UNITED STATES

SECURITIES AND EXCHANGE COMMISSION

WASHINGTON, D.C. 20549

FORM 8-K

CURRENT REPORT

Pursuant to Section 13 or 15(d) of the Securities Exchange Act of 1934

Date of Report (Date of earliest event reported): **January 27, 2018**

PTC THERAPEUTICS, INC.

(Exact Name of Company as Specified in Charter)

Delaware	**001-35969**	**04-3416587**
(State or Other Jurisdiction of Incorporation)	(Commission File Number)	(IRS Employer Identification No.)

100 Corporate Court **South Plainfield, NJ** (Address of Principal Executive Offices)	**07080** (Zip Code)

Company's telephone number, including area code: **(908) 222-7000**

Not applicable

(Former Name or Former Address, if Changed Since Last Report)

Check the appropriate box below if the Form 8-K filing is intended to simultaneously satisfy the filing obligation of the registrant under any of the following provisions (*see* General Instruction A.2. below):

o Written communications pursuant to Rule 425 under the Securities Act (17 CFR 230.425)

o Soliciting material pursuant to Rule 14a-12 under the Exchange Act (17 CFR 240.14a-12)

o Pre-commencement communications pursuant to Rule 14d-2(b) under the Exchange Act (17 CFR 240.14d-2(b))

o Pre-commencement communications pursuant to Rule 13e-4(c) under the Exchange Act (17 CFR 240.13e-4(c))

Indicate by check mark whether the registrant is an emerging growth company as defined in Rule 405 of the Securities Act of 1933 (§230.405 of this chapter) or Rule 12b-2 of the Securities Exchange Act of 1934 (§240.12b-2 of this chapter).

Emerging growth company o

If an emerging growth company, indicate by check mark if the registrant has elected not to use the extended transition period for complying with any new or revised financial accounting standards provided pursuant to Section 13(a) of the Exchange Act. o

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 preliminary data from Part 1 of 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 Current Report on Form 8-K (this "Report"). A copy of 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), "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" (the "SUNFISH poster"), 2) Chiriboga et al. (D. Kraus as presenting author) "Preliminary Evidence for Pharmacodynamics 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" (the "JEWELFISH poster"), and 3) Poirier et al. (L. Mueller as presenting author), "Relationship Between Central and Peripheral SMN Protein Increase Upon Treatment with RO7034067 (RG7916)" (the "SMN protein poster"), 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, who is a third-party investigator in the trial, and was neither prepared nor presented by or 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, who is a third-party investigator in the trial. 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. Agnes Poirier 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 "filed" for purposes of Section 18 of the Securities Exchange Act of 1934, as amended (the "Exchange Act"), or otherwise subject to the liabilities of that section, nor shall it be deemed 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 evaluation of the Phase 2 clinical studies of RG7916 in 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 impact every aspect of the disease. The Company's actual results, performance or achievements could differ materially from those expressed or implied by forward-looking statements it makes 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 or FIREFISH studies and the outcome of 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 are urged to carefully consider all such factors. 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 actual results or changes in plans, prospects, assumptions, estimates or projections, or other circumstances occurring after the date of this Current Report on Form 8-K except as required by law.

Item 9.01. Financial Statements and Exhibits.

(d) Exhibits

Exhibit No.	Description
99.1	Press Release, dated January 27, 2018
99.2	Presentation at the International Scientific Congress on Spinal Muscular Atrophy by Dr. Giovanni Baranello from the Fondazione Istituto Neurologico Carlo Besta in Milan, Italy
99.3	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
99.4	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
99.5	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

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.

PTC Therapeutics, Inc.

Date: January 29, 2018

By: /s/ Mark E. Boulding

Name: Mark E. Boulding

Title: Executive Vice President and Chief Legal Officer

Preliminary Data from FIREFISH trial in Type 1 SMA Infants Presented at the International Scientific Congress on Spinal Muscular Atrophy

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[1,2]. 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 Stuart W. Peltz, 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 pivotal study evaluating the safety and efficacy of RG7916 in babies aged 1–7 months at enrollment 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. 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 infants are promising,” stated Dr. Giovanni Baranello, Fondazione Istituto Neurologico Carlo Besta in Milan, Italy. “These data, in conjunction with earlier poster presentations at the Congress from the trials in patients with type 2/3 SMA, are supportive of safety and sustained increase in SMN protein levels. Clinical trials in SMA patients require a globalization of clinical research; particularly, it is essential for a coordinated multidisciplinary team to support the babies and their families and to ensure the best standard of care to promote the higher benefit to affected children from potential new treatments.”

In addition to the oral presentation, three posters were on display during the Congress: updated pharmacodynamic and safety data from SUNFISH part 1, preliminary evidence for pharmacodynamic effects of RG7916 in JEWELFISH, and preclinical data demonstrating the relationship between central and peripheral SMN protein increase upon treatment with RG7916. The data presented demonstrate systemic and dose-dependent increase of SMN protein levels. The data from mice and other species suggest that SMN protein level increases seen in the blood of patients following RG7916 treatment reflect SMN protein level increases in the CNS, muscle and other key issues affected in SMA. In addition, RG7916 has been safe and well tolerated at all doses and there have been no drug-related safety findings leading to withdrawal.

