# The cost of trials used to support the initial FDA approval of risdiplam (Evrysdi)

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**Introduction** ..... **2**
Table 1: Trials cited in FDA clinical review ..... 3
Table 2: Trials with a start date before FDA approval, not cited in clinical review ..... 3
Challenges of estimating trial costs ..... 3
**U.S. Orphan Drug Tax Credit (ODTC)** ..... **5**
**U.S. Priority Review Voucher** ..... **5**
**Costs of Trials, per patient** ..... **5**
The 2015 Battelle/PhRMA study of trial costs ..... 5
Battelle/PhRMA Study Table A-1. Estimated Locally-Based Per Patient Costs by Selected Disease Areas and Phase (2013 values) ..... 6
The 2020 Moore, Heyward, Anderson and Alexander study published in BMJ Open ..... 7
BMJ Open Study Table 3: Per patient estimated pivotal trial costs by therapeutic area (in current US dollars, for years 2015 to 2017) ..... 8
Table 3: Assumptions regarding per patient costs of risdiplam trials undertaken before FDA approval ..... 8
**Costs of Trials, by year** ..... **9**
**Estimated Costs of Each Trial** ..... **9**
SUNFISH trial (NCT02908685) ..... 9
Table 4: Allocation of the cost of the SUNFISH trial and relevant ODTC rate, by year ..... 10
The FIREFISH trial (NCT02913482) ..... 10
The cost allocation and relevant ODTC for the Firefish trial is as follows: ..... 10
Table 5: Allocation of the cost of the FIREFISH trial and relevant ODTC rate, by year ..... 10
The JEWELFISH trial (NCT03032172) ..... 10
Table 6: Allocation of the cost of the JEWELFISH trial and relevant ODTC rate, by year ..... 11
**Four additional Roche trials for risdiplam that were started before the initial approval of risdiplam but were not included in the FDA Clinical Review** ..... **11**
Table 7: Four Roche trials for risdiplam begun prior to FDA approval but excluded from the FDA clinical review for the initial approval of risdiplam ..... 11
Table 8: Allocation of the cost of three pre-approval Phase 1 trials and relevant ODTC rate, by year ..... 12
RAINBOWFISH (NCT03779334) trial costs ..... 12
Table 9: Allocation of the cost of the RAINBOWFISH trial and relevant ODTC rate, by year ..... 13
**Estimated Cost of Trials, based on BMJ Open median cost for CNS trials** ..... **14**
Table 10: Allocation of the cost of trials, by year ..... 14
Table 11: Cost of each trial, prior to FDA marketing approval, and prior to Orphan Drug Tax Credit: Scenarios based on BMJ Open median cost for CNS trials ..... 14

Table 12: Orphan Drug Tax Credit: Scenarios based on BMJ Open median cost for CNS trials....15
Cost of all seven trials with start dates before approval, through FDA approval (initial approval or expanded indication for RAINBOWFISH): Scenario based BMJ Open median cost for CNS trials....15
**Sensitivity Analysis....15**
Scenario based upon on BMJ Open 25th percentile cost for CNS trials....15
Scenario based upon on BMJ Open 75th percentile cost for CNS trials....16
**Summary and Concluding Comments....16**

# Introduction

Risdiplam is a drug used to treat spinal muscular atrophy (SMA). The drug is marketed as Evrysdi by Hoffmann-La Roche, and is one of three important treatments that can slow or stop the progression of the disease. The other treatments are nusinersen, marketed as Spinraza by Biogen, and the gene therapy onasemnogene abeparvovec-xioi, marketed as Zolgensma by Novartis. All three treatments benefited from significant research funding from charities and governments, are extremely expensive, and have severely limited access globally. Risdiplam is the only non-invasive SMA therapy.

The initial US FDA approval date for Evrysdi was August 7, 2020. Total sales of Evrysdi through the end of 2024 were CHF4,826, including sales of CHF1,631 in 2024.

As of April 13, 2025, the US NIH ClinicalTrials.Gov register of clinical trials identifies 32 trials involving risdiplam, including 20 sponsored by industry, 14 sponsored specifically by Roche (by Roche or its subsidiary Genentech), and 12 trials sponsored by non-profit organizations. Twenty-three of the trials were interventional and 8 were observational.

Roche is listed as the sponsor of 7 trials with a start date before the August 7, 2020 FDA approval, including 5 trials (Two Phase 2 and three Phase 1) that had a primary completion date before August 7, 2020.

The FDA clinical review used to support the approval of Evrysdi describes three trials: the two pivotal trials SUNFISH and FIREFISH (both with a primary completion date before FDA approval), and JEWELFISH (a trial with a primary completion date of 2025).

