PROPOSAL FOR THE ADDITION OF RISDIPLAM TO THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF CHILDREN AND ADULTS WITH SPINAL MUSCULAR ATROPHY

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Section 1: Summary statement of the proposal

This submission is made in support of the inclusion of risdiplam as a medicine on the WHO Model List of Essential Medicines (EML) and the Essential Medicines List for Children (EMLc), for the treatment of spinal muscular atrophy (SMA) in both pediatric and adult patients.

SMA is a debilitating condition, characterized by the degeneration of lower motor neurons, skeletal muscle atrophy, and progressive generalized weakness usually leading to early death. As of 2024, risdiplam (marketed as Evrysdi by Hoffmann-La Roche) is among three disease-modifying treatments available to treat SMA, alongside nusinersen (marketed as Spinraza by Biogen), and onasemnogene abeparvovec (marketed as Zolgensma by Novartis), the latter being a gene therapy. Despite the effectiveness of all marketed SMA treatments, access worldwide remains severely limited.

Risdiplam offers several advantages over other SMA treatments, including the convenience of not requiring refrigeration when in powder form, and its ease of administration, as it is taken orally once daily after a meal using a provided oral syringe. Unlike other therapies, which require invasive procedures or specialized equipment, risdiplam's oral administration is especially suited for resource-limited settings. Furthermore, risdiplam holds potential for a low-cost generic version due to its relatively inexpensive manufacturing process, which makes it a compelling candidate for inclusion in the EML.

The recent RAINBOWFISH study, a pivotal trial in infants with genetically confirmed presymptomatic SMA, further underscores the transformative impact of early risdiplam treatment. The study revealed that most infants treated with risdiplam before the onset of SMA symptoms achieved critical motor milestones, such as sitting, standing, and walking, within normal developmental windows. By 12 months, 80% of infants in the primary efficacy group were able to sit without support—a stark contrast to the natural progression of untreated SMA, where no such milestones would typically be reached. After two years, all infants with 2 copies of the SMN2 gene could sit independently, and many had progressed to standing and walking. These results demonstrate that risdiplam can prevent or significantly mitigate the severe disabilities associated with SMA, offering affected children the potential for a normal developmental trajectory and drastically improving their quality of life.

This application differs from the November 2022 risdiplam application in several key ways. First, this application emphasizes the impact of SMA on patients and their families, illustrating the significant improvements in the quality of life that risdiplam can offer (Section 6). Second, the review incorporates evidence of comparative efficacy and comparative safety, along with the pivotal clinical trials (Section 8). Thirdly, and most critically, this submission highlights the critical importance of presymptomatic treatment to minimize the level of disability and mortality related to SMA, underscored by the latest results from the October 2024 RAINBOWFISH study (Section 8).

We strongly recommend the inclusion of risdiplam on the core EML. Additionally, we recommend that the World Health Organization (WHO) consider a new category for essential yet expensive medicines alongside the recommendation for the government to take measures to obtain an affordable version of the medicine.

Section 2: Consultation with WHO technical department

We understand that this submission will be shared with the relevant WHO technical department(s) ahead of the expert committee.

Section 3: Other organization(s) consulted and/or supporting the submission

In relation to the application, persons and organizations have been consulted: Kacper Ruciński (SMA Foundation Poland), SMA Europe, WeCareJourney.org, and Familias AME Argentina.

Section 4: Key information summary for the proposed medicine

INN	Risdiplam
ATC code	M09AX10
Indication	Treatment of Spinal Muscular Atrophy
ICD-11 code	8B61 Spinal Muscular Atrophy

Dosage form	**Strength**	**EML**	**EMLc**
Powder for oral solution	0.75 mg/ml	Yes	Yes
Table (dispersible)	5 mg	Yes	Yes

A systematic assessment of the age-appropriateness of the dosage forms and strengths of risdiplam for children using the pediatric quality target product profile assessment tool is attached in Annex A.

Introduction of New Tablet Form

In addition to the existing oral solution, risdiplam is expected to be available in a new bioequivalent tablet form, pending FDA approval (anticipated early 2025). The single dispersible 5mg tablet offers several advantages, including a 2-year shelf life, stability and storage at room temperature, and no requirements for reconstitution prior to administration (1). The simplified storage enhances accessibility, particularly in low- and middle-income country (LMIC) settings.

In the event that the FDA approves the tablet formulation before the next expert committee, we will provide an update on the regulatory status and supporting data. If approval is not granted in time, a separate application for the new tablet formulation will be submitted for consideration in 2027.

Section 5: Listing as an individual medicine

This proposal relates to the listing of an individual medicine.

Why is risdiplam preferred over alternative SMA treatments?

Besides risdiplam, there are two other existing treatments on the market, onasemnogene abeparvovec (Zolgensma) and nusinersen (Spinraza). Risdiplam stands out among existing treatments for several reasons.

Nusinersen (Spinraza) is administered via intrathecal injection and is indicated for the treatment of pediatric and adult SMA patients. Due to the intrathecal injection, it is however not suitable for patients with spinal deformities or previous scoliosis surgery and it typically requires a proper hospital setting. Onasemnogene abeparvovec (Zolgensma), on the other hand, is an AAV9 gene replacement therapy used to treat children less than 2 years old (or less than 13.5kg) and requires handling and administration in a hospital setting with adequate containment level, which can pose challenges in LMIC contexts where hospital access, resources, and infrastructure may be limited.

In contrast, risdiplam is an oral medication that is administered at home, providing significant ease of use and immediate applicability following diagnosis. This home-based administration model is particularly advantageous for LMICs, as it reduces the need for specialized hospital

visits and supports broader accessibility for patients. Typically, patients treated with risdiplam in HIC are seen by their treating physicians once every six months for their routine standard-of-care checks.

In terms of storage and feasibility for generic availability, risdiplam's oral formulation is less complex than intrathecal injections or gene therapies. It does not need refrigeration until the powder is reconstituted and even after reconstitution can be kept at room temperature for up to five days. The active ingredient is a small molecule that is simple to produce. This simplicity enhances its potential for broader distribution and cost reduction over time, making it more feasible for generic manufacturing and subsequent price decreases.

Furthermore, risdiplam has a very good safety profile and does not have the specific safety concerns associated with the other treatments. For instance, onasemnogene abeparvovec carries an FDA black box warning due to its potential for causing serious liver damage (2). Additionally, onasemnogene abeparvovec requires careful patient selection, specialized hospital settings, and delayed administration in those with elevated anti-AAV9 antibody titers, concomitant infections, or other underlying conditions including liver function abnormalities. This treatment also needs prolonged corticosteroid treatments to dampen the immune reaction against the AAV9 vector, which carry additional safety risks and burdens (3). It also requires class I MOGM contention and preparation in a specialized hospital setting.

Nusinersen involves intrathecal administration, which is associated with its own safety concerns, especially in very young patients with spinal deformities. The repeated lumbar punctures necessary for ongoing treatment carry risks, such as infection. In some cases, depending on the patient’s needs, anesthesia or sedation may be required to perform these lumbar punctures, introducing further risks. Patients need these procedures three times a year, which increases the cumulative risk.

The European Medicines Agency (EMA) highlights that risdiplam fulfills an unmet treatment need (4), particularly for patients under 2 months of age with severe phenotypes where immediate treatment is critical to prevent irreversible damage. The oral administration of risdiplam allows for prompt treatment initiation, which is essential for this vulnerable patient group. Moreover, risdiplam offers a prophylactic option for treating pre-symptomatic babies, including siblings of affected children identified prenatally or at birth, thereby potentially halting disease progression before symptoms manifest. In this regard, the speed of application of risdiplam is crucial, as it directly translates into the maximum developmental stages that can be achieved. In severe cases, even a delay of a couple of days can result in significant losses, such as the ability to swallow. The early intervention of risdiplam can thus make a critical difference in the development outcomes of infants with SMA.

In conclusion, the proposal to list risdiplam as an individual medicine is strongly supported by its efficacy, ease of use, applicability in LMIC contexts, straightforward storage requirements, feasibility for generic production, and safety profile.

Section 6: Information supporting the public health relevance

Proposed indication(s) and target population(s)

Risdiplam is approved in over 100 countries for the treatment of 5q spinal muscular atrophy (SMA) in patients from birth or from 2 months of age. Currently, no alternative medicines are listed on the Model Lists for the treatment of SMA.

SMA is an autosomal recessive neurodegenerative disease characterized by the degeneration of lower motor neurons in the spinal cord, with subsequent skeletal muscle atrophy and progressive generalized weakness usually leading to early death. In the absence of treatment, and despite being classified as a rare disease, SMA is the most common monogenic cause of death among infants (5).

SMA is linked to a homozygous mutation in the survival motor neuron 1 (*SMN1*) gene (6), which codes for survival motor neuron protein (SMN), a protein critical for motor neuron survival. All SMA patients also have at least one copy of the survival motor neuron 2 (*SMN2*) gene, which produces a small amount of *SMN* protein, which is critical for motor neuron survival. The number of copies of the *SMN2* gene correlates with disease severity, with lower *SMN2* copy numbers associated with an earlier onset and a more severe phenotype.

There has been a historical division of SMA into types (0 to 4) based on the age of onset and the maximum motor function achieved in untreated patients. However, this categorization does not capture the changes in disease course due to treatment with existing SMA therapies (7). The following table provides an overview of the historical classification of SMA.

Table 1: Historical Classification of SMA (7)

SMA type	Typical age at presentation (range)	Maximal motor function achieved with supportive care	Feeding and communication	Pulmonary function	Survival[a] with supportive care
0	Fetal	Nil	Nil	Very poor	Days–weeks
1	3 months (0–6 months)	No sitting or rolling	Poor, requires support	Poor, requires support	Months (median ~10 months)
2	12 months (7–18 months)	Sits, no walking	Variably affected	Reduced, often needs support	Years (median >20 years)
3	3 years (1.5–10 years)	Walks (limited)	Normal	No symptoms, mild reduction possible	Normal
4	>18 years	Walks (normal)	Normal	Normal	Normal

SMA, spinal muscular atrophy. [a]Survival includes 'event-free survival' (ventilation support for <16 h/day for ≥14 days).

In summary, the target population for risdiplam is patients with 5q spinal muscular atrophy (SMA) who present with clinical symptoms of SMA types 1, 2, or 3 regardless of the number of *SMN2* gene copies, or who possess between one and four *SMN2* gene copies regardless of symptom severity. It is approved for use across all age groups.

Epidemiological data

Prevalence and Incidence

SMA has an estimated incidence of 1 in 10,000 live births (8). This is an approximate incidence, with variations seen in many populations. For example, in Middle Eastern and African Countries, the incidence is estimated to be 20 times higher (9–11). Additionally in a population of Egyptian Karaites in Israel, SMA Type 1 was found in 1 in 400 infants (12). A systematic review, accounting for varying populations and regions of focus, concluded that SMA incidence ranged from 5.1 to 16.6 cases per 100,000 live births (13). The carrier frequency of the mutations in *SMN1* ranges from 2-3% in the general population (9).

Approximately 60% of SMA cases manifest in infancy, resulting in the most severe phenotype and often leading to fatal outcomes within the first two years of life. An additional 20–27% of patients achieve the ability to sit independently, though not to walk, prior to symptom onset. In about 12–20% of cases, the disease presents after the patient has become ambulatory (14,15).

In a Global SMA Patient Registry representing 29 countries, the sex distribution of SMA was equal (7). The prevalence of SMA is reported at 1-2 per 100,000 persons, with significant variability between countries. Prevalence is impacted by the drastically shorter life expectancy in the infantile-onset SMA (seen in ~50-60% of affected patients) (8).

These estimates are challenging due to the outdated studies that rely on clinical rather than genetic diagnosis, and the small cohorts of patients that are oftentimes limited to European populations. Despite this, it is clear that the incidence, prevalence, and severity of SMA point towards a pervasive health problem.

Mortality

SMA is globally the second most common fatal autosomal recessive disorder (16). A large US database study found that mortality was twice as high among SMA cases compared to non-SMA controls (5). This higher mortality rate was observed among all age groups, as well as with patients with different SMA subtypes. In contrast to prior smaller-scale studies, this recent study observed a statistically significant increase in mortality among SMA patients compared with controls.

While mortality across SMA is twice as high compared to non-SMA control, the mortality rate for SMA patients also depends on when SMA symptoms manifest. For instance, the most frequent subtype, SMA 1, in the absence of treatment is characterized by >90% mortality by 2 years of age (7).

Impact of SMA

SMA impacts individuals differently depending on the severity of their condition but is universally marked by progressive muscle weakness and loss of function. Without treatment, this deterioration progresses over time, leading to reduced stamina, increased fatigue, and pain. Everyday tasks become challenging for those with SMA. Activities that most people take for granted, like swallowing, breathing, or moving their limbs, become challenging or impossible for those living with SMA.

The condition usually affects essential physiological functions, such as swallowing and respiration; nearly all early-onset patients require mechanical ventilation and many require parenteral nutrition. Additionally, respiratory insufficiency increases vulnerability to infections, leading to extended stays in intensive care, sometimes for months. Common orthopedic complications include joint contractures and scoliosis, which significantly impair mobility, and body positioning and often require surgical intervention. Mobility aids like motorized wheelchairs, hoists, and toileting devices are crucial in daily care, while structural home adaptations or relocations are often necessary to ensure wheelchair accessibility; alternatively, families may decide to move homes.

SMA imposes a significant physical, psychological, social, and financial burden on both patients and their families. In the absence of access to treatment, these challenges are aggravated by the awareness of an impending death as well as a deep sense of injustice when life-saving

treatments are beyond reach. In this context, a 2017 survey of over 800 European families affected by SMA revealed that stabilization of the disease progression alone would already represent a meaningful therapeutic outcome (17).

Risdiplam offers the potential to slow, halt, or, in many cases, reverse disease progression, preserving motor function and thus positively transforming the physical health and psychosocial well-being of patients over the long term. Beyond its therapeutic effects, risdiplam's administration at home reduces the need for frequent hospital visits and specialized care, easing both the physical and emotional toll on patients and families and enhancing their quality of life.

