Item 7.01. Regulation FD Disclosure.

On January 27, 2018, PTC Therapeutics, Inc. (the "Company") issued a press release (the "press release") announcing the presentation of results from the FIREFISH trial in Type 1 SMA infants at the International Scientific Congress on Spinal Muscular Atrophy in Krakow, Poland. The full text of the press release issued in connection with the announcement is furnished as Exhibit 99.1 to this Report. The presentation is also attached to this Report as Exhibit 99.2 and is incorporated by reference into this Item 7.01.

Additionally, copies of three posters that were presented at the conference, 1) Mercuri et al. (L. Servais as presenting author) "Clinical Efficacy and Safety Data from SUNFISH Part 1, a Study Evaluating the Oral SMN2 Splicing Modifier RG7916 in Patients with Type 2 or 3 Spinal Muscular Atrophy" (the "SUNFISH poster"), 2) Chiriboga et al. (D. Kraus as presenting author) "Preliminary Evidence for Plasma SMN Protein Increase Upon Treatment with RO7034067 (RG7916)" (the "SMN protein poster"), and 3) Poirier et al. (L. Mueller as presenting author), "Relations between Blood Cell Uptake and Clinical Response of Patients with Type 2 and 3 Spinal Muscular Atrophy" are attached to this Report as Exhibits 99.3, 99.4 and 99.5, respectively, and are incorporated by reference into this Item 7.01.

The presentation was authored and given by Dr. Giovanni Baranello from the Fondazione Istituto Neurologico Carlo Besta in Milan, Italy. He was neither an investigator in the FIREFISH trial nor presented on behalf of the Company. The SUNFISH poster was authored by Dr. Eugenio Mercuri from the Paediatric Neurology and Nemo Center at Catholic University and Policlinico Gemelli in Rome, Italy. He was neither an investigator in the trial nor presented on behalf of the Company. The JEWELFISH poster was authored by Dr. Claudia A. Chiriboga from the Department of Neurology at Columbia University Medical Center in New York, NY, who is a third-party investigator in the trial. The SMN protein poster was authored by Dr. Daniela Zorzi from the Roche Innovation Center in Basel, Switzerland. The SUNFISH poster and the JEWELFISH poster were neither prepared nor presented by or on behalf of the Company. The Company is providing the presentation and the posters as a convenience for investors for informational purposes.

The information in this Current Report on Form 8-K, including Exhibits 99.1, 99.2, 99.3, 99.4 and 99.5 shall not be deemed to be "filed" with the Securities and Exchange Commission, nor shall it be deemed to be incorporated by reference in any filing under the Securities Act of 1933, as amended, or the Exchange Act, except as expressly set forth by specific reference in such a filing.

Forward Looking Statements:

All statements, other than those of historical fact, contained in this Current Report on Form 8-K, including those contained in Exhibits 99.1, 99.2, 99.3, 99.4 and 99.5, are forward-looking statements, including regarding any advancement of the joint development program in SMA with PTC, Roche, and SMAF, in particular as related to the timing of enrollment, completion and availability of data from either the SUNFISH Part 1 or the JEWELFISH trials; the clinical utility and potential advantages of RG7916, including its potential to impact every aspect of the disease. The Company’s actual results may differ from these forward-looking statements as a result of a variety of risks and uncertainties, including those related to the initiation, enrollment, conduct and availability of data from either the SUNFISH Part 1 or the JEWELFISH trials, as well as any such studies; and the factors discussed in the “Risk Factors” section of the Company’s most recent Quarterly Report on Form 10-Q as well as any updates to these risk factors filed from time to time in the Company’s other filings with the SEC. You should carefully consider the information in the “Risk Factors” section of the Company’s most recent Quarterly Report on Form 10-Q and other documents filed from time to time with the SEC. The forward-looking statements contained herein represent the Company’s views only as of the date of this Current Report on Form 8-K and the Company does not undertake or plan to update or revise any such forward-looking statements to reflect any change in our views, except as required by law.
Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

<table>
<thead>
<tr>
<th>Exhibit No.</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>99.1</td>
<td>Press Release, dated January 27, 2018</td>
</tr>
<tr>
<td>99.2</td>
<td>Presentation at the International Scientific Congress on Spinal Muscular Atrophy by Dr. Giovanni Baranello from the Fondazione Istituto Neurologico Carlo Besta in Milan, Italy</td>
</tr>
<tr>
<td>99.3</td>
<td>SUNFISH poster presented at the International Scientific Congress on Spinal Muscular Atrophy, authored by Dr. Eugenio Mercuri from the Paediatric Neurology and Nemo Center at Catholic University and Policlinico Gemelli in Rome, Italy</td>
</tr>
<tr>
<td>99.4</td>
<td>JEWELFISH poster presented at the International Scientific Congress on Spinal Muscular Atrophy, authored by Dr. Claudia A. Chiriboga from the Department of Neurology at Columbia University Medical Center in New York, NY</td>
</tr>
<tr>
<td>99.5</td>
<td>SMN protein poster presented at the International Scientific Congress on Spinal Muscular Atrophy, authored by Dr. Agnes Poirier from the Roche Innovation Center in Basel, Switzerland</td>
</tr>
</tbody>
</table>

Signature

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this Report to be signed on its behalf by the undersigned hereunto duly authorized.

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Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this Report to be signed by the undersigned hereunto duly authorized.
SOUTH PLAINFIELD, N.J., Jan. 27, 2018 – PTC Therapeutics, Inc. (NASDAQ: PTCT) today announced the presentation of early interim data from Part 1, the dose-finding portion of the FIREFISH study. FIREFISH is a two-part seamless, open-label, multicenter study to investigate the safety and efficacy of RG7916 in infants and babies with Type 1 SMA. RG7916 has been safe and well tolerated at all doses and there have been no drug-related safety findings leading to withdrawal. In addition, data on the ability to swallow and requirements for tracheostomy or permanent ventilation, together with overall survival were also presented. Previously published natural history data indicate that in a comparable historic cohort the median age of event-free survival for SMA Type 1 infants to be between 8 and 10.5 months. The presentation was given by Dr. Giovanni Baranello, Fondazione Istituto Neurologico Carlo Besta in Milan, Italy, at the International Scientific Congress on Spinal Muscular Atrophy in Kraków, Poland, and will be made available via a link under the investor relations section of the PTC website, www.ptcbio.com/smaeurope.

