New Clinical Results with Fitusiran and Givosiran

58th Annual Meeting of the American Society of Hematology

December 4, 2016

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Agenda

Welcome
- Christine Regan Lindenboom
  Vice President, Investor Relations & Corporate Communications

Introduction
- John Maraganore, Ph.D.
  Chief Executive Officer

Fitusiran Clinical Results
- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President of R&D, Chief Medical Officer

Acute Hepatic Porphyrias Disease Overview
- Monty Bissell, M.D.
  Professor of Medicine and Chief of Gastroenterology, UCSF Medical Center

Givosiran Clinical Results
- Akshay Vaishnaw, M.D., Ph.D.
  Executive Vice President of R&D, Chief Medical Officer

Q&A Session

Alnylam Forward Looking Statements

This presentation contains forward-looking statements, within the meaning of Section 27A of the Securities Act of 1933 and Section 21E of the Securities Exchange Act of 1934. There are a number of important factors that could cause actual results to differ materially from the results anticipated by these forward-looking statements. These important factors include our ability to discover and develop novel drug candidates and delivery approaches and successfully demonstrate the efficacy and safety of our product candidates; pre-clinical and clinical results for our product candidates; actions or advice of regulatory agencies; delays, interruptions or failures in the manufacture and supply of our product candidates; our ability to obtain, maintain and protect intellectual property, enforce our intellectual property rights and defend our patent portfolio; our ability to obtain and maintain regulatory approval, pricing and reimbursement for products; our progress in establishing a commercial and ex-United States infrastructure; competition from others using similar technology and developing products for similar uses; our ability to manage our growth and operating expenses, obtain additional funding to support our business activities and establish and maintain business alliances; the outcome of litigation; and the risk of government investigations; as well as those risks more fully discussed in our most recent quarterly report on Form 10-Q under the caption “Risk Factors.” If one or more of these factors materialize, or if any underlying assumptions prove incorrect, our actual results, performance or achievements may vary materially from any future results, performance or achievements expressed or implied by these forward-looking statements. All forward-looking statements speak only as of the date of this presentation and, except as required by law, we undertake no obligation to update such statements.

John Maraganore, Ph.D.
Chief Executive Officer

Introduction

Akshay Vaishnaw, M.D., Ph.D.
Executive Vice President of R&D, Chief Medical Officer

Fitusiran Clinical Results

Fitusiran

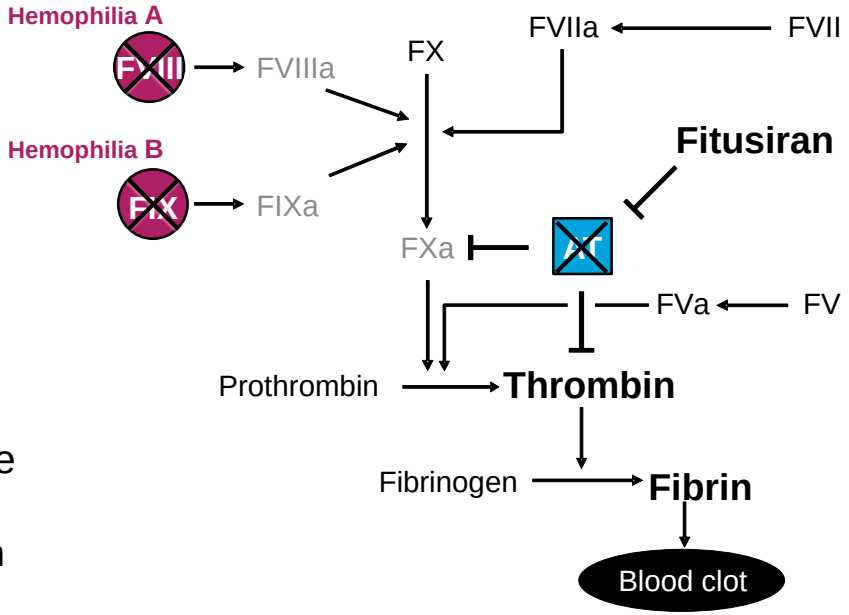
Investigational RNAi Therapeutic for Treatment of Hemophilia

Fitusiran (ALN-AT3)

- SC-administered small interfering RNA (siRNA) therapeutic targeting antithrombin (AT)
  - Non-biologic, chemically-synthesized, with targeting ligand to specifically deliver to liver—site of AT synthesis
  - Harnesses natural RNA interference (RNAi) mechanism for regulation of plasma AT levels

Therapeutic hypothesis

- Hemophilia A and B are bleeding disorders characterized by ineffective clot formation due to insufficient thrombin generation
- Fitusiran is designed to lower AT, with goal of promoting sufficient thrombin generation to restore hemostasis and prevent bleeding
  - Observation of ameliorated bleeding phenotype in patients with co-inheritance of thrombophilic traits in hemophilia[1-4]
  - Supported by pre-clinical data[5] and emerging Phase 1 clinical results[6,7]



[1]Kurnik K, et al. *Haematologica*. 92:982-985 (2007); [2]Ettingshausen E, et al. *Thromb Haemost*. 85:218-220 (2001); [3]Negrier C, et al. *Blood*. 81:690-695 (1993); [4]Shetty S, et al. *Br J Haematol.* 138:541-544 (2007); [5]Seghal A, et al. *Nat Med*. 21:492-497 (2015); [6]Pasi KJ, et al. *Blood. 2015, 126:551*; [7]Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4)

Fitusiran Phase 1 and Phase 2 OLE Study Design

Part A: Single-Ascending Dose (SAD) │Randomized 3:1, Single-blind, Placebo-Controlled, Healthy Volunteers

Part B: Multiple-Ascending Dose (MAD), Weekly dosing │ Open-label, Patients with Hemophilia A or B

Part C: MAD, Monthly dosing │ Open-label, Patients with Hemophilia A or B*

Part D: MAD – Monthly dosing │ Open-label, Patients with Hemophilia A or B with Inhibitors

- Patients eligible to roll over onto Phase 2 OLE starting on Day 84
- Individual patient dose adjustment may be allowed (per Safety Review Committee)

OLE, Open-Label Extension; qM, monthly; SC, subcutaneous
*ClinicalTrials.gov Identifier: NCT02035605; Pasi KJ, et al. Haemophilia. 2016, 22(Suppl 4)
†ClinicalTrials.gov Identifier: NCT02554773

Interim Fitusiran Phase 1 (Part D) Study Results*
Safety/Tolerability† in Patients with Inhibitors