Risdiplam: an affordable possibility

There are currently no SMA treatments included in the EML or EMLc. Of the three existing treatments for SMA, besides the combination of its ease of use, applicability in LMIC contexts, straightforward storage requirements, risdiplam also offers the best chance to obtain a low-cost generic version in the near future. Until the arrival of these new SMA treatments, only supportive care has been available and no treatments targeted the underlying cause of SMA.

KEI reviewed prices in numerous countries, revealing a range from USD $108 to $225 per mg. In the USA, for instance, the daily price of risdiplam is USD $1,125. Although these prices may not reflect potential non-transparent discounts and rebates available to some payers, they underscore the significant cost barrier to accessing risdiplam.

In one upper-middle income country (China), where a significantly lower price for risdiplam was negotiated, patients or their families are traveling from other countries to receive a six-month supply at approximately USD $8.82 per mg or $43 a day —only 3.8% of the US daily price. Despite this localized price reduction, risdiplam is not affordable and remains out of reach for many families.

Risdiplam is distinct from the other two SMA treatments due to its potential for affordable generic production. As a small molecule drug, its manufacturing process, while not the simplest, requires relatively low quantities of API. Compared to Spinraza and Zolgensma, risdiplam's formulation and distribution are considerably more straightforward. It can be shipped in powder form and reconstituted into a solution by a local pharmacy or at home, making it accessible for home administration.

KEI, a registered not-for-profit organization, aims to further enhance access to risdiplam by partnering with a firm to manufacture the drug under Good Manufacturing Practice (GMP) conditions, conduct bioequivalence studies, and establish mechanisms to distribute risdiplam globally. This initiative is part of KEI's ongoing commitment to making essential medications affordable and accessible to all who need them.

Section 7: Treatment Details

Dosage regimen and duration of treatment

Risdiplam is an oral solution that is preferably reconstituted by a healthcare professional prior to being dispensed. It is taken orally once daily after a meal, using the reusable oral syringe provided, at approximately the same time each day. The dosage of risdiplam for SMA patients is determined by their age and their body weight.

Table 2: Dosing Regimen by Age and Body Weight

Dosage form	**Strength**	**EML**	**EMLc**
Powder for oral solution			
< 2 months	0.15 mg/kg	Yes	Yes
2 months to < 2 years of age	0.20 mg/kg	Yes	Yes
≥ 2 years of age (< 20 kg)	0.25 mg/kg	Yes	Yes
≥ 2 years of age (≥ 20 kg)	5 mg	Yes	Yes

Risdiplam is intended for long-term indefinite treatment, contingent upon the patient's clinical response, and should be administered continuously as prescribed. Regular care and monitoring are needed by healthcare providers, not only to track progress with risdiplam but also to look after other complications associated with SMA, such as pulmonary services and care, gastrointestinal and nutritional care, and orthopedic care. In LMIC contexts, patients are often referred to national hospitals with a pediatric neurologist who will oversee their care.

Requirements to ensure appropriate use of the medicine

Patient Eligibility Criteria

Risdiplam is widely approved for patients with a genetically confirmed diagnosis of 5q SMA. Specifically, risdiplam is recommended for treatment of patients with a clinical diagnosis of SMA types 1, 2 or 3 or with pre-symptomatic SMA and with 1 to 4 copies of the *SMN2* gene.

Following recent study results (see RAINBOWFISH in Section 8) risdiplam has been further approved by several regulatory authorities, including by the FDA and EMA, for use in patients under 2 months of age. The option to use risdiplam below the age of 2 months allows for the

beginning of patients' treatment immediately after diagnosis or even before the onset of symptoms in presymptomatic patients, thus preventing the onset of symptoms and tackling the progression of the diseases.

Diagnostic and/or monitoring test requirements

The testing for SMA varies by country context. In around 30 countries, SMA is tested at birth through routine newborn screening programs. This screening identifies a homozygous mutation in the *SMN1* gene.

Where newborn screening is not available, the diagnosis of SMA should be suspected for any infant with unexplained weakness or hypotonia. Additional clues suggesting the diagnosis in infants, children, or adults include a history of motor difficulties, loss of motor skills, proximal muscle weakness, hyporeflexia or areflexia, tongue fasciculations, and signs of lower motor neuron disease on examination (18). However, SMA confirmation through genetic testing is required as part of the prescription of risdiplam to patients - except when it is prescribed as a prophylactic treatment.

Genetic testing for SMA is performed in a genetic lab using a blood sample. A range of methods can be used, such as qPCR, ddPCR, PCR-HRM, MLPA, and various SMA testing kits are available commercially. The cost of sample testing can range from 3–5 USD in newborn screening programs to USD 50–500 for individual tests in diagnostic labs. In LMIC contexts, the samples are sent to neighboring countries with the requisite genetic laboratory to run the genetic test.

Around 95% of SMA patients are detected in mass screening programs that utilize fast, low-cost PCR tests. Individual genetic diagnostics of symptomatic patients detect 100% of SMA cases when such methods as MLPA, ddPCR or gene sequencing are used.

Regular multidisciplinary care is needed for patients with SMA (e.g., physiotherapy, orthopedic management, respiratory management, gastroenterologist support). When treated with risdiplam, patients require clinical evaluations to assess the therapeutic effect and motor function improvements along with safety monitoring.

Treatment Administration Requirements and Setting

Risdiplam is administered orally in the form of a liquid solution.[1] To ensure proper dosing, both age and weight must be considered. The risdiplam powder is dissolved into water, usually by a pharmacist, and the solution must be prepared and accurately measured using the provided oral syringes. The dosing of risdiplam should be after a meal to enhance the drug absorption.

Risdiplam does not need to be administered in a hospital. It can be administered in various settings, including at home. This flexibility in administration enhances the accessibility and the

[1] Risdiplam can also be given through a gastrostomy tube or a nasogastric tube.

convenience for patients and caregivers. For at-home administration, caregivers require some initial training to prepare and administer the medication.

Risdiplam oral solution, once reconstituted, should be stored in a refrigerator at 2°C to 8°C and protected from light. It can be kept refrigerated for up to 64 days. If refrigeration is not available, the reconstituted risdiplam solution is stable at room temperatures, up to 40°C, for a combined total of 5 days. The powder form (unreconstituted medicine) can be stored at room temperature (15°C to 25°C) away from light for up to 12 months, provided it is kept in its carton.

Healthcare professionals, typically pediatric neurologists, with expertise in managing SMA should be responsible for prescribing risdiplam. These specialists are best equipped to diagnose SMA accurately, assess disease severity, and monitor the treatment response. Notably, these specialists are sparse in lower-income settings, where expertise in SMA is scarce and limited to large urban centers which may be too far for some patients to receive a timely and accurate diagnosis and management.

Section 8: Review of evidence for benefits and harms

RAINBOWFISH: Primary efficacy and safety data in risdiplam-treated in infants with presymptomatic spinal muscular atrophy (SMA) (19,20)

The RAINBOWFISH results are long-awaited and were anticipated by the previous expert committee. Due to their importance, they have been placed at the forefront of this section. Following a description of the study, we highlight the importance of these results.

Study Design

RAINBOWFISH is a multicenter, open-label, single-arm study for infants up to six weeks old with genetically confirmed 5q-autosomal recessive SMA, without clinical signs of SMA at baseline. The primary endpoint of the study is the proportion of infants sitting without support for at least five seconds after month 12. The secondary endpoints included the development of clinically manifested SMA, survival and permanent ventilation, achievement of motor milestones, motor function, growth measures, nutritional status, and additional clinical parameters.

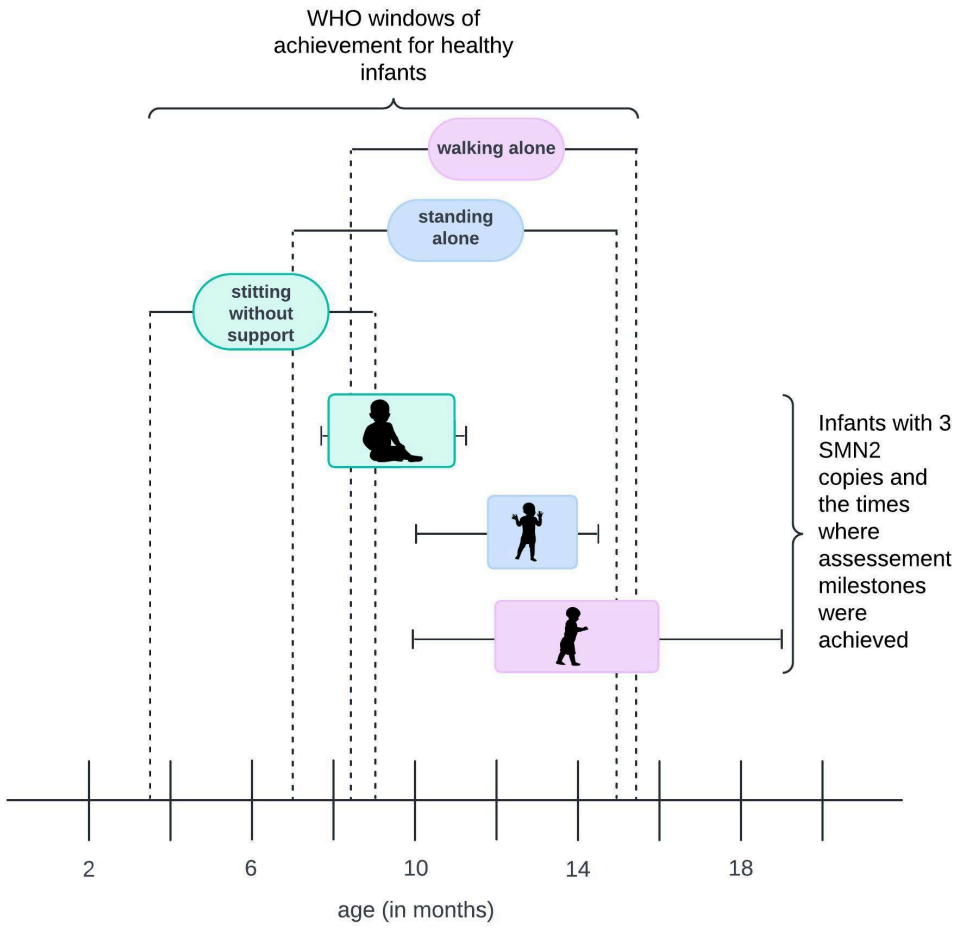
Results

The two-year data was presented in October 2024, 26 infants were enrolled, with a median age of 25 days at the first dose of which 62% were female and 38% were male. These infants have between 2 and 4 copies of SMN2 (2 copies n=8, 3 copies n=13, and ≥4 copies n=5). A total of 25 of the infants completed one year of treatment and 24 completed two years of treatment.

- **Primary endpoint:** At month 12, 4 out of 5 (80%) of infants in the primary efficacy population (those with 2 SMN2 copies) could sit without support for at least five seconds. This significantly exceeds the expected performance of 5% based on the natural history of untreated Type 1 SMA.

- **Secondary endpoints:** By month 12, 22 out of 23 (96%) of infants achieved motor milestones, including sitting without support. By year two, all infants with 2 SMN2 copies could sit unaided, and 3 of 5 (60%) could stand alone while 2 of 5 (40%) were able to walk independently. Infants with ≥3 SMN2 copies achieved 100% of the motor milestones, such as standing, sitting, and walking within the WHO windows of typical development. As illustrated below (Image 1), along with reaching all motor milestones, most infants with 3 SMN2 copies achieved age-appropriate motor milestones within the WHO windows of typical development. Additionally, all infants retained their ability to swallow and feed orally throughout the study, and cognitive development (assessed by Bayley Scales of Infants and Toddler Development) was within normal ranges.

Image 1: Infants with 3 SMN2 copies reach motor milestone developments within WHO windows of development



Safety

There were no deaths due to treatment and no adverse events that led to withdrawal or treatment discontinuation. The majority of adverse events were not considered treatment related, but rather reflective of the age of the infants. The most common adverse events were teething, COVID-19, pyrexia, gastroenteritis, eczema, and constipation. These adverse events were also consistent with previous studies of risdiplam.

Importance of presymptomatic (RAINBOWFISH) study results

These early results indicate the value in early treatment with risdiplam before SMA symptoms appear. Patients with SMA have motor neuron degeneration before the onset of symptoms. Once symptoms manifest, risdiplam cannot reverse them but can only help to prevent further progression. Early intervention with risdiplam, therefore, offers the best opportunity to counteract the effects of the disease, providing infants with pre-symptomatic SMA a significantly better chance of living with minimal disease progression and a better quality of life. More concretely, infants who received prophylactic risdiplam have the chance to live without the disabilities associated with SMA, an unparalleled advancement.

Presymptomatic study results are especially important in countries where newborn screening for SMA is not available. In these settings, siblings of affected children identified prenatally at birth or as presymptomatic can be treated immediately in the first few days of life, at a presymptomatic stage. This is advantageous in countries with higher rates of consanguinity and higher birth rates, where preimplantation genetic diagnosis is not feasible or available.

Treating presymptomatic children and preventing the onset of SMA symptoms has a highly positive impact on reducing the use of healthcare resources and the economic burden associated with the disease. Early treatment drastically reduces the need for medical resources to manage the complications of SMA, thereby significantly lowering healthcare costs and improving the allocation of healthcare resources, which is even more critical for LMIC. Thus, presymptomatic treatment not only benefits the patients and their families but also alleviates the overall strain on healthcare systems.

Clinical trials

Clinical trial information from the two main clinical components is briefly summarized below.

FIREFISH was an open-label, two-part study that evaluated the efficacy and safety of risdiplam in a total of 62 infants with Type 1 SMA (onset between 28 days and 3 months). At Month 12,

32.8% of patients achieved the primary endpoint of sitting without support for at least 5 seconds. By Month 24, 60.3% of patients achieved this milestone. Additionally, 87.1% of patients survived without permanent ventilation at Month 12, and 83.8% at Month 24. Typically, infants with Type 1 SMA are never able to sit independently and do not survive beyond the age of two years without permanent ventilation.