“It is exciting to show for the first time that an oral small molecule demonstrates early signs of clinical benefit,” stated Ross H. Diamond, Ph.D., Chief Executive Officer of PTC Therapeutics. “We believe a drug that distributes to both the CNS and peripheral tissues can provide an important benefit to children suffering from this devastating, fatal disease. We anticipate that the trial will transition to the pivotal portion in the coming months.”

FIREFISH (NCT02913482) is a multi-center, open-label, seamless study investigating the safety and efficacy of RG7916 in infants aged 1–7 months with Type 1 SMA and two SMN2 gene copies. The exploratory Part 1 (n=8–24) is assessing the safety, tolerability, pharmacokinetics and pharmacodynamics of RG7916 at different dose levels. In Part 1, patients receive RG7916 for at least 4 weeks (or 2 weeks after steady-state is achieved) of daily administration; patients then enter an extension phase with RG7916 for a further 2 weeks. The confirmatory Part 2 (n=40) will assess the safety and efficacy of RG7916 at the dose level selected from Part 1 over 24 months. The primary endpoint for Part 2 is the proportion of infants sitting without support for 5 seconds, assessed by the Gross Motor Scale of the BSID-III, after 12 months of treatment.
"This early interim analysis of survival and the delay to milestone events that are hallmarks of the progression of SMA in patients with type 1 SMA, is an important milestone that provides insights into the natural history of SMA.

In conjunction with other patient recruitment at the Congress that took place in Paris, France on December 5, 2017, an update of early and anticipated results in SMA patients treated with RG7916 was presented in a plenary session. This analysis is a critical step in advancing our understanding of the natural history of SMA and in informing the development of future clinical trials in this disease.

"The U.S. Food and Drug Administration has granted orphan drug designation to RG7916 for the treatment of SMA. This designation is based on early preclinical and clinical data that support the potential of RG7916 to address the underlying genetic defect in SMA by increasing SMN protein levels.

RG7916 is a small molecule that directly targets the underlying molecular deficiency of SMA by modulating SMN2 splicing to increase expression of full-length SMN protein. The data presented demonstrate exposure-dependent increases in SMN protein levels, which are consistent with the natural history of SMA. These data are also consistent with the results of the SUNFISH study, which demonstrated that RG7916 significantly increased SMN protein levels in patients with type 2 SMA. RG7916 is currently being evaluated in a phase 2/3 clinical trial in patients with type 1 SMA.

The SMA program was initially developed by PTC Therapeutics in partnership with the SMA Foundation. In November 2011, Roche gained an exclusive worldwide license to the PTC/SMA Foundation SMN2 alternative splicing program. The development of these compounds is being led by Roche and supported by a partnering agreement with PTC Therapeutics.

The SMA program is currently being developed by PTC Therapeutics in partnership with the SMA Foundation. The development of these compounds is being led by Roche and supported by a partnering agreement with PTC Therapeutics.

Kolb S, et al. Amer Neuro Assoc 2017; 883-891
Finkel R, et al. Amer Acad Neurol 2014; 810-817

About Spinal Muscular Atrophy (SMA)
SMA is a genetic disorder that occurs in babies and causes significant muscle weakness and degeneration. It is caused by a deficiency in a protein called SMN, which is necessary for the production of key structures in nerve cells and muscles. SMA is classified into four types based on severity and age of onset. There is no cure for SMA, and treatment options are limited. However, progress in understanding the underlying causes of SMA and the development of new therapies offer hope for future patients.

The SMA program is currently being developed by PTC Therapeutics in partnership with the SMA Foundation. The development of these compounds is being led by Roche and supported by a partnering agreement with PTC Therapeutics.

Kolb S, et al. Amer Neuro Assoc 2017; 883-891
Finkel R, et al. Amer Acad Neurol 2014; 810-817
muscle atrophy and death in its most severe form. It is estimated that this devastating disease affects 1 in every 11,000 children born.

**About the SMA Clinical Trials**

**FIREFISH**: An open-label, two-part clinical trial. Part 1 is a dose escalation study to enroll infants for a minimum of 4 weeks. The primary objective of Part 1 is to assess the safety profile of RG7916 in infants and determine the dose for Part 2. Part 2 is a single-blind study in approximately 40 infants with Type 1 SMA for 24 months, followed by an open-label extension.

**SUNFISH**: A double-blind, two-part, placebo-controlled trial Part 1 enrolled patients with Type 2 or 3 SMA to evaluate safety, tolerability, and PK/PD of a dose of RG7916. Part 2, in non-ambulatory patients with Type 1 or 2 SMA, will consist of safety and efficacy of the RG7916 dose level selected from Part 1.

**JEWELFISH**: An exploratory, open-label study to establish the safety and tolerability of RG7916 in people who have previously participated in a study with another therapy targeting SMN2 splicing.

**About PTC Therapeutics**

PTC is a global biopharmaceutical company focused on the discovery, development, and commercialization of novel medicines using our expertise in RNA biology. PTC’s internally discovered pipeline addresses multiple therapeutic areas, including rare disorders, oncology, and inflammation. PTC’s leading-edge technology, known as PTCiRNA technology, fundamentally changes the way we think about designing medicines to treat genetic diseases. The PTCiRNA approach has enabled PTC to develop innovative drugs for a number of rare diseases in neuromuscular disease, oncology, and inflammatory disorders. PTC has discovered all of its compounds currently under development using its proprietary technologies. Since its founding 20 years ago, PTC’s mission has focused on developing treatments to fundamentally change the lives of patients living with rare genetic disorders. The company was founded in 1998 and is headquartered in South Plainfield, New Jersey. For more information on the company, please visit our website www.ptcbio.com.