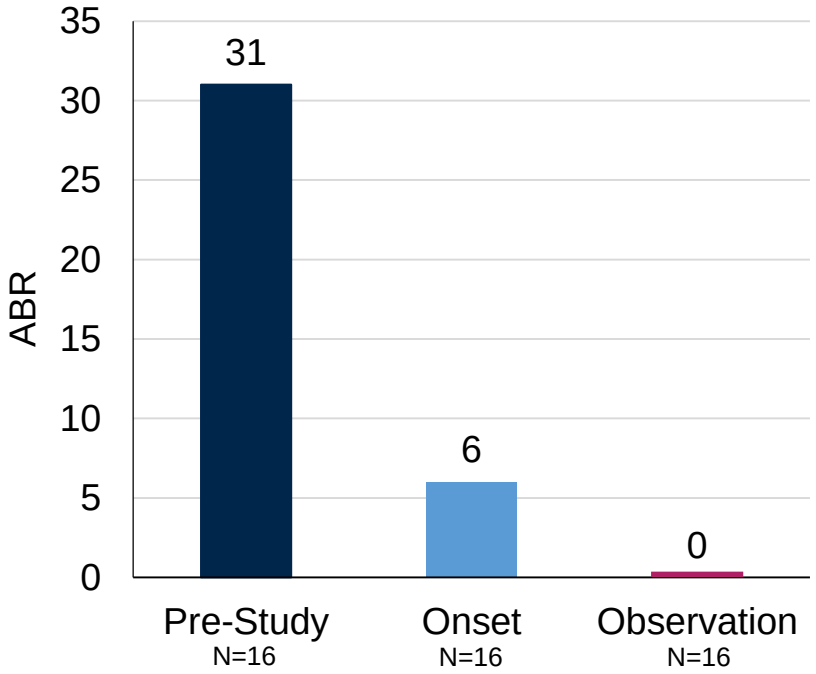
Fitusiran generally well tolerated in inhibitor patients

- No discontinuations due to AEs or drug-related SAEs
- No thromboembolic events
- All AEs mild or moderate in severity
  - Non-laboratory AEs reported in ≥2 patients: injection site reactions (ISRs) 7/16 (44%) and cough 2/16 (13%)
  - ISRs all mild; mostly pain and/or erythema at injection site
- ALT increases >3x ULN observed in 3 patients
  - All asymptomatic, with no concurrent elevations of bilirubin >2x ULN
  - All patients had medical history of HCV
  - Reversible, all patients currently with ALT <3x ULN
- Non-clinically significant D-dimer increases observed in some patients; none associated with laboratory signs of pathological clot formation (changes in platelets, fibrinogen, and/or PT/INR)
- No clinically significant changes in other laboratory parameters
- No instances of anti-drug antibody (ADA) formation
- All bleed events successfully managed with bypassing agents (rFVIIa, aPCC)
- As of data cut-off, 7 patients transitioned to Phase 2 OLE; fitusiran continues to be generally well tolerated

*Data cut-off 06Oct2016
AE, adverse events; SAE, serious adverse events
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events

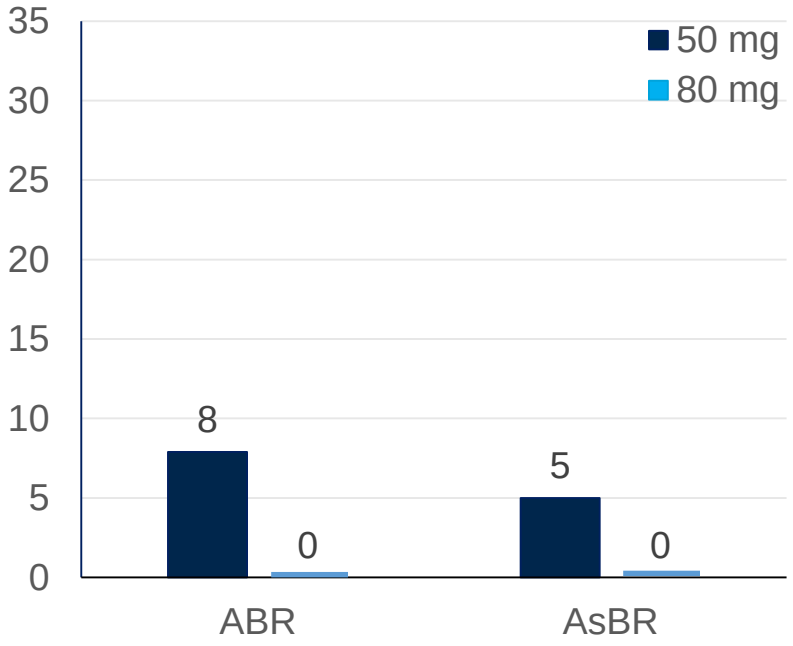
Interim Fitusiran Phase 1 (Part D) and OLE Study Results*
Summary of Median ABRs

All Inhibitor Patients



- Median ABR, Pre-study period: 31
- Median ABR, Observation period: 0
  - Patients reporting no bleeds: 9/16 (56%)
  - Patients report no spontaneous bleeds (AsBR = 0): 11/16 (69%)

Observation Period, 50 mg vs 80 mg



- 50 mg: Median ABR = 8, median AsBR = 5
- 80 mg: Median ABR = 0, median AsBR = 0
  - Patients reporting no bleeds: 7/10 (70%)
  - Patients report no spontaneous bleeds (AsBR = 0): 9/10 (90%)

*Data cut-off 06Oct2016
OLE, open-label extension; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleed rate

Interim Fitusiran Phase 1 (Part D) and OLE Study Results*
Summary and Next Steps

Fitusiran generally well tolerated in hemophilia A and B patients with inhibitors
- No SAEs related to study drug; no thromboembolic events
- All AEs were mild or moderate in severity; ISRs most common AE, all mild

Encouraging results in hemophilia patients with inhibitors
- Once-monthly subcutaneous dosing at 50 mg and 80 mg achieves dose-dependent AT lowering of ~80%
- Exploratory post-hoc analysis of bleed events demonstrates median ABR = 0 for all patients
  - 9/16 (56%) patients bleed-free and 11/16 (69%) patients experiencing zero spontaneous bleeds
- Data suggest 80 mg may provide greater bleed prevention
  - 7/10 (70%) patients bleed-free and 9/10 (90%) patients experiencing zero spontaneous bleeds

Dosing in hemophilia patients with inhibitors continues in Phase 2 OLE
- 7 inhibitor patients now enrolled
- Up to 7 months of continuous dosing

Plan to advance fitusiran to pivotal studies in early 2017

*Data cut-off 06Oct2016
OLE, open-label extension; SAE: serious adverse events; AE, adverse events; ISR, injection site reactions; AT, anti-thrombin; ABR, annualized bleeding rate;

