Sponsor Presentation

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Joint Meeting of the Pediatric Advisory Committee and the Pediatric Ethics Subcommittee

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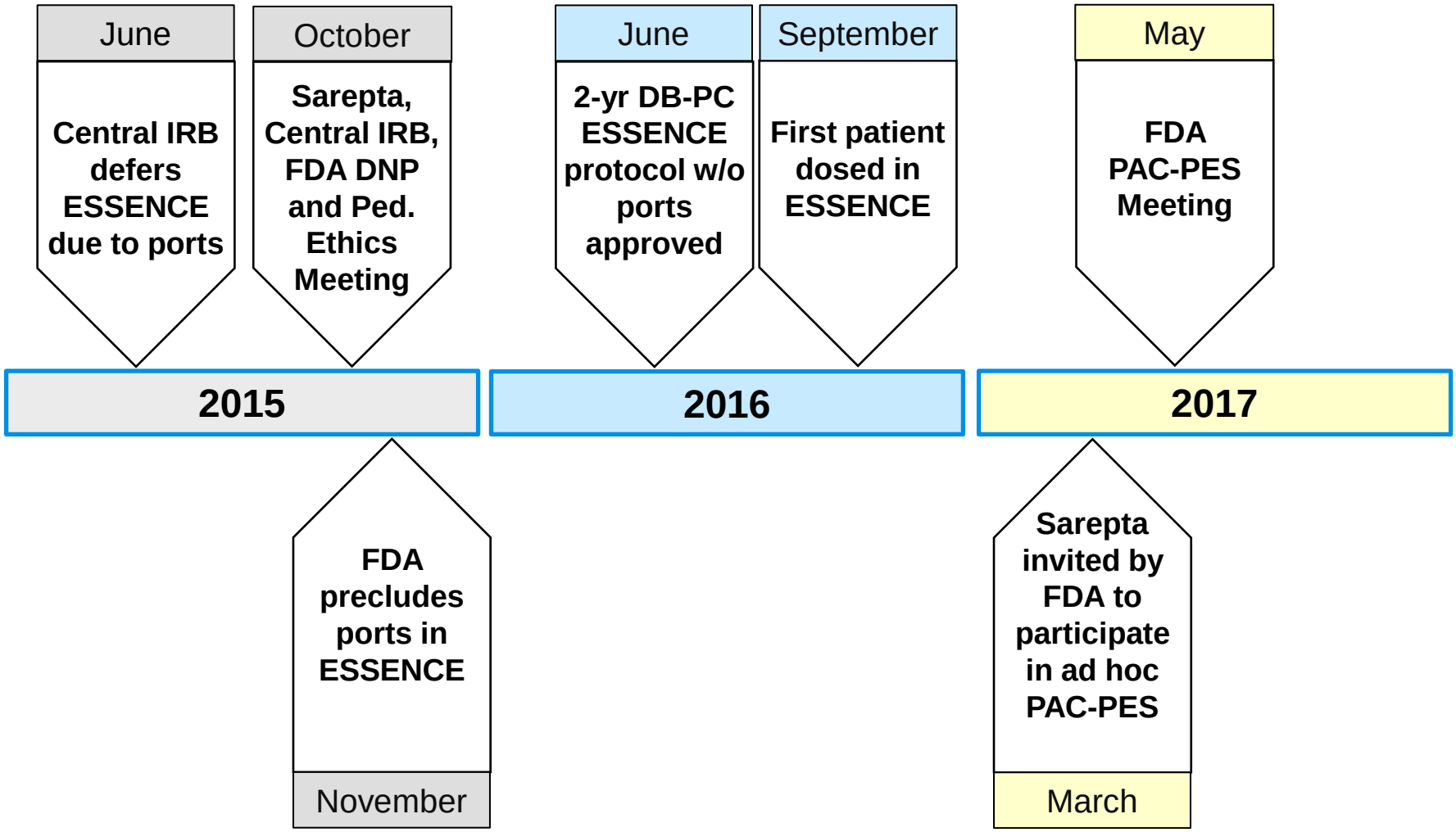
Agenda

- Introduction
- Regulatory history
- Duchenne muscular dystrophy (DMD) and investigational product background
- ESSENCE trial design
- Sarepta port experience
- Impact of port prohibition
- Proposed protocol language and process