Table 3: FIREFISH summary

Population	Study Design	Primary Endpoint	Results (Primary Endpoint)	Secondary Endpoints	Results (Secondary Endpoints)
Infantile-Onset SMA (Type 1)	Open-label, 2-part study (n=62, 58 received recommended dose)	Proportion of patients sitting without support for ≥5 seconds at 12 months	32.8% (Month 12), 60.3% (Month 24)	Survival without permanent ventilation (defined as ≥16 hours/day ventilation for >21 days)	87.1% alive without permanent ventilation at Month 12, 83.8% at Month 24; at Month 24, 28% (16/58) achieved a standing measure

SUNFISH was a randomized, double-blind, placebo-controlled study involving 180 patients with Type 2 or Type 3 SMA. The primary endpoint was a change from baseline in the Motor Function Measure 32 (MFM32) score at Month 12. Patients treated (n=120) with risdiplam showed a 1.36-point improvement in MFM32, compared to a -0.19 change in the placebo group (n=60). Additionally, 38.3% of risdiplam-treated patients had a 3-point or greater improvement in motor function, compared to 23.7% in the placebo group.

Table 4: SUNFISH summary

Population	Study Design	Primary Endpoint	Results (Primary Endpoint)	Secondary Endpoints	Results (Secondary Endpoints)

Type 2 and Type 3	Randomized, double-blind, placebo-controlled study (n=180)	Change from baseline to Month 12 in MFM32 score	1.36-point improvement in MFM32 score for risdiplam versus -0.19 for placebo (p=0.0156)	Proportion of patients with a 3-point improvement in MFM32 Change in Revised Upper Limb Module (RULM) score	38.3 (risdiplam) versus 23.7% (placebo) achieved ≥3-point improvement in MFM32 (p=0.0469) 1.61-point improvement in RULM score for risdiplam versus 0.02 for placebo (p=0.0469)

Search strategy and selection criteria comparative effectiveness and comparative safety

A literature search was conducted to identify relevant studies evaluating the comparative effectiveness and safety of risdiplam. The following databases were searched: PubMed, Cochrane Library, and PROSPERO. The search was conducted in June 2024. The search terms used included “risdiplam,” “comparative effectiveness,” “comparative safety,” “spinal muscular atrophy,” “systematic review,” “literature review,” “comparative efficacy,” and “meta-analysis.”

Selection criteria were established to ensure the relevance of the studies. Included studies were those that compared risdiplam with one of the two other SMA treatments, or the standard of care and reported on outcome measures related to the effectiveness and/or safety of risdiplam. Additionally, studies were excluded if they were non-peer-reviewed articles, opinion pieces, or duplicates.

The initial search yielded a total of 56 studies. After screening titles and abstracts for relevance, 48 studies were excluded based on the criteria mentioned above. Full-text reviews were conducted for the remaining 10 studies, out of which 2 were duplicates. Thus, a total of 8 unique studies were included for further analysis. Additionally, the publication status of systematic reviews listed in PROSPERO was verified, resulting in the exclusion of 3 ongoing and unpublished studies.

To further narrow down the included studies, the studies were further prioritized to be able to present the most relevant evidence, the following criteria were used to prioritize the studies:

- **Quality Assessment:** All remaining studies were assessed using the GRADE approach. Studies with higher quality ratings were prioritized.

- **Relevance and Scope:** The studies were evaluated for their direct comparison of risdiplam and the comprehensiveness of their analysis.

Based on the above criteria, three studies were included in the review (see below). Additionally, evidence from the RAINBOWFISH non-randomized study has also been presented and summarized to supplement the evidence.

Summary of available evidence for comparative effectiveness and comparative safety

STUDY 1 - Long-Term Comparative Efficacy and Safety of Risdiplam and Nusinersen in Children with Type 1 Spinal Muscular Atrophy (21)

Design

This study evaluated the long-term efficacy and safety of risdiplam versus nusinersen in children with Type 1 SMA using indirect treatment comparison methodology. Specifically, an unanchored matching-adjusted indirect comparison (MAIC) was conducted to adjust for differences in population baseline characteristics and reduce potential bias.

Sponsor

The study was industry-sponsored by F. Hoffmann-La Roche Ltd.

Setting and Geographic Location

The data for risdiplam were derived from the FIREFISH trial, while the data for nusinersen came from the ENDEAR and SHINE trials. The trials were conducted across multiple international sites.

Study Period

The analysis included children with at least 36 months of follow-up data.

Patient Eligibility Criteria

Children with type 1 SMA were included. The FIREFISH trial included children aged 1–7 months at enrollment, and similar age criteria were applied in the ENDEAR trial.

Randomization

The FIREFISH trial was a single-arm study, while the ENDEAR trial was randomized and double-blind with a sham procedure-control.

Patient Characteristics

- **Demographic and Clinical Characteristics:** Detailed demographic data were not provided in the summary, but adjustments for baseline characteristics such as age, genetic factors, and disease severity were made using the MAIC methodology.
- **Gender/Sex and Ethnicity Representation:** Specific representation of different ethnicities was not explicitly mentioned. The study accounts for gender in their baseline characteristics.

Treatment Details

- **Intervention Group (Risdiplam):** Data from 58 children who participated in the FIREFISH trial.
- **Comparison Group (Nusinersen):** Published aggregate data from 81 children in the ENDEAR and SHINE trials.

Outcomes Investigated

- **Survival Outcomes:** Overall survival and event-free survival (time to death or need for permanent ventilation).
- **Motor Function Outcomes:** Achievement of motor milestones using the Hammersmith Infant Neurological Examination (HINE-2) and the Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders (CHOP-INTEND).
- **Safety Outcomes:** Time to the first serious adverse event (SAE).

Findings

- **Survival:** Risdiplam was associated with a 78% reduction in the rate of death and an 81% reduction in the rate of death or permanent ventilation compared to nusinersen.
- **Motor Function:** Risdiplam-treated children had a 45% higher rate of achieving a HINE-2 motor milestone response and an 186% higher rate of achieving a ≥4-point improvement in CHOP-INTEND compared to nusinersen-treated children.
- **Safety:** Risdiplam-treated children had a 57% reduction in the rate of SAEs compared to nusinersen-treated children. The long-term data support the superiority of risdiplam over nusinersen in children with type 1 SMA, with significant improvements in survival rates, motor function, and safety outcomes.

Table 5: Summary of Findings including Evidence and Bias Assessment

Outcome	Risdiplam (FIREFISH)	Nusinersen (ENDEAR, SHINE)	Relative Effect (95% CI)	Absolute Effect (per 1000 patients)	Quality of Evidence (GRADE)	Assessment of Bias[2]
Survival	Improved survival rates	Observed survival rates	HR 0.22 (0.12-0.41)	780 fewer deaths	High	Low: High-quality evidence from indirect comparison using MAIC.
Event-Free Survival	Improved event-free survival	Observed event-free survival	HR 0.19 (0.10-0.35)	810 fewer events	High	Low: High-quality evidence from indirect comparison using MAIC.
Motor Function (HINE-2)	Higher rate of motor milestone achievement	Observed motor milestone achievement	OR 1.45 (1.10-1.90)	450 more achieving milestones	Moderate	Medium: Indirect comparison; possible baseline differences.
Motor Function (CHOP-INTEND)	Higher rate of achieving ≥4-point improvement	Observed rate of achieving ≥4-point improvement	OR 2.86 (2.00-4.10)	1860 more achieving ≥4-point improvement	Moderate	Medium: Indirect comparison; possible baseline differences.
Serious Adverse Events (SAEs)	Lower rate of SAEs	Observed rate of SAEs	HR 0.43 (0.28-0.65)	570 fewer SAEs	High	Low: High-quality evidence from indirect comparison using MAIC.

Certainty of Evidence

- **Survival:** High quality. Consistent findings and robust methodology.
- **Event-Free Survival:** High quality. Consistent findings and robust methodology.
- **Motor Function (HINE-2):** Moderate quality. Indirect comparison and potential baseline differences.

[2] Assessment of Bias:

- Low: The risk of bias is low when there is confidence that the study results are valid and not influenced by systematic errors.
- Medium: The risk of bias is medium when there is some concern regarding the validity of the study results due to potential factors such as confounding or selection bias.
- High: The risk of bias is high when there are significant concerns regarding the validity of the study results, indicating a need for cautious interpretation.

- **Motor Function (CHOP-INTEND):** Moderate quality. Indirect comparison and potential baseline differences.
- **Serious Adverse Events (SAEs):** High quality. Consistent findings and robust methodology.

STUDY 2 - Safety and Efficacy of Nusinersen and Risdiplam for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials (22)

Study Design

This study performed a systematic review and meta-analysis of the efficacy and safety of nusinersen and risdiplam in treating SMA using data from randomized controlled trials (RCTs)

Sponsor

This study was supported by the Shenyang Science and Technology Program, grant number 20-205-4-090.

Setting and Geographic Location

The trials included in this review were conducted across multiple international sites.

Study Period

The literature search included studies published up to July 2023.

Patient Eligibility Criteria

The review included RCTs with SMA patients treated with nusinersen or risdiplam and compared with a placebo group.

Randomization

All included trials were randomized, double-blind, and placebo-controlled.

Patient Characteristics

- **Demographic and Clinical Characteristics**: The review included 728 patients with SMA types 1, 2, and 3.
- **Gender/Sex and Ethnicity Representation**: Specific representation of different ethnicities was not detailed.

Treatment Details

The included studies reported data from patients treated with nusinersen or risdiplam compared to placebo.

Outcomes Investigated:

- **Motor Function Outcomes:** Hammersmith Functional Motor Scale—Expanded (HFMSE), Revised Upper Limb Module (RULM), 32-item Motor Function Measure (MFM32), and Hammersmith Infant Neurological Evaluation Section 2 (HINE-2).
- **Safety Outcomes:** Incidence of adverse events (AEs) and severe adverse events (SAEs).

Findings

- **Motor Function Outcomes**: Both Nusinersen and Risdiplam show significant efficacy in improving motor functions in SMA patients.
- **Safety Outcomes**: No significant difference in the incidence of AEs and SAEs between the two drugs and placebo.

Table 6: Summary of Findings including Evidence and Bias assessment

Outcome	Nusinersen	Risdiplam	Quality of Evidence (GRADE)	Assessment of Bias
HFMSE	WMD: 4.90 (3.17, 6.63)	WMD: 0.87 (0.05, 1.68)	High	Low: RCTs with consistent results.
MFM32	Not assessed	WMD: 1.48 (0.58, 2.38)	Moderate	Medium: Some heterogeneity, but overall consistent results.
RULM	WMD: 3.70 (3.30, 4.10)	WMD: 1.29 (0.57, 2.01)	High (Nusinersen)	Low: RCTs with consistent results.
			Moderate (Risdiplam)	Medium: Some heterogeneity, but overall consistent results.

HINE-2	WMD: 5.21 (4.83, 5.60)	Not assessed	High	Low: RCTs with consistent results.
Adverse Events	OR: 0.57 (0.15, 2.14)	OR: 1.08 (0.55, 2.13)	High	Low: RCTs with consistent results.
Severe Adverse Events	OR: 0.54 (0.22, 1.30)	OR: 1.11 (0.66, 1.88)	High	Low: RCTs with consistent results.

Certainty of Evidence

- **Motor Function Outcomes Nusinersen** (HFMSE, RULM, HINE-2): High-quality evidence due to consistent findings across multiple RCTs with low risk of bias.
- **Motor Function Outcomes Risdiplam** (HFMSE, MFM32, RULM): Moderate-quality evidence due to some heterogeneity and medium risk of bias, but still supported by RCTs indicating moderate improvement.
- **Safety Outcomes** (AEs and SAEs for both drugs): High-quality evidence showing no significant difference in the incidence of adverse and severe adverse events compared to placebo, with consistent results across RCTs and low risk of bias.

STUDY 3 - How does risdiplam compare with other treatments for Types 1–3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison (23)

Study Design

The systematic review includes a range of studies comparing risdiplam with other treatments for SMA Types 1-3, specifically focusing on indirect treatment comparisons (ITCs) due to the lack of head-to-head trials. The included trials are:

1. **FIREFISH (NCT02913482)**: Phase II/III, open-label, single-arm trial of risdiplam.
2. **ENDEAR (NCT02193074)**: Phase III, randomized, double-blind, sham-procedure controlled trial of nusinersen.
3. **STR1VE-US (NCT03306277)**: Phase III, open-label, single-arm trial of onasemnogene abeparvovec.
4. **SUNFISH (NCT02908685)**: Phase III, randomized controlled trial of risdiplam.

5. **CHERISH (NCT02292537)**: Phase III, randomized, double-blind, sham-procedure controlled trial of nusinersen.

Sponsor

The study was sponsored by F. Hoffmann-La Roche Ltd.

Setting and Study Period

The studies were conducted internationally across various clinical sites. The study periods varied from 2 years to 8 years.

Patient Eligibility Criteria

Included patients with Type 1 SMA (infants with onset before 6 months of age) and Types 2 and 3 SMA (patients with later onset and variable motor function).

Randomization

ENDEAR, SUNFISH and CHERISH were randomized controlled trials, while FIREFISH and STR1VE-US were single-arm trials.

Patient Characteristics

The studies included diverse patient populations, but detailed demographic and clinical characteristics (such as age, gender, and ethnicity) were primarily matched to the type of SMA. Notably, FIREFISH and ENDEAR included infants with Type 1 SMA, while SUNFISH and CHERISH included older patients with Types 2 and 3 SMA.

Treatment Details

- **Risdiplam**: Oral SMN2 splicing modifier.
- **Nusinersen**: Intrathecal SMN2-targeting antisense oligonucleotide.
- **Onasemnogene abeparvovec**: Intravenous gene therapy using an adeno-associated virus.

Duration of Treatment and Follow-up

The duration of treatment varied by trial but was between 2 and 8 years.

Outcomes Investigated

The primary outcomes were motor function improvement and survival rates. Secondary outcomes included respiratory function, nutritional status, and quality of life measures.

Findings

- **Type 1 SMA**: Risdiplam showed improved survival and motor function compared to nusinersen, though comparisons with onasemnogene abeparvovec were less conclusive due to population differences.
- **Types 2 and 3 SMA**: Comparisons were challenging due to heterogeneity in study populations, but risdiplam showed promising results in improving motor function.