The U.S. Food and Drug Administration granted orphan drug designation to RG7916 for the treatment of patients with SMA. RG7916 directly targets the underlying molecular deficiency of SMA by modulating SMN2 splicing to increase expression of full-length SMN2 mRNA from the SMN2 gene. An interim analysis from the first part of SUNFISH of the five cohorts treated with RG7916 for 28 days or longer demonstrated an exposure-dependent increase in SMN protein. SMA is characterized by reduced levels of SMN protein, motor neuron loss, and muscle atrophy. To date, RG7916 remains well-tolerated in patients at all doses and there have been no drug-related safety findings leading to withdrawal.

The SMA program was initially developed by PTC Therapeutics in partnership with the SMA Foundation in 2006 to accelerate the development of a treatment for SMA. 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 executed by Roche and overseen by a joint steering committee with members from PTC, Roche, and the SMA Foundation.

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

About Spinal Muscular Atrophy (SMA)

Spinal muscular atrophy (SMA) is a genetic neuromuscular disorder that is the leading genetic cause of mortality in infants and toddlers caused by a missing or defective survival of motor neuron 1 (SMN1) gene, which results in reduced levels of SMN protein. The homologous SMN2 gene is predominantly spliced to a truncated mRNA, and only produces small amounts of functional SMN protein. Insufficient levels of SMN protein are responsible for the loss of motor neurons within the spinal cord leading to

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 in at least 8 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-arm 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 several RG7916 dose levels. The pivotal SUNFISH Part 2, in non-ambulant patients with Type 2 or 3 SMA, will evaluate 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 and oncology. 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.

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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 timing of enrollment, completion and evaluation of the Phase 2 clinical studies of RG7916 in 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 impact every aspect of the disease; the timing and outcome of PTC's regulatory strategy and process; PTC's strategy, future expectations, plans and prospects, future operations, future financial position, future revenues or projected costs; and the objectives of management. Other forward-looking statements may be identified by the words "potential," "will," "promise," "expect," "plan," "target," "anticipate," "believe," "estimate," "intend," "may," "project," "possible," "would," "could," "should," "continue," and similar expressions.

PTC's actual results, performance or achievements could differ materially from those expressed or implied by forward-looking statements it makes 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 or FIREFISH studies and the outcome of such studies; events during, or as a result of, these studies that could delay or prevent further development of RG7916, including future actions or activities under the SMA joint development program; our expectations for regulatory approvals; PTC's scientific approach and general development progress; and the factors discussed in the "Risk Factors" section of PTC's most recent Quarterly Report on Form 10-Q as well as any updates to these risk factors filed from time to time in PTC's other filings with the SEC. You are urged to carefully consider all such factors.

As with any pharmaceutical under development, there are significant risks in the development, regulatory approval and commercialization of new products, including with respect to PTC's joint development program in SMA with Roche and the SMAF. There are no guarantees that any product candidate under the joint development program will receive regulatory approval in any territory or prove to be commercially successful. The forward-looking statements contained herein represent PTC's views only as of the date of this press release and PTC does not undertake or plan to update or revise any such forward-looking statements to reflect actual results or changes in plans, prospects, assumptions, estimates or projections, or other circumstances occurring after the date of this press release except as required by law.

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 Baranello[1], J Day[2], A Klein[3], E Mercuri[4], L Servais[5], N Deconinck[6], R Masson[1], H Kletzl[7], C Czech[7], M Gerber[7], Y Cleary[7], F Lee[7], K Gelblin[7], S Nave[7], K Gorni[7] and O Khwaja[7]

1. Carlo Besta Neurological Research Institute Foundation, Developmental Neurology Unit, Milan, Italy; 2. Department of Neurology, Stanford University, Palo Alto, CA, USA; 3. University Children's Hospital Basel, Basel, Switzerland; Inselspital, Bern, Switzerland; 4. Paediatric Neurology and Nemo Center, Catholic University and Policlinico Gemelli, Rome, Italy; 5. Institute of Myology, Paris, France; Reference Center for Neuromuscular Disease, Centre Hospitalier Régional de La Citadelle, Liège, Belgium; 6. Queen Fabiola Children's University Hospital and Université Libre de Bruxelles, Brussels, Belgium; Neuromuscular Reference Center UZ Ghent; Ghent, Belgium; 7. 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); CLMI070X2201 (Novartis); AVXS-101-CL-302 (Avexis); SMA-001 (Catalyst); PI in the following clinical trials in Duchenne Muscular Dystrophy: FOR_DMD; DSC/14/2357/48 (Italfarmaco); VBP15-004 (Reveragen); PTC124-GD-025o_DMD (PTC Therapeutics).