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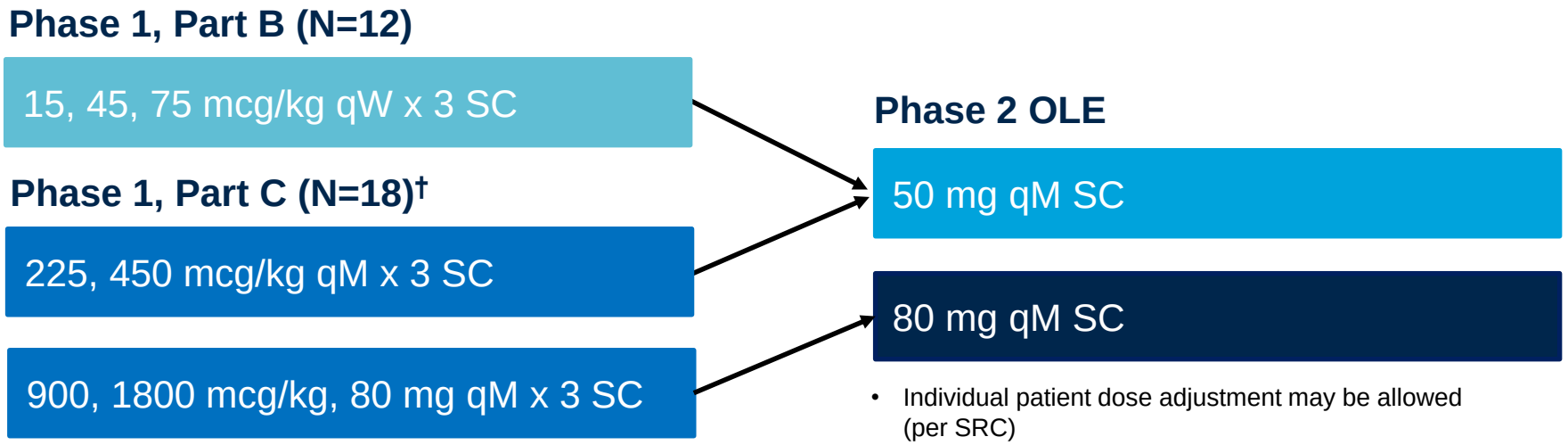
Fitusiran Phase 2 OLE Study Design
Patients with Hemophilia without Inhibitors

Patients previously dosed in Phase 1* study eligible to roll over onto Phase 2 Open-Label Extension (OLE)^ study



- As of data cut-off of 06Oct2016, 16 patients from Phase 1, Parts B & C have transitioned to Phase 2 OLE
  - Days between doses in Phase 1 and Phase 2 OLE ranged from 30 (no interruption in dosing) to 461

OLE, open-label extension; qW, weekly; qM, monthly; SC, subcutaneous
*ClinicalTrials.gov Identifier:NCT02035605; Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4)
^ClinicalTrials.gov Identifier: NCT02554773
†5 patients participating in Part C previously participated in Part B

Interim Fitusiran Phase 2 OLE Study Results*
Safety/Tolerability† in Patients without Inhibitors

Fitusiran generally well tolerated with up to 14 months continuous administration at 50-80 mg qM

- No discontinuations due to AEs or drug-related SAEs
- No thromboembolic events
- All AEs mild or moderate in severity
  - Non-laboratory AEs reported in ≥2 patients: 4/16 (25%) injection site reactions (ISRs) and vomiting 2/16 (13%)
  - ISRs all mild; mostly pain and/or erythema at injection site
- ALT increases >3x ULN were observed in 3 patients
  - All asymptomatic, with no concurrent elevations of bilirubin >2x ULN
  - All patients had medical history of HCV
  - With currently available follow-up, 2 patients with declining ALT through continued dosing
- No laboratory evidence of pathologic clot formation (changes in D-dimer, platelet count, fibrinogen, and/or PT/INR)
- No clinically significant changes in other laboratory parameters
- No instances of anti-drug antibody (ADA) formation
- All bleed events successfully managed with replacement factor
- Safety profile generally consistent with observations in Phase 1 study[1]

*Data cut-off 06Oct2016;
AE, adverse events; SAE, serious adverse events
†Adverse event grouping based on MedDRA-coded terms, excluding bleed events
1. Pasi KJ, et al. *Haemophilia.* 2016, 22(Suppl 4)

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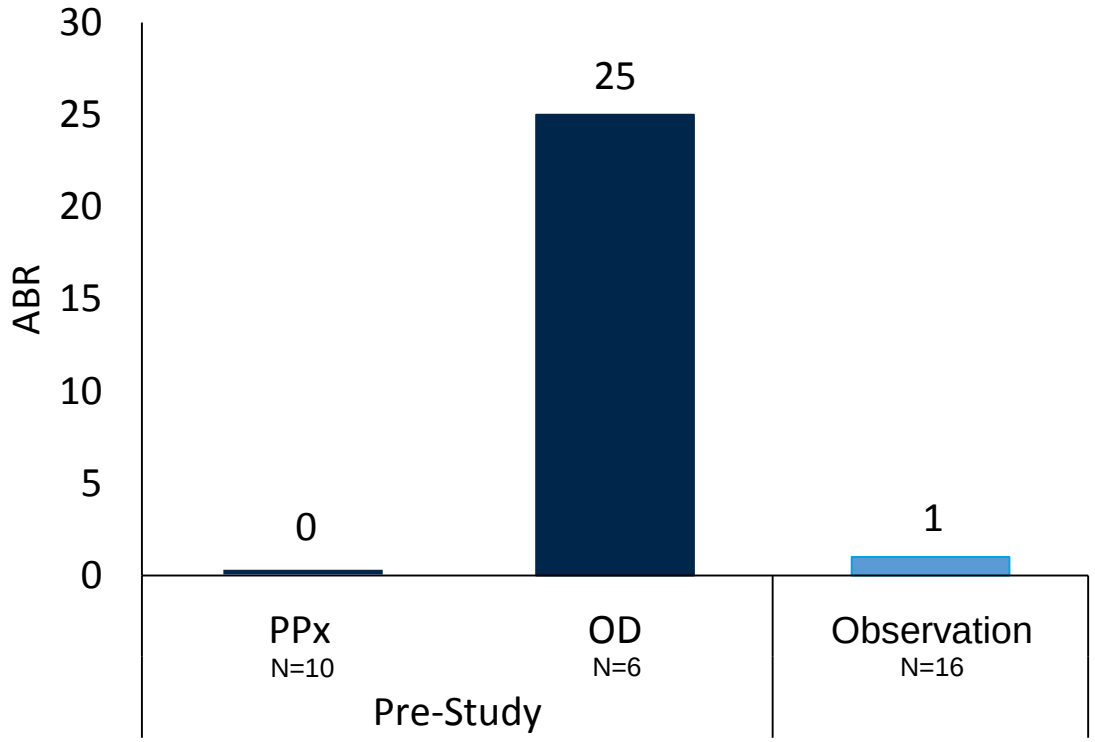
Interim Fitusiran Phase 2 OLE Study Results*

Summary of Median ABRs in Patients without Inhibitors



- Median ABR, Observation period = 1
  - Patients reporting no bleeds: 8/16 (50%)
  - Patients reporting no spontaneous bleeds (AsBR = 0): 11/16 (69%)
- Median duration in observation period = 170 days (5.7 months)