Table 7: Summary of Findings including Evidence and Bias Assessment

Outcome	Risdiplam (FIREFISH, SUNFISH)	Nusinersen (ENDEAR, CHERISH)	Onasemnogene abeparvovec (STR1VE-US)	Relative Effect (95% CI)	Absolute Effect	Quality of Evidence (GRADE)	Assessment of Bias
Survival (Type 1 SMA)	Improved	Baseline	Baseline	HR: 0.70 (0.50-0.90)	30% relative reduction	Moderate	Medium: Indirect comparisons and heterogeneity among studies
Motor Function (CHOP INTEND, Type 1 SMA)	Significant improvement	Moderate improvement	Baseline	MD: 4.5 points (2.0-7.0)	15% absolute improvement	High	Low: Consistent results across studies
Motor Function (HFMSE, Types 2/3 SMA)	Moderate improvement	Moderate improvement	N/A	MD: 2.5 points (1.0-4.0)	10% absolute improvement	Moderate	Medium: variability among studies
Respiratory Function	Improved	Baseline	Baseline	Not available	Not available	Low	Low: limited data and indirect comparisons

Quality of Life	Improved	Improved	Baseline	Not available	Not available	Moderate	Low: limited data and indirect comparisons

Certainty of Evidence

- **Survival (Type 1 SMA):** Moderate certainty due to indirect comparisons and heterogeneity.
- **Motor Function (Type 1 SMA):** High certainty due to consistent results across studies.
- **Motor Function (Types 2/3 SMA):** Moderate certainty due to variability among studies.
- **Respiratory Function and Quality of Life:** Low to moderate certainty due to indirect comparisons and limited data.

Synthesis of Findings: comparative effectiveness and comparative safety

The three studies included in this review provide a comprehensive evaluation of the comparative effectiveness and safety of risdiplam versus nusinersen and onasemnogene abeparvovec. Below is a brief synthesis of the results from the three reviews included in this section to demonstrate the comparative effectiveness and safety of risdiplam.

Comparative Effectiveness: Across all studies, risdiplam consistently showed significant improvements in motor function and survival outcomes compared to nusinersen. For Type 1 SMA, risdiplam demonstrated superior motor milestone achievements and overall survival benefits. The findings suggest that risdiplam may offer a more effective treatment option for SMA, particularly for patients with Type 1 SMA.

Comparative Safety: Risdiplam was associated with a lower rate of serious adverse events (SAEs) compared to nusinersen, highlighting its favorable safety profile. The safety outcomes from the meta-analysis also supported the high safety profile of risdiplam, with no significant differences in adverse events compared to placebo.

Comparison with onasemnogene abeparvovec: The evidence for risdiplam's effectiveness compared to onasemnogene abeparvovec was less conclusive due to population differences and indirect comparisons. However, risdiplam showed promising results in improving motor function for Types 2 and 3 SMA.

Assessment of applicability of the available evidence across diverse populations and settings

The included meta-analyses along with data from the RAINBOWFISH study, encompass a broad spectrum of patient populations and healthcare settings. These trials were conducted across multiple international sites, spanning diverse regions such as China, Ukraine, Serbia, Australia, Brazil, and others, thereby capturing varying healthcare contexts, resources, and infrastructure.

While the majority of studies primarily focused on pediatric populations, with a subset including adult patients (primarily with Type 2 or Type 3 SMA), the trials collectively represent a wide range of demographics. Although detailed demographic data were not consistently reported in the meta-analyses, examination of the individual trials reveals a diverse patient population with representation across different ethnicities, races, patients requiring nutritional support, those needing pulmonary care, and a balanced distribution across gender.

However, it is important to note that the absence of dedicated studies focusing on special patient groups, such as pregnant or breastfeeding individuals, limits the applicability of the findings to these populations.

Section 9: Summary of recommendations in current clinical guidelines

Currently, there are no specific recommendations for risdiplam in current WHO guidelines for the treatment of SMA. Two articles published in Neuromuscular Disorders from 2018 form the basis of the standard of care for SMA patients (24,25). These guidelines on the standard of care were developed by a multidisciplinary committee of international experts. However, these connecting articles were published before the approval of risdiplam and the more widespread use of SMA drugs targeting the underlying cause of SMA. The second guideline article (part 2, also published in 2018) briefly discusses the approval of Nusinersen by the FDA (in December 2016), providing an overview of its administration and the early positive clinical outcomes. However, the standard of care outlined in these articles has not been updated since 2018 and does not include disease-modifying treatments for SMA.

Section 10: Summary of available data on comparative cost and cost-effectiveness

Price of Risdiplam

An overview of 2024 data on the price of risdiplam in a range of countries where the medicine is available can be found in Annex B. This table, compiled by KEI, provides detailed insights into the costs across different regions. Additional historical data on the price of risdiplam is available at drugsdatabase.info/drug-prices. This data illustrates the significant variation in risdiplam pricing globally, with prices ranging from USD $8.82 to $225.07 per mg.

Costs of Manufacturing Risdiplam

The WHO Essential Medicines List (EML) tends to favor older small-molecule drugs with large patient populations, resulting in lower API costs that may not represent small-scale production drugs. In a 2018 study, Hill, Barber, and Gotham estimated API costs for various drugs on the WHO EML, showing a wide range from $2/kg to $669,376/kg, with the latter being an extreme outlier (26). Most API prices are below $10,000/kg, with 98% under this threshold, 83% below $1,000/kg, and 38% under $100/kg. The median API price is $152/kg.

Upon confidential consultations with companies and chemistry experts, KEI has estimated that the API Costs-of-Goods (COGs) for risdiplam would be around $25,000-$30,000/kg, potentially reducing to about $8,500/kg within the next 3-5 years with continued development. Given the low dose of treatment (around 5mg/day), a reasonable treatment cost per patient is achievable even at the higher estimate of $25,000-$30,000/kg for the API. This is drastically lower than Roche's current price in high-income countries, which ranges from $108,000,000/kg to $225,000,000/kg.

For risdiplam, the generic API price is expected to be significantly higher compared to other APIs due to its small patient population and low annual dosage. Despite this, the generic price will still be much more affordable compared to its branded version and not present the same level of economic challenges highlighted in the above national and academic cost-effectiveness summaries. Indeed, as mentioned in Section 6, in China Roche's risdiplam is priced drastically lower - thus showcasing that the branded version of the drug is for sale at an affordable price (only 3.8% of the US daily price) and has the potential for more widespread affordability and accessibility.

Special Access Programs for Risdiplam

As of July 2023, there were 2,163 patients that participated in Roche's Compassionate Use Program (CUP) for risdiplam across 59 countries, 23 of these are LMICs (27). The CUP has strict eligibility requirements, for example, if patients are eligible for available therapies other than risdiplam, these patients are excluded from the risdiplam CUP. Additionally, due to the restriction of patient-eligibility criteria as part of the CUP, not all countries from all geographic regions were able to participate in the CUP. The CUP, by no means, covers a large proportion of patients that need access. Indeed, in some lower-income countries, the CUP has ended, meaning that now that all the 'spots' have been filled, no new children diagnosed with SMA will be eligible for treatment under the CUP.

Patients who are unable to participate in Roche's CUP or afford risdiplam may opt to travel to countries where the price per bottle is much less. For example, patients have been known to travel from all over the world to China in order to get a more affordable supply of risdiplam at approximately USD 520 per bottle. This is a substantially lower price than its neighboring country India, where the price is approximately USD 7,400 per bottle.

In many countries, particularly LMIC, **hundreds of children with SMA continue to be born and die or suffer from the burden of comorbidities because they lack access to SMA treatments**. This lack of access results in a significant unmet medical need, where children are deprived of life-altering treatment. This disparity underscores the inadequacy of relying solely on CUP, which leaves many patients behind.

Comparative Cost & Budget Impact from National Economic Analyses

United Kingdom: NICE (28)

In the UK, risdiplam has a list price of £7,900 per 60 mg (80 ml) vial.

NICE conducted a cost-effectiveness analysis[3] comparing risdiplam to best supportive care (BSC). The Incremental Cost-Effectiveness Ratio (ICER) for risdiplam compared to BSC was estimated as follows:

- **SMA Type 1:** above £50,000 per QALY gained
- **SMA Types 2 or 3**: significantly higher than £30,000 per QALY gained

The analysis concluded that while risdiplam shows significant clinical benefits, its ICERs are substantially high, indicating that the treatment is not cost-effective at its current price. The

[3] A new cost effectiveness analysis of nusinersen and risdiplam for SMA will be published by NICE in December 2024.

committee also states that the cost-effectiveness estimates are higher than what NICE usually considers an acceptable use of NHS resources. However, because of the unmet need for effective treatments for SMA, risdiplam was recommended via the Managed Access Agreement (MAA) to enable data collection to address uncertainties in the evidence.

The document did not specify a detailed budget impact analysis. However, it is clear that the high cost of risdiplam would have a significant impact on the overall drug budget for treating SMA.

Recommendation

NICE ultimately recommended risdiplam for reimbursement by the NHS for treating SMA in patients aged 2 months and older, provided that certain conditions are met, including a confidential discount to its list price.

Canada: CADTH (29)

Risdiplam is priced at $193.9725 per mg in Canada. The annual cost for patients aged 2 years and older (weighing 20 kg or more) is approximately $354,000. For younger patients (ages 2 months to 2 years), the annual cost is around $93,456.

A cost analysis was done comparing risdiplam to nusinersen and best supportive care (BSC). The analysis focused on QALYs and life-years over different time horizons. The incremental cost-effectiveness ratio (ICER) for risdiplam compared to BSC was calculated as follows:

- **SMA Type 1**: $1,203,108 per QALY.
- **SMA Types 2 or 3**: $37,378,163 per QALY.

They further concluded that risdiplam was associated with lower costs and more QALYs compared to nusinersen. Indeed, a price reduction of 30% for nusinersen still resulted in risdiplam continuing to be dominant, this was partially due to the intrathecal injections required with nusinersen.

Due to risdiplam's high ICERs, CADTH concluded that substantial price reductions would be needed to view risdiplam as cost-effective. Indeed, they noted that a price reduction of 99% is needed to achieve a conventional cost-effectiveness threshold of $50,000 per QALY. The table below, which summarized CADTH's results, illustrates that despite SMA Types 2 and 3 having a lower annual cost per patient, they have a much higher ICER compared to SMA Type 1. This indicates that treatments for SMA Types 2 or 3 are less cost-effective relative to their costs and benefits.

Table 8: Summary of CADTH results

Parameter	SMA Type 1	SMA Types 2 or 3

Annual Cost (per patient)	$354,000	$93,456
ICER (per QALY)	$1,203,108	$37,378,163
Required Price Reduction	Up to 99%	Up to 99%

CADTH highlighted one significant limitation in their analysis, which was the uncertainty around the magnitude of clinical benefit. When conducting their analysis, they commented that there remains some uncertainty because there is an absence of direct comparative data with BSC or nusinersen.

Budget Impact

CADTH estimated that the 3-year budget impact of risdiplam would be $87,744,812, accounting for the underestimation of treatment retention rates and coverage under public plans. They note that there may be cost savings among SMA type 1 patients, however, the high cost of risdiplam is expected to increase the overall drug budget for the full indicated population.

Recommendation

In conclusion, CADTH recommended risdiplam to be reimbursed by public drug plans for the treatment of SMA in patients aged 2 months and older, if certain conditions are met. Currently, the reimbursement of risdiplam varies by province and territory in Canada.

Ireland: NCPE (30)

NCPE used a Markov model with monthly cycles to stimulate the progression or regression associated with SMA through various motor milestones. Their analysis covered both Type 1 SMA and Types 2 and 3 SMA, using different comparators for each.

Type 1 SMA

For Type 1 SMA, the comparators were Best Supportive Care (BSC), nusinersen, and onasemnogene abeparovec. The results of the cost-effectiveness analysis are summarized in Table 9.

Table 9: Cost-Effectiveness Analysis for SMA Type 1

Treatment	Total Costs (€)	QALYs	Incremental Cost (€)	Incremental QALYs	ICER (€ per QALY)

Risdiplam	4,814,569	9.71	-	-	-
Best Supportive Care (BSC)	472,701	2.43	4,341,868	7.28	596,547
Nusinersen	3,422,009	7.98	1,392,560	1.73	806,307
Onasemnogene Abeparovec (OA)	3,091,817	9.48	1,722,753	0.24	7,326,448

Types 2 and 3 SMA

For SMA Types 2 and 3, the comparators were BSC and nusinersen. The results are detailed in Table 10.

Table 10: Cost-Effectiveness Analysis for SMA Types 2 and 3

Comparison	Total Costs (€)	Total QALYs	Incremental Costs (€)	Incremental QALYs	ICER (€ per QALY)
Risdiplam	5,602,712	0.27	-	-	-
BSC	1,657,143	-0.47	3,945,569	0.74	5,339,479
Nusinersen	5,307,779	0.11	294,933	0.16	1,829,157

Budget Impact

The price of wholesale risdiplam (60mg/80ml) is €8,450 per bottle (list price), with an annual per-patient drug cost to the Health Service Executive (HSE) estimated at €264,371. The Applicant's estimated 5-year gross budget impact for risdiplam was €107 million compared to €132m for nusinersen.

Recommendation

Based on this analysis, the NCPE recommended that risdiplam not be considered for reimbursement until its cost-effectiveness could be improved. The final decision on reimbursement is, however, made by the HSE. The HSE has offered conditional reimbursement to risdiplam, as of September 2023. There is thus a special program where a clinician must submit an individual reimbursement application for each patient for use as a monotherapy in the treatment of SMA (31).

The Netherlands: Zorginstituut Nederland (32)

The Zorginstituut conducted a cost-effectiveness analysis comparing risdiplam to best supportive care (BSC) and treatments like nusinersen. The incremental cost-effectiveness ratio (ICER) for risdiplam compared to BSC was calculated as follows:

- **SMA Type 1**: €362,300 per QALY.
- **SMA Types 2 or 3**: €416,471 per QALY.