**For More Information**

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**Forward Looking Statements**

All statements, other than those of historical fact, contained in this press release, are forward-looking statements, including statements regarding: any advancement of the joint development program in SMA with PTC, Roche, and SMAF, in particular as related to the completion of enrollment, completion and evaluation of the Phase 2 clinical studies of RG7916 in Type 1 SMA patients and the period during which the...
results of the studies will become available; the clinical utility and potential advantages of RG7916, including its potential to improve or cure any of the diseases for which they are being developed, may be adversely affected by the results of the studies. In addition, there may be other factors beyond the control of PTC that could impact PTC's ability to conduct the SUNFISH and FIREFISH studies, including the ability of the companies involved in the studies to obtain necessary regulatory approvals, to complete the studies within the time frame planned, and to complete the studies successfully. Other factors that could adversely impact PTC's ability to conduct the SUNFISH and FIREFISH studies include the availability of a sufficient number of patients with spinal muscular atrophy who are eligible to participate in the studies, the availability of a sufficient number of investigators and sites to conduct the studies, and the willingness of patients to participate in the studies. PTC's scientific approach and general development progress may be adversely affected by the results of the studies. In addition, the timing and outcome of PTC's regulatory strategy and process may be adversely affected by the results of the studies. PTC's strategy, future expectations, plans and prospects, future operations, future financial position, future revenues or projected costs, and other factors described in this press release may be adversely affected by the results of the studies. These factors may include the timing and outcome of regulatory filings and approvals, the availability and duration of regulatory exclusivity periods, the availability and duration of patent protection, the availability of adequate funding, the availability of adequate manufacturing capacity, the availability of adequate supply of clinical trials materials, the ability to market and sell future products, the ability to attract and retain the necessary personnel, and the ability to obtain and enforce patents. Other factors that could adversely affect PTC's ability to conduct the SUNFISH and FIREFISH studies or the results of the studies include the ability of PTC to obtain and maintain adequate insurance coverage, the ability of PTC to obtain and maintain adequate supply of clinical trials materials, the ability of PTC to obtain and maintain adequate supply of patients, and the ability of PTC to obtain and maintain adequate manufacturing capacity. Other factors that could adversely affect PTC's ability to conduct the SUNFISH and FIREFISH studies or the results of the studies include the ability of PTC to obtain and maintain adequate supply of patients, and the ability of PTC to obtain and maintain adequate manufacturing capacity.
FIREFISH, A MULTI-CENTER, OPEN-LABEL TRIAL TO INVESTIGATE THE
SAFETY AND EFFICACY OF RG7916 IN BABIES WITH TYPE 1 SMA:
STUDY UPDATE AND REAL-LIFE EXPERIENCE OF STUDY
IMPLEMENTATION

G Baranello1, J Day2, A Klein3, E Mercrut4, I Servais5, N Deconinck6,
R Masson1, H Klatz1, C Czech7, M Gerber7, Y Cleary7, F Lee8, K Gebilin9,
S Nave1, K Gorni1 and O Khwaja1

1, 2, 3. Centro Neurologico Neurochirurgico, University of Milan; 4, 5. Department of Neurology
Stanford University, Palo Alto, CA, USA; 6, 7. University Children’s Hospital Basel, Switzerland;
8, 9. Roche Pharmaceutical Research and Early Development, Roche Innovation Center, Basel, Switzerland.
Disclosures

GB is PI in the following clinical trials in SMA: BP39055 and BP39056 (Roche); CLM37052201 (Novartis); AVXS-101 (Avexis); SMA-001 (Galapagos); PTC319-351 (PTC Therapeutics).

JF reports grants from JCR Pharmaceuticals, PTC, Aevia, Novartis, and Shire; consulting fees from JCR Pharmaceuticals, Roche, and Shire; and is a consultant for JCR Pharmaceuticals. JF has served as a consultant for JCR Pharmaceuticals; Aevia; Genzyme; and Genzyme Therapeutics. He has served on the advisory board of JCR Pharmaceuticals, Genzyme, and Genzyme Therapeutics. He has received stock options for Genzyme Therapeutics.

AL has received grants for genetic testing of spinal muscular atrophy type II patients from Roche and Genzyme, and stock options from Genzyme.

AK has received speaker and consulting fees from Biogen, PTC, Roche, and Santhera and is PI for a P. Hoffmann-La Roche and Santhera study.

DI is a consultant for F. Hoffmann-La Roche, Aevia, IONIS, and Biogen, and PI for IONIS and F. Hoffmann-La Roche studies.

LS is PI of SMA studies for Roche, Biogen, and Aevia. He has attended SABs of Biogen and Aevia and received consulting fees from Biogen.

RM has no disclosures to report.

HC, CD, MG, XG, FL, KD, and OK are current employees of F. Hoffmann-La Roche.

RG7916 is an investigational medicine and benefit/risk profile has not been fully established. The information presented is early interim data.
Introduction

• SMA is a severe, progressive neuromuscular disease leading to loss of motor function and reduced life expectancy.

• Increasing evidence suggests that SMA may be a multi-system disorder, where cells and tissues throughout the body, including motor neurons, may be selectively vulnerable to low SMN protein levels.

• RG7916 is an orally administered, centrally and peripherally distributed SMN2 pre-mRNA splicing modifier that increases SMN protein levels.
  - Preclinical data show similar RG7916 concentrations in blood, brain, and muscle tissues (Poster IIH, A. Putler et al.);
  - Similar SMN protein increases in brain and muscle in SMA mouse models following RG7916 administration (Poster IIH).

• Proof-of-mechanism of oral SMN2 splicing modifiers was previously established in preclinical models and in Type 2 and 3 SMA patients with RG7916 (Poster IIH, E. Beroukh et al.).

• The FIREPHON study aims to assess the safety and efficacy of RG7916 in babies with Type 1 SMA. This study is sponsored by F. Hoffmann-La Roche Ltd.
RG7916 modifies SMN2 splicing to produce functional SMN protein in central and peripheral compartments.
**FIREFISH: Study overview**

**Type 1 SMA 1-7 months old**

**Part 1**: Dose-finding
- Patients enrolled for Part 2
- Open-label
- Dose level selected

**Part 2**: Confirmatory
- Dose level selected for Part 2
- Active treatment
- RG7916

**Open-Label Extension**
- Active treatment
- Continued treatment
- RG7916

**Key Inclusion criteria**
- Candidate confirmation of homozygous deletion or compound heterozygous allele(s) of function of SMN2
- Clinical features as per progressive SMA type 1 criteria (10 days to 7 months of age)
- No prior participation in trials or studies of investigational drug
- Inability to tolerate gastrostomy or require ventilator or tracheostomy
- Has a medical history of a severe or fatal event related to SMA
- Recent history of a severe or fatal event related to SMA

**Key Exclusion criteria**
- Any history of drug intolerance
- Any history of a severe event related to SMA
- Patient has undergone a heart operation
- Any severe event related to SMA