*Data cut-off 06Oct2016

PPx, prophylaxis; OD, on demand; ABR, annualized bleeding rate; AsBR, annualized spontaneous bleeding rate

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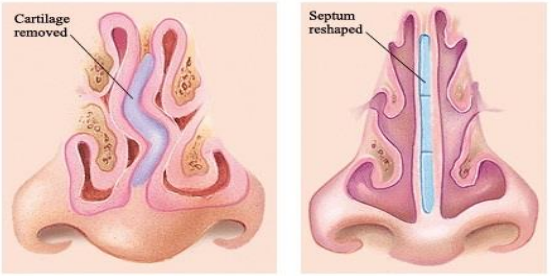
Initial Surgical Case Experience on Fitusiran
Elective Septoplasty



Patient

- C1-3, severe hemophilia A
- Dose level: 50 mg
- Last available AT level prior to procedure: 13% relative to baseline

Procedure

- Factor utilization: investigator reports cumulative periprocedural utilization of recombinant factor VIII as 20% of that typically used
- Investigator reported* hemostatic efficacy ratings based on ISTH score[1]
  - Intraoperative: Excellent
  - 24 h post-operative: Excellent
  - 7 days post-operative: Excellent
- Safety
  - No AEs reported in this patient during procedure or 64 days of subsequent continued follow up

*Per investigator's retrospective report

1. Khorsand N, et al. *J Thromb Haemost.* 14:211–4 (2016)

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Interim Fitusiran Phase 2 OLE Study Results*
Summary and Next Steps

Fitusiran generally well tolerated in hemophilia A and B patients without inhibitors
- No SAEs related to study drug; no thromboembolic events
- All AEs were mild or moderate in severity; ISRs most common AE, all mild

Transition from Phase 1 to Phase 2 OLE demonstrates key attributes of fitusiran pharmacology, including reversibility and clamped AT lowering

Evidence of clinical activity
- Once-monthly subcutaneous dosing at 50 mg and 80 mg achieves dose-dependent AT lowering of ~80% and thrombin generation levels approaching the lower end of normal range
- Exploratory post-hoc analysis of bleeding events demonstrates median ABR = 1 and median AsBR = 0
  - 8/16 (50%) patients bleed-free and 11/16 (69%) patients experiencing zero spontaneous bleeds

First surgical case experience on fitusiran
- Elective septoplasty successfully performed in severe hemophilia A patient without inhibitors
- Reduced factor utilization reported by investigator

Plan to advance fitusiran to pivotal studies in early 2017

*Data cut-off 06Oct2016
SAE: serious adverse events; AE, adverse events; ISR, injection site reactions; AT, anti-thrombin; ABR, annual bleed rate; OLE, open-label extension

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Monty Bissell, M.D.
Professor of Medicine and Chief of Gastroenterology,
UCSF Medical Center

Acute Hepatic Porphyrias Disease Overview

Acute Hepatic Porphyria Disease Overview

Acute Hepatic Porphyria (AHP)[1,2]

- Inborn errors of heme synthesis from liver enzyme defects
- AIP most common, with prevalence 2-5 per 100,000, approximately 5-10% manifest
  - Autosomal dominant mutation in hydroxymethylbilane synthase (HMBS)

Disease Pathophysiology

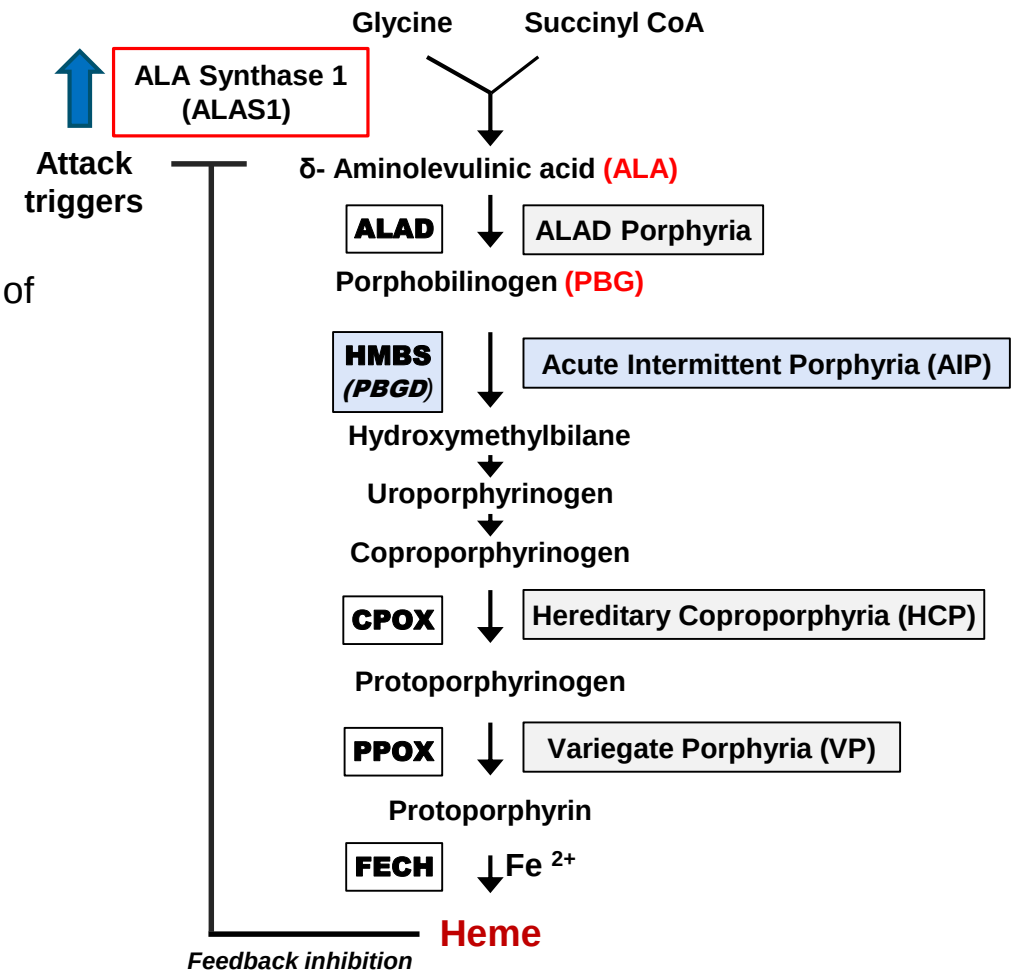
- Increased ALAS1 levels leads to accumulation of toxic heme intermediates ALA/PBG that cause acute attacks

Attack Manifestations

- Autonomic Nervous System
  - Severe abdominal pain, hypertension
- Central Nervous System
  - Mental status changes, seizures
- Peripheral Nervous System
  - Muscle weakness, paralysis