Table 11: Comparative cost-effectiveness

Parameter	SMA Type 1	SMA Types 2 and 3	Combined Analysis
ICER (Discounted)	€362,300 per QALY	€416,471 per QALY	Not specified
ICER (Undiscounted)	€590,143 per QALY	€678,497 per QALY	Not specified
Cost per LY (Discounted)	€198,559	€1,381,226	Not specified
Cost per LY (Undiscounted)	€314,994	€1,864,012	Not specified
Required Price Reduction	Approximately 94%	Approximately 78%	Approximately 85%

Budget Impact

The Zorginstituut expected the net budget impact of risdiplam for three years of €5 million (3).

Recommendation

The document concludes that while risdiplam offers significant clinical benefits for patients with SMA, its high ICERs indicate that it is not cost-effective at the current price. Substantial price reductions are necessary to achieve conventional cost-effectiveness thresholds. The analysis suggests that risdiplam provides value for money only if its price is significantly reduced, ensuring it is accessible and affordable while delivering its clinical benefits effectively. Despite this analysis, risdiplam is included in the basic health insurance package and is reimbursed (33).

Australia: PBAC (34)

The drug cost for Risdiplam at $33,000 per patient per month, based on the published price and an assumed dose of 5 mg per day.

A cost-effectiveness analysis comparing risdiplam to best supportive care (BSC) and treatments like nusinersen.

Table 12: ICER and QALY Data for Risdiplam

SMA Type	Discounted ICER per QALY	Undiscounted ICER per QALY	Discounted Cost per LY Gained	Undiscounted Cost per LY Gained
Type 1	€362,300	€590,143	€198,559	€314,994
Types 2 & 3	€416,741	€678,497	€1,381,226	€1,864,012

SMA Type 1: The high ICER values indicate that risdiplam is quite expensive per QALY gained compared to alternatives, suggesting that it is not cost-effective under usual thresholds unless significant price reductions are applied.

SMA Types 2 & 3: Similarly, these types also show high ICERs, reflecting that the cost per QALY gained is substantially higher than typical thresholds for cost-effectiveness.

PBAC also conducted a cost minimization analysis to assess the economic impact of prescribing risdiplam compared to nusinersen for patients with SMA Types 1, 2 and 3a who are under 19 years of age at treatment initiation. The annual costs are as follows: First Year:

- **First Year:** Risdiplam shows a cost advantage of -$264,000 due to the higher frequency of nusinersen loading doses.
- **Subsequent Years:** Annual cost savings narrow, with Risdiplam being more expensive by $66,000 per year.

Overall, both treatments converge to an average cost of $396,000 when averaged over 5 years. Thus while there is an initial cost-saving for risdiplam, the long-term economic benefit is dependent on sustained cost savings beyond the drug costs, such as potential savings in administration and associated healthcare costs.

Recommendation

Based on the high ICER values and the need for a significant price reduction (up to 85% for certain patient groups), the document suggests that risdiplam at its current price does not offer value for money compared to alternatives like BSC and needs a substantial price reduction to be considered cost-effective.

Despite its high price, PBAC concluded that risdiplam should be listed for Types 1, 2 or 3, who are aged 18 years and under at treatment initiation, on the basis that it should be available only under special arrangements.

Brazil: Conitec (35)

For each new case of SMA, the average annual cost in the first 5 years was calculated at R$412,498.44. When examining the cost-effectiveness of risdiplam, Conitec was using the following prices:

Table 13: Risdiplam prices Brazil

Presentation	Unit Price Proposed by the Applicant	Maximum Selling Price to the Government 18%[2]	Price Practiced in Public Purchases[3]
Powder for oral solution 0.75 mg/mL (80 mL) of risdiplam	R$ 25,370.00 per unit, excluding taxes	R$ 44,173.02 Not available	Not available

An economic model based on a Markov cohort simulation compared the cost-effectiveness of risdiplam, nusinersen, and supportive care over a 10-year period from the perspective of the Brazilian SUS in the context of Type 1 SMA. Risdiplam demonstrated extended dominance over nusinersen. As a result, they excluded risdiplam in the new simulation of economic evaluation comparing risdiplam with BSC.

Table 14: Risdiplam vs BSC (Type 1 SMA)

Technology	Treatment Cost (R$)	Utility (QALY)	Incremental Cost	Incremental Effectiveness	ICER (R$/QALY)
Supportive Care	21,483.26	0.26	-	-	-
Risdiplam	3,227,472.67	0.89	3,205,989.52	0.63	5,094,220.37

Based on this model risdiplam has an incremental cost-effectiveness ratio (ICER) of R$5,094,220.37 per QALY gained.

Budget Impact

The budget impact analysis for Type 1 SMA projected substantial savings over the initial 5 years post-incorporation into SUS (Brazil's publicly funded healthcare system), followed by cost increases as the prevalence of risdiplam-treated patients increased. Budget impact analysis projected savings of R$262,395,692.94 over the first 5 years, shifting to a cost increase in subsequent years due to patient population growth. As the years progress and the prevalence of pre-existing cases increases, these savings translate into budgetary impact. The annual cost for a patient already in maintenance treatment with the maximum dose of risdiplam versus an equivalent patient on nusinersen is R$761,100.00 versus R$483,138.00. These calculations, however, disregard the costs of supportive care.

Recommendation

Conitec concludes with the recommendation to incorporate risdiplam into SUS for the treatment of Type 1 SMA patients.

France: Haute Autorité de Santé (36)

Price data was confidential and thus redacted. Compared to the current alternatives, risdiplam is evaluated alongside nusinersen and best supportive care (BSC). The cost per year of life gained for Type I SMA is €327,728 compared to BSC, and for Type II/III non-ambulant SMA, risdiplam is less cost-effective than nusinersen, with a high cost per quality-adjusted life year (QALY).

The target population for risdiplam in France is approximately 1,200 patients, leading to a significant budget impact. Over five years, the budget is expected to increase by 26.7%, translating to millions of euros in additional healthcare expenditure. The economic analysis conducted by the Haute Autorité de Santé (HAS) shows that, although risdiplam may offer improved compliance and a favorable side-effect profile, it is not cost-effective compared to existing treatments like nusinersen and onasemnogene abeparvovec.

Recommendation

Despite not being cost-effective, HAS has granted a favorable reimbursement status for Types 1. 2 and non-ambulant Type 3 SMA, while excluding reimbursement for Type 4.

Portugal: INFARMED (37)

While no figures are provided in the INFARMED document, they state that the analysis found that the cost of treatment with risdiplam is lower than the cost of treatment with nusinersen, which is beneficial for the National Health Service (SNS).

The INFARMED document recommends the financing of Risdiplam for the treatment of SMA types 1, 2, and 3 for patients aged 2 months and older, based on its recognized beneficial effects.

Scotland: Scottish Medicine Consortium (38)

As listed in the 2022 report, the yearly cost of risdiplam in Scotland was listed at up to £239,633 per year. The estimate was that there would be 22 eligible patients for risdiplam in year 1 and increase to 63 patients by year 5. Risdiplam is fully reimbursed under Scotland's ultra-orphan medicines scheme (39).

Information on the budget impact was not published due to commercial confidence issues.

New Zealand: PHARMAC (40)

PHARMAC New Zealand has decided to fund risdiplam from May 1, 2023. They estimate that in the first year, 30 to 50 people will be eligible for funded treatment with either nusinersen or risdiplam. The expectation is that each year, an additional four people may be diagnosed with SMA and eligible for treatment.

The listed price for a pack size of 80 milliliters of oral solution is set at $14,100.00. Additionally, there will be a confidential rebate applied to lower the net price of risdiplam.

Comparative Cost & Budget Impact from Academic Analyses

A comprehensive literature search was conducted to identify relevant economic analyses on the treatment of SMA. The databases searched included PubMed and Google Scholar. The search was conducted in June 2024. The search terms used included "cost-effectiveness," "health economics," “comparative cost,” “risdiplam,” “economic analysis,” and “budget impact.” Included studies were those that conducted a full economic evaluation (cost-effectiveness, cost-utility, or cost-benefit analysis) of risdiplam. Additionally, studies were excluded if they were non-peer-reviewed, duplicates, and not in English.

The initial search yielded a total of 20 studies. After screening titles and abstracts for relevance, 14 studies were excluded based on the criteria mentioned above. Thus, a total of 6 studies were included below to summarize the comparative cost and budget impact of risdiplam.

STUDY 1 - Cost-Effectiveness of Risdiplam Versus Nusinersen for Treating Patients with Spinal Muscular Atrophy Type 1 in China (41)

Study Design: This study employed a cost-effectiveness analysis using a six-state Markov model to compare the costs and outcomes of risdiplam, an at-home oral therapy, and nusinersen, an injectable therapy, for treating SMA Type 1.

Time Horizon: The model used a 10-year time horizon.

Population Characteristics: The population included patients diagnosed with SMA Type 1 in China, characterized by severe motor and respiratory impairment due to the disease's early onset.

Data Sources: Clinical data for risdiplam was sourced from the FIREFISH clinical trial, while data for nusinersen was derived from a matching-adjusted indirect comparison using the same trial. Utility values were estimated based on EQ-5D-3L responses from Chinese pediatric neurologists.

Base-Case Analysis: Patients treated with risdiplam gained 1.42 more life-years and 1.41 more quality-adjusted life years (QALYs) compared to those treated with nusinersen. The total direct medical costs for risdiplam were CNY 207,486 lower than for nusinersen, making risdiplam the dominant treatment.

Sensitivity Analyses: The study results indicated robustness across various sensitivity analyses, consistently showing risdiplam as a cost-effective alternative to nusinersen.

Conclusion: Due to increased QALYs and lower costs, risdiplam is a dominant alternative over nusinersen for SMA Type 1 patients in China.

STUDY 2 - Cost-Effectiveness of Technologies for the Treatment of Spinal Muscular Atrophy: A Systematic Review of Economic Studies (42)

Study Design: This systematic review aggregated data from 20 economic studies evaluating the cost-effectiveness of four treatments for SMA: best supportive therapy, nusinersen, risdiplam, and onasemnogene abeparvovec.

Time Horizon: The time horizons varied among the included studies, with some adopting short-term (5 years) and others long-term (lifetime) perspectives.

Population Characteristics: The studies reviewed involved patients with SMA Types I and II across various countries, focusing on different age groups and severity levels of the disease.

Data Sources: Structured search in 4 databases along with a manual search to include complete economic studies that evaluated nusinersen, risdiplam, onasemnogene abeparvovec, and the best support therapy from the health system's perspective were selected.

Willingness-to-Pay Thresholds: Thresholds varied widely, with comparisons made against country-specific thresholds, the 50,000 USD/QALY and 100,000 USD/QALY benchmarks, and the 3 GDP per capita/QALY thresholds.

Base-Case Analysis: The review found that nusinersen, risdiplam, and onasemnogene abeparvovec were generally not cost-effective compared to best supportive therapy. However, risdiplam and onasemnogene abeparvovec were often considered cost-effective compared to nusinersen. There was no consensus on the superior treatment between risdiplam and onasemnogene abeparvovec, as results were mixed.

Sensitivity Analyses: Results indicated significant variability, with cost-effectiveness, highly dependent on the willingness-to-pay threshold and specific country context. For instance, onasemnogene abeparvovec was considered cost-effective at higher thresholds in some studies but not in others.

Conclusion: The pharmacoeconomic analyses show that the technologies are not cost-effective compared with the best support therapy. The lack of controlled studies for risdiplam and onasemnogene abeparvovec hamper any conclusions about their face-to-face comparison.

STUDY 3 - Budget Impact Analysis Comparing Costs of Nusinersen and Risdiplam for Type 3 Spinal Muscular Atrophy Patients (43)

Study Design: This study conducted a budget impact analysis (BIA) to evaluate the economic implications of introducing risdiplam as a treatment for Type 3 SMA patients compared to the current standard, nusinersen.

Time Horizon: The analysis was performed over a 3-year time horizon.

Population Characteristics: The target population consisted of Type 3 SMA patients in a rare diseases reference center.

Data Sources: Public databases were utilized to estimate the target population and to model two market scenarios: one where patients are treated with nusinersen and another with risdiplam.

Base-Case Analysis: The analysis showed that the introduction of risdiplam was projected to generate a 3-year savings of €3411.50. Specifically, there could be significant savings in the administration costs for patients under the age of 2 with a weight of 5kg, estimated at

€26,382.08. These savings primarily result from the lower costs associated with the oral administration of risdiplam compared to the more invasive administration methods required for nusinersen.

Sensitivity Analyses: The results were consistent, showing potential cost savings with the use of risdiplam primarily due to its oral administration route, which reduces administration costs compared to nusinersen's intrathecal delivery.

Conclusion: Budget impact analysis indicates that risdiplam and nusinersen SMA therapies have overlapping costs, but the oral administration of risdiplam could be a decisive factor for the therapeutic switch from nusinersen.

STUDY 4 - Cost-Effectiveness of Risdiplam for Patients with Types 1 - 3 Spinal Muscular Atrophy (SMA) in France (44)

Study Design: This study utilized a cost-effectiveness analysis (CEA) to evaluate the economic impact of risdiplam for patients with Types 1, 2, and 3 SMA in France.

Time Horizon: The model was designed with a lifetime time horizon to capture long-term costs and health outcomes.

Population Characteristics: The study included a diverse population of SMA patients categorized into Types 1, 2, and 3, representing different severities and ages of onset.

Data Sources: Two six-state semi-Markov models were adapted to the French collective perspective to evaluate the incremental cost-effectiveness ratio (ICER) of risdiplam. Costs and outcomes were discounted at 2.5% with direct medical costs derived from a French database (SNDS).

Willingness-to-Pay Thresholds: The willingness-to-pay threshold used in the study was based on the French healthcare system's standard threshold for cost-effectiveness, typically around €50,000 per QALY gained.

Base-Case Analysis: Risdiplam was found to increase quality-adjusted life years (QALYs) across all SMA types. In comparison to BSC, risdiplam increased LYGs (5.81) and costs (€2,005,518), resulting in an ICER of €345,217/LYG for SMA Type 1. Risdiplam also resulted in more life years gained compared to nusinersen and had a lower cost for equivalent life years compared to onasemnogene abeparovec.

Sensitivity Analyses: Sensitivity analyses confirmed the robustness of the results, showing that risdiplam remained cost-effective under various assumptions and scenarios.

