPR), a member-level estimation calculated as the proportion of days' supply provided during a given period, for the year 2021. The numerator is the number of days' supply obtained, starting at the date of the first fill of the year, and the denominator is the total number of days between the first fill and December 31, 2021. This method assumes the medication is prescribed for weekly, continuous use, and that the member took their medication as prescribed.

Cost Estimates

The cost estimates represent the projected annual total national costs associated with covering exon-skipping drugs for treatment of Medicaid members with DMD. We modeled the costs based on the DMD prevalence and drug uptake and adherence observed in the TAF Medicaid claims data, as well as current wholesale acquisition cost for the drug and statutorily required rebate percentages, and the prevalence of relevant gene mutations reported elsewhere.[25-28] Because the prevalence of the condition, uptake, use patterns of these treatments, and mortality vary by age, we used an age-based model where all inputs were allowed to vary by age. For prevalence, we used six 5-year age brackets from 0 to 29 years of age and the prevalence rates observed in the data for each age group. For the uptake rate and inputs related to drug use patterns, we created three 10-year age brackets from 0 to 29 years of age. We used the uptake rates observed in the data for each of these age groups for the drugs approved in 2019 or before (eteplirsen and golodirsen). For viltolarsen and casimersen (approved shortly before or during our 2021 study period), we modified the uptake rates, assuming the uptake for viltolarsen will increase by 10% of its uptake rate in 2021 and casimersen uptake rate will increase by 25%. Similarly, because we do not observe a full year of use patterns for casimersen, we assumed the rate of incident users for this drug will mimic that of eteplirsen. We used the adherence rates observed in the data in each age group for each drug when there were sufficiently large number of patients (more than 10) in the age group. When there were 10 or fewer patients in an age group using a treatment, we assumed the percentages observed for the other treatments will apply proportionally to the percentages in other age groups. To account for the high incident mortality

rate for this disease, we used mortality rates from the literature that evaluated incident mortality among DMD patients by age.[29] Similarly, because the cost of the drug is dependent on the treatment dosage based on patient body weight, we used the price that would correspond to the dose that the patients in each of the six 5-year age brackets would need based on the median weight for males in that age group reported by the Centers for Disease Control and Prevention.[30] The list of exon-skipping treatments and the associated annual prices are described in Exhibit C1. The other model inputs and sources are summarized in Exhibit C2.

EXHIBIT C1

Exon-skipping treatments and prices

Treatment	Dosage form (strength)	Annual price[a], $
Eteplirsen	Solution; IV (100 mg/2 mL [50 mg/mL] or 500 mg/10 mL [50 mg/mL])	748,800
Golodirsen	Solution; IV (100 mg/2 mL [50 mg/mL])	748,800
Viltolarsen	Solution; IV (250 mg/5 mL [50 mg/mL])	703,872
Casimersen	Solution; IV (100 mg/2 mL [50 mg/mL])	748,800

Note. [a] Costs are annualized based on 30 kg (66 pounds) body weight and assuming patients are taking the recommended weekly dose. An average Medicaid DMD patient using an exon-skipping treatment is 15 years old and is likely to have a higher body weight and higher annual treatment cost. See Exhibit C2 for annualized prices for patients of different ages (and associated average body weights).

EXHIBIT C2

Cost modeling inputs: prevalence and uptake

	Prevalence (members with DMD), N[a,b]	Eligible patients with variant, %[25-28]	Uptake (eligible patients using drug), %[b,c]	Incident mortality rate (per 1,000)[31,c]
Eteplirsen	6,205	13	28	2.5
Golodirsen	6,205	8	13	2.5
Viltolarsen	6,205	8	7	2.5
Casimersen	6,205	8	19	2.5
Sensitivity analysis bounds	5,896 to 6,591	Rate ± 20%	eteplirsen, 20% to 35% golodirsen, 6% to 20% viltolarsen, 3% to 15% casimersen, 10% to 30%	n/a

Notes. [a] Includes estimated patient populations in Alabama, Utah, and Mississippi at the national prevalence rate. [b] Source: TAF data. [c] Inputs vary by age; only the averages are shown.