**Detailed study information**
- clinicaltrials.gov/ct2/show/NCT02913482
- www.roche-sma-clinicaltrials.com

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## FIRESH: Outcome measures

<table>
<thead>
<tr>
<th>Primary endpoint</th>
<th>Part 1</th>
<th>Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Safety, tolerability, PK and PD of RG7916</td>
<td>Safety, tolerability, PK and PD of RG7916</td>
<td>% infants sitting without support for 5 seconds at 12-months assessed by Gross Motor Scale of the BSDS III</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Secondary endpoints</th>
<th>Part 1</th>
<th>Part 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Motor function (HINE-2, CHOP-INTENEX)</td>
<td>Motor function (HINE-2, CHOP-INTENEX)</td>
<td></td>
</tr>
<tr>
<td>Pharmacodynamic PK</td>
<td>Pharmacodynamic PK</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>Time-to-death or permanent ventilation</td>
<td>Time-to-death or permanent ventilation</td>
<td></td>
</tr>
<tr>
<td>Respiratory Plethysmography (RP)</td>
<td>Respiratory Plethysmography (RP)</td>
<td></td>
</tr>
<tr>
<td>Compound Muscle Action Potential Negative Peak Amplitude (CMAP)</td>
<td>Compound Muscle Action Potential Negative Peak Amplitude (CMAP)</td>
<td></td>
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</tbody>
</table>
Patient demographics and baseline characteristics from the first 13 patients and study status

- Part 1 (dose-finding) screening ongoing with a total of 10 patients enrolled*
- 10 active sites: Italy, France, USA, Belgium, Switzerland, Turkey
- Data presented here are from the first 13 patients recruited
- Part 2 expected to start Q1 2018

*Status Jan 5, 2018

<table>
<thead>
<tr>
<th>All Treatments (N=13)</th>
<th></th>
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<tbody>
<tr>
<td>Age at first dose (months)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>6.9 (6.3–6.9)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>10 (76.9)</td>
</tr>
<tr>
<td>Weight at baseline (g)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>6720 (5650–7600)</td>
</tr>
<tr>
<td>Age at diagnosis (months)</td>
<td>Median (IQR)</td>
</tr>
<tr>
<td></td>
<td>3.5 (2.1–4.6)</td>
</tr>
</tbody>
</table>
### Summary of clinical outcomes

<table>
<thead>
<tr>
<th>No patients have required tracheostomy or permanent ventilation*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No patient has lost the ability to swallow</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Able to swallow, n</td>
</tr>
<tr>
<td>Unable to swallow, n</td>
</tr>
</tbody>
</table>

*Permanent ventilation defined as ≥16 hours of assisted ventilation per day for ≥15 days or continuous intubation ≥30 days.

**Permanent ventilation defined as ≥16 hours of assisted ventilation per day for more than 2 weeks or continuous intubation ≥30 days.
Summary of safety outcomes

- Overall 10 (77%) out of 13 patients experienced at least one adverse event. Most events were mild in intensity and resolved despite ongoing treatment.
- Adverse events reported in more than one patient were pyrexia (n=3), upper respiratory tract infection (n=3), diarrhoea (n=2), vomiting (n=2), and erythema (n=2).
- Serious adverse events were reported in four patients: respiratory tract infection viral, pneumonia & neutropenia, acute respiratory failure and hypoxia.
- Ophthalmological monitoring conducted every 2 months did not show any evidence of the retinal toxicity seen in preclinical monkey studies in any patient exposed to RG57916.

- Fatal events were reported in two patients:
  - Respiratory tract infection viral with fatal outcome on study Day 21.
  - Cardiac arrest and respiratory arrest with fatal outcome on study Day 236.*

*Event reported after cut-off date November 15, therefore not included in serious adverse events count.

Reference: interim safety summary BP39056 part 1 dated 08/01/2018
Tips from real-life experience during the implementation of the FIREFISH study

- Working with patients with Type 1 SMA presents several challenges, mainly related to the age and the severity of the disease
- Challenges can affect the infants, family, and staff involved in the studies
- As SMA (and especially Type 1) is a rare and devastating disease, we are facing a GLOBALIZATION of clinical research
  - Families in countries where competing trials and therapies (e.g., nusinersen) are not available may ask to be recruited to studies or to access therapies
  - This may accelerate recruitment and development of new treatments
  - Give access to potential treatment to a higher number of patients
Tips from real-life experience during the implementation of the FIREFISH study

- Real-life experience from investigators must be used to best support patients and families during the FIREFISH trial.
- The importance of support from advocacy groups and patient/family organizations.
- Key considerations when conducting a study in Type 1 SMA include:
  - The need to coordinate a multi-disciplinary team of healthcare specialists dealing with such young babies.
  - The support to relocate families away from their home country.
  - The importance of assuring standard-of-care practices whilst patients participate in the trial.
Family relocation

- Families in countries where competing trials and therapies (e.g., nusinersen) are not available may ask to be recruited to studies or to access therapies
- Resource limitations and cultural differences
- Relocation is important for the safety of the child and for the good conduct of the study
SMA standard of care implementation has increased survival and improved quality of life of children and their families.
Clinical trials involving relocation should ensure multidisciplinary management

- A proactive and anticipatory approach is essential to modify the course of the disease
- Changing phenotype should be paralleled and supported by the implementation of standard of care (e.g., postural control or standing frame as long as the child reaches new motor milestones, etc)

The application of SoC remains essential despite the emerging therapies

- Need of consistency of management within the study (involving different sites in different countries)
- Need for training and dissemination of experience among sites and countries
Conclusions

- To date, RG7916 has been safe and well tolerated at all doses and there have been no drug-related safety findings leading to withdrawal in any SMA patients exposed to RG7916.
- Ophthalmologic monitoring did not show any evidence of the retinal toxicity seen in preclinical monkey studies in any patient exposed to RG7916.
- Early interim clinical data reported:
  - No patient lost the ability to swallow.
  - No patient has required tracheostomy or reached permanent ventilation.
- Important considerations in conducting such clinical studies:
  - Coordination of a multi-disciplinary team.
  - Family education.
  - Application of standard-of-care practices.
- Study updates will continue to be communicated at congresses in 2018.
- Part 2 of the study is expected to start in Q1 2018.
Acknowledgments