Treatment and Unmet Need

- Acute treatment and prophylaxis with human hemin (IV)
- Unmet need for more efficacious and safer therapies for prophylaxis



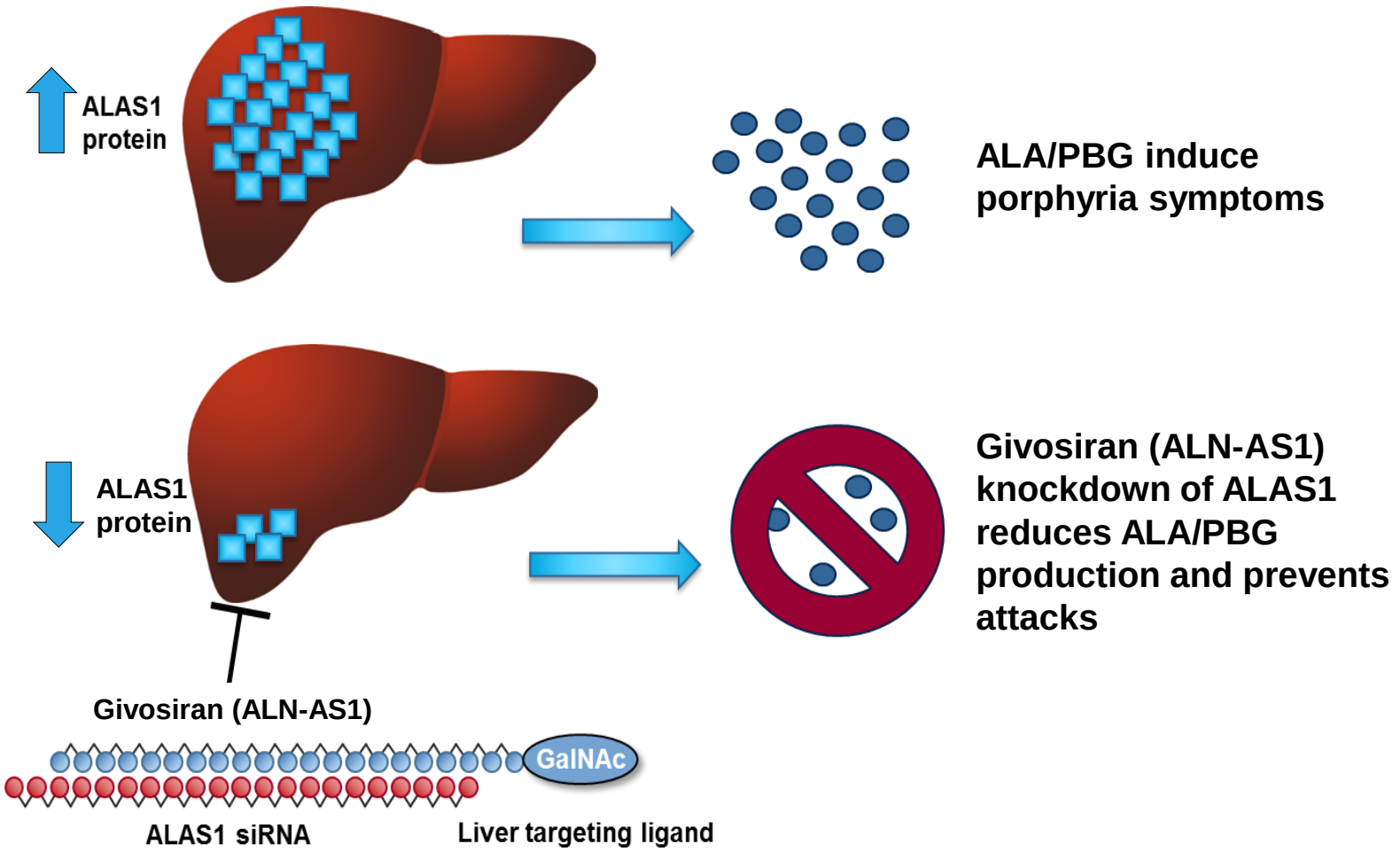
[1]Bonkovsky HL, et al. Am J Med. 2014;127(12):1233-41. [2]Elder G, et al. J Inherit Metab Dis. 2013;36(5):849-57.

Akshay Vaishnaw, M.D., Ph.D.
Executive Vice President of R&D, Chief Medical Officer

Givosiran Clinical Results

Givosiran: Investigational RNAi Therapeutic
Therapeutic Hypothesis

Knockdown of Liver ALAS1 Protein to Reduce ALA/PBG



Givosiran Phase 1 Study: Parts A and B
Study Design and Objectives

Part A: Single-Ascending Dose (SAD) | Randomized 3:1, Single-blind, Placebo-controlled, in Asymptomatic High Excreter Patients (ASHE)

- 0.035* mg/kg x 1 SC, N=4 ✓
- 0.10 mg/kg x 1 SC, N=4 ✓
- 0.35 mg/kg x 1 SC, N=4 ✓
- 1.0 mg/kg x 1 SC, N=4 ✓
- 2.5 mg/kg x 1 SC, N=4 ✓

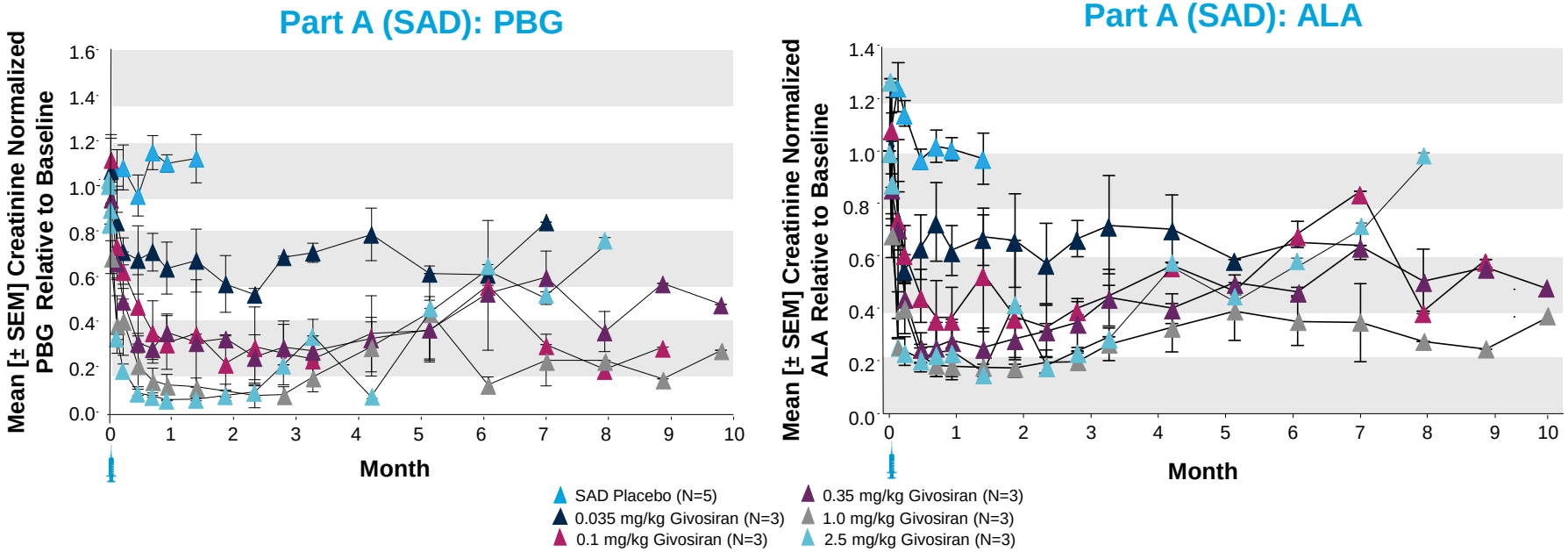
Part A and B Study Objectives:
- Primary: safety
- Secondary: PK and PD (ALA, PBG)
- Exploratory: ALAS1 mRNA by cERD