Conclusion: Based on the last available information, risdiplam is projected to be a high-value treatment alternative to nusinersen and onasemnogene abeparovec in France.

STUDY 5 - Budget Impact Analysis of Risdiplam for the Treatment of Spinal Muscular Atrophy in Colombia (45)

Study Design: This study performed a budget impact analysis (BIA) to evaluate the financial implications of introducing risdiplam for treating SMA in Colombia.

Time Horizon: The analysis considered a time horizon of five years.

Population Characteristics: The target population included SMA patients across different types, specifically Types 1, 2, and 3, reflecting the distribution and demographic characteristics of the Colombian SMA population.

Data Sources: Data sources included Colombian public databases and published literature reviews.

Base-Case Analysis: The introduction of risdiplam was projected to increase the overall budget due to its high acquisition cost. The adoption of risdiplam resulted in a budget impact of USD $439,862 and $969,311 in years 1–5, respectively. However, it showed potential for cost savings in administration and supportive care when compared to alternative therapies.

Sensitivity Analyses: Various scenarios were tested, confirming that while the initial drug costs were high, long-term savings in healthcare resource utilization could offset some of these expenses.

Conclusion: Risdiplam provides an alternative treatment option for Colombian SMA patients.

STUDY 6 - Risdiplam for the Treatment of Spinal Muscular Atrophy: Impact on the National Healthcare Service During the First 15 Months of Commercialization in Italy (46)

Study Design: This study employed a budget impact analysis (BIA) to assess the financial implications of introducing risdiplam for treating SMA in Italy.

Time Horizon: The analysis covered the first 15 months following the commercialization of risdiplam.

Population Characteristics: The study focused on patients with SMA Types 1, 2, and 3, including those with a clinical diagnosis of SMA 5q and varying copies of the SMN2 gene.

Data Sources: A Cost Offset Calculator was developed using the AIFA monitoring register and internal data. Two 1-month cycle Markov models were used to estimate clinical outcomes and costs of SMA patients receiving either risdiplam or nusinersen. Health-state occupancy was determined using risdiplam clinical data and indirect comparisons for nusinersen. Direct costs included drug acquisition, administration, and disease monitoring. Resource use data and unit costs were retrieved from published literature and Italian sources.

Base-Case Analysis: The introduction of risdiplam led to a significant impact on the national budget. The Cost Offset Calculator estimated savings of €15.3 million for drug acquisition and administration along with savings of €256,000 for healthcare resource consumption. The drug acquisition cost reflects the savings from the costs of acquiring and administering alternative treatments that risdiplam replaced and eliminating the need for more expensive administration methods. The savings listed for healthcare resource consumption refer to savings from reduced need for hospital visits, professional administration, and a potential for the decrease in the frequency of intensive care needed.

Sensitivity Analyses: Various scenarios confirmed that while the initial drug costs were high, long-term savings in healthcare resource utilization, particularly in hospital visits and supportive care, could offset these costs.

Conclusion: The introduction of risdiplam led to significant savings in drug acquisition, administration, and healthcare resource use. However, the overall budget impact remains substantial due to the high cost of the drug.

Summary of Comparative Cost and Cost Effectiveness

The various comparative cost and cost-effectiveness analyses of risdiplam showcase a consistent pattern. Both academic and national studies of risdiplam demonstrate its high cost that results in substantial incremental cost-effectiveness ratios (ICERs). For example, NICE and CADTH report ICER’s well above willingness-to-pay limits, highlighting the need for significant price reductions. The NCP Ireland and the Zorginstituut Nederland also highlighted high ICERs. Despite the high cost, all of the health assessment agencies mentioned above have recommended risdiplam for reimbursement (but with varying qualifications for this reimbursement).

For example, despite their analysis of the high cost of risdiplam, both Canada and the UK offer risdiplam under their public health systems, pursuant to special access plans and strict eligibility requirements. The budget impact analyses, such as those from India and Colombia, point out the financial burden of risdiplam but also suggest the potential for longer-term savings in the form of healthcare resource utilization due to its oral administration. Overall, risdiplam does present economic challenges at its current high price, but its ability to offer at-home treatment makes it a valuable treatment for SMA.

Section 11: Regulatory status, market availability and pharmacopoeial standards

Regulatory status of the proposed medicine

Risdiplam is approved to treat patients two months of age and older with SMA in more than 100 countries and the dossier is under review in a further 13 countries as of June 2024 (47). In several countries, regulatory agencies have updated and expanded the approval of risdiplam to include babies under 2 months of age.

In 2022, the U.S. FDA was the first to approve risdiplam's label extension (48). This expanded indication was based on positive interim data from RAINBOWFISH (see the discussion of the study under Section 8 non-randomized studies).

After the FDA, other regulatory agencies followed suit and similarly expanded risdiplam's approval, as of July 2024 these include:

- EMA (EU) (49);
- Swissmedic (Switzerland) (50);
- MHRA (UK) (51);
- ANVISA (Brazil) (52);
- Medsafe (New Zealand) (40).

Market availability of the proposed medicine

Risdiplam is available in many countries, with an intended market reach of 120 countries. There are no generics available but large price discrepancies exist between countries, leading to some patients and families traveling to countries that have a lower price for risdiplam and importing it through personal importation. Additionally, many families have relocated their lives to countries where treatment is accessible.

Roche and PTC Therapeutics, Inc. have filed numerous patents covering risdiplam. In the U.S. FDA Orange Book, Roche lists two patents, each titled "Compounds for treating spinal muscular atrophy" and each assigned to Roche and PTC Therapeutics (US9586955 and US9969754).

To examine the patent status of risdiplam, we made use of both WIPO PCT applications, which identify where patents have been filed at the national level, as well as identifying patents listed

in Pat-INFORMED, another WIPO database. According to this data, see in Annex C, there are 67 different offices where patents have been filed titled “Compounds for threatening spinal muscular atrophy,” which relate to risdiplam. While there are 67 distinct offices, this includes both the European Patent Office and the Eurasian Patent Organization offices,[4] which add an additional 44 and 9 countries, respectively. This means that Roche / PTC Therapeutics have relevant risdiplam patents in 120 countries.

Some countries, such as Argentina, are not members of the PCT and were not listed as having patents in Pat-INFORMED. As such, it is possible that these three databases do not account for all the offices that have granted a patent titled “Compounds for treating spinal muscular atrophy”. Additionally, besides the rights Roche and PCT Therapeutics have in patents, they also have regulatory rights in test data, market data, and orphan drug exclusivity in several justifications.

As mentioned in Section 6 of this application, KEI intends to pursue the de-risked development of a generic version of risdiplam. As part of this process, KEI has initially asked Roche, on multiple occasions, for a voluntary license to manufacture and sell a generic version of risdiplam. Roche has denied our request on three separate occasions. Despite this rejection and the wide-reaching patent landscape for risdiplam, KEI’s risdiplam project will not be hindered by existing exclusivities. Instead, the project can operate out of a jurisdiction where intellectual property rights will not block the development and distribution of generic risdiplam.

Pharmacopoeial standards

Not listed in the International, British, European, or United States Pharmacopoeia.

Section 12: New EML category

The current structure of the EML is inadequate for addressing pricing and affordability issues effectively. KEI has consistently urged the WHO to establish a category for essential products that are inaccessible due to high prices, recognizing the crucial role of government intervention in pricing.

The case of risdiplam exemplifies this need. Roche sells the drug at an exorbitant $108,000,000 to $225,000,000 per kg of API, resulting in an unsustainable cost for patients. However, risdiplam can be produced at a fraction of this price. Listing risdiplam on the EML without

[4] The EPO provides examinations for 39 European member states, one extension state, and four validation states. The EAPO members are the Republics of Azerbaijan, Armenia, Belarus, Georgia, Kazakhstan, Kyrgyz, Moldova and Tajikistan, and the Russian Federation.

addressing both Roche's high prices and the potential for lower generic costs disregards critical concerns for payers and patients.

KEI has repeatedly called on the WHO to create an EML category for drugs that are medically essential but financially out of reach:

- 2007, March 2. KEI asked the WHO Expert Committee on the Selection and Use of Essential Medicines and the WHO Department of Medicines Policy and Standards “to create a new category in the 'WHO Model List of Essential Medicines' (EML) for products that would be essential “if available from competitive generic suppliers at generic prices.” (53)

- 2012, February 28. KEI submission to the WIPO Standing Committee on the Law of Patents (SCP) on Patents and Health, asks WIPO members, “What would the WHO EML look like if there was a new category for products that are cost effective if available from generic suppliers?” (54)

- 2013, January 14. Proposal for the inclusion of trastuzumab in the WHO Model List of Essential Medicines for the treatment of HER-2 positive breast cancer. KEI requested the WHO Expert Committee on the Selection and Use of Essential Medicines to “identify the measures that will be necessary to expand access to the drug at affordable prices, including the measures necessary to overcome intellectual property barriers, a biosimilar pathway for drug registration, including a WHO prequalification process for trastuzumab, and also the efficient procurement strategies that have proved to be useful in bringing down prices for HIV drugs.” (55)

- 2015, April 20. At the Open Session of the 20th Expert Committee on the Selection and Use of Essential Medicines, KEI reiterated its proposal that the WHO create a category in the EML for products that would be essential, if available at affordable prices. (56)

- 2016, December. A KEI proposal for the inclusion of enzalutamide in the WHO Model List of Essential Medicines of the treatment of metastatic castration resistant prostate cancer requested the WHO to “consider the cost effectiveness of the drug when available from competitive generic suppliers.” (57)

- 2016. December. The KEI Proposal for The Inclusion Of Trastuzumab Emtansine (TDM1) In the WHO Model List of Essential Medicines for the Treatment of HER2-Positive Locally Advanced or Metastatic Breast Cancer stated: “For the WHO to consider a recommendation on T-DM1, it is important to consider the possibility of biosimilar products [...]”. (58)

- 2017, March 27. A KEI statement at the 21st meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines, asked for a new EML category for drugs that are medically essential but face challenges regarding affordability, noting that

governments and patients would take this as a signal to implement policies to make these medically effective drugs affordable (59).

- 2017, October 13. KEI provided comments to WHO Director General Tedros on the Draft Concept Note Concerning the WHO General Programme of Work. KEI noted that “The WHO Expert Committee has been asked, several times, to create a category in the EML for products that would be essential, if available at affordable prices. If drugs are medically effective, but expensive, they should be placed in an EML category for drugs that are medically essential but face challenges regarding affordability. Governments and patients would take this as a signal to implement policies to make these medically effective drugs affordable.” (60)

- 2019, January. Proposal for the inclusion of enzalutamide and abiraterone acetate in the WHO Model List of Essential Medicines for the treatment of metastatic castration resistant prostate cancer. KEI requested the WHO to “consider the cost-effectiveness both for cases where the drugs are expensive, from the originator, and when the drugs are less expensive from generic suppliers, including looking at reasonable scenarios for generic prices falling over time.” (61)

- 2019, April 1. A KEI statement to the 22nd meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines states “[i]f drugs are medically effective, but expensive, they should be placed in an EML category for drugs that are medically essential but face challenges regarding affordability. Governments and patients would take this as a signal to implement policies to make these medically effective therapies affordable. A system of medical guidance that consistently ignores or excludes new drugs for cancer needs to be reformed, and new options for dealing with affordability and access are needed if we are serious about achieving equality of health outcomes.” (61)

- 2020, December. Proposal for the inclusion of enzalutamide in the WHO Model List of Essential Medicines for the Treatment of Metastatic Castration-Resistant Prostate Cancer. KEI requested the WHO to “consider the cost-effectiveness for both cases: when the drugs are expensive (from the originator), and when the drugs are less expensive (from generic suppliers), including looking at reasonable scenarios for generic prices falling over time.”(62)

- 2021, April 29. KEI made a presentation to the WHO Essential Medicines List Cancer Medicines Working Group, noting “[t]he WHO EML evaluation deals with efficacy directly, but prices indirectly, often on an ad hoc basis, or not at all, despite the relevance and importance to users of the list.” KEI notes that “prices for products are not a state of nature, policies can make a difference.” KEI proposes the WHO separate the evaluation of efficacy and prices, and (1) Identify medicines that are useful medically, (2) include on the EML main list products that are both medically useful and already affordable, and (3) include a new category for products that are medically useful, but that may have high

prices, and that should be added to a national list when and if measures are undertaken to acquire products at affordable prices." (63)

- 2021, June 21. KEI made a statement to the Open Session of the 23rd Meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines. The WHO Expert Committee has been asked, several times, to create a category in the EML for products that would be essential, if available at affordable prices. A pathway for affordable antineoplastics would expand treatment options for patients, including the inclusion of second-line treatments [...] If drugs are medically effective, but expensive, they should be placed in an EML category for drugs that are medically essential but face challenges regarding affordability. Governments and patients would take this as a signal to implement policies to make these medically effective therapies affordable." (64)

- 2022, January 26. KEI made a statement on the Political declaration of the third high-level meeting of the General Assembly on the prevention and control of noncommunicable diseases and WHO's roadmap for the global action plan for the prevention and control of NCDs at the 150th session of the World Health Organization's Executive Board. KEI proposes the Executive board support the establishment of a standing EML Working Group on pricing and consider a category for "effective but expensive category of drugs, including policy interventions that can make products more affordable." (65)

- 2022. November 15. Proposal for the Inclusion of Risdiplam in the WHO Model List of Essential Medicines for the Treatment of Spinal Muscular Atrophy. KEI noted that "[a]ny decision to list risdiplam on the EML which does not recognize both the high price from Roche and the opportunities for lower generic prices ignores two of the most important facts relevant to third-party payers and patients." (66)