The two pivotal trials cited in the FDA review that had primary completion dates before approval had an enrollment of 293 patients total. The JEWELFISH trial, which had a primary completion date in 2025, had an enrollment of 174 patients.

### Table 1: Trials cited in FDA clinical review

| NCT Number / Name | Start Date / Primary Completion | Enrollment |
|---|---|---|
| NCT02908685 / SUNFISH | Oct 19, 2016<br>Sep 6, 2019 | 231 |
| NCT02913482 / FIREFISH | Dec 23, 2016<br>Nov 14, 2019 | 62 |
| NCT03032172 / JEWELFISH | Mar 3, 2017<br>Feb 7, 2025 | 174 |

The NIH trial registry also has four additional trials that began prior to FDA approval but which were not cited in the clinical review (Table 2). Of these, the 3 trials with a primary completion date before FDA approval had a combined enrollment of 94 patients. The trial with a primary completion in 2023 had an enrollment of 26 patients.

### Table 2: Trials with a start date before FDA approval, not cited in clinical review

| NCT Number | Start Date / Primary Completion | Enrollment |
|---|---|---|
| NCT02633709 | Jan 7, 2016<br>Aug 4, 2016 | 33 |
| NCT03920865 | May 16, 2019<br>Jan 2, 2020 | 26 |
| NCT03988907 | Jun 18, 2019<br>Sep 29, 2019 | 35 |
| NCT03779334 | Aug 7, 2019<br>Feb 20, 2023 | 26 |

## Challenges of estimating trial costs

KEI has asked Roche to share information on the costs of the clinical trials used to support the registration of Evrysdi. Roche has declined to do so.

In the absence of information from Roche, an estimate will be made of the costs of the trials undertaken before FDA approval.

Prior to FDA approval, the development of risdiplam involves investments by charities, companies and the US government Orphan Drug Tax Credit subsidy. After FDA approval Roche was able to sell risdiplam at high prices, and make a profit from the product sales as well as the priority review voucher (PRV) awarded by the US FDA.

There are many challenges in estimating trial costs. The drug itself is relatively inexpensive to manufacture, particularly given the very small doses used in treatment. For patients on a trial, Roche typically will not receive reimbursements for the drug until FDA approval, but under many national healthcare systems, can receive reimbursements for routine or standard patient care, for a government sanctioned Phase II or III trial.

Routine medical expenses that would occur regardless of trial participation are often billed to insurers, public or private, and include, for example, routine labs or imaging already part of standard care, supportive therapies (respiratory care, feeding assistance), hospitalizations for SMA-related issues not caused by trial participation, and SMA care components such as respiratory and nutritional support, if consistent with routine care.

It is worth noting that one recent study of SMA patients undertaken by consultants to Novartis found that the costs of care for patients who are compliant with treatment was far lower than for patients who are non-compliant, providing a compelling economic rationale for third party payers to support trials[1] (and also offering insights into the medical costs one might expect for patients who are enrolled in a trial).

The cost of risdiplam itself is excluded from reimbursements as an investigational product. The trial sponsor (Roche) would give risdiplam to patients in a trial for free, up until regulatory approval. For a trial that begins before approval and extends beyond approval, there will be a period where Roche receives nothing for supplying risdiplam, followed by a period when the product is reimbursable, at a highly profitable price.

The costs for Roche of manufacturing the drug are not significant, with a year of treatment requiring less than 2 grams of risdiplam API, which can probably be manufactured by Roche at less than $50,000 per kilo, or $50 per gram. Even if our manufacturing cost estimate (which is informed by discussion of potential generic manufacturers) is off by an order of magnitude, the cost of providing the drug in a trial is not significant.

The non-reimbursable costs that a sponsor must bear include such items as study coordinators, protocol-specific procedures, imaging or lab costs, data management, site payments, and CRO and monitoring fees.

[1] "Median and mean all-cause total health care costs (PPPY) and all-cause medical service costs (PPPY) were greater for patients who were nonadherent to risdiplam than those who were adherent, a trend that extended across SMA types 2–4 (Table 3; Fig. 3). Specifically, median all-cause total health care costs PPPY of nonadherent versus adherent patients were 16-fold greater for SMA type 2 ($356,524.60 vs. $21,475.40), four-fold greater for SMA type 3 ($56,113.00 vs. $14,909.10), and three-fold greater for SMA type 4 ($16,817.00 vs. $4,594.10). Similarly, median all-cause medical service costs PPPY of nonadherent versus adherent patients were 11-fold greater for SMA type 2 ($354,854.50 vs. $21,402.80), five-fold greater for SMA type 3 ($54,218.80 vs. $10,188.70), and three-fold greater for SMA type 4 ($4,206.90 vs. $1,328.50)." Source: Patel, A., Toro, W., Yang, M. et al. Risdiplam utilization, adherence, and associated health care costs for patients with spinal muscular atrophy: a United States retrospective claims database analysis. Orphanet J Rare Dis 19, 494 (2024). https://doi.org/10.1186/s13023-024-03399-0.

