Panel II: SMA Drugs in Development

- **Thomas Blaettler MD**, Global Clinical Development Team Leader, F. Hoffmann-La Roche
- **Lawrence Charnas, MD, PhD**, Sr. Translational Medicine Expert, Musculoskeletal Diseases, Novartis Institutes for Biomedical Research
- **Wildon Farwell MD, MPH,** Medical Director, Neurology Early Clinical Development, Biogen
- **Omar Khwaja, MD PhD**, Head of Rare Disease, Research and Early Development, F. Hoffmann-La Roche
- **Stacy Rudnicki MD**, Director of Clinical Research and Development, Cytokinetics
- **Eugene Schneider MD**, Executive Director, Clinical Development, Isis Pharmaceuticals
- **Douglas M. Sproule,** MD MSc, Vice President, Clinical Development, AveXis Inc.

Thomas Blaettler, MD

CLINICAL DEVELOPMENT UPDATE: OLESOXIME

Olesoxime

- An investigational medicine, taken orally as a liquid
- Targets maintenance of motor neuron function
- Studied in a placebo-controlled, double-blind clinical trial in people with Type 2 and non-ambulatory Type 3 SMA aged 3–25[1]

Development status

- Roche consulted the FDA and EMA on the adequacy of the clinical evidence to establish the benefit–risk profile of olesoxime for the treatment of SMA
- As a result, Roche will be conducting a Phase 3 study

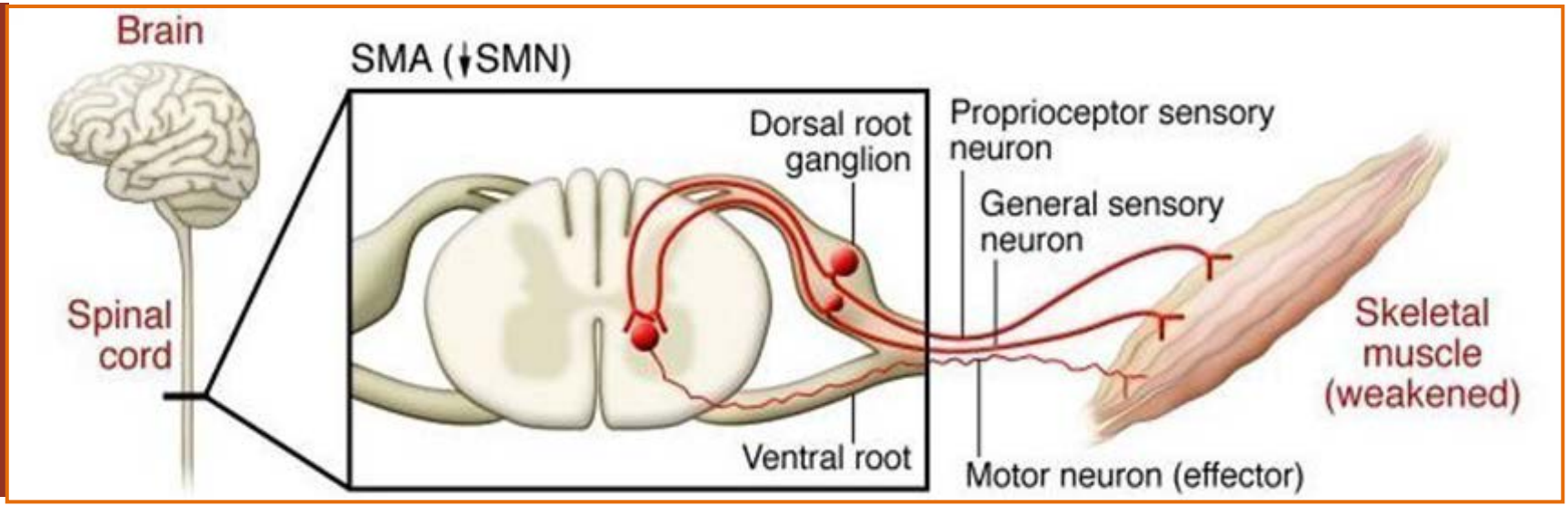
Open-label OLEOS study

- An open-label extension of the Phase 1 and 2 olesoxime trials, named OLEOS, is currently recruiting patients[2]
- OLEOS will evaluate the long-term safety, tolerability and effectiveness of olesoxime in people with Type 2 and non-ambulatory Type 3 SMA who took part in the Phase 1 and 2 studies[2]

Planned Phase 3 study

- A Phase 3 study of olesoxime in people with Type 2 and Type 3 SMA is planned to start in 2017

1. https://clinicaltrials.gov/ct2/show/NCT01302600; 2. https://clinicaltrials.gov/ct2/show/NCT02628743.