Section 13: Reference List

1. Kletzl H, Heinig K, Jaber B, Lomeli B, Yeung W, Young A, et al. P232 Bioavailability and bioequivalence of Risdiplam tablets in healthy volunteers. Neuromuscular Disorders. 2023 Oct 1;33:S93.
2. FDA. Package Insert - Zolgensma [Internet]. 2024. Available from: https://www.fda.gov/media/126109/download
3. Zorginstituut Nederland. Package advice risdiplam (Evrysdi®) for the treatment of 5q spinal muscular atrophy (SMA) [Internet]. 2020 [cited 2024 Jul 24]. Available from: https://english.zorginstituutnederland.nl/publications/reports/2022/07/15/package-advice-risdiplam-evrysdi
4. Hoffmann-La Roche. PRIME designation granted by European Medicines Agency for Roche's risdiplam for treatment of spinal muscular atrophy (SMA) [Internet]. 2018. Available from: https://assets.roche.com/imported/875639.pdf
5. Viscidi E, Juneja M, Wang J, Wang N, Li L, Farwell W, et al. Comparative All-Cause Mortality Among a Large Population of Patients with Spinal Muscular Atrophy Versus Matched Controls. Neurol Ther. 2022 Mar;11(1):449–57.
6. Lunn MR, Wang CH. Spinal muscular atrophy. The Lancet. 2008 Jun 21;371(9630):2120–33.
7. Mercuri E, Sumner CJ, Muntoni F, Darras BT, Finkel RS. Spinal muscular atrophy. Nat Rev Dis Primers. 2022 Aug 4;8(1):1–16.
8. Verhaart IEC, Robertson A, Wilson IJ, Aartsma-Rus A, Cameron S, Jones CC, et al. Prevalence, incidence and carrier frequency of 5q–linked spinal muscular atrophy – a literature review. Orphanet J Rare Dis. 2017 Dec;12(1):124.
9. Prior TW, Leach ME, Finanger E. Spinal Muscular Atrophy. In: GeneReviews® [Internet]. University of Washington, Seattle; 2020 [cited 2024 Jul 25]. Available from: https://www.ncbi.nlm.nih.gov/sites/books/NBK1352/
10. Naofal ME, Tayoun AA. P456: Genetic testing and screening for spinal muscular atrophy in the Middle East. Genetics in Medicine Open [Internet]. 2023 Jan 1 [cited 2024 Oct 18];1(1). Available from: https://www.gimopen.org/article/S2949-7744(23)00503-4/fulltext
11. Bemanalizadeh M, Mansouri V. Beyond Numbers: A Call to Action for Accurate Estimation of Spinal Muscular Atrophy in the Middle East and North Africa Region - Pediatric Neurology. Pediatric Neurology [Internet]. [cited 2024 Oct 18]; Available from: https://www.pedneur.com/article/S0887-8994(24)00349-7/abstract
12. Fried K, Mundel G. High incidence of spinal muscular atrophy type I (Werdnig - Hoffmann disease) in the Karaite community in Israel. Clin Genet. 1977 Oct;12(4):250–1.
13. Jones C, Oskoui M, Zielinski D, Vinikoor L, Farwell W. PP09.1 – 2352: Systematic review of incidence and prevalence of spinal muscular atrophy (SMA). European Journal of Paediatric Neurology. 2015 May 1;19:S64–5.
14. Verhaart IEC, Robertson A, Leary R, McMacken G, König K, Kirschner J, et al. A multi-source approach to determine SMA incidence and research ready population. J Neurol. 2017 Jul 1;264(7):1465–73.
15. Ogino S, Wilson R, Gold B. New insights on the evolution of the SMN1 and SMN2 region: simulation and meta-analysis for allele and haplotype frequency calculations | European Journal of Human Genetics. Eur J Hum Genet. 2004;12:1015–23.
16. Rabea F, El Naofal M, Chekroun I, Khalaf M, Zaabi NA, AlZaabi K, et al. Spinal muscular atrophy genetic epidemiology and the case for premarital genomic screening in Arab populations. Commun Med. 2024 Jun 15;4(1):1–6.
17. Rouault F, Christie-Brown V, Broekgaarden R, Gusset N, Henderson D, Marczuk P, et al. Disease impact on general well-being and therapeutic expectations of European Type II and

Type III spinal muscular atrophy patients - ScienceDirect. Neuromuscular Disorders. 27(5):428–38.
18. Arnold WD, Kassar D, Kissel JT. Spinal muscular atrophy: Diagnosis and management in a new therapeutic era. Muscle & Nerve. 2015 Feb;51(2):151–67.
19. Finkel R, Farrar M, Servais L, Vlodavets D, Zanoteli E, Al-Muhaizea M, et al. RAINBOWFISH: Primary efficacy and safety data in risdiplam-treated infants with presymptomatic spinal muscular atrophy (SMA). In Orlando, USA; 2024.
20. Servais L, Finkel RS, Vlodavets D, Zanoteli E, Al-Muhaizea M. RAINBOWFISH: 2-year efficacy and safety data of risdiplam in infants with presymptomatic SMA [Internet]. 2024. Available from: https://medically.roche.com/content/dam/pdmahub/restricted/neurology/wms-2024/WMS-2024-presentation-servais-RAINBOWFISH-2-year-efficacy-and-safety.pdf
21. Kokaliaris C, Evans R, Hawkins N, Mahajan A, Scott DA, Sutherland CS, et al. Long-Term Comparative Efficacy and Safety of Risdiplam and Nusinersen in Children with Type 1 Spinal Muscular Atrophy. Adv Ther. 2024 Jun 1;41(6):2414–34.
22. Qiao Y, Chi Y, Gu J, Ma Y. Safety and Efficacy of Nusinersen and Risdiplam for Spinal Muscular Atrophy: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. Brain Sci. 2023 Oct 7;13(10):1419.
23. Ribero VA, Daigl M, Martí Y, Gorni K, Evans R, Scott DA, et al. How does risdiplam compare with other treatments for Types 1-3 spinal muscular atrophy: a systematic literature review and indirect treatment comparison. J Comp Eff Res. 2022 Apr 1;11(5):347–70.
24. Mercuri E, Finkel RS, Muntoni F, Wirth B, Montes J, Main M, et al. Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care. Neuromuscular Disorders. 2018 Feb 1;28(2):103–15.
25. Finkel RS, Mercuri E, Meyer OH, Simonds AK, Schroth MK, Graham RJ, et al. Diagnosis and management of spinal muscular atrophy: Part 2: Pulmonary and acute care; medications, supplements and immunizations; other organ systems; and ethics. Neuromuscular Disorders. 2018 Mar 1;28(3):197–207.
26. Hill AM, Barber MJ, Gotham D. Estimated costs of production and potential prices for the WHO Essential Medicines List. BMJ Global Health. 2018 Jan 1;3(1):e000571.
27. Kantaria R, Baker K, Beckley-Kartey S, Gorni K, Montrocher-Ober I, Vindevoghel L. Global Risdiplam Compassionate Use Program for Patients with Type 1 or 2 Spinal Muscular Atrophy. Clinical Therapeutics. 2024 Apr 1;46(4):374–8.
28. NICE. Risdiplam for treating spinal muscular atrophy [Internet]. NICE; 2021 [cited 2024 Jul 24]. Available from: https://www.nice.org.uk/guidance/ta755
29. CADTH. CADTH Reimbursement Review: Risdiplam (Evrysdi). Canadian Journal of Health Technologies [Internet]. 2021 Nov;1(11). Available from: https://www.cadth.ca/sites/default/files/DRR/2021/SR0661-combined-report-final.pdf
30. National Centre For Pharmacoeconomics. Technical Summary Risdiplam [Internet]. 2022. Available from: https://ncpe.ie/wp-content/uploads/2022/03/Technical-summary-Risdiplam-HTAID-21006.pdf
31. HSE. Managed Access Protocol – Risdiplam (Evrysdi®) for the treatment of 5q Spinal Muscular Atrophy [Internet]. 2023. Available from: https://www.hse.ie/eng/about/who/cspd/medicines-management/managed-access-protocols/risdiplam-evrysdi/risdiplam-evrysdi-managed-access-protocol.pdf
32. Zorginstituut Nederland. Pakketadvies sluisgeneesmiddel risdiplam (Evrysdi) [Internet]. 2022. Available from: https://www.zorginstituutnederland.nl/binaries/zinl/documenten/adviezen/2022/07/15/pakketadvies-sluisgeneesmiddel-risdiplam-evrysdi/Brief+aan+minister+van+VWS+over+pakketadvies+sluisgeneesmiddel+risdiplam+%28Evrysdi%29.pdf

33. Ministerie van Volksgezondheid W en S. Advice - Extension of reimbursement conditions for risdiplam (Evrysdi®) - Report - National Health Care Institute [Internet]. Ministerie van Volksgezondheid, Welzijn en Sport; 2023 [cited 2024 Jul 24]. Available from: https://english.zorginstituutnederland.nl/publications/reports/2023/12/20/advice-extension-of-reimbursement-conditions-for-risdiplam-evrysdi
34. PBAC. Risdiplam, Powder for oral solution 0.75mg per 1ml, 80ml, Evrysdi. 2021.
35. Conitec. Risdiplam para o tratamento de atrofia muscular espinhal (AME) tipo I [Internet]. 2022. Available from: http://antigo-conitec.saude.gov.br/images/Relatorios/2022/20220314_Relatorio_709_risdiplam_AMEtipoI.pdf
36. Haute Autorité de Santé. AVIS ECONOMIQUE EVRYSDI (risdiplam) Amyotrophie spinale (SMA) [Internet]. 2021. Available from: https://www.has-sante.fr/upload/docs/application/pdf/2021-10/evrysdi_20072021_avis_economique.pdf
37. Infarmed. RELATÓRIO PÚBLICO DE AVALIAÇÃO EVRYSDI (RISDIPLAM). 2023.
38. Scottish Medicines Consortium. risdiplam 0.75mg/mL powder for oral solution (Evrysdi®) [Internet]. 2022. Available from: https://www.scottishmedicines.org.uk/media/6976/risdiplam-evrysdi-final-jan-2022-amended-040722-for-website.pdf
39. NHS. National Services Scotland. 2024 [cited 2024 Jul 24]. Ultra-orphan medicines. Available from: https://www.nss.nhs.scot/specialist-healthcare/financial-risk-share/ultra-orphan-medicines/
40. Pharmac. Pharmac | Te Pātaka Whaioranga | NZ Government. 2023 [cited 2024 Jul 24]. Decision to fund risdiplam (Evrysdi) for spinal muscular atrophy. Available from: https://pharmac.govt.nz/news-and-resources/consultations-and-decisions/decision-2023-04-11-risdiplam
41. Hu J, Sutherland CS, Ribero VA, Zhu L, Hou X, Xia Y, et al. POSC94 Cost-Effectiveness of Risdiplam Versus Nusinersen for Treating Patients with Spinal Muscular Atrophy Type 1 in China. Value in Health. 2022 Jan 1;25(1):S105.
42. Motta-Santos A, Noronha K, Reis C, Freitas D, Carvalho L, Andrade M. Cost-Effectiveness of Technologies for the Treatment of Spinal Muscular Atrophy: A Systematic Review of Economic Studies. Value in Health Regional Issues. 2024 Jul 1;42:100985.
43. Uda ME, Rivano M, Aledda L, Maioli MA, Lombardo F. Budget impact analysis: comparing the costs of nusinersen and risdiplam in the treatment of type 3 spinal muscular atrophy patients. Eur J Hosp Pharm [Internet]. 2023 Oct 27 [cited 2024 Jul 24]; Available from: https://ejhp.bmj.com/content/early/2023/10/28/ejhpharm-2023-003733
44. Boussahoua M, Sutherland CS, Ribero VA, Enache R, Lay KL, Dissez CL, et al. EE173 Cost-Effectiveness of Risdiplam for Patients with Types 1 - 3 Spinal Muscular Atrophy (SMA) in France. Value in Health. 2022 Dec 1;25(12):S87.
45. Vásquez E, Lasalvia P, Suárez F, Quitian D. EE397 Budget Impact Analysis of Risdiplam for the Treatment of Spinal Muscular Atrophy in Colombia. Value in Health. 2022 Dec 1;25(12):S133.
46. Ghetti G, Neri I, Ferrario M. EE704 Risdiplam for the Treatment of Spinal Muscular Atrophy: Impact on the National Healthcare Service During the First 15 Months of Commercialization in Italy. Value in Health. 2023 Dec 1;26(12):S190.
47. SEC. Form 10-K PTC Therapeutics, INC. [Internet]. 2023 [cited 2024 Jul 24]. Available from: https://www.sec.gov/ix?doc=/Archives/edgar/data/1070081/000155837024002196/tmb-20231231x10k.htm
48. FDA. Label: EVRYSDI® (risdiplam) for oral solution [Internet]. 2022. Available from:

https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/213535s003s005lbl.pdf
49. EMA. Evrysdi: Procedural steps taken and scientific information after the authorisation [Internet]. Available from: https://www.ema.europa.eu/en/documents/procedural-steps-after/evrysdi-epar-procedural-steps-taken-scientific-information-after-authorisation_en.pdf
50. Swissmedic. Evrysdi® (active substance: risdiplam): Indication extension in Switzerland [Internet]. 2023 [cited 2024 Jul 24]. Available from: https://www.swissmedic.ch/swissmedic/en/home/ueber-uns/publikationen/public-summary-swiss-par/public-summary-swiss-par-evrysdi-01.html
51. National Institute for Health Care Excellence. Risdiplam for treating spinal muscular atrophy [Internet]. 2021. Available from: https://www.nice.org.uk/guidance/ta755/resources/risdiplam-for-treating-spinal-muscular-atrophy-pdf-82611377117125
52. ANVISA. Consultas: Evrysdi [Internet]. [cited 2024 Jul 24]. Available from: https://consultas.anvisa.gov.br/#/bulario/detalhe/1392295?nomeProduto=EVRYSDI
53. KEI Staff. 2007 KEI Letter to WHO on the Essential Medicines List [Internet]. Knowledge Ecology International. 2007 [cited 2024 Jul 24]. Available from: https://www.keionline.org/38114
54. Balasubramaniam T. KEI submission to WIPO patent committee commenting on the US proposal on patents and health [Internet]. Knowledge Ecology International. 2012 [cited 2024 Jul 24]. Available from: https://www.keionline.org/21803
55. KEI, University of California, Universities Allied for Essential Medicines, Third World Network, Young Professionals Chronic Disease Network. Proposal for the Inclusion of Trastuzumab In the WHO Model List of Essential Medicines for the Treatment of HER2-Positive Breast Cancer [Internet]. 2013. Available from: https://keionline.org/sites/default/files/Trastuzumab_Herceptin_EMLapplication_13jan2013.pdf
56. Balasubramaniam T. KEI statement to WHO 20th Expert Committee on the Selection and Use of Essential Medicines [Internet]. Knowledge Ecology International. 2015 [cited 2024 Jul 24]. Available from: https://www.keionline.org/22732
57. KEI Staff. 2016 KEI application to WHO to put enzalutamide on the Essential Medicines List (EML) [Internet]. Knowledge Ecology International. 2016 [cited 2024 Jul 24]. Available from: https://www.keionline.org/38119
58. KEI Staff. KEI's 2016 Application for T-DM1 on the WHO EML [Internet]. Knowledge Ecology International. 2016 [cited 2024 Jul 24]. Available from: https://www.keionline.org/38116
59. Balasubramaniam T. KEI statement: 21st meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines [Internet]. Knowledge Ecology International. 2017 [cited 2024 Jul 24]. Available from: https://www.keionline.org/23316
60. KEI Staff. KEI Comments on the Draft Concept Note Concerning the WHO General Programme of Work [Internet]. Knowledge Ecology International. 2017 [cited 2024 Jul 24]. Available from: https://www.keionline.org/23450
61. Balasubramaniam T. KEI statement: 22nd meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines [Internet]. Knowledge Ecology International. 2019 [cited 2024 Jul 24]. Available from: https://www.keionline.org/30248
62. Abinader LG, Cassedy C, Balasubramaniam T, Love J. Proposal for the Inclusion of Enzalutamide in the WHO Model List of Essential Medicines for the Treatment of Metastatic Castration Resistant Prostate Cancer [Internet]. 2020. Available from: https://www.keionline.org/wp-content/uploads/KEI.WHO_.EML_.Enzalutamide.2020.pdf
63. KEI Staff. WHO expands the list of essential medicines and proposes a new working group to address ways to make highly priced essential medicines more affordable and