## U.S. Orphan Drug Tax Credit (ODTC)

The United States provides a tax credit for qualifying clinical trials for rare diseases, the Orphan Drug Tax Credit (ODTC). The credit is available for trials conducted inside the United States and for trials outside the United States when there is an insufficient U.S. testing population (an assumption that is assumed to be true for all risdiplam trials due to the rarity of the disease). The credit applies after the FDA provides an Orphan Designation for the product, in this case on January 4, 2017, and before the FDA approval of the product. The FDA has two approvals for risdiplam, an August 7, 2020[2] approval for treatment of patients 2 months or older, and an FDA approval on May 27, 2022[3] for patients between birth and 2 months of age.[4]

The tax credit is equal to 50 percent of qualifying trial expenses incurred through December 31, 2017, and 25 percent thereafter.

## U.S. Priority Review Voucher

On August 7, 2020, the date of the initial FDA approval, Roche was awarded a Rare Pediatric Disease Priority Review Voucher[5] (tracking number, PRV NDA 213535).

The Rare Pediatric Disease Priority Review Voucher (PRV) program is a U.S. FDA incentive designed to encourage development of drugs and biologics for serious or life-threatening rare diseases that primarily affect children.

The voucher allows the holder to obtain a priority review of a new drug application, when it would not otherwise qualify, something that drug companies value because it shortens the review period before a less important product can be sold. The PRV both allows earlier market entry and extends the effective period of the monopoly by several months. The PRV can be sold to third parties. In 2020 the market value of a PRV was roughly $100 million.

## Costs of Trials, per patient

The costs of the trials per patient are the most important assumptions to be made. A range of possible costs are presented, informed by two studies.

### The 2015 Battelle/PhRMA study of trial costs

The first is a Battelle/PhRMA study of trial costs, published in March 2015.

- **Study:** Biopharmaceutical Industry-Sponsored: Clinical Trials: Impact on State Economies. Prepared by Battelle Technology Partnership Practice, for Pharmaceutical Research and Manufacturers of America (PhRMA), March 2015.

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[2] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/213535Orig1s000ltr.pdf
[3] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/213535Orig1s003,%20s005ltr.pdf
[4] https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=548116; https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213535s003s005lbl.pdf
[5] https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2020/213535Orig1s000ltr.pdf

**Study period:** 2013.
Link: http://orclinicalresearch.com/wp-content/uploads/2018/12/battelle-2015-study.pdf

From the Battelle/PhRMA study:

> Because detailed state-level data on total biopharmaceutical industry-sponsored clinical trial spending do not exist, estimates were produced by combining several data sources. The number of industry sponsored clinical trials was tabulated directly from the data available in ClinicalTrials.gov. . . .
>
> Per-patient cost data was obtained from Cutting Edge Information (CEI), a clinical trials data and operations consultancy. While there is no one agreed-upon objective source for trial site cost data, the CEI survey-based data, was one of the most robust available sources providing detailed cost information for a range of clinical trial activities . . .
>
> The information obtained from CEI allowed for the development of Phase-based per-patient cost estimates for seven specific disease areas and an eighth "other" category for trials not related to one of the disease areas (Table A-1). These initial per-patient cost estimates by phase and disease area were then examined by industry representatives and adjustments were made to these figures to account for outliers among the CEI survey responses as well as to better reflect industry experience for certain disease areas. . . .

The Battelle/PhRMA study reported the estimated costs of conducting clinical research at local trials sites in the United States in its Table A-1, on page A-3.

The Battelle/PhRMA estimates are presented for Phase 0, 1, 2, 3 and 4 stages of development, and for eight disease areas. The estimates are adjusted for inflation, in 2013 USD dollars. The per patient average cost, for all phases and all diseases was $36,500. The highest cost was $69,000 for Phase 3 oncology trials. The estimate for central nervous system/Brain/Pain trials was $34,000 for Phase 1, $39,500 for Phase 2, and $40,500 for Phase 3, similar to the averages reported for all diseases.