Part B: Multiple-Ascending Dose (MAD) | Randomized 3:1, Single-blind, Placebo-controlled, in ASHE Patients

- 0.35 mg/kg, qMx2 SC, N=4 ✓
- 1.0mg/kg, qMx2 SC, N=4 ✓

Clinicaltrials.gov: NCT02452372
*0.035 mg/kg cohort dosed after 0.10 and 0.35 mg/kg cohorts

Updated Givosiran Phase 1 (Parts A,B) Study Results*



Parts A and B Study Summary

Study Status

- Dosing is complete (n=23†), patients in follow up to monitor ALA/PBG recovery

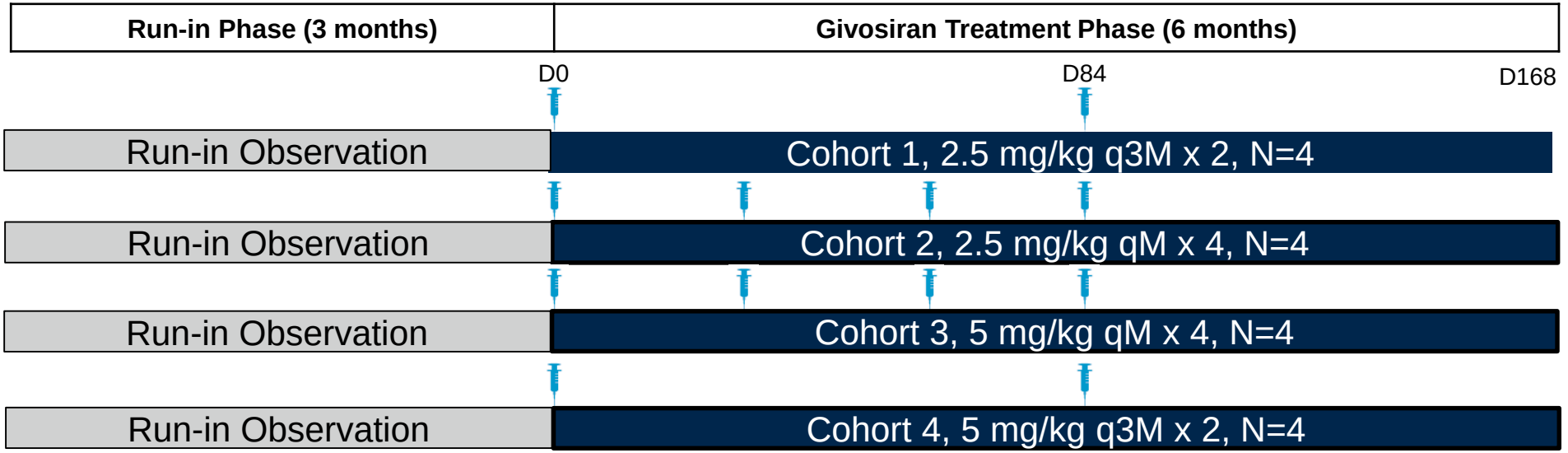
Results

- Givosiran was generally well tolerated
  - No discontinuations or serious adverse events related to study drug
  - No clinically significant changes in physical examination or laboratory tests
    - 2 mild and transient injection site reactions
- Givosiran led to rapid, dose-dependent, and prolonged urinary PBG and ALA lowering after single (SAD) or multiple doses (MAD) (data not shown)

*Data transfer date: 07 Nov 2016

SAD, Single-Ascending Dose; †5 subjects had >1 treatment assignment: 2 subjects repeated Part A; 3 subjects enrolled in Parts A and B

Givosiran Phase 1 Study: Part C Overview*



Study Design

- Placebo-controlled, double-blind, randomized 3:1, multiple dose study in AIP patients with recurrent attacks
- Key Inclusion Criteria:
  - Genetic confirmation of AIP
  - ≥ 2 attacks in past 6 months if on-demand treatment or willing to stop hemin prophylaxis during study. One attack in run-in required for randomization.

Objectives

- Safety and tolerability of givosiran
- Characterize givosiran PK and PD

Exploratory Objectives

- Clinical activity of givosiran on attack characteristics and treatment
- Characterize circulating ALAS1 mRNA from the liver in urine and serum

*Data cut-off is D168 for Cohort 1 (unblinded) and D84 for Cohort 2 (blinded)
Clinicaltrials.gov: NCT02452372

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Interim Givosiran Phase 1 (Part C) Study Results*
Demographics and Baseline Disease Activity: Cohorts 1 and 2

Demographics (N=8)	
Age, years; mean (range)	39.4 (21-60)
Sex: Female, n (%)	7 (88)
Race: White/Caucasian, n (%)	8 (100)
Patient Reported Attack Number in last 12 mos; mean (range)	17.9 (0-50)
Hemin prophylaxis use prior to study, n (%)	5 (62)
Baseline Disease Activity (N=8)	
Baseline PBG, mmol/mol Cr; mean (min, max)	48.6 (12.3, 88.2)
Baseline ALA, mmol/mol Cr; mean (min, max)	23 (2.6, 36.7)

*Data transfer date: 07 Nov 2016
ULN: ALA <3.9 or 3.8 mmol/mol Cr; PBG < 1.6 or 1.5 mmol/mol Cr depending on site

Interim Givosiran Phase 1 (Part C) Study Results*
Safety and Tolerability in AIP Patients with Recurrent Attacks

No drug-related SAEs in Cohorts 1-4

Cohorts 1 and 2

- No discontinuations due to AEs
- During treatment period, all randomized patients (8/8) reported at least 1 non-porphyria attack AE
  - Majority of AEs mild or moderate in severity
  - AEs reported in ≥3 patients were abdominal pain, nausea, vomiting, nasopharyngitis, and headache (3 patients each)
  - Possibly or definitely related AEs reported in ≥ 2 cases were injection site reaction and myalgia; all mild
  - No clinically significant changes in vital signs, EKG, clinical laboratory parameters or physical examination

