patients and after treatment initiation for nusinersen-treated patients. **Results:** A total of 349 SMA1 patients (median age=1 year; 55.6% female) with median follow-up of 7.9 months were included. The proportion of patients receiving mechanical ventilation, nutritional support, and physical therapy/rehabilitation was 46.4%, 46.1%, and 22.6%. Patients had, on average, 59.4 days with medical visits/year (14.1 inpatient, 13.4 respiratory failure-related). The 45 nusinersen-treated patients had, on average, 56.6 days with medical visits/year (4.6 inpatient, 11.4 respiratory failure-related). Excluding nusinersen-related costs, mean healthcare costs PPPY were $137,627 (median: $43,167) for all patients and $92,618 ($29,425) for nusinersen-treated patients. Mean nusinersen-related costs were $191,909 ($144,487) per month for the first 3 months post-initiation and $36,882 ($16,132) per month thereafter. **Conclusions:** HRU and costs associated with SMA1 are substantial, even among patients treated with nusinersen.

P.063

SUNFISH Part 1 results and Part 2 trial design in patients with type 2/3 spinal muscular atrophy (SMA) receiving risdiplam (RG7916)

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Background: SMA is characterized 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 pre-mRNA splicing of *SMN2* to increase SMN protein levels. **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 2/3 SMA. Part 1 (n=51) assesses safety, tolerability, pharmacokinetics and pharmacodynamics of different risdiplam dose levels. Pivotal Part 2 (n=180) assesses safety and efficacy of the risdiplam dose level selected based on Part 1 results. **Results:** Part 1 results showed a sustained, >2-fold increase in median SMN protein versus baseline following 1 year of treatment. Adverse events were mostly mild, resolved despite ongoing treatment and reflected underlying disease. No drug-related safety findings have led to withdrawal (data-cut 06/17/18). SUNFISH Part 1 exploratory endpoint results and Part 2 study design will also be presented. **Conclusions:** To date, no drug-related safety findings have led to withdrawal. Risdiplam led to sustained increases in SMN protein levels.

P.064

FIREFISH Part 1: 1-year results on motor function in infants with Type 1 spinal muscular atrophy (SMA) receiving risdiplam (RG7916)

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doi: 10.1017/cjn.2019.164

Background: SMA is characterized 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 pre-mRNA splicing of *SMN2* to increase SMN protein levels. **Methods:** FIREFISH (NCT02913482) is an ongoing, multicenter, open-label operationally seamless study of risdiplam in infants aged 1–7 months with Type 1 SMA and two *SMN2* gene copies. Exploratory Part 1 (n=21) assesses the safety, tolerability, pharmacokinetics and pharmacodynamics of different risdiplam dose levels. Confirmatory Part 2 (n=40) is assessing the safety and efficacy of risdiplam. **Results:** In a Part 1 interim analysis (data-cut 09/07/18), 93% (13/14) of babies had ≥4-point improvement in CHOP-INTEND total score from baseline at Day 245, with a median change of 16 points. The number of infants meeting HINE-2 motor milestones (baseline to Day 245) increased. To date (data-cut 09/07/18), no drug-related safety findings have led to patient withdrawal. No significant ophthalmological findings have been observed. **Conclusions:** In FIREFISH Part 1, risdiplam improved motor function in infants with Type 1 SMA.

P.065

AVXS-101 gene-replacement therapy (GRT)) in presymptomatic spinal muscular atrophy (SMA): study update

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Background: SMA is a neurodegenerative disease caused by biallelic deletion/mutation of *SMN1*. Copies of a similar gene (*SMN2*) modify disease severity. In a phase 1 study, *SMN* GRT onasemnogene abeparvovec (AVXS-101) improved outcomes of symptomatic SMA patients with two *SMN2* copies (2x*SMN2*) dosed ≤6 months. Because motor neuron loss can be insidious and disease progression is rapid, early intervention is critical. This study evaluates AVXS-101 in presymptomatic SMA newborns. **Methods:** SPR1NT is a multicenter, open-label, phase 3 study enrolling ≥27 SMA patients with 2–3x*SMN2*. Asymptomatic infants ≤6 weeks receive a one-time intravenous AVXS-101 infusion ($1.1x10^{14}$ vg/kg). Safety and efficacy are

assessed through study end (18 [2x*SMN2*] or 24 months [3x*SMN2*]). Primary outcomes: independent sitting for ≥30 seconds (18 months [2x*SMN2*]) or assisted standing (24 months [3x*SMN2*]). **Results:** From April–September 2018, 7 infants received AVXS-101 (4 female; 6 with 2x*SMN2*) at ages 8–37 days. Mean baseline CHOP-INTEND score was 41.7 (n=6), which increased by 6.8, 11.0, 18.0, and 22.5 points at day 14 (n=4), month 1 (n=3), 2 (n=3), and 3 (n=2). Updated data available at the time of the congress will be presented. **Conclusions:** Preliminary data from SPR1NT show rapid motor function improvements in presymptomatic SMA patients.