Introduction

- ESSENCE is a Phase 3 placebo-controlled safety and efficacy study of SRP-4045 and SRP-4053 in pediatric DMD patients
  - Approximately 2-year placebo-controlled period
  - First long-term placebo-controlled study
- Central IRB deferred approval due to port use in placebo patients; consultation sought with FDA
- FDA precluded port use per 21 CFR 50.53 citing greater than minimal risk without prospect of direct benefit in placebo patients
- Prior trial experience suggests a significant proportion of patients ultimately require ports
- Precluding ports has negative impact on patients and trial conduct
- Propose allowing port use at investigator discretion

IRB and Regulatory History of ESSENCE Port Preclusion



Not to scale

Duchenne Muscular Dystrophy (DMD) Overview

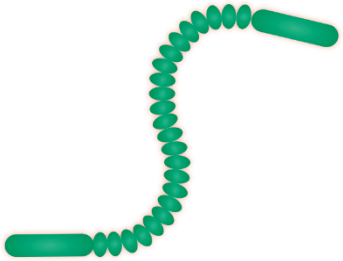
- Most common muscular dystrophy, and most common fatal genetic disorder diagnosed in children
- Rare/orphan disease affecting ~1 in 3500 - 5000 males worldwide[1]
- Caused by mutations in *DMD*, the dystrophin gene, on X chromosome
  - Most common are large out of frame exon deletions (~80%)
  - Results in little or no dystrophin, a key structural protein that stabilizes muscle fiber membranes
- Progressive, ultimately fatal disease with multiple comorbidities

[1]MMWR 2009;58(40):1119-22

Exon Skipping Aims to Restore Reading Frame to Enable Production of Dystrophin Protein

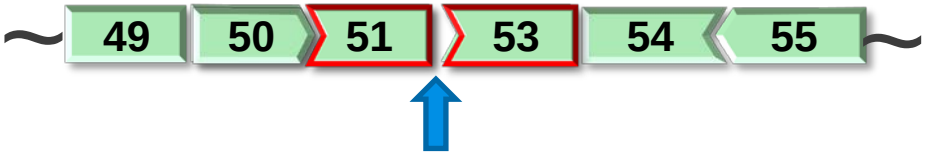
SRP-4053: exon 53 skipping *SRP-4045: exon 45 skipping*