Cohort 3

- After data transfer date, one patient experienced an SAE of acute pancreatitis complicated by pulmonary embolism resulting in death
  - Event assessed as unlikely related to givosiran or placebo by investigator due to presence of gallbladder sludge
  - Safety Review Committee in agreement with assessment

*Data transfer date: 07 Nov 2016

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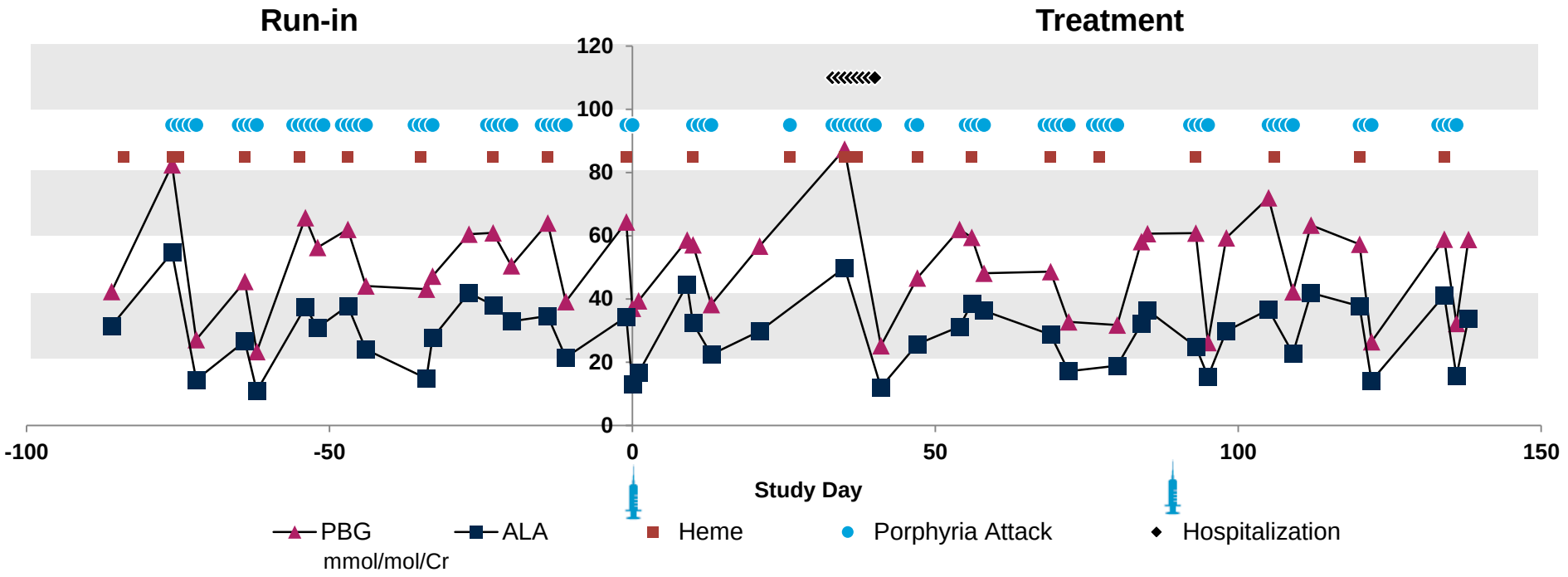
Interim Givosiran Phase 1 (Part C) Study Results*

Clinical Activity Data: Cohort 1, Placebo Patient

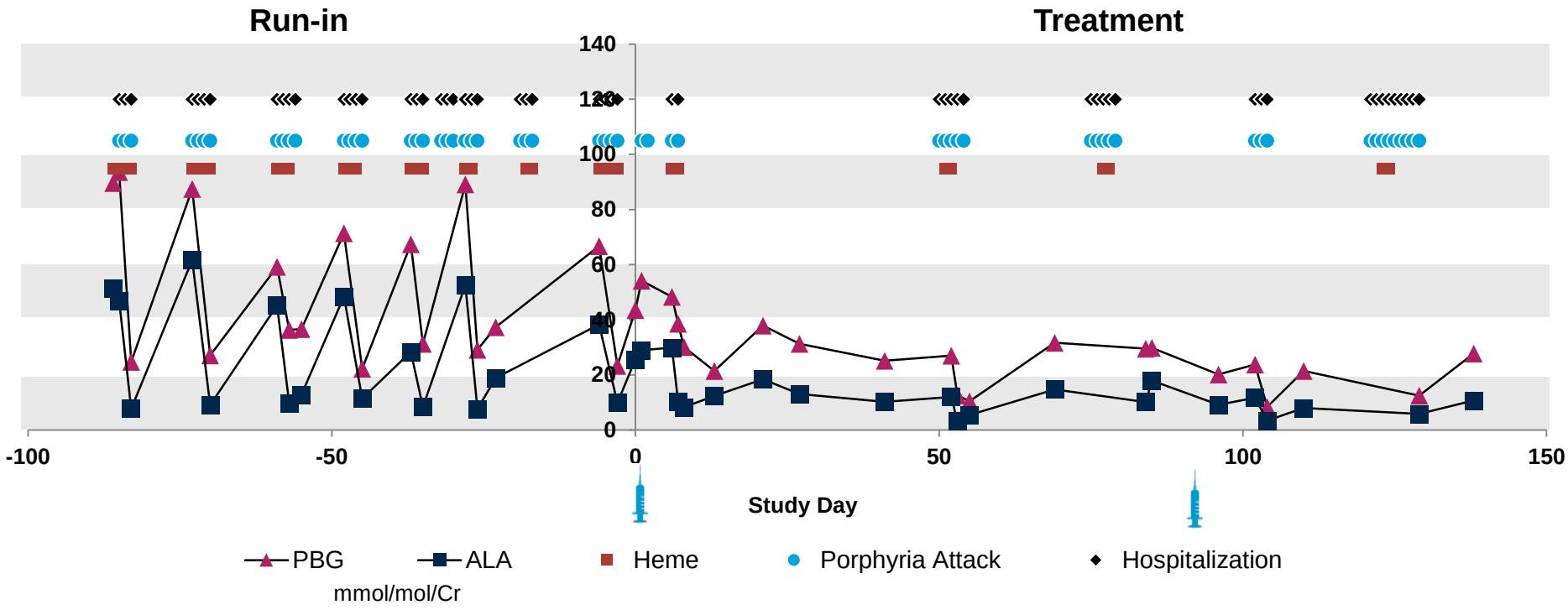


Period	Weeks	Attacks	Attacks Annualized	Max Attack-Free Interval (Days)	Hemin Doses	Hemin Doses Annualized
Run-In	12	8	34	9	10	43
Treatment	22	11	26	16	12	29