Abbreviations. DMD: Duchenne muscular dystrophy; FDA: US Food and Drug Administration; n/a: not applicable; TAF: T-MSIS Analytic Files; T-MSIS: Transformed Medicaid Statistical Information System.

EXHIBIT C3

Cost modeling inputs: drug costs

	Eteplirsen	Golodirsen	Viltolarsen	Casimersen
Price per mg, $ [a]	16	16	6	16
Body weight assumed, kg				
Ages 2 to 4	15.7	15.7	15.7	15.7
Ages 5 to 9	26.1	26.1	26.1	26.1
Ages 10 to 14	49.0	49.0	49.0	49.0
Ages 15 to 19	70.7	70.7	70.7	70.7
Ages 20 to 29	81.3	81.3	81.3	81.3
Annual drug cost, $ [b]				
Ages 2 to 4	391,872	391,872	368,360	391,872
Ages 5 to 9	651,456	651,456	612,369	651,456
Ages 10 to 14	1,223,040	1,223,040	1,149,658	1,223,040
Ages 15 to 19	1,765,670	1,765,670	1,659,730	1,765,670
Ages 20 to 29	2,029,248	2,029,248	1,907,493	2,029,248
Federal rebates, % [32,c]	23.1	23.1	23.1	23.1

Notes. [a] This information came from IPD Analytics. [b] These values were calculated by Center researchers. [c] Does not include state-negotiated supplemental rebates.
Abbreviations. SSA: Social Security Administration.

EXHIBIT C4

Cost modeling inputs: adherence

	Adherent users, % [a,b]	Prevalent users, % [a,b,c]	Avg. MPR if adherent [b]	Avg. MPR if nonadherent [b]
Eteplirsen	76	70	0.95	0.51
Golodirsen	75	70	0.95	0.35
Viltolarsen	69	70	0.98	0.40
Casimersen	69	70	0.98	0.48
Sensitivity analysis bounds	55% to 90%	55% to 85%	0.90 to 1	0.2 to 0.8

Notes. [a] Inputs vary by age; only the averages are shown. [b] This information comes from TAF data. [c] Prevalent users are those who have been using the drug from the first month of the year on; the remaining users are incident users who have started using the drug within the year, after the first month.
Abbreviations. MPR: Medication Possession Ratio; TAF: T-MSIS Analytic Files; T-MSIS: Transformed Medicaid Statistical Information System.

As our focus is direct drug costs, we did not include the costs of drug dispensing and monitoring. Due to lack of published data, we also did not include cost offsets associated with replacement of treatment-as-usual. Similarly, we did not include cost implications of treatment effectiveness in terms of recovery, reduced health care service use, or mortality.

We performed sensitivity analyses using Monte Carlo simulations, taking into consideration uncertainty in the model inputs, and reporting the range that contained 95% of the simulated cost values as the confidence bounds for our cost estimate. The lower and upper bounds considered for prevalence and percentage of patients eligible varied by treatment, while uptake, adherence, percentage of prevalent users, and MPRs were allowed to vary by both treatment and age group. We also performed 2-way scenario analyses to show how the cost estimate changes under different uptake and adherence scenarios. These different uptake and adherence scenarios considered costs when uptake and adherence rates were higher or lower by the same percentage across all age groups compared with the base case. The results of these scenario analyses are shown in Appendix G.

For our per-member per-month (PMPM) cost estimates, we used the member month counts we observed in the 2021 data, excluding any dually enrolled members. For the state and federal breakdown of the costs, we first calculated the percentage of the members with DMD in CHIP and adult Medicaid Expansion enrollment categories. We then calculated the average Federal Medical Assistance Percentage (FMAP) rates across states weighted by the number of DMD patients in each enrollment category and applied the corresponding matching rates to the relevant portion of the total costs for Medicaid and CHIP members. We applied the 90% FMAP exception for the portion of the costs by the members with adult Medicaid Expansion enrollment.

