Background

- Spinal muscular atrophy (SMA) is a severe, progressive, inherited neuromuscular disease leading to loss of motor function and reduced life expectancy.1
- SMA is caused by reduced levels of the survival motor neuron (SMN) protein due to deletions and/or mutations of the SMN1 gene.1
  - A second SMN gene, SMN2, produces only low levels of functional SMN protein.2
  - Increasing preclinical evidence indicates that SMA is a multisystem disorder.3
  - Therapies that increase SMN protein levels systematically may have broader therapeutic benefit than those targeting motor neurons alone.
- Risdiplam (RG7916; RO7034067) is an orally administered, centrally and peripherally distributed small molecule that modulates SMN2 pre-mRNA splicing to increase SMN protein levels.4

Study design

- JEWELFISH (NCT03032172)1 is a multicenter, open-label study primarily evaluating the safety and tolerability of once-daily oral administration of risdiplam in patients aged from 6 months to 60 years with SMA who have previously enrolled in Study BP29420 (MOONFISH5) with the splicing modifier RO6885247 or received previous treatment with nusinersen or elexiscence.6

Patients in JEWELFISH show a diversity of copy number, SMA type and ambulatory status

<table>
<thead>
<tr>
<th>All patients (N=12)</th>
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</thead>
<tbody>
<tr>
<td>Age at screening, years, median (range)</td>
<td>20 (13–52)</td>
</tr>
<tr>
<td>Gender, female/male, n (%)</td>
<td>3/9 (25.0/75.0)</td>
</tr>
<tr>
<td>Risdiplam treatment duration, median days (range)</td>
<td>303 (57–512)</td>
</tr>
<tr>
<td>SMA Type 2, n (%)</td>
<td>6 (50); 6 (50)</td>
</tr>
<tr>
<td>SMA2 copy number, n (%)</td>
<td>2 (1); 3 (3); 4 (1); 5 (1); 6 (1)</td>
</tr>
<tr>
<td>Previous therapy, n (%)</td>
<td>RO6885247 (MOONFISH)7</td>
</tr>
<tr>
<td>SMA Type 3, n (%)</td>
<td>Nusinersen</td>
</tr>
<tr>
<td>Unknown</td>
<td>5 (41.7)</td>
</tr>
<tr>
<td>Ambulatory, n (%)</td>
<td>MFM32 at baseline, median (range)</td>
</tr>
</tbody>
</table>

Risdiplam treatment has been well tolerated in JEWELFISH

- To date, risdiplam has been well tolerated, and there have been no drug-related safety findings leading to withdrawal in any patient with SMA exposed to risdiplam.
- Safety data is available from 12 patients exposed to study drug from 57–512 days:
  - Ophthalmological monitoring did not show any evidence of the retinal findings seen in preclinical monkey studies.
  - 41 mild or moderate events were reported in 10 patients.
  - The most frequent events were nasopharyngitis (5 events in 2 patients), pyrexia (3 events in 2 patients) and headache (3 events in 2 patients).
  - 4 no SAEs were reported; no adverse trends were reported after a review of all available safety laboratory results, vital signs and ECG data.
  - Study treatment was not changed in response to any AEs.

Abbreviations

- AEs, adverse events; AUCmax, area under curve; AUC0–24h, area under curve 0–24 hours; Cmax, maximum observed plasma concentration; Cmin, trough plasma concentration; ECG, electrocardiogram; MFM32, motor function measure; MRI, messenger ribonucleic acid; PD, pharmacodynamics; PK, pharmacokinetics; SAEs, serious adverse events; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

Acknowledgments

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References


Presented at the 23rd International Annual Congress of the World Muscle Society, Mendoza, Argentina, October 2–6, 2018.
JEWELFISH: Risdiplam (RG7916) increases SMN protein in non-naïve patients with SMA

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Updated protocol is currently being submitted and approvals can be expected by Q4 2018 – Q2 2019 at selected sites.

Inclusion and exclusion criteria

<table>
<thead>
<tr>
<th>Key inclusion criteria</th>
<th>Key exclusion criteria</th>
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<tbody>
<tr>
<td>• Males and females 6 months to 60 years of age inclusive (at screening)</td>
<td>• Concomitant participation in any investigational drug or device study</td>
</tr>
<tr>
<td>• Confirmed diagnosis of 5q-autosomal recessive SMA, including:</td>
<td>• Participation in any investigational drug or device study, with the exception of studies with olesoxime or nusinersen, within 90 days of screening or five half-lives of the drug, whichever is longer</td>
</tr>
<tr>
<td>- genetic confirmation of homozygous deletion or heterozygosity predictive of loss of function of the SMN1 gene</td>
<td>• History of gene or cell therapy</td>
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<tr>
<td>- clinical history, signs, or symptoms attributable to SMA.</td>
<td>• Recently initiated treatment for SMA (&lt;6 weeks prior to enrollment) with oral salbutamol or another beta 2-adrenergic agonist taken orally</td>
</tr>
<tr>
<td>• Previous enrollment in Study BP29420 (MOONFISH) with the splicing modifier RO6885247 or previous treatment with any of the following:</td>
<td>• Recent history (&lt;1 year) of ophthalmologic disease</td>
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<tr>
<td>- nusinersen (defined as having received ≥4 doses of nusinersen, provided that the last dose was received ≥90 days prior to screening)</td>
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<tr>
<td>- olesoxime (provided that the last dose was received ≤12 months and ≥90 days prior to screening).</td>
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</tbody>
</table>

Abbreviations

6MWT, six-minute walk test; AUC, area under curve; BSID-III, Bayley Scales of Infant Development, Third Edition; Cmax, maximum observed plasma concentration; Ctrough, trough plasma concentration; HINE-2, Hammersmith Infant Neurological Examination Module 2; MFM, Motor Function Measure; PD, pharmacodynamics; PK, pharmacokinetics; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMAIS, SMA independence Scale; SMN, survival of motor neuron.

Primary endpoints

- Safety
- PK:
  - Cmax
  - AUC
  - Ctrough of risdiplam and metabolites.

Secondary endpoints

- PK-PD relationship (PD investigations will include analyses of SMN2 mRNA splice forms and SMN protein)

Exploratory endpoints

- Efficacy:
  - motor functions and milestones (MFM for patients 2–60 years, RULM for patients 2–60 years, 6MWT for patients 6–60 years, BSID-III for patients 6 months–2 years, HINE-2 for patients 6 months–2 years)
  - respiratory function
  - patient-reported (for patients 12–60 years) and caregiver-reported (for patients aged 2–60 years) SMAIS

Supplementary page

(This page provides additional online content and will not be included in the main poster. Attendees will be able to view and download this page by scanning the QR code on the main poster.)