SMN protein levels before and after treatment with risdiplam (RG7916) in patients with Type 1 to 3 SMA compared to healthy subjects

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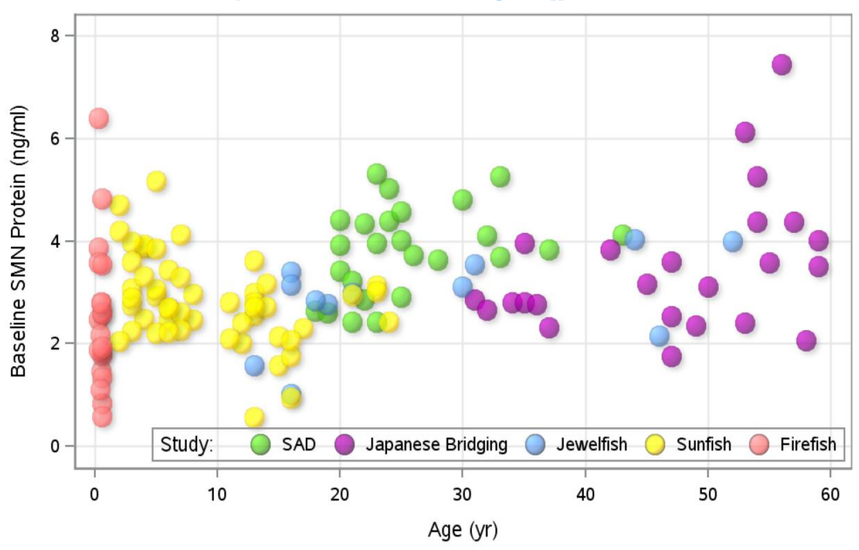
Background

- Spinal muscular atrophy (SMA) is characterized by motor neuron loss and muscle atrophy, due to reduced levels of the survival of motor neuron (SMN) protein from loss of function (deletions and/or mutations) of the *SMN1* gene.[1] While *SMN1* produces full-length SMN protein in healthy people, a second gene, *SMN2*, produces only low levels of functional SMN protein in patients with SMA.[2]
- 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, resulting in an increase of functional SMN protein.[3]
- Preclinical data suggest that the SMN protein increase seen in patients' blood following risdiplam treatment reflect SMN protein level increase in CNS, muscle and other key tissues affected in SMA.[4]
- SMN protein levels in whole blood were compared between patients with SMA Type 1, 2 or 3 and healthy subjects, prior and after treatment with risdiplam, between copy numbers, across a wide age range, and in longitudinal data over time.

Methods

- Risdiplam is currently under investigation in the following clinical studies: FIREFISH (Type 1 SMA, age 1-7 months at enrollment; NCT02913482), SUNFISH (Type 2/3 SMA, age 2-25 years; NCT02908685) and JEWELFISH (previously treated Type 2/3 SMA, age 12-60 years; NCT03032172).
- Whole blood samples were collected from all patients with SMA for measurement of SMN protein at baseline prior to treatment and at several time-points during treatment with risdiplam.
- SMN protein in blood was also analyzed from healthy participants in two Phase 1 studies with risdiplam: a Single Ascending Dose (SAD) study (NCT02633709), and a Japanese Bridging study (NCT03040635) which compared the pharmacokinetic profile in Caucasian and Japanese subjects.
- SMN protein was quantified in whole blood using an immunoassay developed by Roche Diagnostics on the Elecsys® platform.[5] All SMN protein samples were collected under standardized procedures across studies and were analyzed with the same assay, which enables a robust comparison across trials.

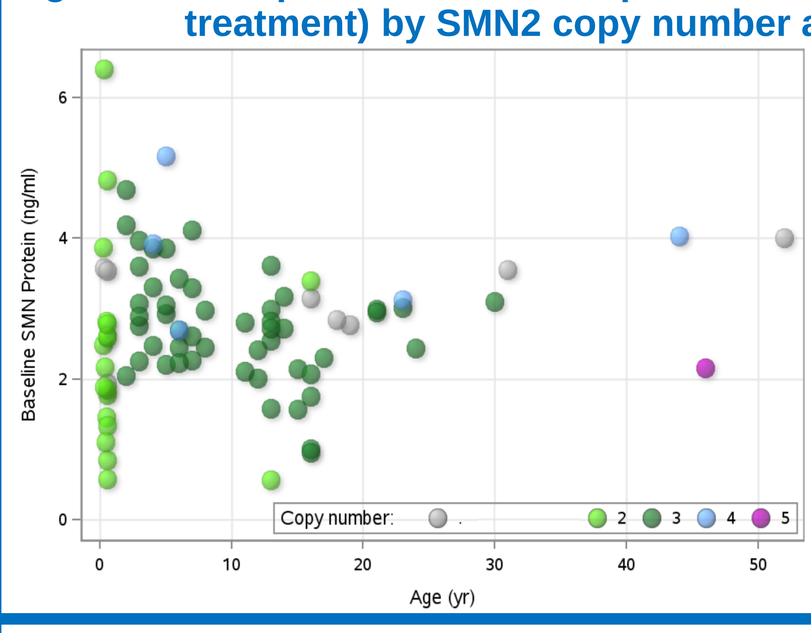
Figure 1: SMN protein in blood of patients with SMA and healthy subjects versus age (prior to treatment)



Healthy Subjects
n= 49, age 18 - 60 years
SAD: Single Ascending Dose study , n=25, age 18 - 43 years (76% White, 12% Asian, 12% Black)
Japanese Bridging: single dose study in Japanese subjects , n=24, age 31 - 60 years

Patients with SMA
n=84, age 3.3 months - 52 years
FIREFISH: 21 SMA Type 1 patients , age 3.3 - 7 months
SUNFISH: 51 SMA Type 2 and 3 patients, age 2 - 24 years
JEWELFISH: 12 non-naive SMA patients, age 13 - 52 years

Figure 2: SMN protein in blood of patients with SMA (prior to treatment) by SMN2 copy number and age



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Grey dots depict patients with unknown copy number.