The drug spending estimates for 2021 were based on converting the total number of days' supply in 2021 pharmacy and outpatient services claims for each of these 4 drugs into a dollar cost. We identified the number of fills and total days' supply for DMD patients by age. We estimated treatment dosage (mg needed) for each fill based on the median body weight for patient age and multiplied the dosage with the per-mg drug wholesale acquisition price, applying the statutorily required rebates to calculate estimated cost associated with each fill. We used the FMAP rates from 2021 and the enrollment status of the DMD patients to calculate the federal and state share of the calculated costs.

For states with unusable data quality for identifying CHIP enrollment, we used the average percentage of CHIP enrollment in other states. Similarly, for expansion states with unusable data quality for identifying Medicaid adult expansion enrollment, we used the average of adult expansion enrollment share in other expansion states.

Limitations

Our cost estimates are based on the prevalence of DMD and treatment uptake and use patterns we identified in the claims data. Given that the T-MSIS TAF do not include clinical information relevant to

identifying individuals eligible for exon-skipping treatments, we had to approximate the clinical indication using a claims data-based approach. As such, the accuracy of our estimates depends on the completeness and reliability of the claims and the information recorded in the data (e.g., diagnosis and procedure codes in the inpatient and outpatient claims, and the NDC codes in pharmacy and outpatient claims) as well as enrollment and demographic information (e.g., dual enrollment, age) given for each member. We do not observe the exact genetic variant of DMD in the data, and relied on the percentage of DMD patients with the specific variants reported elsewhere to estimate the number of patients amenable to each exon-skipping therapy.

For the 3 states for which we have no data on DMD prevalence, our cost estimates assume that DMD prevalence and the treatment uptake and use patterns in these states are similar to what is observed in other states. Our cost estimates do not include supplemental rebates, and the estimated total cost is broken down by state and federal share without any consideration for third-party liability or other insurance payments.

APPENDIX D

MEDICAID MEMBERS WITH AND WITHOUT DMD, 2021

EXHIBIT D

Medicaid members with and without Duchenne muscular dystrophy, 2021

		Members with DMD			Members without DMD
State	Total Medicaid population	n	per 100,000 members	%	n
United States	*81,439,192*	*6,041*	*7.4*	*0.01*	*81,433,151*
Alabama[a]	--	--	--	--	--
Alaska	231,442	18	7.8	0.01	231,424
Arizona	2,066,692	162	7.8	0.01	2,066,530
Arkansas	975,462	81	8.3	0.01	975,381
California	14,068,016	746	5.3	0.01	14,067,270
Colorado	1,496,614	127	8.5	0.01	1,496,487
Connecticut	964,247	59	6.1	0.01	964,188
Delaware	264,062	36	13.6	0.01	264,026
District of Columbia	--	--	--	--	--
Florida	3,976,922	275	6.9	0.01	3,976,647
Georgia	2,258,383	169	7.5	0.01	2,258,214
Hawaii	391,262	16	4.1	0.00	391,246
Idaho	402,324	40	9.9	0.01	402,284
Illinois	3,187,612	219	6.9	0.01	3,187,393
Indiana	1,748,824	135	7.7	0.01	1,748,689
Iowa	753,318	89	11.8	0.01	753,229
Kansas	426,693	54	12.7	0.01	426,639
Kentucky	1,613,908	116	7.2	0.01	1,613,792
Louisiana	1,693,162	80	4.7	0.00	1,693,082
Maine	328,619	31	9.4	0.01	328,588
Maryland	1,506,988	77	5.1	0.01	1,506,911
Massachusetts	1,798,991	151	8.4	0.01	1,798,840
Michigan	2,687,982	193	7.2	0.01	2,687,789
Minnesota	1,197,056	120	10.0	0.01	1,196,936
Mississippi	--	--	--	--	--
Missouri	1,093,093	127	11.6	0.01	1,092,966
Montana[b]	280,337	20	7.1	0.01	280,317
Nebraska	323,274	61	18.9	0.02	323,213
Nevada	792,178	33	4.2	0.00	792,145
New Hampshire	227,212	31	13.6	0.01	227,181
New Jersey	1,886,202	120	6.4	0.01	1,886,082
New Mexico	857,354	45	5.2	0.01	857,309
New York	6,262,027	327	5.2	0.01	6,261,700

