Update from SUNFISH Part 1: Safety, Tolerability and PK/PD from the Dose-Finding Study, Including Exploratory Efficacy Data in Patients with Type 2 or 3 Spinal Muscular Atrophy (SMA) Treated with Risdiplam (RG7916)

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Objective:
To determine safety, tolerability and PK/PD in patients with Type 2 or 3 SMA who received risdiplam for the duration of the SUNFISH Part 1 dose-finding study, and exploratory efficacy data in patients treated for at least 1 year in Part 1.

Background:
SMA is caused by reduced levels of survival of motor neuron (SMN) protein from deletions and/or mutations of the *SMN1* gene. While *SMN1* produces full-length SMN protein, a second gene, *SMN2*, produces low levels of functional SMN protein. Risdiplam (RG7916/RO7034067) is an investigational, orally administered, centrally and peripherally distributed small molecule that modulates *SMN2* pre-mRNA splicing towards the production of full-length *SMN2* mRNA to increase SMN protein levels.

Design/Methods:
SUNFISH (NCT02908685) is an ongoing multicenter, double-blind, placebo-controlled, operationally seamless study (randomized 2:1, risdiplam:placebo) in patients aged 2–25 years, with Type 2 or 3 SMA. Part 1 (n=51) assesses safety, tolerability and PK/PD of different risdiplam dose levels. Pivotal Part 2 (n=180) is assessing the safety and efficacy of the risdiplam dose level that was selected based on results from Part 1.

Results: SUNFISH Part 1 included patients of broad age ranges and clinical characteristics (functional level, scoliosis and contractures). To date, a sustained, >2-fold increase in median SMN protein versus baseline was seen after 1 year of risdiplam. Adverse events have been mostly mild, resolved despite ongoing treatment and reflect the underlying disease. No drug-related safety findings have led to withdrawal. Safety, tolerability and PK/PD will be presented from all patients in Part 1. Exploratory efficacy will be presented in patients treated for ≥1 year.

Conclusions: To date, risdiplam has been shown to be well tolerated and leads to sustained increases in SMN protein. Despite not being designed and powered to detect efficacy, patients on risdiplam experienced improvement over 12 months on the Motor Function Measure versus natural history.