JD reports grants from: AMO Pharmaceuticals; aTyr; AveXis; Biogen; Bristol Meyers Squibb; Cytokinetics; Ionis Pharmaceuticals; Roche Pharmaceuticals; Sanofi-Genzyme; and Sarepta Therapeutics. He has served as a consultant for: AMO Pharmaceuticals; AveXis; Biogen; Cytokinetics; Ionis Pharmaceuticals; Roche Pharmaceuticals; Pfizer; Sarepta Therapeutics; Santhera Pharmaceuticals. He has patents licensed to Athena Diagnostics for genetic testing of myotonic dystrophy type 2 (US patent 7442782) and spinocerebellar ataxia type 5 (US patent 7527931).

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

EM is a consultant for F. Hoffmann-La Roche, AveXis, IONIS and Biogen, and PI for Biogen/IONIS and F. Hoffmann-La Roche studies.

LS is a PI of SMA studies for Roche, Biogen, and Avexis. He has attended SAB of Biogen and Avexis and received consultancy fees from BiogenND.

RM has no disclosures to report.

HK, CC, MG, YC, FL, KGelblin, SN, KGorni 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.

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

Introduction

- SMA is a severe, progressive neuromuscular disease leading to loss of motor function and reduced life expectancy[1]
- 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[3,4]
- 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 tissue (***Poster P48, A. Poirier et al.***)
  - Similar SMN protein increase in brain and muscle in SMA mouse models following RG7916 administration (***Poster P48***)
- Proof-of-mechanism of oral SMN2 splicing modifiers was previously established in preclinical models[5] and in Type 2 and 3 SMA patients with RG7916[6] (***Poster P46, E. Mercuri et al.***)
- The FIREFISH 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.

SMA, spinal muscular atrophy; SMN, survival of motor neuron.

1. Mercuri E, et al. *Lancet Neurol* 2012;11:443–452; 2. Acsadi G, et al. *J Neurosci Res* 2009;12:2748–2756;
3. Singh RN, et al. *Biochim Biophys Acta* 2017;1860:299–315; 4.Hamilton G and Gillingwater TH. *Trends Mol Med* 2013;19:40–50;
5. Naryshkin N, *et al. Science* 2014; 345:688–693; 6. Clinicaltrials.gov NCT02633709 Accessed December 2017

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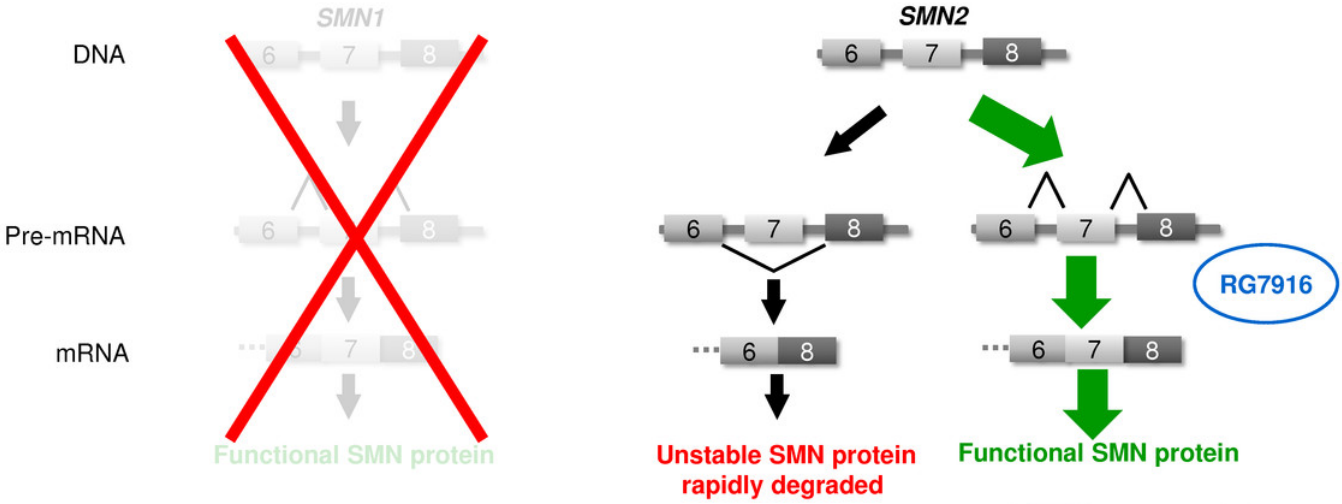
RG7916 mechanism of action

RG7916 modifies *SMN2* splicing to produce functional SMN protein in central and peripheral compartments



Pinard E, *et al. J Med Chem;* 2017;60:4444–4457.