Figure 3: SMN protein in blood of SMA patients (before and after 4 weeks of treatment with risdiplam, all dose levels) and healthy subjects

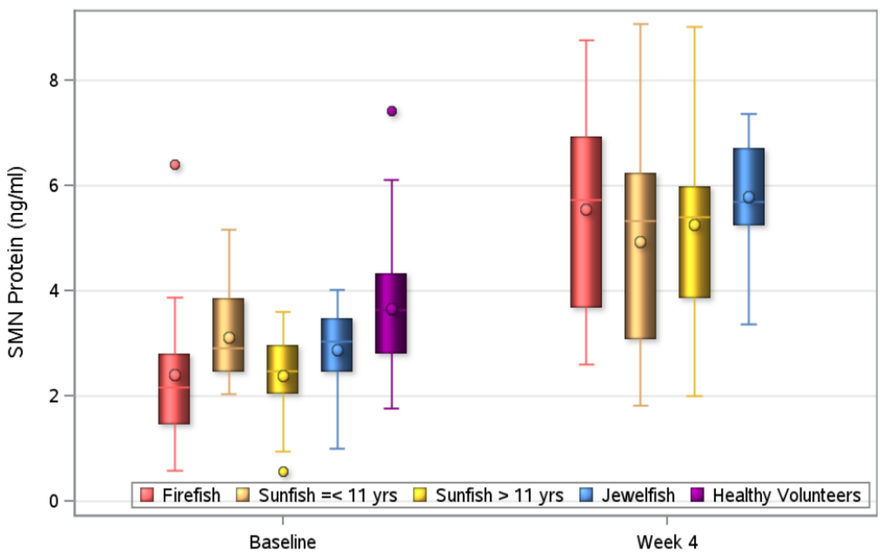

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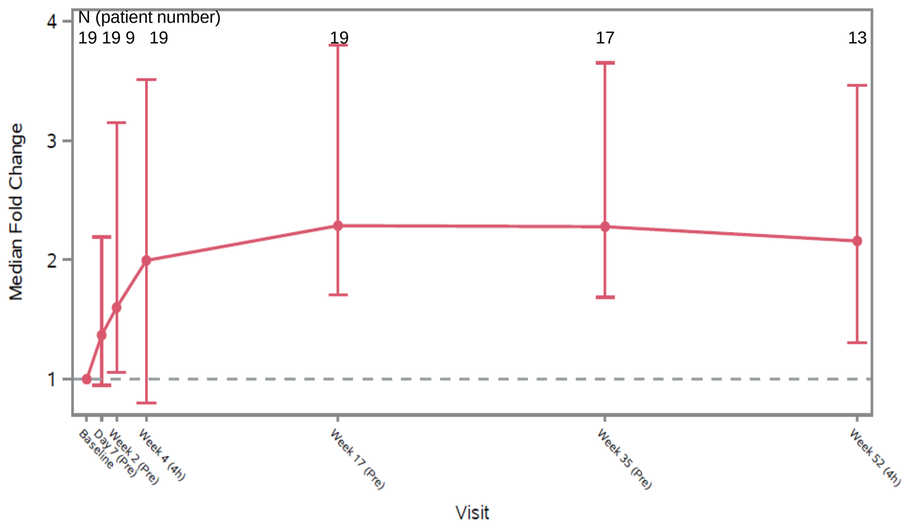
Figure 4: SMN protein increase is maintained over time with continued risdiplam treatment



SUNFISH Part 1, SMA Type 2 and 3 patients, at dose level selected for Part 2
Median change from baseline. Error bars show the minimum and maximum values.

Results

- Prior to treatment, blood SMN protein levels were lower in patients with SMA Type 1 versus Type 2/3, and patients with SMA showed on average lower levels compared to healthy adult subjects (Fig. 1 and 3).
- A trend for higher baseline SMN protein in younger patients was observed, particularly in the large data-set of SUNFISH patients with SMA Type 2 and 3 (Fig. 1 and 3). SMN2 copy number did not seem to drive SMN protein blood level, although limited data is available for 4 and 5 copy numbers (Fig. 2).
- Patients with SMA Type 1, 2 and 3 reach SMN protein levels in the range of healthy adult subjects (Fig. 3), or higher, after 4 weeks of treatment with risdiplam.
- The increase in SMN protein was maintained during continued risdiplam treatment, with long-term data currently available for a treatment duration of one year (Fig. 4).

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Conclusions

- A correlation of baseline SMN protein in blood was observed with SMA type (Type 2/3 versus Type 1) respectively the patient's age.
- After treatment with risdiplam, an increase in SMN protein to levels of adult healthy subjects, or higher, was obtained for patients across all 3 types of SMA; the largest increase (up to 6.5 fold) was observed for SMA Type 1 infants. The increase in SMN protein was maintained over time with continued treatment.
- This increase in SMN protein is expected to lead to significant clinical benefit, which is currently assessed in the ongoing Parts 2 of the FIREFISH and SUNFISH clinical trials.

References

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Abbreviations

CNS, central nervous system
SAD, Single Ascending Dose
SMA, spinal muscular atrophy
SMN, survival of motor neuron

Acknowledgments

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