## Battelle/PhRMA Study Table A-1. Estimated Locally-Based Per Patient Costs by Selected Disease Areas and Phase (2013 values)

| Disease Area | Phase 0 | Phase 1 | Phase 2 | Phase 3 | Phase 4 | Avg. All Phases |
|---|---|---|---|---|---|---|
| Cardiovascular/Circulatory | $9,500 | $21,500 | $25,000 | $26,000 | $9,500 | $20,500 |
| Central Nervous System/Brain/Pain | $15,000 | $34,000 | $39,500 | $40,500 | $15,000 | $36,000 |
| Diabetes/Metabolic/Nutrition | $7,000 | $16,000 | $18,500 | $19,000 | $7,000 | $17,500 |
| Hematology | $11,500 | $26,000 | $30,000 | $31,000 | $11,500 | $26,000 |
| Infectious | $6,500 | $15,000 | $17,500 | $18,000 | $6,500 | $16,500 |
| Oncology | $25,500 | $57,000 | $67,500 | $69,000 | $25,500 | $59,500 |

| | | | | | | |
|---|---|---|---|---|---|---|
| Respiratory | $11,500 | $26,000 | $30,500 | $31,000 | $11,500 | $30,000 |
| Other | $13,000 | $29,500 | $34,500 | $35,000 | $13,000 | $30,500 |
| Avg. All Diseases | $16,500 | $38,500 | $40,000 | $42,000 | $16,500 | $36,500 |
| | | | | | | |
| *Source: Battelle, based on survey data from Cutting Edge Information.* | | | | | | |

## The 2020 Moore, Heyward, Anderson and Alexander study published in BMJ Open

The second study was published in the British Medical Journal, *BMJ Open*, in 2020, and provides estimates of the costs of pivotal trials used to support the approval of new drugs, over the period 2015 to 2017.

- **Study**: Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015-2017: a cross-sectional study.
  **Study period:** 2015 to 2017
  **Citation:** Moore TJ, Heyward J, Anderson G, Alexander GC. Variation in the estimated costs of pivotal clinical benefit trials supporting the US approval of new therapeutic agents, 2015-2017: a cross-sectional study. BMJ Open. 2020 Jun 11;10(6):e038863. doi:10.1136/bmjopen-2020-038863. PMID: 32532786; PMCID: PMC7295430.
  **Link:** https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7295430/

The authors described their methodology as follows:

> We derived the estimates for each trial using the IQVIA CostPro Mid-Level Tool,/10/ a clinical trial cost estimating programme used by pharmaceutical manufacturers. Its estimates were derived from actual data from 2000 final awarded trial proposals and integrates cost information from 200 000 trial sites in 60 countries. For each trial CostPro produced a low, median and high estimate based on industry benchmark data. The programme also provided default values derived from industry benchmarks for occasional missing values, such as number of patients screened. The medical condition treated and related therapeutic areas were defined in the IQVIA CostPro Mid-Level Tool based on a subset of the International Classification of Diseases Version 9. Our preliminary investigation revealed that some trial costs are driven by trial conduct features that are not publicly available. This included the number of amendments to the trial protocol, the number of Institutional Review Boards, and how frequently sites were monitored. After consulting with experienced trialists, we computed two sets of estimates, one assuming more efficient trial conduct, and one less efficient. Our primary outcome variable was the mean (95% CI) of all six estimates, three from each efficiency assumption group. All costs were in current US dollars.
>
> *10.CRO CostPro:Training manual user guide. Plymouth Meeting, PA:IQVIA, 2019.*

Table 3 of the *BMJ Open* study presents the median and the interquartile range (IQR) for the estimates, which were reported for 12 therapeutic areas. All costs were in current (not adjusted

for inflation) US dollars. The median for all 225 trials was $41,413 per patient. The high was $100,271 for 39 oncology trials. The median for 33 trials involving central nervous system (CNS) therapeutics was $39,467, similar to the median for all trials. The 25th percentile and 75 percentile for the CNS trials were $31, 825 and $67,988, respectively.