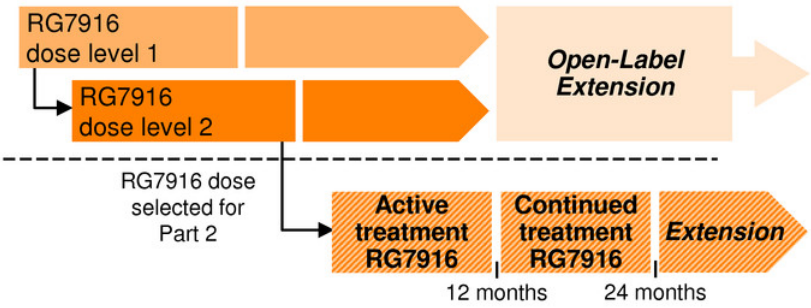
Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

FIREFISH: Study overview

FIREFISH
Type 1 SMA
1–7 months old

Part 1*: Dose-finding
Several RG7916 dose levels
n=8–24

Part 2: Confirmatory
Open-label
Dose level selected from Part 1
n=40



Key inclusion criteria	• Genetic confirmation of homozygous deletion or compound heterozygosity predictive of loss of function of SMN1 • Clinical history, signs or symptoms attributable to SMA type 1 after 28 days but prior to 3 months • Adequate nutrition at time of enrolment and willing to consider tube if required • Two SMN2 gene copies (confirmed by central testing during screening)
Key exclusion criteria	• Concomitant or previous participation in a SMN2 targeting or gene therapy study • Invasive ventilation or tracheostomy • Awake non-invasive ventilation or with awake hypoxemia (SaO_2 < 95%) with or without ventilator support • Hospitalization for pulmonary event within the last 2 months, or planned at the time of screening • Recent history (< 1 year) of ophthalmological disease

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

*Comprises minimum two dose-ranging cohorts; Patients to be enrolled in a stepwise fashion based on PK findings to minimize exposure.
https://clinicaltrials.gov/ct2/show/NCT02913482, accessed Jan 2018.

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FIREFISH: Outcome measures

	Part 1	Part 2
Primary endpoint	• **Safety, tolerability, PK and PD of RG7916** • **Dose selection for Part 2**	**% infants sitting without support for 5 seconds at 12-months assessed by Gross Motor Scale of the BSID-III**
Secondary endpoints		• Motor function (HINE-2, CHOP-INTEND) • Pharmacodynamics/PK • Safety • Time to death or permanent ventilation • Respiratory Plethysmography (RP) • Compound Muscle Action Potential Negative Peak Amplitude (CMAP)

https://clinicaltrials.gov/ct2/show/NCT02913482, accessed Jan 2018.
BSID-III, Bayley Scales of Infant and Toddler development Third Edition; CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders; HINE-2, Hammersmith Infant Neurological Examination Module 2.

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Patient demographics and baseline characteristics from the first 13 patients and study status

- Part 1 (dose-finding) screening ongoing with a total of 16 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

	All Treatments (N=13)
Age at first dose (months)	
Median (IQR)	6.9 (6.3–6.9)
Gender	
Female, n (%)	10 (76.9)
Weight at baseline (g)	
Median (IQR)	6720 (5650–7600)
Age at diagnosis (months)	
Median (IQR)	3.5 (2.1–4.6)

IQR=interquartile range.
Data current as of December 7, 2017.
RG7916 is an investigational medicine and benefit/risk profile has not yet been fully established. The information presented is from early interim analysis.

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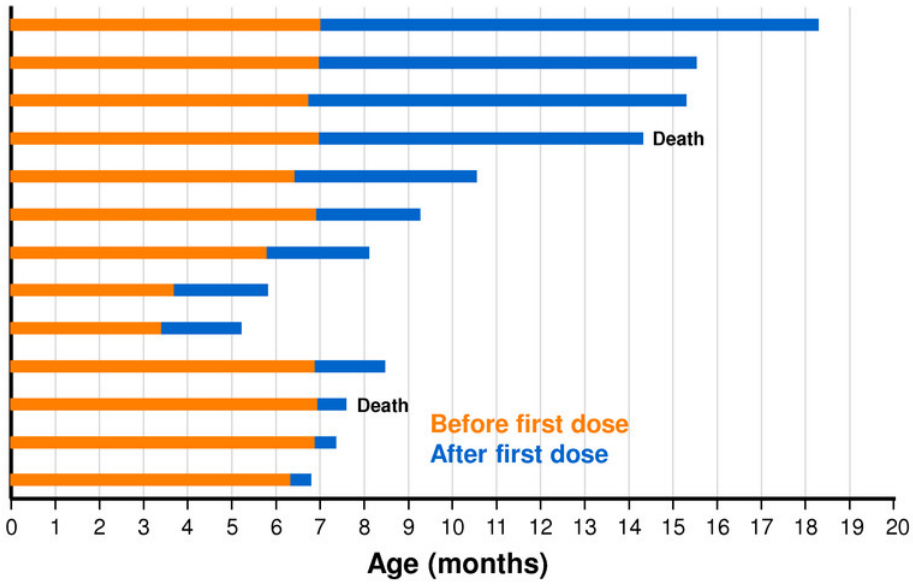
Age of patients and duration of exposure to treatment



Study duration is measured from start date of first dose to date of data extraction. Data current as of December 7, 2017.
RG7916 is an investigational medicine and benefit/risk profile has not yet been fully established. The information presented is from early interim analysis.