We thank all the patients who participate in these studies and their families. We thank our collaborators PTC Therapeutics and SMA Foundation. We thank the FIREFISH, SUNFISH, and JEWELFISH investigators and trial staff.
Doing now what patients need next
Updated pharmacodynamic and safety data from SUNFISH Part 1, a study evaluating the oral SMN2 splicing modifier RG7916 in patients with Type 2 or 3 spinal muscular atrophy

Eugenio Mercursi1, Giovanni Baranello1, Janbernd Kirchauer1, Laurent Servais1, Nathalie Geonnas1, Maria Carmela Pera1, Ann Caroline1, Gillian Armstrong1, Heidermaint Kneiz2, Marianne Gerber2, Christian Czech2, Yuri Cleary3, Margaret Chan4, Sangheeta Jethwa4, Stephanie Nave4, Keenja Gomi5 and Omar Khwaja6

1Pediatric Neurology and Neurocognitive Center, Catholic University and Policlinico Gemelli, Rome, Italy; 2Carlo Besta Neurological Research Institute Foundation, Developmental Neurology Unit, Milan, Italy; 3Department of Neuropediatrics and Muscle Disorders, Medical Center-University of Freiburg, Freiburg, Germany; 4Institute of Myology, Paris, France; 5Reference Center for Neuromuscular Diseases, Centre Hospitalier Régional de La Citédes Bordes, Lille, Belgium; 6Neuromuscular Reference Centre, Department of Paediatrics and Child Neurology, University Hospital Louvain, Belgium; 7DUC St Jozef Antwerp, Antwerp, Belgium; 8Roche Pharmaceuticals Research and Early Development, Roche Innovation Center Basel, Switzerland; 9Roche Products Ltd, Welwyn Garden City, United Kingdom; 10Roche Pharmaceutical Research and Early Development, Roche Innovation Center New York, New York, NY, USA

Background
- Spinal muscular atrophy (SMA) is a severe, progressive neuromuscular disease leading to loss of motor function and reduced life expectancy.
- SMA is caused by mutation or deletion of the survival-of-motor neuron 1 (SMN1) gene; a second SMN gene, SMN2, only produces low levels of functional SMN protein.
- SMA has traditionally been described as a disease of lower motor neurons; however, cells and tissues throughout the body may be vulnerable to reduced levels of SMN protein, and increasing evidence suggests that SMA is a multi-system disorder.6,7
- RG7916 is an orally administered, centrally and peripherally distributed SMN2 pre-mRNA splicing modifier that increases SMN protein levels.
- The SUNFISH study aims to assess the safety and efficacy of RG7916 in people with Type 2 or 3 SMA.
- Here, we report data from Part 1 of the SUNFISH study.

Methods
- SUNFISH study is currently recruiting participants (NCT02990685).
- Study design: SUNFISH is a multicenter, randomized, placebo-controlled, operationally seamless, Phase 2 study evaluating the efficacy and safety of RG7916 in patients with Type 2 or Type 3 SMA (Figure 1 and Table 1).
- Part 1: Exploratory: dose-finding; blinded RG7916 or placebo (2:1) in patients with Type 2 or ambulatory and non-ambulatory Type 3 SMA. First patient dosed October 20th 2016.
- Part 2: Confirmatory: efficacy and safety at the selected dose from Part 1; blinded RG7916 or placebo (2:1) for 12 months followed by open-label RG7916 until commercial availability, in patients with Type 2 or non-ambulatory Type 3 SMA. First patient dosed October 11th 2017.

Table 1: SUNFISH study overview; Type 2 or 3 SMA, 2–25 years

<table>
<thead>
<tr>
<th>Part 1 (n=51)</th>
<th>Part 2 (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inclusion/exclusion criteria</td>
<td>Key inclusion criteria</td>
</tr>
<tr>
<td>Confirmed genetic diagnosis of SMA*</td>
<td>Confirmed genetic diagnosis of SMA*</td>
</tr>
<tr>
<td>Non-ambulant</td>
<td>Able to sit independently and can raise hand to mouth</td>
</tr>
<tr>
<td>Endpoints</td>
<td>Primary endpoints</td>
</tr>
<tr>
<td>Safety, tolerability, PK and PD of RG7916</td>
<td>Change from baseline in MFM32 at Month 12</td>
</tr>
<tr>
<td>Dose selection for Part 2</td>
<td></td>
</tr>
<tr>
<td>Respiratory function at 12 months</td>
<td>SNRIP, MEP, FEV, fVC, fVmax, and PCF</td>
</tr>
<tr>
<td>SNRIP, MEP, FEV, fVC, fVmax, and PCF</td>
<td><strong>Safety</strong></td>
</tr>
</tbody>
</table>

![Figure 1: SUNFISH study design](image1)

![Figure 2: SMN2 mRNA levels versus plasma concentrations of RG7916](image2)

![Figure 3: SMN protein levels](image3)

Conclusions
- To date, RG7916 has been safe and well tolerated at all doses, and there have been no drug-related safety findings leading to withdrawal.
- BiMonthly ophthalmological monitoring did not show any evidence of retinal toxicity seen in preclinical monkey studies.
- Adverse events were mostly mild, resolved despite ongoing treatment and were reflective of the underlying disease.
- RG7916 produced a dose-dependent increase in SMN2 FL mRNA and a concomitant decrease in SMN2Δ7 mRNA (Figure 2).
- In patients with SMA, SMN protein was increased in a dose-dependent manner up to a median of 2.5-fold (Figure 3).
- Increases in SMN protein were sustained up to 250 days (Figure 3).

Table 2: Adverse events occurring in ≥2 patients in at least 1 dose group, Day 1 to 84 by starting dose

<table>
<thead>
<tr>
<th>Aged 2–25 years</th>
<th>Aged 2–11 years</th>
<th>Aged 11–25 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>Dose 1</td>
<td>Dose 2</td>
</tr>
<tr>
<td>Placebo n=16</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose 1 n=37</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose 2 n=32</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Dose 3 n=30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*All adverse events in ≥2 patients with ≥5 events for each age group are summarized below.

Acknowledgments
We would like to thank the patients and their families who participated in this study, as well as the investigators and trial staff involved in the SUNFISH study for their valuable contributions. From Roche Wingham and John Bagnato of the Roche Basler Forschung for their contributions to this study. We thank Dr. Mikko von der Mehden of the Carlo Besta Neurological Research Institute Foundation, Developmental Neurology Unit, Milan, Italy. In support of this study, we would like to thank our collaborators at PTI Therapeutics and the SMA Foundation.
Background
• The SUNFISH study aims to assess the safety and efficacy of RG7916 in people with Type 2 or 3 SMA.
• Here, we report data from Part 1 of the SUNFISH study.