### *BMJ Open* Study Table 3: Per patient estimated pivotal trial costs by therapeutic area (in current US dollars, for years 2015 to 2017)

| Therapeutic area | Trials | Median | (IQR) |
|---|---|---|---|
| Blood | 2 | $310,975.00 | (200 213–421 738) |
| Cardiovascular | 6 | $34,857.00 | (22 922–50 540) |
| Central nervous system | 33 | $39,467.00 | (31 825–67 988) |
| Dermatology | 21 | $24,861.00 | (19 523–30 573) |
| Endocrine/metabolism | 52 | $40,612.00 | (34 874–63 420) |
| Genitourinary | 7 | $39,640.00 | (23 179–47 100) |
| Gastrointestinal | 12 | $27,887.00 | (25 633–55 687) |
| Infectious | 31 | $37,175.00 | (31 497–49 283) |
| Musculoskeletal | 3 | $58,212.00 | (34 811–63 447) |
| Oncology | 39 | $100,271.00 | (80 880–155 714) |
| Ophthalmological | 9 | $23,893.00 | (16 990–29 894) |
| Respiratory | 10 | $53,590.00 | (39 062–59 814) |
| Overall | 225 | $41,413.00 | (29 894–75 047) |

For purposes of estimating the costs of Phase 2 or 3 trials for risdiplam, a range of possible per patient costs will be used, based upon the median and IQR values in the BMJ Open study, for central nervous system trials (CNS), with an upward adjustment of seven percent to reflect inflation, and a downward adjustment of $5,000 for the Phase 1 trials involving healthy volunteers. Each value will be rounded to a multiple of $1,000.

### Table 3: Assumptions regarding per patient costs of risdiplam trials undertaken before FDA approval

| | Median | 25th Percentile | 75th Percentile |
|---|---|---|---|
| Phase I trials with healthy volunteers | $39,000 | $30,000 | $68,000 |
| Phase 2 or 3 | $42,000 | $35,000 | $73,000 |

## Costs of Trials, by year

In the absence of information from Roche, the distribution of expenses is assumed to follow an S-curve pattern:

**Slow Start (Bottom Curve):** In the initial phases of a clinical trial (planning, protocol development, site selection, regulatory submissions, site initiation), cumulative costs and activity are relatively low.

**Rapid Acceleration (Middle Section):** As the trial moves into peak activity – primarily patient recruitment, enrollment, treatment administration, data collection, and site monitoring – the rate of spending and progress accelerates. This is often the most resource-intensive period.

**Leveling Off (Top Curve):** Towards the end of the trial, the rate of new spending slows down, and the cumulative cost curve begins to flatten as it approaches the total project budget.

An additional adjustment is made for trials that take several years to reach full enrollment.

## Estimated Costs of Each Trial

The three trials cited in the FDA Clinical Review were the SUNFISH, FIREFISH and JEWELFISH trials.

### SUNFISH trial (NCT02908685)

Title: A Study to Investigate the Safety, Tolerability, Pharmacokinetics, Pharmacodynamics and Efficacy of Risdiplam (RO7034067) in Type 2 and 3 Spinal Muscular Atrophy (SMA) Participants.
Enrolled: 231 patients.
Study start: October 19, 2016.
Primary completion date: September 6, 2019.
Registry listing: https://clinicaltrials.gov/study/NCT02908685

The SUNFISH trial (NCT02908685) for risdiplam began in **November 2016** and reached its primary completion in **October 2019**, spanning approximately **3 years**. We assume the trial activity followed the below schedule:

- **Year 1 (2016–2017):** Initial setup costs, including site selection, regulatory approvals, and initial patient recruitment.
- **Year 2 (2017–2018):** Peak activity with the majority of patient enrollment, treatment administration, and data collection.
- **Year 3 (2018–2019):** Follow-up assessments, data analysis, and reporting.

The cost allocation, reflecting the November 2016 start, is as follows:

### Table 4: Allocation of the cost of the SUNFISH trial and relevant ODTC rate, by year

| Year | Percentage of cost | Relevant ODTC rate |
|---|---|---|
| 2016 | 10% | 0% |
| 2017 | 35% | 50% |
| 2018 | 35% | 50% |
| 2019 | 20% | 25% |

## The FIREFISH trial (NCT02913482)

Title: Investigate Safety, Tolerability, PK, PD and Efficacy of Risdiplam (RO7034067) in Infants With Type1 Spinal Muscular Atrophy
Enrolled: 62 patients.
Study start: December 23, 2016.
Primary Completion: Nov 14, 2019.
Registry link: https://clinicaltrials.gov/study/NCT02913482

The cost allocation and relevant ODTC for the Firefish trial is as follows:

### Table 5: Allocation of the cost of the FIREFISH trial and relevant ODTC rate, by year

| Year | Percentage of cost | Relevant ODTC rate |
|---|---|---|
| 2017 | 30% | 50% |
| 2018 | 40% | 25% |
| 2019 | 30% | 25% |

## The JEWELFISH trial (NCT03032172)

Title: A Study of Risdiplam (RO7034067) in Adult and Pediatric Participants With Spinal Muscular Atrophy.
Enrolled: 174 patients.
Study start: March 3, 2017.
Primary Completion: February 7, 2025.
Registry link: https://clinicaltrials.gov/study/NCT03032172

The JEWELFISH trial was cited in the FDA clinical review and began before approval, but was completed in 2025, several years later. The trial was not fully enrolled until the summer of 2019, a year before FDA approval. The cost allocations over time are reflected in Table 6.