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Summary of clinical outcomes

No patients have required tracheostomy or permanent ventilation*

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

No patient has lost the ability to swallow

Visit	All Treatments
Baseline	**N=13**
Able to swallow, n	12
Unable to swallow, n	1
Week 8	**N=9**
Able to swallow, n	8
Unable to swallow, n	1
Week 17	**N=4**
Able to swallow, n	4
Unable to swallow, n	0
Week 26	**N=4**
Able to swallow, n	4
Unable to swallow, n	0
Week 35	**N=3**
Able to swallow, n	3
Unable to swallow, n	0

Data current as of December 7, 2017.
RG7916 is an investigational medicine and benefit/risk profile has not yet been fully established. The information presented is from early interim analysis.

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

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=5), upper respiratory tract infection (n=3), diarrhea (n=2), vomiting (n=2), 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 RG7916
- 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

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

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 (eg, 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

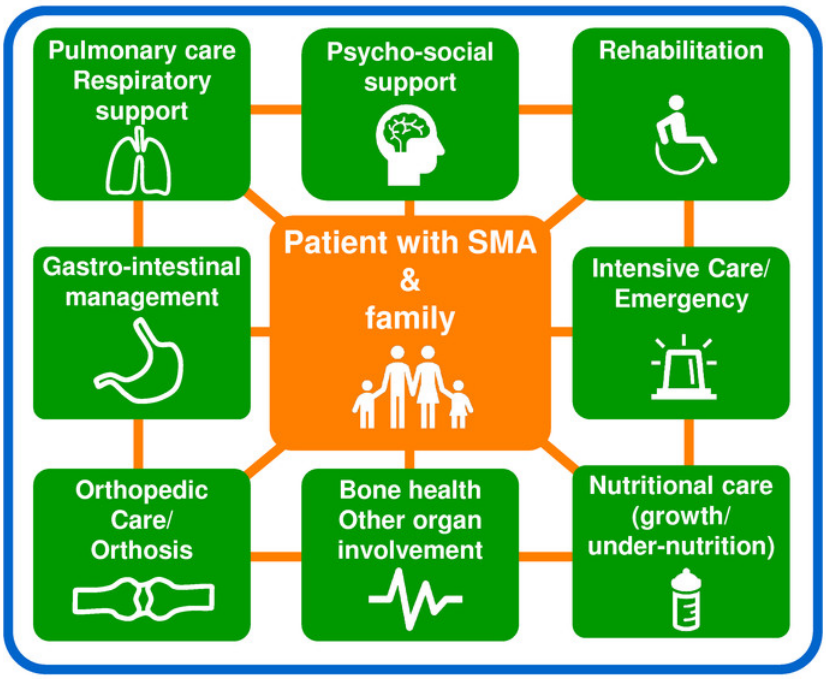
Tips from real-life experience during the implementation of the FIREFISH study

- 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 (eg, 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



Increased survival

Improved quality of life

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

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 (eg, 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

SoC, standard of care.

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:
  - Co-ordination of a multi-disciplinary team
  - Family relocation
  - 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

Roche in collaboration with SMA FOUNDATION and PTC THERAPEUTICS

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 saf a study evaluating the oral SMN2 sp patients with Type 2 or 3 spinal mus

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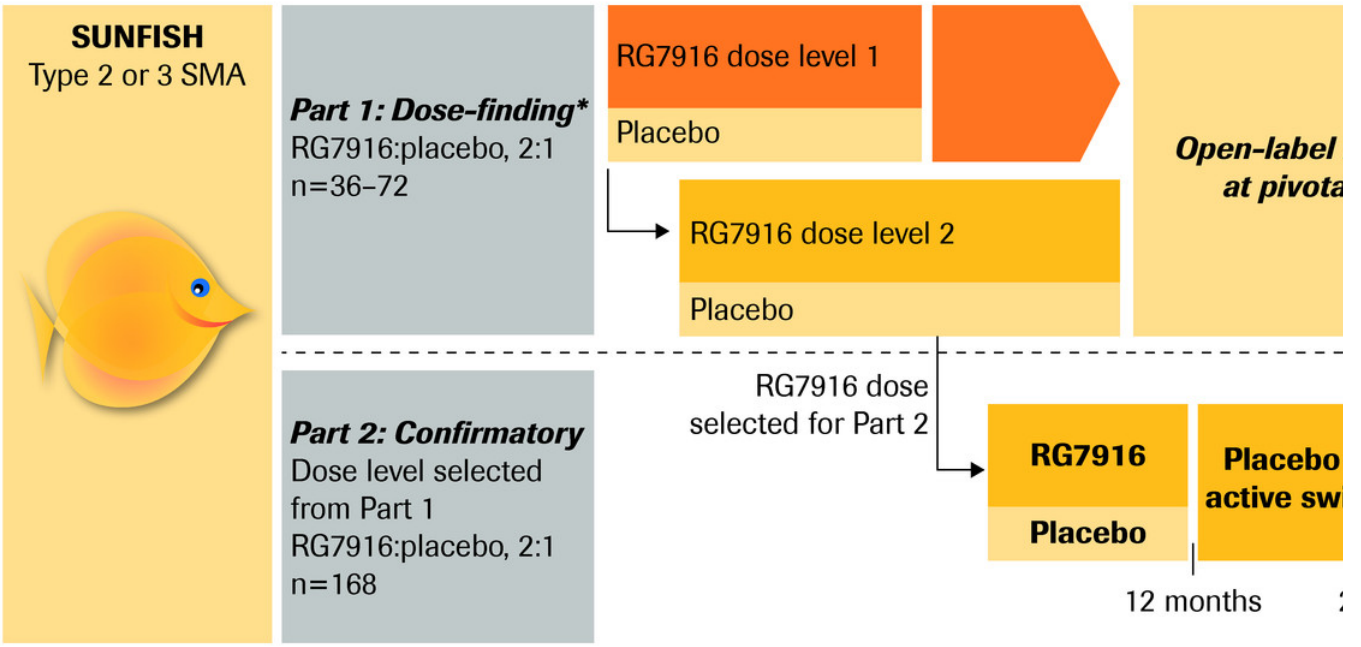
Background