Methods
• Dose selection for Part 2

Abbreviations
AUC, area under curve; C_{max}, maximum plasma concentration; C_{t}, trough plasma concentration; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; HRMs, Hematology/Functional Motor Score; tNH, maximum-expiratory nasal inspiratory flow

References
Preliminary evidence for pharmacodynamic effects of RG7916 in JEWELFISH, a study in patients with spinal muscular atrophy who previously participated in a study with another SMN2-splicing targeting therapy

C.A. Chiriboga1, E. Mercuri2, D. Fischer1, D. Kraus1, M. Alexander3, G. Armstrong4, H. Kletzli5, M. Gerber6, Y. Cleary1, K. Gelbli7, T. Bergauer7, K. Gorni8 and O. Khwaja9

1Department of Neurology, Columbia University Medical Center, New York, NY, USA; 2Pediatric Neurology and Neonatal Center, Catholic University and Policlinico Gemelli, Rome, Italy; 3Department of Neurology, University of Basel Hospital, Basel, Switzerland; 4Roche Pharmaceutical Research and Early Development, Roche Innovation Center, Basel, Switzerland; 5Roche Pharmaceutical Research and Early Development, Roche Innovation Center New York, New York, NY, USA; 6Roche Products Ltd, Welwyn Garden City, UK

Background
- Spinal muscular atrophy (SMA) is a rare hereditary neuro muscular disease caused by loss of function of the survival of motor neuron 1 (SMN1) gene.
- SMA is characterized by progressive degeneration of spinal cord motor neurons, leading to muscle weakness and atrophy.
- While SMN1 produces full-length (FL) SMN protein, a second gene, SMN2, produces only low levels of functional SMN protein.
- RG7916 is an orally available, centrally and peripherally distributed investigational small molecule designed to modify the splicing of the SMN2 pre-mRNA, resulting in increased production of SMN2 FL RNA, and subsequently SMN protein.
- Although SMA has traditionally been viewed as a disease of motor neurons, increasing evidence indicates that SMA is a multi-system or whole-body disorder. Therapies that increase SMN protein levels systemically may have the potential to have broader therapeutic benefit than those targeting the motor neurons alone.
- JEWELFISH is an exploratory, open-label study (NCT03032172) to establish the safety and tolerability of RG7916 in people who have previously participated in a study with another therapy targeting SMN2 splicing.

Study design
- JEWELFISH is a multicenter, open-label study primarily evaluating the safety and tolerability of once-daily oral administration of RG7916 in patients aged 12–60 years with Type 2 or 3 SMA who have previously participated in a study with therapy targeting SMN2 splicing (Table 1).
  - This includes patients previously enrolled in the MOONFISH study with RG7600 and those previously enrolled in studies with续文。
  - Planned enrollment is 24 patients, to include 16 previous MOONFISH patients and 8 previous nonenrollment study patients.
  - JEWELFISH will also investigate the pharmacodynamics (PD) and pharmacokinetics (PK) of RG7916 treatment in non-naive patients.
  - As planned in the study protocol, a Safety Monitoring Committee reviews all safety information from all JEWELFISH participants.

Results
- Data from 3 patients with up to 4 weeks’ exposure are shown.
- To date, no drug-related adverse events leading to study discontinuation have been observed in JEWELFISH, and no stopping rules have been met.
- Preliminary PD: data from 3 JEWELFISH patients show a rapid increase in the SMN2 FL/SMN2 mRNA ratio, with an approximately 2-fold increase at 4 hours after treatment onset. The SMN2 FL/SMN2 mRNA ratio increased up to 4-fold from baseline over 4 weeks of RG7916 treatment (Figure 1).
- SMN protein analysis indicated an increase in SMN concentration over 4 weeks of RG7916 treatment (Figure 2), with an up to 4-fold increase in the SMN ratio compared with baseline in 1 patient and up to 2-fold increase in the other 2 patients (Figure 3).

Conclusions
- All 3 patients showed increases in SMN2 FL/SMN2 mRNA ratio and SMN protein increases of up to 4-fold.
- The JEWELFISH protocol will be amended to the dose level selected for the pivotal Part 2 of SUNFISH.
- Safety and PK/PD data from SUNFISH Part 1 informed the selection of a pivotal RG7916 dose level; see Mercuri E et al. SUNFISH poster.
- To date, RG7916 has been safe and well tolerated at all doses and there have been no drug-related safety findings leading to withdrawal in any SMA patients exposed to RG7916.

Acknowledgments
We would like to thank the patients and their families for participation in these studies. This study is funded by Hoffmann-La-Roche. The authors thank Paul Girouard, Yuni Cleary and Marianne Oertel of Roche Pharmaceutical Research and Early Development, Roche Innovation Center Basel, Switzerland for data analysis support. We would also like to thank our collaborators at PTC Therapeutics and the SMA Foundation. The authors thank Craig Others, PhD, of MedQuick Media UK for providing medical writing support, which was funded by Hoffmann-La-Roche Basel, Switzerland, in accordance with Good Publication Practice (GPP3) guidelines.

Abbreviations
- AUC, area under curve; Cmax, maximum observed plasma concentration; Ctrough, trough plasma concentration; FL, full-length; PD, pharmacodynamics; PK, pharmacokinetics; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

References
reliminary evidence for pharmacodynamic effects of RG7916 in JEWELFISH, a study in patients with spinal muscular atrophy who previously participated in a study with another SMN2-splicing targeting therapy


1Department of Neurology, Columbia University Medical Center, New York, NY, USA; 2Paediatric Neurology and Nemo Center, Catholic University and Policlinico Gemelli, Rome, Italy; 3Department of Neurology, University of Basel Hospital, Basel, Switzerland; 4Roche Pharmaceutical Research and Early Development, Roche Innovation Center, Basel, Switzerland; 5Roche Pharmaceutical Research and Early Development, Roche Innovation Center New York, New York, NY, USA; 6Roche Products Ltd, Welwyn Garden City, UK