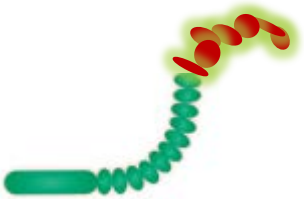
Normal Dystrophin mRNA



Normal Dystrophin Protein

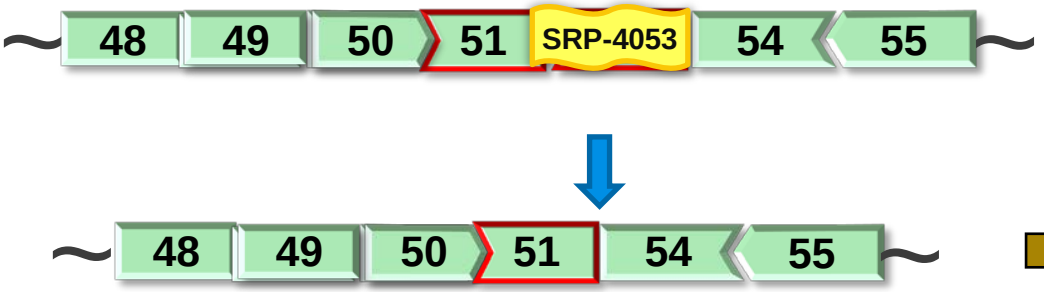
Exon 52 Deletion Disrupts Reading Frame

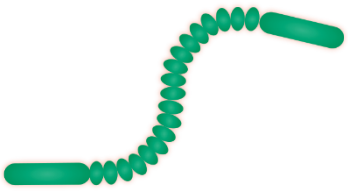




Unstable/No Dystrophin Protein: DMD

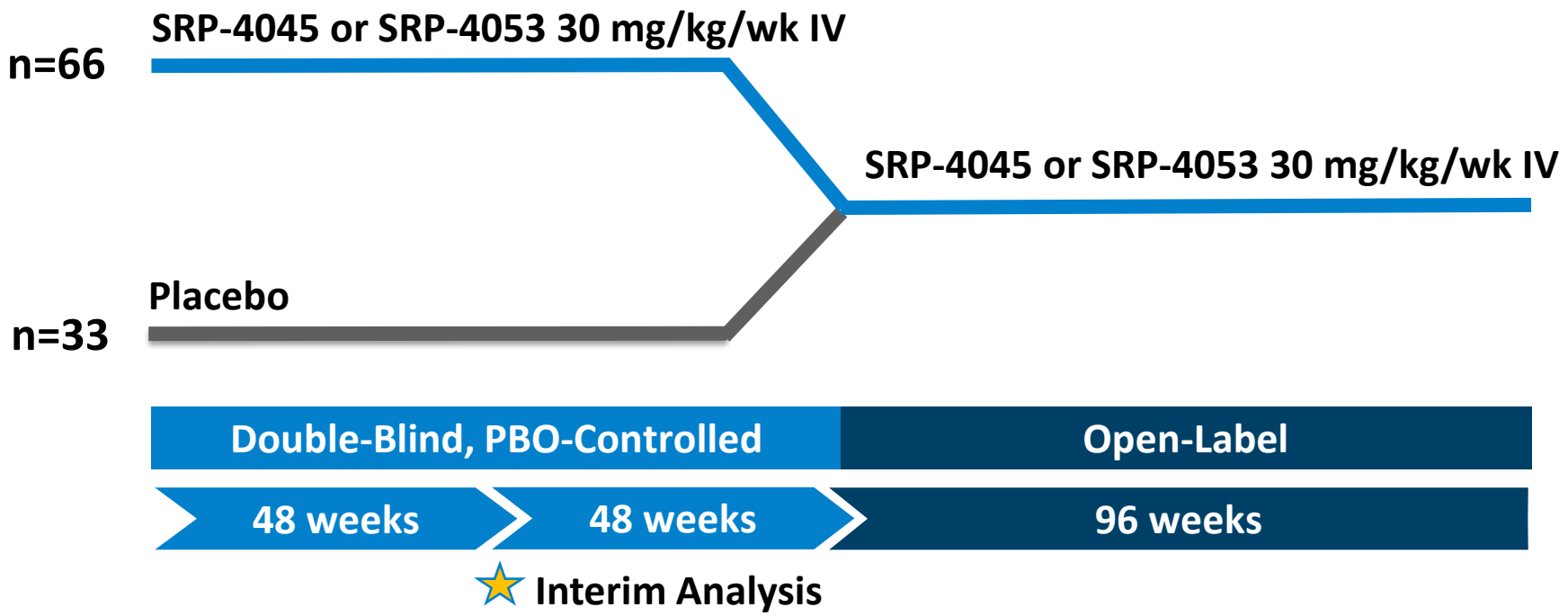
Skipping Exon 53 Restores Reading Frame





Intended to Produce Shortened Dystrophin Protein

ESSENCE is a Double-blind, Placebo-controlled Study



- Patient Population: DMD patients age 7-13 yrs with mutations amenable to exon 45 or 53 skipping
- Primary Endpoint: Change from baseline in 6-minute walk test
- Interim efficacy analysis when 75% of patients reach Week 48

Goals of Venous Access for DMD Patients in ESSENCE

- Maintain venous access in trial
  - Study infusions and safety laboratory draws
- Minimize patients'
  - Pain and suffering
  - Emotional trauma
  - Safety risk
- Protect venous access for future medical/surgical needs