### Table 6: Allocation of the cost of the JEWELFISH trial and relevant ODTC rate, by year

| Year | Enrollment | Percentage of cost, before approval | Percentage of cost, after approval | Relevant ODTC rate (applies until approval) |
|---|---|---|---|---|
| 2017 | 24 | 2.4% | | 50% |
| 2018 | 58 | 5.4% | | 25% |
| 2019 | 150 | 13.9% | | 25% |
| 2020 | 174 | 10.8% | 5.4% | 25% |
| 2021 | 174 | | 16.2% | |
| 2022 | 174 | | 16.2% | |
| 2023 | 174 | | 15.5% | |
| 2024 | 174 | | 14.2% | |
| | | | | |
| Sum | | 32.5% | 67.5% | |

## Four additional Roche trials for risdiplam that were started before the initial approval of risdiplam but were not included in the FDA Clinical Review

There were four additional trials that have a start date before August 7, 2020, and that are included in the NIH ClinicalTrial.gov registry, but not cited in the FDA clinical review. They include three Phase 1 trials involving healthy volunteers, with a combined enrollment of 94 patients, including one trial not eligible for the Orphan Drug Tax Credit (start and completion date before the risdiplam Orphan Drug Designation), and two that were eligible for a 25 percent credit. The fourth trial is the RAINBOWFISH trial, which focused on treating non-symptomatic infants, aged from birth to six weeks.

### Table 7: Four Roche trials for risdiplam begun prior to FDA approval but excluded from the FDA clinical review for the initial approval of risdiplam

| NIH ID | Title | Enrollment | Start Date | Primary Completion |
|---|---|---|---|---|

| | | | | |
|---|---|---|---|---|
| NCT02633709 | Phase 1: A Study to Investigate the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of Risdiplam (RO7034067) Given by Mouth in Healthy Volunteers | 33 | 2016-01-07 | 2016-08-04 |
| NCT03920865 | Phase 1: A Study to Investigate the Effect of Hepatic Impairment on the Pharmacokinetics and Safety and Tolerability of a Single Oral Dose of Risdiplam Compared to Matched Healthy Participants With Normal Hepatic Function | 26 | 2019-05-16 | 2020-01-02 |
| NCT03988907 | Phase 1: A Drug-drug Interaction Study With Risdiplam Multiple Dose and Midazolam in Healthy Participants | 35 | 2019-06-18 | 2019-09-29 |
| NCT03779334 | Phase 2: A Study of Risdiplam in Infants With Genetically Diagnosed and Presymptomatic Spinal Muscular Atrophy (RAINBOWFISH) | 26 | 2019-08-07 | 2023-02-20 |

### Table 8: Allocation of the cost of three pre-approval Phase 1 trials and relevant ODTC rate, by year

| NIH ID | Enrollment | Year of trial | Orphan Drug tax Credit |
|---|---|---|---|
| NCT02633709 | 33 | 2016 | 0% |
| NCT03920865 | 26 | 2019 | 25% |
| NCT03988907 | 35 | 2019 | 25% |

## RAINBOWFISH (NCT03779334) trial costs

Title: A global study of oral risdiplam in pre-symptomatic participants with spinal muscular atrophy (SMA).
Enrollment: 26 patients.
Start date: August 7, 2019.
Primary Completion: February 20, 2023.
FDA approval for the new indication: May 27, 2022.
Registry link: https://clinicaltrials.gov/study/NCT03779334

As of July, 1, 2021, 18 infants were enrolled in the RAINBOWFISH trial, and only 7 had been enrolled for 12 months.[6] As of February 2022, worldwide recruitment was complete.[7] The cost allocations reflect a phasing in of patient enrollment.

The primary completion date was more than 8 months after the US FDA approval for the expanded population of patients between birth and 2 months.

The trial, from its start on August 7, 2019 to primary completion on February 20, 2022, lasted 1,293 days. Of these, 1,024 days were on or prior to FDA approval and 269 days were after.

The Orphan Drug Tax Credit was equal to 25 percent in 2019 through May 27, 2022 and zero thereafter.