Table 1: JEWELFISH study overview

<table>
<thead>
<tr>
<th>JEWELFISH</th>
<th>Type 2 or 3 SMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Key inclusion criteria</td>
<td>• Confirmed diagnosis of 5q-autosomal recessive SMA • Any number of SMN2 gene copies allowed</td>
</tr>
<tr>
<td>Key exclusion criteria</td>
<td>• Participation in any investigational drug or device study, other than an antisense oligonucleotide targeting SMN2 splicing or SMN2 splicing modifier study, within 90 days of screening or 5 half-lives of the drug, whichever is longer • History of gene or cell therapy • Recently initiated treatment (&gt;6 months prior to enrollment) with oral salbutamol or another beta 2-adrenergic agonist taken orally • Recent history (&gt;1 year) of ophthalmologic disease</td>
</tr>
</tbody>
</table>

Primary endpoints

Safety

PK: Mean plasma concentration, Cmax, AUC and Ctrough of RG7916 and metabolites

Secondary endpoints

PD: SMN mRNA and protein levels in blood

Figure 1: SMN2 FL/SMNΔ7 mRNA ratio over time

Figure 3: The SMN protein ratio over time

Background

• Spinal muscular atrophy (SMA) is a rare hereditary neuromuscular disease caused by loss of function of the survival of motor neurons systemically may have the potential to have broader therapeutic benefit than those targeting the motor neurons alone.

• JEWELFISH is an exploratory, open-label study (NCT03032172) to establish the safety and tolerability of RG7916 in people who have previously participated in a study with another therapy targeting SMN2 splicing.5

• JEWELFISH is a multicenter, open-label study primarily evaluating the safety and tolerability of once-daily oral administration of RG7916 to adult and pediatric patients with Type 2 or 3 SMA who have previously participated in a study with therapy targeting SMN2 splicing (Table 1).

— Planned enrollment is 24 patients, to include 16 previous MOONFISH patients and 8 previous nusinersen study patients.

• JEWELFISH will also investigate the pharmacodynamics (PD) and pharmacokinetics (PK) of RG7916 treatment in non-naïve patients.

• As planned in the study protocol, a Safety Monitoring Committee reviews all safety information from all JEWELFISH participants.

Results

• Data from 3 patients with up to 4 weeks’ exposure are shown.

• To date, no drug-related adverse events leading to study discontinuation have been observed in JEWELFISH, and no stopping rules have been met.

• Preliminary data suggests a 1.5- to 2.5-fold increase in the SMN2 FL/SMNΔ7 mRNA ratio compared with baseline in 1 patient and up to 2-fold increase in the other 2 patients (Figure 3).

Conclusions

• Preclinical PD data from SUNFISH Part 1 informed the selection of a pivotal RG7916 dose level; see Mercuri E et al. SUNFISH poster.

• To date, RG7916 has been safe and well tolerated at all doses and there have been no drug-related safety findings leading to withdrawal in any SMA patients exposed to RG7916.

Acknowledgments

We would like to thank the patients and their families for participation in these studies. This study is funded by F. Hoffmann-La-Roche Basel, Switzerland, in accordance with Good Publication Practice (GPP3) guidelines.

Abbreviations

AUC, area under curve; Cmax, maximum observed plasma concentration; Ctrough, trough plasma concentration; FL = full-length; PD, pharmacodynamics; PK, pharmacokinetics; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

References

Relationship between central and peripheral SMN protein increase upon treatment with RO7034067 (RG7916)

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1 Pharmaceutical Sciences, Roche Pharma Research and Early Development, Roche Innovation Center, Basel, Switzerland
2 PTC Therapeutics, South Plainfield, NJ, USA
3 SMA Foundation, New York, NY, USA

Background
- Spinal muscular atrophy (SMA) is caused by deletion and/or mutation of the Survival Motor Neuron 1 (SMN1) gene, resulting in insufficient levels of the SMN protein, which is critical to the survival of motor neurons.1
- Increasing evidence suggests SMN depletion directly affects cells and tissues in both the CNS and the periphery, suggesting that SMA may be a multi-system disorder.2
- RO7034067 (RG7916) is an orally administered, centrally and peripherally distributed SMN2 pre-mRNA splicing modifier that increases SMN protein levels.4,5
  — RO7034067 is under investigation in the SUNFISH (Type 2/3 SMA), FIREFISH (Type 1 SMA) and JEWELFISH (non-naive Type 2/3 SMA) clinical studies.
- RO7034067 was designed to penetrate the CNS (avoiding transporter protein interaction which would restrict this) and peripheral tissues on oral administration.
- We assessed the tissue and CSF distribution of orally administered RO7034067 and effects on SMN protein levels in the CNS and peripheral tissues of preclinical models; this will inform the significance of increases in blood SMN protein levels seen in patients receiving RO7034067.

Methods
- RO7034067 tissue and CSF (to serve as a surrogate for free concentration in the brain) distribution were assessed in adult and juvenile, wildtype fVb mice, Brown Norway BN/Crl rats, Wistar Hannover Crj/W (Han) rats and cynomolgus monkeys (Macaca fascicularis).
- C/C-allele mouse model of mild SMA was derived from FVB.B6-Smnlm5Sil/m1 Smn1/Smn2/Jmpf/J strain and dosed and aged from 4 to 7 weeks old. The Δ7 mice were derived from FVB.Cp(Tg(SMN2Δ7)K2299Rmhi Tg(SMN2Δ9Rmhi) null strain and dosed post-natal Day 3.
- Levels of RO7034067 were quantified using liquid chromatography–tandem mass spectrometry (LC-MS/MS) on triplicate mass spectrometers.
- SMN protein levels were quantified using Homogeneous Time Resolved Fluorescence (Human SMN Assay Kit Classic) as previously described, and normalised to total protein concentrations. Fold increase was calculated vs vehicle.