An open-label multi-part first-in-human study of oral LMI070 in infants with Type I spinal muscular atrophy

Lawrence Charnas & Emilie Voltz on behalf of the SMA Team
Novartis Institutes for Biomedical Research

NOVARTIS

Summary and Conclusions: CLMI070X2201

a) 13 patients treated with LMI070; longest to date is ~14 months

b) No Maximum Tolerated Dose (MTD) has been reached; Adverse Events (AE) have generally been mild and LMI070 has been well tolerated

c) New target organs identified only in a chronic dog toxicology study

d) Patients remain on study with dose modification and additional safety measures

e) Excluding 2 pulmonary deaths, no patients have withdrawn from treatment

f) Increases in CHOP INTEND and maintenance of independent feeding/ventilation are seen

g) Recruitment temporarily paused

h) Novartis is continuing the study of LMI070 as a treatment in Type 1 SMA

NUSINERSEN

Eugene Schneider, MD,
Vice President, Clinical Development

Wildon Farwell, MD,
Neurology Medical Director

IONIS PHARMACEUTICALS

Biogen

Nusinersen

- We are currently in collaboration to develop and potentially commercialize the investigational compound, nusinersen, for the potential treatment of SMA.
- Nusinersen is designed to alter the splicing of the SMN2 gene to increase production of fully functional SMN protein.
- Nusinersen has received orphan drug status and fast track designation from the FDA.
- Currently, Ionis is conducting two Phase 3 nusinersen studies:
  - ENDEAR - a Phase 3 study, in infants with SMA
  - CHERISH - a Phase 3 study in children with SMA
- Currently, Biogen is conducting two additional studies:
  - NURTURE – a Phase 2 study in presymptomatic infants with SMA
  - EMBRACE – a Phase 2 study designed to collect additional data on a small subset of patients with infantile or childhood-onset SMA who do not meet the age and other criteria of ENDEAR & CHERISH

Nusinersen Development Program

Pre-symptomatic Newborns	nurture	Biogen Study
Infant Onset		Phase 2 Open Label *(Infants)*
	endear	Phase 3
	embrace	Biogen Study
	shine	OLE Study for Phase 3 Studies
Childhood Onset	cherish	Phase 3
		Phase 2 Open Label *(Children)*

Robust Clinical Development Program

SP-US-0124

Omar Khwaja, MD, PhD
CLINICAL DEVELOPMENT UPDATE: *SMN2* SPLICING MODIFIERS RG7916 AND RG7800

RG7916

- RG7916 is an investigational medicine being developed by Roche, PTC Therapeutics and the SMA Foundation
- It is taken orally, and designed to selectively target splicing of *SMN2* pre-mRNA to potentially increase production of functional SMN protein[1]

RG7916 Phase 1 study in healthy volunteers

- A Phase 1 study in healthy volunteers supports[2] the progress of RG7916 into clinical studies in people with SMA

Studies of RG7916 in people with SMA

- Studies of RG7916 in people with SMA Types 1–3 are expected to start by the end of 2016

RG7800 – MOONFISH study

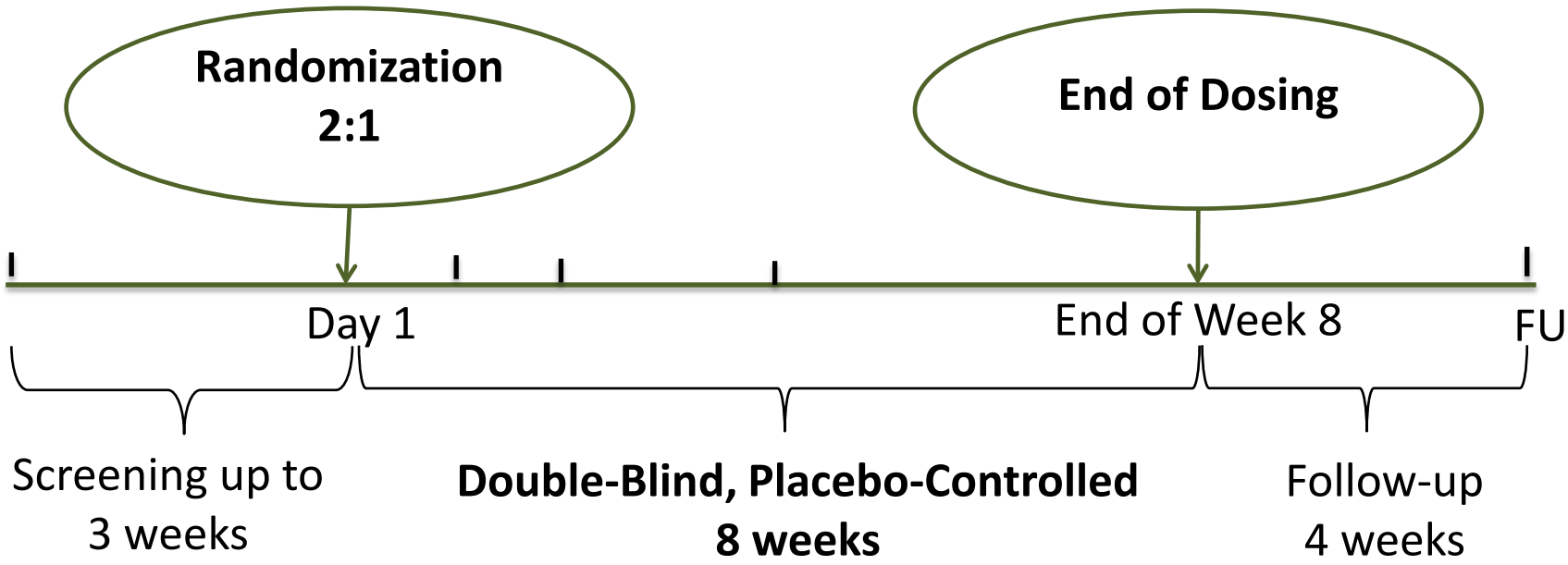
- RG7800 is an investigational medicine designed to target the splicing of *SMN2* pre-mRNA
- The clinical development of RG7800 will remain on hold
- Patients who participated in the MOONFISH study may potentially be eligible to join an open-label study with RG7916