DMD Comorbidities and Treatments Compromise Venous Access

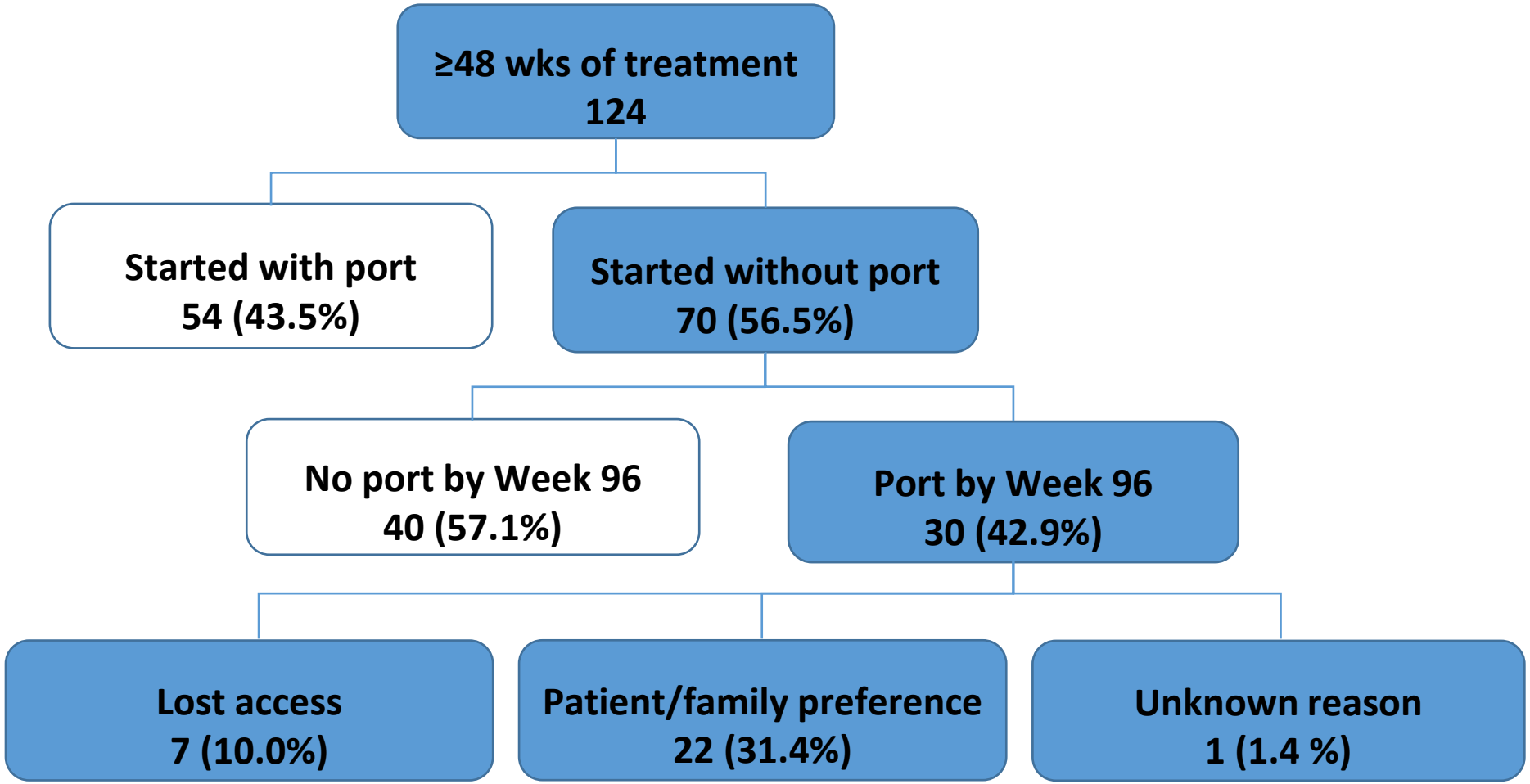
- Mobility limitations and contractures
- Steroid-induced vein fragility and obesity/fat accumulation
- Cognitive/behavioral and psychiatric issues
  - Intellectual and learning disabilities
  - Attention-deficit hyperactivity disorder/impulsivity
  - Anxiety/panic disorder
  - Autism spectrum disorders
  - Steroid-induced mood lability and aggression

Aitkenhead AR. Clinical Anaesthesia. 1999. Churchill Livingstone. Banihani R et al. J Child Neurol. 2015;30(11):1472-82. Bushby K et al. Lancet Neurol. 2010;9(1):77-93.

