Risdiplam (EVRYSDI®) has been approved for the treatment of patients with SMA in more than 80 countries worldwide. To adjust for differing durations of risdiplam exposure across the clinical trials, AEs were also evaluated by exposure time (number of events per 272 days).

<table>
<thead>
<tr>
<th>Types</th>
<th>Number of patients</th>
<th>Total PY at risk (years)</th>
<th>Median age at first dose, years (range)</th>
<th>Median exposure, days (range)</th>
<th>Median age at first dose, years (range)</th>
<th>Median age at first dose, years (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 1</td>
<td>130</td>
<td>3.4</td>
<td>12.6 (9–16)</td>
<td>14.3 (7–24)</td>
<td>13.5 (9–24)</td>
<td>13.5 (9–24)</td>
</tr>
<tr>
<td>Type 2</td>
<td>257</td>
<td>6.3</td>
<td>1.9 (1–4)</td>
<td>4.0 (1–8)</td>
<td>3.4 (1–8)</td>
<td>3.4 (1–8)</td>
</tr>
<tr>
<td>Types 2/3</td>
<td>383</td>
<td>9.1</td>
<td>3.7 (1–16)</td>
<td>5.6 (1–16)</td>
<td>4.9 (1–16)</td>
<td>4.9 (1–16)</td>
</tr>
</tbody>
</table>

Three patients with Type 1 SMA (3.9%) had SAEs reported as related to risdiplam treatment (*P = 0.01 vs Type 2/3). In both pools, the most common SAE was pneumonia (reported in 29.9% of patients with Type 1 SMA and 5.7% of patients with Types 2/3 SMA; *P < 0.001 vs Types 2/3). Note: Data across all studies suggest that risdiplam has a favourable safety profile.

SAEs

The overall rate of SAEs per 100PY was 3.7-fold higher in patients with Type 1 SMA compared with patients with Types 2/3 SMA. The rate of SAE leading to AE leading to treatment withdrawal in one patient.

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SAEs
### Supplementary Material

#### Supplementary Table 1. AEs reported per 100PY in symptomatic patients

| Type 1 SMA | Type 2/3 SMA | All
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FREEDOM</strong></td>
<td><strong>PARTS 1 and 2</strong></td>
<td><strong>PARTS 1 and 2</strong></td>
</tr>
<tr>
<td>Intervention</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Formula</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>AEs</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>ICD-11 preferred term</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

#### Supplementary Table 2. AEs reported per 100PY in presymptomatic patients

<table>
<thead>
<tr>
<th>Type 2/3 SMA</th>
<th>Symptomatic patients</th>
<th>Presymptomatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FREEDOM</strong></td>
<td><strong>PARTS 1 and 2</strong></td>
<td><strong>PARTS 1 and 2</strong></td>
</tr>
<tr>
<td>Intervention</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Formula</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>AEs</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>ICD-11 preferred term</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

#### Supplementary Table 3. AEs reported as related to risdiplam

<table>
<thead>
<tr>
<th>Type 2/3 SMA</th>
<th>Symptomatic patients</th>
<th>Presymptomatic patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FREEDOM</strong></td>
<td><strong>PARTS 1 and 2</strong></td>
<td><strong>PARTS 1 and 2</strong></td>
</tr>
<tr>
<td>Intervention</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>Formula</td>
<td>0</td>
<td>0.0</td>
</tr>
<tr>
<td>AEs</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.8</td>
<td>0.0</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Headache</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>ICD-11 preferred term</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

### Abbreviations

- AEs: Adverse events
- CCOD: Coding not complete at CCOD.
- L: Laboratory
- C: Clinical
- UTRI: Upper respiratory tract infection
- S: Symptomatic
- P: Presymptomatic
- R: Risdiplam
- L: Laboratory
- C: Clinical
Types 2/3 SMA

5 (1.1)
2 (0.5)
3 (0.8)
3 (0.6)
1 (1.3)
22 (5.7)
5 (1.1)
URTI Nasopharyngitis
4 (5.2)
2 (2.6)
4 (0.9)
5 (1.1)
8 (1.7)
2 (2.6)
2 (0.5)
45 (9.7)
2 (0.5)
1 (1.3)
3 (3.9)
4 (5.2)
0
8 (1.7)
6 (1.5)
3 (0.6)
0
3 (3.9)
3 (0.6)
2 (2.6)
4 (0.9)
3 (0.6)
1 (0.3)
2 (0.5)
23 (29.9)
3 (3.9)

E Bertini, Pediatric Neurology Institute, Catholic University and Nemo Pediatrico, Fondazione Policlinico Gemelli IRCCS, Rome, Italy.