P.066

AVXS-101 gene-replacement therapy (GRT) in spinal muscular atrophy type 1 (SMA1): long-term follow-up from the phase 1 clinical trial

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Background: SMA is a neurodegenerative disease caused by biallelic deletion/mutation of the survival motor neuron (*SMN1*) gene. In the phase 1 trial (NCT02122952), *SMN* GRT onasemnogene abeparvovec (AVXS-101) improved outcomes of 15 symptomatic SMA1 patients (3 at a lower dose [cohort 1] and 12 at the proposed therapeutic dose [cohort 2]). This report describes long-term follow-up study design and data from the phase 1 study. **Methods:** Patients in the phase 1 study could rollover into a long-term follow-up study (NCT03421977). The primary objective is to collect long-term safety data (serious adverse events, hospitalizations, and adverse events of special interest). Annual follow-up will occur for 15 years. Additionally, patient record transfers from local clinician(s) will be requested. Safety assessments include medical history and record review, physical examination, clinical laboratory evaluation, and pulmonary assessments. Efficacy assessments include physical examination to assess developmental milestones. **Results:** As of September 27, 2018, the oldest patients are 59.2 (cohort 1) and 52.1 (cohort 2) months old and free of permanent ventilation. Preliminary data, including survival and developmental milestones, will be presented. **Conclusions:** Patients treated with a one-time dose of AVXS-101 continue to gain strength, develop, and achieve new milestones, demonstrating a long-term, durable response.

P.067

Quality of my life: perceptions of boys with Duchenne muscular dystrophy and their parents

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Background: To attain the most comprehensive view of the quality of life (QoL) of a child with Duchenne Muscular Dystrophy (DMD), the completion of a pediatric QoL measure by the child and his/her parent and the assessment of QoL and health-related quality of life (HRQoL) as separate constructs is crucial. Previous QoL research has not assessed HRQoL as a separate construct. By using the Quality of My Life (QoML) questionnaire, our objective was to describe QoL and HRQoL in boys with DMD based on child- and parent-reports. **Methods:** Parent and child dyads identified via the Canadian Neuromuscular Disease Registry received QoML questionnaires (2013-2016). Children and parent-proxy each completed the QoL and HRQoL Visual Analog Scales. Responses were marked on a 10-cm line, with higher scores (max=10) reflecting higher QoL and HRQoL. Descriptive statistics were computed for child- and parent-reports of QoL and HRQoL at three time-points. **Results:** Mean(*SD*) QoL and HRQoL scores for child- and parent-reports were: 1) Baseline (*n*=20 dyads), 8.32(*1.72*) vs. 6.73(*2.23*) and 7.63(*2.51*) vs. 6.73(*2.19*); 2)18-months (*n*=10 dyads, *n*=9 dyads), 7.83(*2.05*) vs 7.66(*1.66*) and 7.62(*2.41*) vs 7.41(*2.16*); 3) 36-months (*n*=15 dyads) 7.38(*2.00*) vs. 6.99(*1.77*) and 7.19(*2.70*) vs. 6.76(*2.26*). **Conclusions:** Boys with DMD report higher QoL and HRQoL compared to their parents.

P.068

Abnormal fatty acid metabolism is a feature of spinal muscular atrophy

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Background: Spinal muscular atrophy (SMA) is a children's neuromuscular disorder. Although motor neuron loss is a major feature of the disease, we have identified fatty acid abnormalities in SMA patients and in preclinical animal models, suggesting metabolic perturbation is also an important component of SMA. **Methods:** Biochemical, histological, proteomic, and high resolution respirometry were used. **Results:** SMA patients are more susceptible to dyslipidemia than the average population as determined by a standard lipid profile in a cohort of 72 pediatric patients. As well, we observed a non-alcoholic liver disease phenotype in apreclinical mouse model. Denervation alone was not sufficient to induce liver steatosis, as a mouse model of ALS, did not develop fatty liver. Hyperglucagonemia in $Smn^{2B/-}$mice could explain the hepatic steatosis by increasing plasma substrate availability via glycogen depletion and peripheral lipolysis. Proteomic analysis identified mitochondrion and lipid metabolism as major clusters. Alterations in mitochondrial function were revealed by high-resolution respirometry. Finally, low-fat diets led to increased survival in $Smn^{2B/-}$mice. **Conclusions:** These results provide strong evidence for lipid metabolism defects in SMA. Further investigation will be required to establish the primary mechanism of these alterations and understand how they lead to additional co-morbidities in SMA patients.