accessible. [Internet]. Knowledge Ecology International. 2021 [cited 2024 Jul 24]. Available from: https://www.keionline.org/36588
64. KEI Staff. KEI statement: 23rd meeting of the WHO Expert Committee on the Selection and Use of Essential Medicines [Internet]. Knowledge Ecology International. 2021 [cited 2024 Jul 24]. Available from: https://www.keionline.org/36362
65. Balasubramaniam T. EB150: Statement of Knowledge Ecology International (KEI) on the Political declaration of the third high-level meeting of the General Assembly on the prevention and control of non-communicable diseases [Internet]. Knowledge Ecology International. 2022 [cited 2024 Jul 24]. Available from: https://www.keionline.org/37274
66. Schouten A, Love J. Proposal for the Inclusion of Risdiplam in the WHO Model List of Essential Medicines for the Treatment of Spinal Muscular Atrophy [Internet]. 2022. Available from: https://cdn.who.int/media/docs/default-source/essential-medicines/2023-eml-expert-committee/applications-for-addition-of-new-medicines/a40_risdiplam.pdf?sfvrsn=16d9d918_2

ANNEX A

Pediatric quality target product profile assessment and findings

Attribute	Risdiplam Solutions (all doses)
Target population (age) (0 to ≤12 years)	**3** Suitable for whole pediatric population
Dose and dose flexibility	**3** Wide range of doses available based on weight and age of patient, allowing for precise dosing adjustments to meet the needs of all pediatric patients.
Patient acceptability 0–5 years	**3** The formulation is well-tolerated by young and older children, with acceptable taste, manageable dosing frequency, and a form that is easy for them to take.

Patient acceptability 6–12 years	
Excipient safety	**2** There are one or two excipients (Benzoate and Mannitol) in the formulation that might pose some risk to sensitive patients, but overall, the safety profile is generally acceptable and well-tolerated.
Administration Considerations	**2** The medication requires some manipulation and measuring, such as reconstituting risdiplam in water in a bottle and administration with a syringe, these steps are manageable for caregivers.
Stability, storage conditions, primary packaging material	**2** While the medication can be stored at room temperature before use, the reconstituted product requires refrigeration and protection from light.

Registration status	**3** The medication has been approved by more than one stringent regulatory authority, indicating it meets high standards of efficacy and safety, providing confidence in its use.

ANNEX B

List of prices of Risdiplam across various countries.

Chemical	Country	Date	Strength	Currency	Price (Unit)	Price (Total)	Conversion	Price (USD)	Price (USD per Unit)	Reference
Risdiplam	Australia	June 18, 2024	60mg/80 ml	AUD	$10,841.89	$10,841.89	0.66	$7,155.65	$119.26	Link
Risdiplam	Cyprus	June 18, 2024	60mg/80 ml	EUR	€8,895.82	€8,895.82	1.07	$9,518.53	$158.64	Link
Risdiplam	China	October 10, 2024	60mg/80 ml	RMB	¥3,780.00	¥3,780.00	0.14	$529.20	$8.82	(not public price)

Risdiplam	Denmark	June 18, 2024	60mg/80 ml	EUR	€10,246.84	€10,246.84	1.07	$10,964.12	$182.74	Link
Risdiplam	Finland	June 18, 2024	60mg/80 ml	EUR	€9,242.83	€9,242.83	1.07	$9,889.83	$164.83	Link
Risdiplam	Norway	June 18, 2024	60mg/80 ml	NOK	82,913.30 kr	82,913.30	0.094	$7,793.85	$129.90	Link
Risdiplam	Norway	June 18, 2024	60mg/80 ml	NOK	105,750.70 kr	105,750.70	0.094	$9,940.57	$165.68	Link
Risdiplam	Slovenia	June 18, 2024	60mg/80 ml	EUR	€7,537.77	€7,537.77	1.07	$8,065.41	$134.42	Link
Risdiplam	Malaysia	October 10, 2024	60mg/80 ml	MYR	40,400.00	40,400.00	0.233	$9,413.20	$156.89	Link
Risdiplam	Netherlands	June 18, 2024	0.75mg/ml	EUR	€752.55	€752.55	1.07	$805.23	$161.05	Link

Risdiplam	Switzerland	June 18, 2024	60mg/80 ml	CHF	CHF7,956.67	CHF7,956.67	1.13	$8,991.04	$149.85	Link
Risdiplam	Switzerland	June 18, 2024	60mg/80 ml	CHF	CHF8,409.80	CHF8,409.80	1.13	$9,503.07	$158.38	Link
Risdiplam	Saudi Arabia	June 18, 2024	60mg/80 ml	SAR	SAR46,543.40	SAR46,543.40	0.27	$12,566.72	$209.45	Link
Risdiplam	France	June 18, 2024	60mg/80 ml	EUR	€9,201.61	€9,201.61	1.07	$9,845.72	$164.10	Link
Risdiplam	USA	June 18, 2024	60mg/80 ml	USD	$13,504.05	$13,504.05	1	$13,504.05	$225.07	Link
Risdiplam	Canada	June 18, 2024	60mg/80 ml	CAN	$13,504.05	$13,504.05	0.73	$9,857.96	$193.97	Link
Risdiplam	Luxembourg	June 18, 2024	60mg/80 ml	EUR	€8,458.71	€8,458.71	1.07	$9,050.82	$193.97	Link

Risdiplam	Luxembourg	June 18, 2024	60mg/80 ml	EUR	€8,712.47	€8,712.47	1.07	$9,322.34	$193.97	Link

ANNEX C

Patents listed in Pat-Informed for “Compounds for treating spinal muscular atrophy”

Jurisdiction	Publication Number	Publication Date	Filing Date	Grant Date	Grant Number
WIPO	WO2015173181	2015-11-19	2015-05-11	-	-
Eurasian Patent Organization	-	-	2020-12-18	2021-05-18	35068
European Patent Office	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Armenia	-	-	2015-05-11	2020-04-23	35068
Austria	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Australia	2015261046	2019-04-18	2015-05-11	2019-07-30	2015261046
Azerbaijan	-	-	2022-02-04	2022-03-21	35068
Belgium	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Bulgaria	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Brazil	BR112016026205-0	2017-08-15	2015-05-11	2021-12-07	BR112016026205-0
Belarus	-	-	2022-02-15	2022-03-15	35068
Canada	2948561	-	2021-05-20	2021-08-27	2948561
Switzerland	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Chile	-	-	2015-05-11	2020-10-22	60.786

China	CN106459092A	2017-02-22	2015-05-11	2019-10-15	ZL201580027306.9
Colombia	-	2017-02-17	2015-05-11	2018-06-14	33849
Costa Rica	-	2017-02-17	2015-05-11	2022-09-07	4241
Czech Republic	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Germany	3663296	2020-06-10	2015-05-11	2023-05-17	602015083642
Denmark	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Algeria	-	-	2015-05-11	2018-01-30	9797
Spain	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Finland	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
France	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
United Kingdom	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Greece	3663296	2020-06-10	2015-05-11	2023-05-17	3112681
Hong Kong	1230197	2017-12-01	2017-04-19	2020-11-20	HK1230197
Croatia	3663296	2020-06-10	2015-05-11	2023-05-17	P20230637
Hungary	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Indonesia	2017/11662	2017-10-20	2015-05-11	2019-05-13	IDP000058655
Ireland	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Israel	-	-	2015-05-11	2020-12-01	270027
India	201647038542A	2017-02-03	2015-05-11	2020-03-11	334397
Italy	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Japan	2017-515863	2017-06-15	2015-05-11	2017-11-02	6236173
Korea, Republic of	-	-	2015-05-11	2021-05-18	10-2256013
Kazakhstan	-	-	2022-08-03	2022-09-20	35068

Lithuania	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Morocco	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Mexico	-	-	2015-05-11	2020-01-14	371050
Malaysia	-	-	2015-05-11	2020-04-01	MY-174284-A
Netherlands	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Norway	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
New Zealand	-	2019-11-29	2015-05-11	2020-03-03	725008
Peru	-	2017-03-16	2015-05-11	2021-08-26	10862
Philippines	WO2015/173181	2015-11-19	2015-05-11	2022-06-27	1-2016-502081
Poland	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Portugal	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Romania	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Serbia	3143025	2017-03-22	2015-05-11	2019-10-09	59718
Russian Federation	-	-	2015-05-11	2022-06-07	40467
Sweden	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Singapore	-	-	2015-05-11	2020-06-02	11201609497T
Slovenia	3663296	2020-06-10	2015-05-11	2023-05-17	3663296
Slovakia	3143025	2017-03-22	2015-05-11	2019-10-09	3143025
Turkey	3663296	2020-06-10	2015-05-11	2023-05-17	TR2023/005919T4
Taiwan, Province of China	201609738	2016-03-16	2015-05-14	2019-08-01	I667239
Ukraine	-	-	2015-05-11	2019-07-25	119670
United States	US-2021-0147447-A1	2021-05-20	2020-11-16	2023-11-28	11827646

Venezuela	-	2016-06-23	2015-05-18	2022-02-18	A059694
Viet Nam	-	-	2015-05-11	2021-03-31	28203
South Africa	-	-	2015-05-11	2022-05-25	2016/07026

Patents listed in Patent Scope under WO2013119916 “Compounds for treating spinal muscular atrophy”

Office	Entry Date	National Number	Published Date	Granted Date
Australia	01.08.2014	2013216870	28.08.2014	16.11.2017
New Zealand	04.08.2014	628186	29.08.2014	01.07.2016
Canada	05.08.2014	2863874	-	16.02.2021
Israel	05.08.2014	233959	-	01.03.2018
Philippines	07.08.2014	12014501786	-	-
Brazil	08.08.2014	112014019750	-	-
Chile	08.08.2014	2014002100	23.10.2015	-
Costa Rica	08.08.2014	CR2014-000376	23.01.2015	-
Thailand	08.08.2014	1401004644	-	-
United States of America	08.08.2014	14377531	-	07.03.2017
Japan	11.08.2014	2014556711	-	-
Mexico	11.08.2014	MX/a/2014/009696	24.02.2015	12.02.2018
Peru	11.08.2014	001250-2014	10.01.2015	27.02.2019
European Patent Office	03.09.2014	2013747100	17.12.2014	27.06.2018
Ecuador	04.09.2014	2014-17269	-	-
Indonesia	08.09.2014	IDP00201405359	18.03.2016	-
Colombia	09.09.2014	14198817	19.09.2014	19.05.2017

Eurasian Patent Organization	09.09.2014	201491505	30.01.2015	30.04.2018
Ukraine	09.09.2014	a201409921	-	11.06.2018
Philippines	13.08.2018	12018501711	-	-
Israel	-	254045	31.10.2017	Divisional 17.08.2017
Republic of Korea	-	1020207020788	04.08.2020	Divisional 16.07.2020

Patents listed in Patent Scope under WO2015173181 “Compounds for treating spinal muscular atrophy”

Office	Entry Date	National Number	Published Date	Granted Date
Australia	07.10.2016	2015261046	27.10.2016	22.08.2019
New Zealand	07.10.2016	725008	28.10.2016	03.03.2020
European Patent Office	17.10.2016	2015721701	22.03.2017	-
Philippines	19.10.2016	12016502081	-	-
Colombia	21.10.2016	NC2016/0003234	17.02.2017	14.06.2018
Peru	25.10.2016	002128-2016	16.03.2017	26.08.2021
Israel	31.10.2016	248653	31.01.2017	-
Mexico	07.11.2016	MX/a/2016/014547	09.03.2017	14.01.2020
Chile	08.11.2016	2016002836	21.04.2017	-
Costa Rica	08.11.2016	CR2016-000518	21.02.2017	07.09.2022
Brazil	09.11.2016	112016026205	-	-
Canada	09.11.2016	2948561	-	-
China	11.11.2016	201580027307	-	15.10.2019
India	11.11.2016	201647038542	03.02.2017	13.03.2020

Japan	14.11.2016	2016567816	-	-
Thailand	14.11.2016	1601006837	-	-
Eurasian Patent Organization	09.12.2016	201692280	31.07.2018	30.04.2020
Ukraine	13.12.2016	a201612716	-	25.07.2019
Republic of Korea	14.12.2016	1020217002966	08.02.2021	-
Serbia	29.11.2019	P-2019/1541	-	31.01.2020
Israel	-	270027	-	Divisional 17.10.2019
Singapore	-	11201609497T	-	02.06.2020