SAEs reported as related to risdiplam treatment

By MedDRA system organ class.

CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021) and JEWELFISH (31 Jan 2022). Error bars ±95% CI.

*In the all-patient population in either SMA type. There were no SAEs reported in the presymptomatic population. CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021) and JEWELFISH.

SAEs reported in ≥3* patients by

Constipation
Aspiration
Back pain
Femur fracture
Vomiting

Lower respiratory tract infection
Influenza
Dehydration
Respiratory failure
Pneumonia

Presymptomatic patients: the risdiplam dose.

Trents, complications, and exacerbations in the same patient, which resolved after 13 and 11 days, respectively, and did not require a change to the risdiplam dose; hypoglycaemia, metabolic acidosis and GI haemorrhage in the same patient, which resolved after 3, 12 and 4 days, respectively, and led to a change to the risdiplam dose; pneumonia and asthma in the same patient, which resolved after 25 days and did not require a change to the risdiplam dose.

Neutropenia in the context of pneumonia, which resolved after 3 and 7 days, respectively, and did not require a change to the risdiplam dose; hypoglycaemia, metabolic acidosis and GI haemorrhage in the same patient, which resolved after 3, 12 and 4 days, respectively, and led to a change to the risdiplam dose; supraventricular tachycardia in the context of hypoxia, which resolved after 1 day and did not require a change to the risdiplam dose.

Supplementary Table 4. SAEs in symptomatic patients

<table>
<thead>
<tr>
<th>SAEs reported by MedDRA preferred term (≥3* patients)</th>
<th>Type 1 N=465</th>
<th>Type 2/3 N=465</th>
<th>All N=930</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=90</td>
<td>N=90</td>
<td>N=180</td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (2.2%)</td>
<td>2 (2.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Aspiration</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Back pain</td>
<td>3 (3.3%)</td>
<td>3 (3.3%)</td>
<td>6 (3.3%)</td>
</tr>
<tr>
<td>Femur fracture</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (4.4%)</td>
<td>4 (4.4%)</td>
<td>8 (4.4%)</td>
</tr>
<tr>
<td>Lower respiratory tract infection</td>
<td>2 (2.2%)</td>
<td>2 (2.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (2.2%)</td>
<td>2 (2.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>2 (2.2%)</td>
<td>2 (2.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Respiratory failure</td>
<td>2 (2.2%)</td>
<td>2 (2.2%)</td>
<td>4 (2.2%)</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
<tr>
<td>Dehydration</td>
<td>1 (1.1%)</td>
<td>1 (1.1%)</td>
<td>2 (1.1%)</td>
</tr>
</tbody>
</table>

Supplementary Figure 1. Overall rates of SAEs over time in symptomatic patients

Supplementary Figure 2a. Rates of most frequent infection AEs over time in symptomatic patients - first 6 months†

Supplementary Figure 2b. Rates of most frequent GI AEs over time in symptomatic patients - first 6 months†

Supplementary Figure 2c. Rates of most frequent GI AEs over time in symptomatic patients - first 6 months†

Ophthalmological evaluations

- Ophthalmological examination by ophthalmologists has not shown evidence of the clinical findings over 6 to 12 months ophthalmological dataset.
- Laboratory evaluation:
- Review of all laboratory results; viral and bacterial did not show any clinically significant adverse or findings.

Abbreviations

- GI AEs per 100PY
- Infection AEs per 100PY
- CCODs: FIREFISH Parts 1 and 2 (23 Nov 2021), SUNFISH Parts 1 and 2 (6 Sep 2021) and JEWELFISH.
- Error bars ±95% CI.