### Table 9: Allocation of the cost of the RAINBOWFISH trial and relevant ODTC rate, by year

| Year | Enrollment | Percentage of cost, before approval | Percentage of cost, after approval | Relevant ODTC rate (applies until approval) |
|---|---|---|---|---|
| 2019 | 7 | 8.7% | | 25% |
| 2020 | 18 | 22.4% | | 25% |
| 2021 | 22 | 27.3% | | 25% |
| 2022 | 26 | 12.9% | 19.4% | 25% |
| 2023 | 26 | | 9.3% | 0 |
| | | | | |
| Sum | | 71.3% | 28.7% | |

[6] RAINBOWFISH: Preliminary efficacy and safety data in risdiplam-treated infants with presymptomatic spinal muscular atrophy (SMA)RS Finkel,1* MA Farrar,2 D Vlodavets,3 E Zanoteli,4 M Al-Muhaizea,5 L Nelson,6 A Prufer,7 L Servais,8–10 Y Wang,11 C Fisher,12 M Gerber,13 K Gorni,14H Kletzl,15 L Palfreeman,12 RS Scalco,16 E Bertini,17 on behalf of the RAINBOWFISH Study Group. https://medically.roche.com/global/en/medical-material/WMS-2022-poster-richard-RAINBOWFISH-preliminary-efficacy-and-safety-data-in-risdiplam-pdf.html

[7] Apr 07 / Roche and Genentech. RAINBOWFISH: A study of risdiplam▼ in infants with presymptomatic spinal muscular atrophy (SMA). Neuroscience Spinal Muscular Atrophy AAN-2022. https://medically.gene.com/global/en/unrestricted/neuroscience/AAN-2022/aan-2022-poster-richard-rainbowfish-a-study-of-risdipla.html

## Estimated Cost of Trials, based on *BMJ Open* median cost for CNS trials

### Table 10: Allocation of the cost of trials, by year

| | Sunfish | Firefish | Jewelfish | Rainbow-fish | Phase 1, NCT 02633709 | Phase 1, NCT 03920865 | Phase 1, NCT 03988907 |
|---|---|---|---|---|---|---|---|
| Enrollment | 232 | 62 | 174 | 26 | 33 | 26 | 35 |
| | | | | | | | |
| 2016 | 10.0% | | | | 100.0% | | |
| 2017 | 35.0% | 30.0% | 2.4% | | | | |
| 2018 | 35.0% | 40.0% | 5.4% | | | | |
| 2019 | 20.0% | 30.0% | 13.9% | 8.7% | | 100.0% | 100.0% |
| 2020 | | | 10.8% | 22.4% | | | |
| 2021 | | | | 27.3% | | | |
| 2022 | | | | 12.9% | | | |

### Table 11: Cost of each trial, prior to FDA marketing approval, and prior to Orphan Drug Tax Credit: Scenarios based on *BMJ Open* median cost for CNS trials

| | Sunfish | Firefish | Jewelfish | Rainbow-fish | Phase 1, NCT 02633709 | Phase 1, NCT 03920865 | Phase 1, NCT 03988907 |
|---|---|---|---|---|---|---|---|
| Enrollment | 232 | 62 | 174 | 26 | 33 | 26 | 35 |
| Per patient cost | $42,000 | $42,000 | $42,000 | $42,000 | $39,000 | $39,000 | $39,000 |
| 2016 | $974,400 | | | | $1,287,000 | | |
| 2017 | $3,410,400 | $781,200 | $175,392 | | | | |
| 2018 | $3,410,400 | $1,041,600 | $394,632 | | | | |
| 2019 | $1,948,800 | $781,200 | $1,015,812 | $95,004 | | $1,014,000 | $1,365,000 |
| 2020 | | | $789,264 | $244,608 | | | |
| 2021 | | | | $298,116 | | | |
| 2022 | | | | $140,868 | | | |
| All years before FDA approval | $9,744,000 | $2,604,000 | $2,375,100 | $778,596 | $1,287,000 | $1,014,000 | $1,365,000 |