1. Naryshkin N, *et al. Science* 2014; 345:688–693; 2. https://clinicaltrials.gov/ct2/show/NCT02633709 .

CK-2127107, a selective activator of the fast skeletal muscle troponin complex, for the potential treatment of SMA

- **Patient population**
  - Patients 12 years of age and older
  - Genetically confirmed SMA Types II, III, or IV
  - 72 patients equally divided between ambulatory and non-ambulatory status

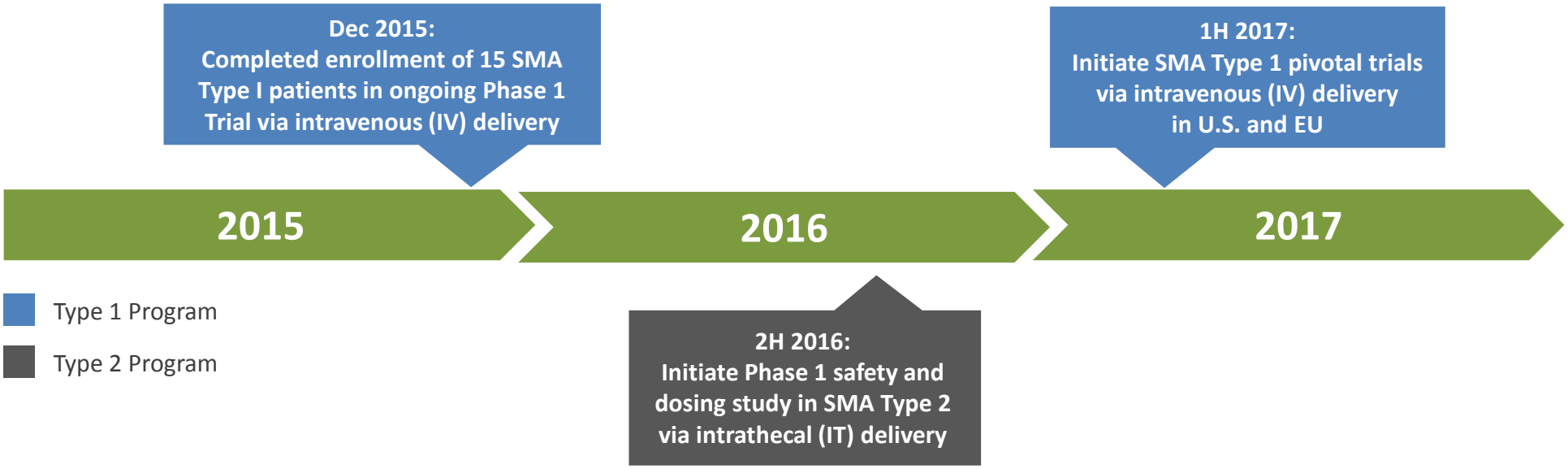
- **Sequential dose escalation, randomized, double blind placebo controlled study**
  - Cohort 1: 150 mg bid compared to placebo
  - Cohort 2: 450 mg bid (proposed) compared to placebo



astellas
Leading Light for Life

Cytokinetics

AVXS-101 Clinical Development Overview



- Ongoing fully-enrolled Phase 1, open-label study of SMA Type 1 infants who received intravenous administration of AVXS-101
- Pivotal trials of intravenous administration of AVXS-101 in SMA Type 1 planned for 2017 in the U.S. and EU
- Study of intrathecal administration of AVXS-101 in SMA Type 2 patients planned for the second half 2016