State	Total Medicaid population	Members with DMD			Members without DMD
		n	per 100,000 members	%	n
North Carolina	2,396,142	169	7.1	0.01	2,395,973
North Dakota	--	--	--	--	--
Ohio	2,926,427	276	9.4	0.01	2,926,151
Oklahoma	1,052,565	81	7.7	0.01	1,052,484
Oregon	1,250,950	63	5.0	0.01	1,250,887
Pennsylvania	3,183,117	321	10.1	0.01	3,182,796
Rhode Island	319,305	14	4.4	0.00	319,291
South Carolina	1,255,882	98	7.8	0.01	1,255,784
South Dakota[b]	123,851	13	10.5	0.01	123,838
Tennessee	1,564,046	153	9.8	0.01	1,563,893
Texas	5,515,970	607	11.0	0.01	5,515,363
Utah[a]	--	--	--	--	--
Vermont	160,890	11	6.8	0.01	160,879
Virginia	1,746,297	166	9.5	0.01	1,746,131
Washington	1,955,277	123	6.3	0.01	1,955,154
West Virginia	567,556	54	9.5	0.01	567,502
Wisconsin	1,241,446	117	9.4	0.01	1,241,329
Wyoming[b]	--	--	--	--	--

Notes. [a] Data not available. [b] Data suppressed (N < 11).
Abbreviation. DMD: Duchenne muscular dystrophy.

APPENDIX E

DEMOGRAPHIC INFORMATION

EXHIBIT E

Availability of race and ethnicity information for Medicaid members included in analyses, 2021

	Medicaid members with DMD	%	Medicaid members without DMD	%
Total	*6,041*	-	*81,433,152*	-
Race or ethnicity available	4,121	68.2	56,444,189	69.3
Race or ethnicity NR[a]	1,219	20.2	6,360,567	22.9
Race or ethnicity missing[b]	701	11.6	18,628,396	7.8

Notes. [a] We did not report race/ethnicity data from states that have unusable or high concern data quality for race/ethnicity information, including Arizona, Connecticut, District of Columbia, Iowa, Louisiana, Massachusetts, New York, Oregon, Rhode Island, South Carolina, Tennessee, and Wyoming. [b] Missing in states for which race and ethnicity data is reported.

Abbreviations. DMD: Duchenne muscular dystrophy; NR: not reported.

APPENDIX F

TREATMENT UPTAKE, 2021

EXHIBIT F1

Uptake of Exon-skipping drugs among Medicaid members with DMD, 2021

ETEPLIRSEN	All members with DMD	Members eligible for eteplirsen[a]	Members using eteplirsen	% uptake among eligible members[b]
Total members	*6,041*	*785*	*216*	*27.5*
Age range, years				
0 to 9	1,208	157	54	34.4
10 to 17	2,470	321	96	29.9
18 to 29	2,363	307	66	21.5

GOLODIRSEN	All members with DMD	Members eligible for golodirsen[a]	Members using golodirsen	% uptake among eligible members[b]
Total members	*6,041*	*483*	*59*	*12.2*
Age range, years				
0 to 9	1,208	97	14	14.5
10 to 17	2,470	198	32	16.2
18 to 29	2,363	189	13	6.9

VILTOLARSEN	All members With DMD	Members eligible for viltolarsen[a]	Members using viltolarsen	% uptake among eligible members[b]
Total members	*6,041*	*483*	*28*	*5.8*
Age range, years				
0 to 9	1,208	97	11	11.4
10 to 17	2,470	198	n/a[c]	
18 to 29	2,363	189	n/a[c]	