Data on Port Usage Systematically Collected During Sarepta DMD Trials

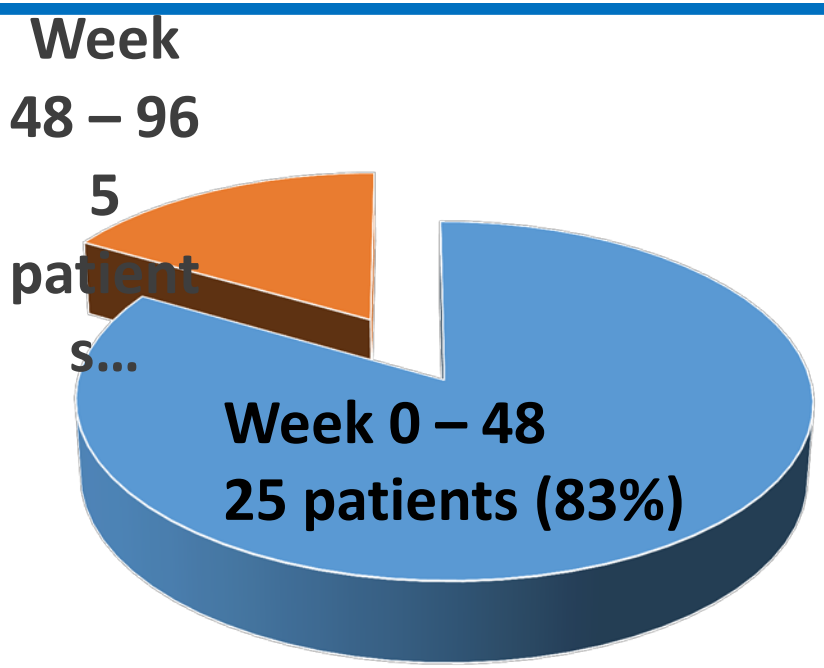
- Port placement, replacement and removal
- Reason for port placement
  - Initial access
  - Loss of IV access
  - Patient/family preference
  - Physician preference
  - Other

Nearly Half of Patients Needed Ports by 2 Years in Sarepta US DMD Trials



Eteplirsen trial data as of 02 Dec 16
Study 4045-101 data as of 28 Jan 17

Most On-treatment Port Placements Occurred in First Year



- Majority (83%) had port placed within 48 weeks
- Median time to port placement: ~15 weeks (103.5 days)

Eteplirsen trial data as of 02 Dec 16
Study 4045-101 data as of 28 Jan 17

Eteplirsen: Potential Port-Associated Adverse Events in ≥ 2 Patients

Preferred Term	Eteplirsen, n (%)	
	Patients with Ports (N=86)	All IV Patients (N=148)
Catheter site pain	9 (10.5)	15 (10.1)
Catheter site bruise	7 (8.1)	7 (4.7)
Infusion site pain	4 (4.7)	8 (5.4)
Peripheral swelling	3 (3.5)	5 (3.4)
Thrombosis in device	3 (3.5)	4 (2.7)
Catheter site hemorrhage	2 (2.3)	2 (1.4)
Catheter site inflammation	2 (2.3)	2 (1.4)
Catheter site pruritus	2 (2.3)	2 (1.4)
Catheter site rash	2 (2.3)	2 (1.4)
Catheter site related reaction	2 (2.3)	2 (1.4)
Procedural pain	2 (2.3)	34 (23.0)
Rash	2 (2.3)	30 (20.3)

- 86/148 patients used a port
- 32/86 patients with port-associated AE(s)
- Majority mild and unrelated
- No port-associated SAEs

Data as of 02 Dec 2016

Study 4045-101: Potential Port-Associated Adverse Events in ≥ 1 Patient

Preferred Term	4045-101 Port Patients (N=11); n (%)
Procedural pain	**5 (45.5)**
Bacteremia, septic embolus, vena cava thrombosis*	**1 (9.1)**
Catheter site inflammation	**1 (9.1)**
Device dislocation	**1 (9.1)**
Musculoskeletal pain	**1 (9.1)**
Rash pruritic	**1 (9.1)**

** 3 SAEs in 1 patient*

- 11/12 patients used a port
- 5/11 patients with port-associated AE(s)
- Majority of events were mild and unrelated to SRP-4045

Data as of 28 Jan 2017

Precluding Ports May Have Consequences

- Emotional and psychological impact
- Physical risk
  - Restraining patients for IVs increases fracture risk
- Avoidable dropouts could reduce the value of patients' contribution
- High dropout rate requires larger sample size
  - Larger sample size impacts feasibility
  - Trial validity may be compromised if too many missing values

Proposed Protocol Language: Ports Optional and Used Only When Necessary

“In the event it becomes necessary, venous access methods such as midline catheter, central line, or portacath may be used at the Investigator’s discretion, contingent upon approval by local and/or country-specific regulatory body(ies).”

Summary

- Maintaining IV access challenging in some DMD patients when frequent infusions are required
- Providing investigator discretion regarding port placement
  - Minimizes physical and emotional suffering for patients
  - Reduces risk of permanent loss of venous access
  - Prevents dropouts due to loss of venous access; preserves validity of trial

Proposal: Allow optional port use on a case-by-case basis per judgment of investigator and family