- Spinal muscular atrophy (SMA) is a severe, progressive neuromuscular diseas of motor function and reduced life expectancy.[1]
- SMA is caused by mutation or deletion of the survival of motor neuron 1 (*SMI* a second SMN gene, *SMN2*, only produces low levels of functional SMN prote
- SMA has traditionally been described as a disease of lower motor neurons; ho and tissues throughout the body may be vulnerable to reduced levels of SMN increasing evidence suggests that SMA is a multi-system disorder.[3,4]
- RG7916 is an orally administered, centrally and peripherally distributed *SMN2* splicing modifier that increases SMN protein levels.
- The SUNFISH study aims to assess the safety and efficacy of RG7916 in peopl Type 2 or 3 SMA.
- Here, we report data from Part 1 of the SUNFISH study.

Methods

- **SUNFISH study is currently recruiting participants (NCT02908685)**.
- **Study design:** SUNFISH is a multicenter, randomized, placebo-controlled, op seamless, Phase 2 study evaluating the efficacy and safety of RG7916 in patie Type 3 SMA (Figure 1 and Table 1).
  - **Part 1**. Exploratory: dose-finding; blinded RG7916 or placebo (2:1) in patie or ambulatory and non-ambulatory Type 3 SMA. First patient dosed Octobe
  - **Part 2**. Confirmatory: efficacy and safety at the selected dose from Part 1; bl or placebo (2:1) for 12 months followed by open-label RG7916 until commer in patients with Type 2 or non-ambulatory Type 3 SMA. First patient dosed O

Figure 1: SUNFISH study design



*Part 1 of SUNFISH comprises 2 age groups (2–11 and 12–25 years); for each age group a minimum of two doses will be te

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

	Part 1 (n=51)	Part 2 (n=168)
Inclusion/exclusion criteria		
Key inclusion criteria	▪ Confirmed genetic diagnosis of SMA*	▪ Confirmed genetic diagnosis o ▪ Non-ambulant ▪ Able to sit independently and c to mouth
Key exclusion criteria	▪ Previous participation in an *SMN2*-targeting study or gene therapy study ▪ Planned (within 18 months) or previous (<1 year prior) sur scoliosis or hip fixation	
Endpoints		
Primary endpoints	▪ Safety, tolerability, PK and PD of RG7916 ▪ Dose selection for Part 2	▪ Change from baseline in MFM Month 12
Selected secondary endpoints		**Motor function at 12 months** ▪ HFMSE, RULM, stabilization or in MFM32, MFM domain score **Respiratory function at 12 mo** ▪ SNIP, MIP†, MEP†, FEV_1†, FVC† a

PK/PD

- *SMN2* mRNA and SMN protein
- C_{max}, C_{trough} and AUC of RG7916

QoL at 12 months

- SMAIS‡

Safety

*5q-autosomal recessive SMA. †Patients aged 6–25 years only. ‡In patients aged ≥12 years only.

Abbreviations

AUC, area under curve; C_{max}, maximum plasma concentration; C_{trough}, trough plasma concentration; FEV_1, forced expir
second; FL, full-length; FVC, forced vital capacity; HFMSE, Hammersmith Functional Motor Scale Expanded; MEP, ma
pressure; MFM, Motor Function Measure; MIP, maximum inspiratory pressure; PCF, peak cough flow; PD, pharmacody
pharmacokinetic; QoL, Quality of Life; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy; SMAIS, Sp
Atrophy Independence Scale; SMN, survival of motor neuron; SNIP, sniff nasal inspiratory pressure.