CASIMERSEN	All members with DMD	Members eligible for casimersen[a]	Members using casimersen	% uptake among eligible members[b]
Total members	*6,041*	*483*	*73*	*15.1*
Age Range, years				
0 to 9	1,208	97	18	18.6
10 to 17	2,470	198	36	18.2
18 to 29	2,363	189	19	10.1

Notes. [a] Assuming 13% of the members with DMD are amenable to exon 51 skipping, 8% are amenable to exon 53 skipping, and 8% are amenable to exon 45 skipping.[1,2,3,4] [b] Percentage of estimated members with the relevant gene mutation. [c] Suppressed (N < 11).
Abbreviation. DMD: Duchenne muscular dystrophy.

EXHIBIT F2

Medication adherence, means, and proportions, stratified by treatment, 2021

	Total Medicaid members	Mean MPR	Adherent[b], %
All drugs			
Fully enrolled[a]	*352*	*0.90*	*76*
All members with fills	*370*	*0.89*	*74*
By drug, all members with fills			
Eteplirsen	216	0.88	76
Golodirsen	59	0.88	75
Viltolarsen	28	0.84	68
Casimersen	73	0.94	70

Notes. [a] Fully enrolled members are those with calculated 365 days of enrollment in the year 2021, [b] ≥ 0.8 MPR.
Abbreviation. MPR: medication possession ratio.

APPENDIX G

COST SCENARIO ANALYSES

EXHIBIT G1

Estimated annual cost of eteplirsen (in $M) under different uptake and adherence scenarios

	Uptake		BASE CASE		
Adherence	14%	22%	**28%**	34%	42%
53%	76	122	154	184	231
61%	80	127	161	192	241
68%	84	134	168	201	251
BASE CASE **76%**	88	139	**175**	210	262
84%	90	145	182	218	273
91%	94	150	189	227	282

EXHIBIT G2

Estimated annual cost of golodirsen (in $M) under different uptake and adherence scenarios

	Uptake		BASE CASE		
Adherence	7%	10%	**13%**	16%	20%
53%	17	29	38	45	57
60%	21	35	41	50	63
68%	23	36	45	52	66
BASE CASE **75%**	23	38	**47**	55	70
83%	25	40	49	58	75
90%	26	41	52	62	79

EXHIBIT G3

Estimated annual cost of vitolarsen (in $M) under different uptake and adherence scenarios

	Uptake		BASE CASE		
Adherence	4%	6%	**7%**	8%	11%
48%	7	13	16	20	24
55%	9	15	17	22	25
62%	11	17	21	24	28
BASE CASE **69%**	12	17	**21**	25	30
76%	12	19	23	26	30
83%	12	19	23	28	32

EXHIBIT G3

Estimated annual cost of casimersen (in $M) under different uptake and adherence scenarios

	Uptake		BASE CASE		
Adherence	10%	15%	**19%**	23%	29%
48%	32	50	62	76	94
55%	33	51	66	79	98
62%	35	54	69	83	102
BASE CASE **69%**	36	56	**72**	86	107
76%	38	59	75	90	112
83%	39	60	79	93	116

REFERENCES

1. Mendell JR, Rodino-Klapac LR, Sahenk Z, et al. Eteplirsen for the treatment of Duchenne muscular dystrophy. *Ann Neurol*. 2013;74(5):637-647. doi: 10.1002/ana.23982.

2. ClinicalTrials.gov. NCT01396239. A randomized, double-blind, placebo-controlled, multiple dose efficacy, safety, tolerability and pharmacokinetics study of AVI-4658 (eteplirsen),in the treatment of ambulant subjects with Duchenne muscular dystrophy. 2011; https://classic.clinicaltrials.gov/ct2/show/NCT01396239. Accessed November 10, 2023.

3. US Food and Drug Administration. Prescribing label. Exondys 51. 2016; https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/206488s027s028s029lbl.pdf. Accessed March 2, 2024.

