Background
- Spinal muscular atrophy (SMA) is a severe, progressive, inherited neuromuscular disease leading to loss of motor neuron function and reduced life expectancy.1
- SMA is caused by reduced levels of the survival of motor neuron (SMN) protein due to deletions or mutations of the SMN1 gene.2
  - A second SMN gene, SMN2, produces only low levels of functional SMN protein.3
  - Increasing preclinical evidence indicates that SMA is a multisystem disease.4
  - Therapies that increase SMN protein levels systemically may have broader therapeutic benefit than those targeting motor neurons alone.5
- Risdiplam (RG7916) is an orally administered, centrally and peripherally distributed SMN2 pre-mRNA splicing modifier that increases the levels of functional SMN protein.6

Study design
- JEWELFISH (NCT03032172)1 is an ongoing, multicenter, open-label study to assess the safety, tolerability and PK/PD relationship of once-daily oral administration of risdiplam in patients aged from 6 months to 60 years with SMA previously enrolled in Study BP29420 (MOONFISH)1 with the splicing modifier RO6885247 or received previous treatment with nusinersen (SPINRAZA)2,3,4; aleinoxime or onasemnogene abeparvovec-zolfin (ZOLGENSMA).5

Patients in JEWELFISH show a diversity of copy number, SMA type, ambulatory status and previous treatment
- SMA type, n (%)
  - Type 1, 14/10 (58.3/41.7)
  - Type 2, 22/23 (48.9/51.1)
  - Type 3, 2/7 (22.2/77.8)
- Gender, female/male, n (%)
  - Male, 18/16 (62.9/37.1)
  - Female, 6/10 (37.1/62.9)
- SMN2 copy number, n (%)
  - n=24, 12 (50.0)
  - n=23, 5 (21.7)
  - n=22, 2 (8.9)
  - n=21, 4 (18.2)
- SMN protein analysis from 18 patients. Analysis on new data following recruitment is ongoing.

Primary endpoints
- Safety
- PK: Mean plasma concentration
- Cmax, AUC and Cmin of risdiplam and metabolites

Secondary endpoints
- PK/PD relationship (PD investigations will include analyses of SMN2 pre-mRNA splice forms and SMN protein levels)

*Target recruitment.

Risdiplam treatment led to rapid and sustained increases in SMN protein levels in patients with Type 2 and Type 3 SMA

To date,* no drug-related safety findings have led to withdrawal in any JEWELFISH patients
- Safety data is available from 45 patients exposed to risdiplam from 0–28.9 months.
- Preclinical safety findings were not observed in any patient:
  - ophthalmologic monitoring in all clinical studies of risdiplam has not shown any evidence of the retinal findings seen in preclinical monkey studies
  - hematologic parameters have remained stable over time and no drug-induced skin findings have been observed.
- 12 AEs have been reported in 26 patients.
  - The most frequently reported AEs were upper respiratory tract infection (8 patients), headache (8 patients) and nausea (5 patients).
  - Two serious AEs were reported, which resolved with ongoing risdiplam treatment (femoral neck fracture, upper respiratory tract infection).
- No adverse trends have been reported after a review of all available safety laboratory results, vital signs and ECG data.
  - The overall AE profile of treatment in non-naive patients is consistent with that in treatment-naïve patients1
  - — The most frequently reported AEs among patients in JEWELFISH previously treated with nusinersen (n=24) were upper respiratory tract infection (7 patients) headache (6 patients) and nausea (5 patients).
  - — The most frequently reported AEs among patients in SUNFISH Part 1 (N=51) were pyrexia (27 patients), cough (17 patients), vomiting (17 patients) and upper respiratory tract infection (18 patients).

Abbreviations
- AEs, adverse events; AUC, area under the curve; Cmax, max observed plasma concentration; Cmin, trough plasma concentration; ECG, electrocardiogram; MFM, motor function measure; PD, pharmacodynamics; PK, pharmacokinetics; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

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- We would like to thank the patients and their families for participation in these studies.

References
4. ClinicalTrials.gov. NCT02240355 (Accessed September 2019);
6. JEWELFISH is currently recruiting globally.

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Image 1:
- Risdiplam treatment led to rapid and sustained increases in SMN protein levels in patients with Type 2 and Type 3 SMA.

Image 2:
- PD data has shown a sustained, >2-fold increase in median SMN protein versus baseline over 12 months of treatment.

Image 3:
- To date,* there have been no drug-related AEs leading to withdrawal in any SMA patients exposed to risdiplam.

Image 4:
- JEWELFISH is currently recruiting globally.

Image 5:
- The data cut-off was 29 May 2019.

Image 6:
- The data cut-off was 28 June 2019.