Presented at the International

Preliminary evidence for pharm RG7916 in JEWELFISH, a study muscular atrophy who previou with another *SMN2*-splicing ta

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Background

- Spinal muscular atrophy (SMA) is a rare hereditary neuromuscular disease caused b loss of function of the survival of motor neuron 1 (*SMN1*) gene.[1]
- SMA is characterized by progressive degeneration of spinal cord α-motor neurons, leading to muscle weakness and atrophy.[2]
- While *SMN1* produces full-length (FL) SMN protein, a second gene, *SMN2*, produce only low levels of functional SMN protein.[1]
- RG7916 is an orally available, centrally and peripherally distributed investigational sm molecule designed to modify the splicing of the *SMN2* pre-mRNA, resulting in increa production of *SMN2 FL* mRNA, and subsequently SMN protein.[3]
- Although SMA has traditionally been viewed as a disease of motor neurons, increasi evidence indicates that SMA is a multi-system or whole-body disorder.[4] Therapies th 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 tolerability of RG7916 in people who have previously participated in a study with ano therapy targeting *SMN2* splicing.[5]

Study design

- JEWELFISH is a multicenter, open-label study primarily evaluating the safety and

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 target *SMN2* splicing (Table 1).

  - This includes patients previously enrolled in the MOONFISH study with RG7800 a those previously enrolled in studies with nusinersen.
  - Planned enrollment is 24 patients, to include 16 previous MOONFISH patients an 8 previous nusinersen study patients.
- JEWELFISH will also investigate the pharmacodynamics (PD) and pharmacokinetics 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 PD data from 3 JEWELFISH patients show a rapid increase in the *SMN2 FL/SMNΔ7* mRNA ratio, with an approximately 2-fold increase at 4 hou after treatment onset. The *SMN2 FL/SMNΔ7* mRNA ratio increased up to 4-fold fro 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 compa 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/SMNΔ7* 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[6].
- Safety and PK/PD data from SUNFISH Part 1 informed the selection of a pivotal RG 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 RG

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writing support, which was funded by F. Hoffmann-La Roche Basel, Switzerland, in accordance with Good Publication Practice (GPP3) guidelines.

Abbreviations

AUC, area under curve; C_{max}, maximum observed plasma concentration; C_{trough}, trough plasma concentrati
FL = full-length; PD, pharmacodynamics; PK, pharmacokinetics; SMA, spinal muscular atrophy; SMN, surviv
of motor neuron.

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Relationship between central an upon treatment with RO7034067

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Background

- Spinal muscular atrophy (SMA) is caused by deletion and/or mutation of t Motor Neuron 1 (*SMN1*) gene, resulting in insufficient levels of the SMN p critical to the survival of motor neurons.[1]
- Increasing evidence suggests SMN depletion directly affects cells and tiss CNS and the periphery, suggesting that SMA may be a multi-system disor
- RO7034067 (RG7916) is an orally administered, centrally and peripherally *SMN2* pre-mRNA splicing modifier that increases SMN protein levels.[3-4]
  - RO7034067 is under investigation in the SUNFISH (Type 2/3 SMA), FI SMA) and JEWELFISH (non-naïve Type 2/3 SMA) clinical studies.
- RO7034067 was designed to penetrate the CNS (avoiding transporter pr interaction which would restrict this) and peripheral tissues on oral adm
- We assessed the tissue and CSF distribution of orally administered RO7(effects on SMN protein levels in the CNS and peripheral tissues of precl this will inform the significance of increases in blood SMN protein levels patients receiving RO7034067.

Methods

- RO7034067 tissue and CSF (to serve as surrogate for free concentration in the were assessed in adult and juvenile, wildtype FvB mice, Brown Norway B Wistar Hannover Crl:WI (Han) rats and cynomolgus monkeys (*Macaca fa*
- C/C-allele mouse model of mild SMA was derived from FVB.129(B6)-Sm SMN2)Mrph/J strain and dosed from ~7 weeks old. The Δ7 mice was de

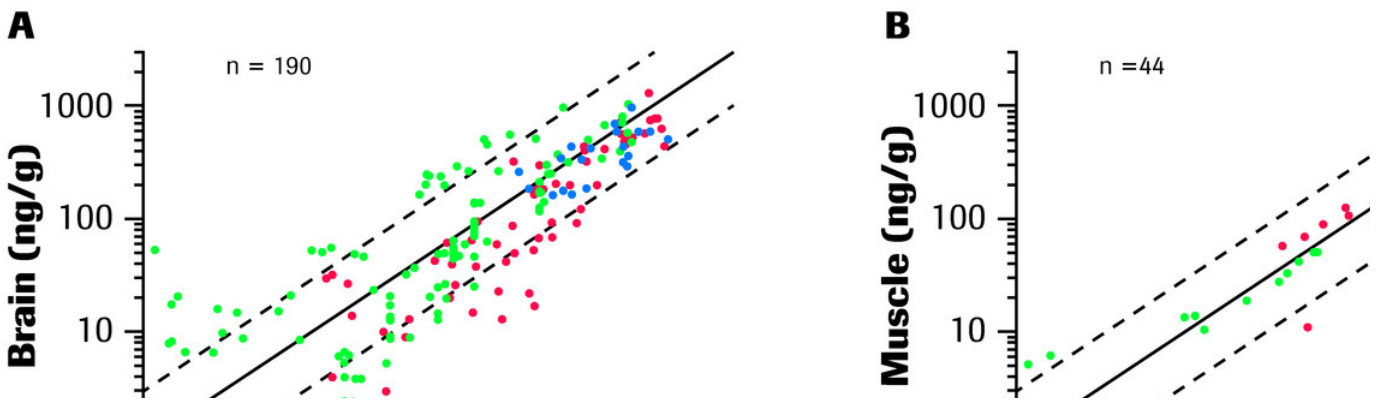
FVB.Cg-Tg(SMN2*delta7)4299Ahmb Tg(SMN2)89Ahmb strain and dosed post-natal Day 3.