4. Mendell JR, Goemans N, Lowes LP, et al. Longitudinal effect of eteplirsen versus historical control on ambulation in Duchenne muscular dystrophy. *Ann Neurol*. 2016;79(2):257-271. doi: 10.1002/ana.24555.

5. ClinicalTrials.gov. NCT01540409. Open-label, multiple-dose, efficacy, safety, and tolerability study of eteplirsen in subjects with Duchenne muscular dystrophy who participated in Study 4658-US-201. 2012; https://classic.clinicaltrials.gov/ct2/show/NCT01540409. Accessed November 10, 2023.

6. US Food and Drug Administration. Prescribing label. Vyondys 53. 2019; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/211970s002lbl.pdf. Accessed March 2, 2024.

7. Frank DE, Schnell FJ, Akana C, et al. Increased dystrophin production with golodirsen in patients with Duchenne muscular dystrophy. *Neurology*. 2020;94(21):e2270-e2282. doi: 10.1212/WNL.0000000000009233.

8. ClinicalTrials.gov. NCT02310906. A 2-part, randomized, double-blind, placebo-controlled, dose-titration, safety, tolerability, and pharmacokinetics study (part 1) followed by an open-label efficacy and safety evaluation (part 2) of SRP-4053 in patients with Duchenne muscular dystrophy amenable to exon 53 skipping. 2014; https://clinicaltrials.gov/study/NCT02310906. Accessed March 2, 2024.

9. ClinicalTrials.gov. NCT02740972. A phase II, dose finding study to assess the safety, tolerability, pharmacokinetics, and pharmacodynamics of NS-065/NCNP-01 in boys with Duchenne muscular dystrophy (DMD). 2016; https://clinicaltrials.gov/study/NCT02740972. Accessed March 3, 2024.

10. US Food and Drug Administration. Prescribing label. Viltepso. 2020; https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/212154s002lbl.pdf. Accessed March 2, 2024.

11. Clemens PR, Rao VK, Connolly AM, et al. Safety, tolerability, and efficacy of viltolarsen in boys with Duchenne muscular dystrophy amenable to exon 53 skipping: a phase 2 randomized clinical trial. *JAMA Neurol*. 2020;77(8):982-991. doi: 10.1001/jamaneurol.2020.1264.

12. ClinicalTrials.gov. NCT02500381. A double-blind, placebo-controlled, multi-center study with an open-label extension to evaluate the efficacy and safety of SRP-4045 and SRP-4053 in patients with Duchenne muscular dystrophy. 2015; https://clinicaltrials.gov/study/NCT02500381. Accessed November 10, 2023.

13. US Food and Drug Administration. Prescribing label. Amondys 45. 2021; https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/213026s005lbl.pdf. Accessed March 2, 2024.

14. ClinicalTrials.gov. NCT03992430. A Randomized, double-blind, dose finding and comparison study of the safety and efficacy of a high dose of eteplirsen, preceded by an open-label dose escalation, in patients with Duchenne muscular dystrophy with deletion mutations amenable to exon 51 skipping. 2019; https://clinicaltrials.gov/study/NCT03992430. Accessed November 11, 2023.

15. US Food and Drug Administration. Ongoing: non-malignant hematological, neurological, and other disorder indications accelerated approvals. 2023; https://www.fda.gov/drugs/accelerated-approval-program/ongoing-non-malignant-hematological-neurological-and-other-disorder-indications-accelerated. Accessed November 10, 2023.

16. ClinicalTrials.gov. NCT04060199. A phase 3 randomized, double-blind, placebo-controlled, multi-center study to assess the efficacy and safety of viltolarsen in ambulant boys with Duchenne muscular dystrophy (DMD). 2019; https://clinicaltrials.gov/study/NCT04060199. Accessed November 11, 2023.

17. Medicaid.gov. Medicaid data quality (DQ) atlas. 2024; https://www.medicaid.gov/dq-atlas/welcome. Accessed April 12, 2024.