Results
- Single or repeated, daily oral (PO) or intraperitoneal (IP) administration of RO7034067 for up to 38 weeks showed similar total drug levels in brain, muscle and CSF of mice (n=90), rats (n=148) and monkeys (n=24) (Figure 1).
  — An excellent correlation was observed between plasma levels of RO7034067 and levels in brain, muscle and CSF over a wide range of concentrations.
- Following oral administration for 7 days in cynomolgus monkeys, RO7034067 distributed to key tissues and organs including the CNS which could be affected in SMA (Figure 2).
  — Total plasma concentrations (794 ng/ml) were very similar to those in brain (783 ng/ml) and muscle (688 ng/ml) whereas CSF drug levels (53.5 ng/ml) were within the range of free compound in plasma (119 ng/ml).
- After oral administration of RO7034067 to adult C/C-allele mice (n=4 per dose; 1, 3 or 10 mg/kg/day for 10 days), and Δθ mice (n=6 or 7 per dose; 0.1, 0.3, 1 or 3 mg/kg/day for 7 days), the SMN protein increase from baseline was parallel in brain and muscle (Figure 3).
- Following oral administration of a structurally similar SMN2 splicing modifier, RO6885247 (RG8000) in C/C-allele mice, comparable fold increases in SMN protein levels in blood, muscle and brain were observed in Figure 4.

Conclusions
- RO7034067 distributes well into the CNS, CSF and peripheral tissues, including muscle, blood and brain, in mice, rats and monkeys following single or repeat oral or IP dosing.
- Oral administration of RO7034067 increased SMN protein levels to a similar magnitude in the brain and muscle of C/C and Δ7 mouse models of SMA.
- In addition, oral administration of a structurally similar SMN2 splicing modifier, RO6885247, resulted in parallel increases in SMN protein levels in the brain, blood, and muscle of C/C-allele mice.
- The data from mice and other species suggest that SMN protein level increases seen in the blood of patients following RO7034067 (RG7916) treatment reflect SMN protein level increases in CNS, muscle and other key tissues affected in SMA.

Abbreviations
- AAALAC, Association for Assessment and Accreditation of Laboratory Animal Care International; CNS, central nervous system; CSF, cerebral spinal fluid; IP, intraperitoneal injection; PO, per oral; MDRD, multi-drug resistance gene; SMA, spinal muscular atrophy; SMN, survival motor neuron.

Acknowledgements
- We would like to thank the Jackson Laboratory for providing the FVB.B6-Smnlm5Sil/m1 Smn1/Smn2/Jmpf/J strain and FVB.Cp(Tg(SMN2Δ7)K2299Rmhi Tg(SMN2Δ9Rmhi) null strain, and the Charlie River Laboratories for providing the Wistar Hannover Crj/W (Han) strain. We would also like to thank our collaborators at PTC Therapeutics and the SMA Foundation. The study was sponsored by F Hoffmann-La Roche AG, Basel, Switzerland. Writing and editorial assistance was provided by Vassa Schiza, PhD, of MedPharm Media, USA and was funded by F Hoffmann-La Roche Basel, Switzerland, in accordance with Good Publication Practice (GPP3) guidelines. All animal experiments were carried out in AAALAC-certified facilities, and protocols were approved by the Institutional Animal Care and Use Committee.
Relationship between central and peripheral SMN protein increase upon treatment with RO7034067 (RG7916)

Agnès Poirier1, Marla Weetall2, Hasane Ratni1, Katja Heinig1, Nikolai Naryshkin2, Sergey Paushkin3, Lutz Mueller1

2 PTC Therapeutics, South Plainfield, NJ, USA
3 SMA Foundation, New York, NY, USA

Figure 1: RO7034067 tissue vs. plasma concentration

RO7034067 plasma concentration vs. concentration in brain (Figure 1A; n=190), muscle (Figure 1B; n=44) and CSF (Figure 1C; n=35) of mice, rats and monkeys following single or repeat PO or IP administration.

Conclusions
• RO7034067 distributes well into the CNS, CSF and peripheral tissues, including muscle, blood and brain, in mice, rats and monkeys. RO7034067 is capable of increasing SMN protein levels in various tissues and a significant correlation was found between plasma and tissue concentrations.

Abbreviations
• MRD1, multi-drug resistance gene; SMA, spinal muscular atrophy; SMN, survival motor neuron.

References

Acknowledgements
• We would like to thank the Jackson Laboratory for providing the FVB.129(B6) Smn1tm5(Smn1/SMN2)Mrph/J strain and FVB.C57Bl6J Smn1tm5(Smn1/SMN2)Mrph/J strain. These animals were housed and maintained in LAC-certified facilities, and protocols were approved by the Institutional Animal Care and Use Committee.

Background
• Spinal muscular atrophy (SMA) is caused by deletion and/or mutation of the Survival Motor Neuron 1 (SMN1) gene, resulting in insufficient levels of the SMN protein, which is critical to the survival of motor neurons. Increasing evidence suggests SMN depletion directly affects cells and tissues in both the CNS and the periphery, suggesting that SMA may be a multi-system disorder.

• RO7034067 (RG7916) is an orally administered, centrally and peripherally distributed SMN2 pre-mRNA splicing modifier that increases SMN protein levels. RO7034067 is under investigation in the SUNFISH (Type 2/3 SMA), FIREFISH (Type 1 SMA) and JEWELFISH (non-naïve Type 2/3 SMA) clinical studies.

Methods
• In adult C/C-allele mice (n=4 per dose) dosed 1, 3 or 10 mg/kg/day PO for 10 days, and in Δ7 mice (n=6 or 7 per dose) dosed 0.1, 0.3, 1 or 3 mg/kg/day PO from post-natal 3 through 90 days, increases in blood, muscle and brain were observed in (Figure 4). Figure 2. RO7034067 tissue distribution in cynomolgus monkeys

RO7034067 concentration in plasma (ng/ml), CSF (ng/ml) and tissues (ng/g) of cynomolgus monkeys (n=2) at Day 7 following daily PO dosing (3mg/kg/day for 7 days).

RO7034067 (ng/ml or ng/g)

<table>
<thead>
<tr>
<th>Plasma</th>
<th>Monkey 1</th>
<th>Monkey 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle</td>
<td>Heart</td>
<td>Bone marrow</td>
</tr>
<tr>
<td>Free plasma</td>
<td>1000</td>
<td>1000</td>
</tr>
</tbody>
</table>

AUC0–24h@day6 = 8740 ng/h/ml

Figure 4. SMN protein fold increase from baseline in blood, brain and muscle of adult C/C-allele mice after oral administration of RO6885247 (10 mg/kg/day) PO for up to 30 days. Figure 3. SMN protein levels fold increase from baseline in brain vs. muscle in SMA mouse models following oral administration of RO7034067

0 1 2 3 4
0 1 2 3 4
0 5 10 20 25 30
0 1 2 3 4

SMN protein brain (fold inc) SMN protein muscle (fold inc) SMN protein blood (fold inc)