**Table 12: Orphan Drug Tax Credit: Scenarios based on *BMJ Open* median cost for CNS trials**

| | Sunfish | Firefish | Jewelfish | Rainbow-fish | Phase 1, NCT 02633709 | Phase 1, NCT 03920865 | Phase 1, NCT 03988907 |
|---|---|---|---|---|---|---|---|
| Enrollment | 232 | 62 | 174 | 26 | 33 | 26 | 35 |
| Per patient cost | $42,000 | $42,000 | $42,000 | $42,000 | $39,000 | $39,000 | $39,000 |
| 2016 | | | | | | | |
| 2017 | $243,600 | | | | $321,750 | | |
| 2018 | $852,600 | $195,300 | $43,848 | | | | |
| 2019 | $852,600 | $260,400 | $98,658 | | | | |
| 2020 | $487,200 | $195,300 | $253,953 | $23,751 | | $253,500 | $341,250 |
| 2021 | | | $197,316 | $61,152 | | | |
| 2022 | | | | $74,529 | | | |
| | | | | | | | |
| All years before FDA approval | $2,436,000 | $651,000 | $593,775 | $159,432 | $321,750 | $253,500 | $341,250 |

Cost of all seven trials with start dates before approval, through FDA approval (initial approval or expanded indication for RAINBOWFISH): Scenario based *BMJ Open* median cost for CNS trials

- Cost of trials through FDA approval, before Orphan Drug Tax Credit: $19,167,696.
- Orphan Drug Tax Credit, assuming all locations are eligible for the credit: $4,756,707.
- Cost of trials through FDA approval, net of Orphan Drug Tax Credit: $14,410,989.

## Sensitivity Analysis

### Scenario based upon on *BMJ Open* 25th percentile cost for CNS trials

- Cost of trials through FDA approval, before Orphan Drug Tax Credit: $15,738,080.
- Orphan Drug Tax Credit, assuming all locations are eligible for the credit: $3,905,173.
- Cost of trials through FDA approval, net of Orphan Drug Tax Credit: $11,832,908.

### Scenario based upon on *BMJ Open* 75th percentile cost for CNS trials

- Cost of trials through FDA approval, before Orphan Drug Tax Credit: $33,335,424.
- Orphan Drug Tax Credit, assuming all locations are eligible for the credit: $8,272,646.
- Cost of trials through FDA approval, net of Orphan Drug Tax Credit: $25,062,779.

## Summary and Concluding Comments

This is an estimate of trial costs for risdiplam that relies on third party estimates of the per-patient costs of trials of similar drugs. Roche controls access to the actual outlays on the trials, and unfortunately has declined to share that information. One topic that most published studies on trial costs do not address is the extent to which portions of trial costs are reimbursed by public or private insurance and reimbursement programs, or the extent to which the US Orphan Drug Tax Credit has been used as a subsidy. Policy makers should consider mandating disclosure of trial costs and subsidies as a condition of market entry or reimbursements.

The estimates presented in this research note are based upon:

1. **Enrollment data from the NIH ClinicalTrials.Gov trial registry.** There were 588 patients enrolled in seven trials that had a start date before the first FDA approval for risdiplam. Five of the trials, with 388 patients enrolled, had a primary completion date before FDA approval. For the two trials that began before FDA approval and were completed after FDA approval that had 200 patients enrolled, the pre-approval costs were included, and the post approval costs were not.
2. **Assumptions regarding the per patient trial costs.** The assumptions regarding per patient trial costs are based primarily on a study published in *BMJ Open*, which modeled the costs of pivotal trials that the FDA relied upon for new therapeutic agents approved by the FDA from 2015 to 2017. The *BMJ Open* study included data from 225 trials, including 33 trials (involving 14 drugs) for the treatment of the Central Nervous System (CNS).
3. **Allocation of the trial costs over the period from the trial start to the primary completion dates.** The allocation over time followed a slight S-curve allocation.

For the base case, using the *BMJ Open* median per patient cost for CNS trials, the cost of risdiplam clinical trials through FDA approval was $19.2 million, before considering the Orphan Drug Tax Credit, and $14.4 million after the credit.

In the sensitivity analysis, the total trial costs (before the Orphan Drug Tax Credit) ranged from $15.7 million (for the 25th percentile case), to $33.3 million (for the 75th percentile case). The Orphan Drug Tax Credit, if applied to all trial costs, lowered the range of net cost to $11.8 million to $25.1 million.

Note that the FDA priority review voucher (PRV), awarded on August 7, 2020, was worth approximately $100 million that year, more than five times the estimated Roche outlays on trials at that date, before taking into account the US Orphan Drug Tax Credit subsidy. If the actual trial

cost were five times higher than the base case estimate, Roche would have recovered all of its trial costs the day of FDA approval, when taking into account the value of the PRV.

For additional context on the role of a charity, the SMA Foundation (SMAF), in supporting pre-clinical development of risdiplam, see: Arianna Schouten, Timeline: Development of Risdiplam, KEI Research Note 2025:1, April 7, 2025.  LInk: https://www.keionline.org/timeline-development-of-risdiplam