18. Centers for Medicare and Medicaid Services. TAF technical guidance: Claims files. 2022; https://resdac.org/sites/datadocumentation.resdac.org/files/2022-06/TAF-TechGuide-Claims-Files.pdf. Accessed April 12, 2024.

19. Szabo S, Klimchak A, Qian C, Popoff E, Iannaccone S, Gooch K. Characterizing commercially- and Medicaid-insured registrants with Duchenne muscular dystrophy (DMD) in the United States (US) (1231). *Neurology*. 2020;94(15_supplement):1231. doi: 10.1212/WNL.94.15_supplement.1231 Accessed 2024/02/22.

20. US Food and Drug Administration. National drug code directory. 2024; https://www.accessdata.fda.gov/scripts/cder/ndc/index.cfm. Accessed April 12, 2024.

21. Klimchak AC, Szabo SM, Qian C, Popoff E, Iannaccone S, Gooch KL. Characterizing demographics, comorbidities, and costs of care among populations with Duchenne muscular dystrophy with Medicaid and commercial coverage. *J Manag Care Spec Pharm*. 2021;27(10):1426-1437. doi: 10.18553/jmcp.2021.27.10.1426 Accessed 2023/11/10.

22. Kronick R, Gilmer T, Dreyfus T, Lee L. Improving health-based payment for Medicaid beneficiaries: CDPS. *Health Care Financ Rev*. 2000;21(3):29-64.

23. Chronic Conditions Data Warehouse. Chronic conditions. 2017; https://www2.ccwdata.org/web/guest/condition-categories-chronic. Accessed April 26, 2024.

24. Centers for Medicare and Medicaid Services. Billing and coding: Outpatient physical and occupational therapy services. 2024; https://www.cms.gov/medicare-coverage-database/view/article.aspx?LCDId=33631&articleId=56566&NCSelection=NCD&KeyWord=negative+pressure&KeyWordLookUp=Doc&KeyWordSearchType=Exact&kq=true. Accessed April 26, 2024.

25. US Food and Drug Administration. FDA grants accelerated approval to first drug for Duchenne muscular dystrophy. 2016; https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-drug-duchenne-muscular-dystrophy. Accessed September 8, 2023.

26. US Food and Drug Administration. FDA grants accelerated approval to first targeted treatment for rare Duchenne muscular dystrophy mutation. 2019; https://www.fda.gov/news-events/press-announcements/fda-grants-accelerated-approval-first-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation. Accessed September 8, 2023.

27. US Food and Drug Administration. FDA approves targeted treatment for rare Duchenne muscular dystrophy mutation. 2020; https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation. Accessed November 10, 2023.

28. US Food and Drug Administration. FDA approves targeted treatment for rare Duchenne muscular dystrophy mutation. 2021; https://www.fda.gov/news-events/press-announcements/fda-approves-targeted-treatment-rare-duchenne-muscular-dystrophy-mutation-0#:~:text=Today%2C%20the%20U.S.%20Food%20and,provide%20information%20for%20making%20proteins. Accessed September 8, 2023.

29. Broomfield J, Hill M, Guglieri M, Crowther M, Abrams K. Life Expectancy in Duchenne Muscular Dystrophy. *Neurology*. 2021;97(23):e2304-e2314. doi: doi:10.1212/WNL.0000000000012910.

30. Fryar CD, Carroll MD, Gu Q, Afful J, Ogden CL. Anthropometric reference data for children and adults : United States, 2015-2018. 2021;3(46). https://stacks.cdc.gov/view/cdc/100478.

31. Broomfield J, Hill M, Guglieri M, Crowther M, Abrams K. Life expectancy in duchenne muscular dystrophy: reproduced individual patient data meta-analysis. *Neurology*. 2021;97(23):e2304-e2314. doi: 10.1212/WNL.0000000000012910 Accessed 2024/04/26.

32. US Social Security Administration. Payment for Covered Outpatient Drugs. 1990; https://www.ssa.gov/OP_Home/ssact/title19/1927.htm. Accessed May 15, 2024.

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