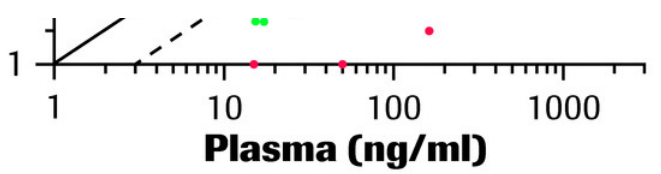
- Levels of RO7034067 were quantified using liquid chromatography–tand spectrometry (LC-MS/MS) on triple quadrupole mass spectrometers.
- SMN protein levels were quantified using Homogeneous Time Resolved (Human SMN Assay Kit Cisbio) as previously described, and normalised concentrations. Fold increase was calculated vs vehicle.

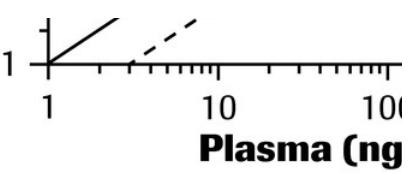
Results

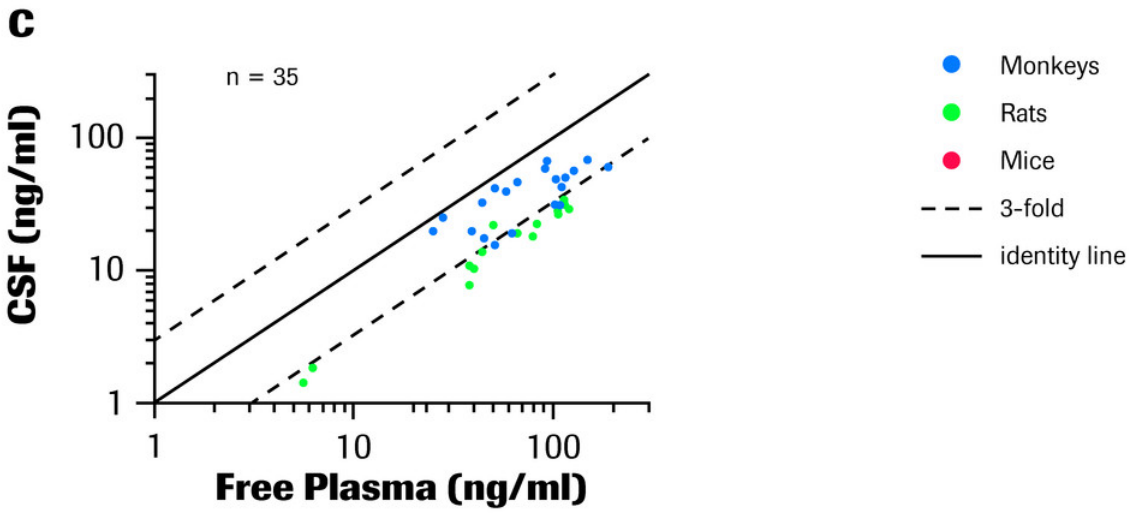
- Single or repeated, daily oral (PO) or intraperitoneal (IP) administration c for up to 39 weeks showed similar total drug levels in brain, muscle and (n=90), rats (n=148) and monkeys (n=24) (Figure 1).
  - An excellent correlation was observed between plasma levels of RO7(levels in brain, muscle and CSF over a wide range of concentrations.
- Following oral administration for 7 days in cynomolgus monkeys, RO703 distributed to key tissues and organs including the CNS and muscle that affected in SMA (Figure 2).
  - Total plasma concentrations (794 ng/ml) were very similar to those in ng/g) and muscle (668 ng/g), whereas CSF drug levels (53.5 ng/ml) w range of free compound in plasma (119 ng/ml).
- After oral administration of RO7034067 to adult C/C-allele mice (n=4 pe or 10 mg/kg/day for 10 days), and Δ7 mice (n=6 or 7 per dose; 0.1, 0.3, kg/day for 7 days), the SMN protein increase from baseline was parallel muscle (Figure 3).
- Following oral administration of a structurally similar SMN2 splicing mod RO6885247 (RG7800) in C/C-allele mice, comparable fold increases in S levels in blood, muscle and brain were observed in (Figure 4).

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
and monkeys following single or repeat PO or IP administration.