*Data transfer date: 07 Nov 2016

Interim Givosiran Phase 1 (Part C) Study Results*

Clinical Activity Data: Cohort 1, Givosiran – Patient 1

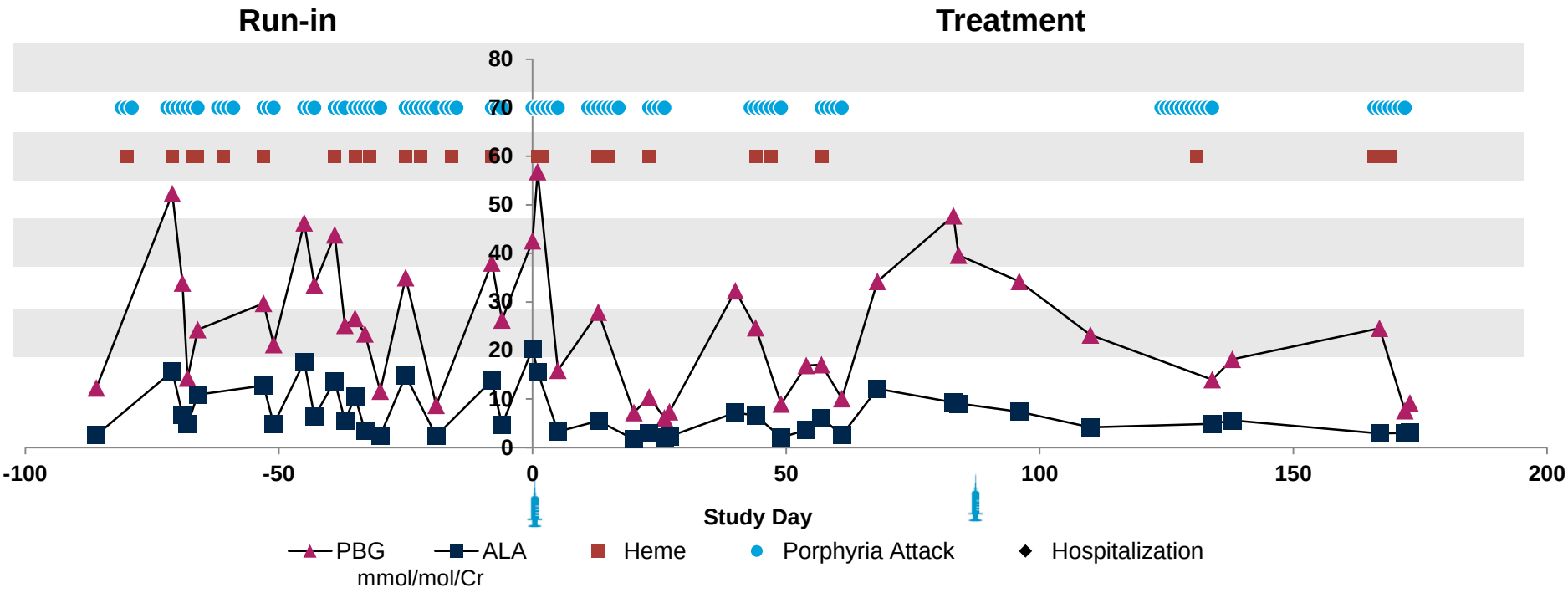


Period	Weeks	Attacks	Attacks Annualized	Max Attack-Free Interval (Days)	Hemin Doses	Hemin Doses Annualized
Run-In	12	9	38	10	24	102
Treatment	22	6	14	42	8	19

*Data transfer date: 07 Nov 2016

Interim Givosiran Phase 1 (Part C) Study Results*

Clinical Activity Data: Cohort 1, Givosiran – Patient 2

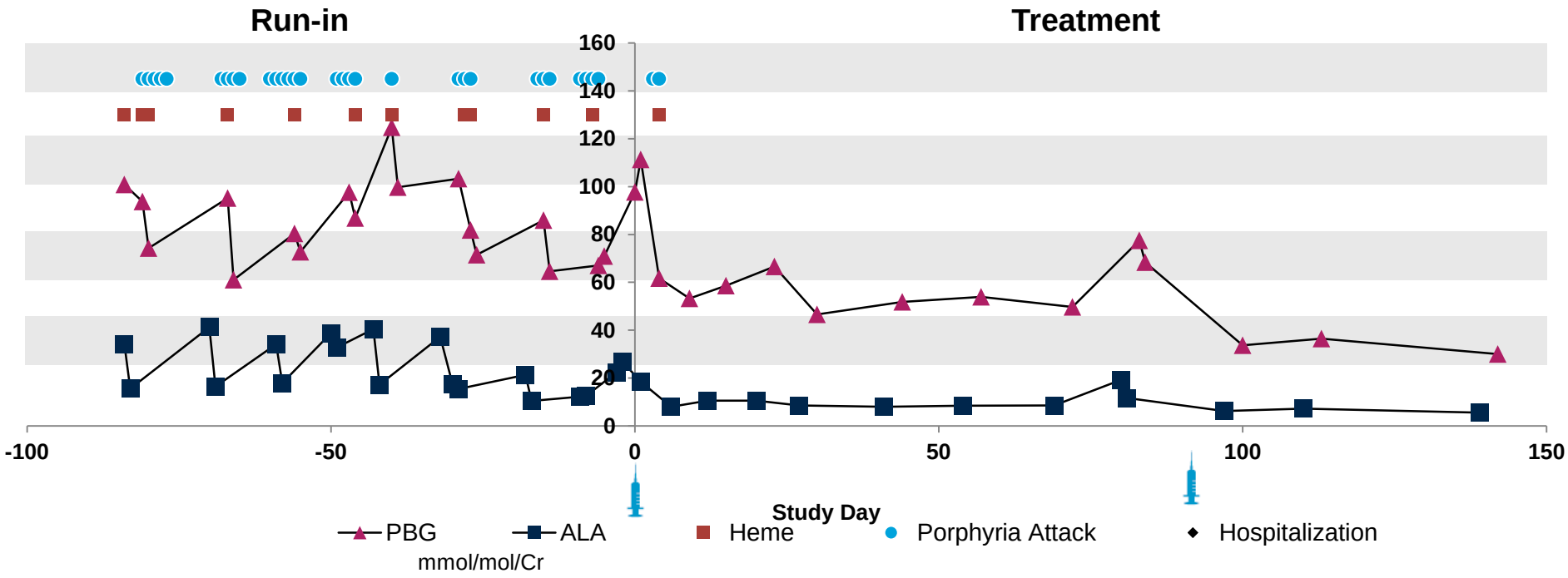


Period	Weeks	Attacks	Attacks Annualized	Max Attack-Free Interval (Days)	Hemin Doses	Hemin Doses Annualized
Run-In	12	11	47	6	13	55
Treatment	25	7	15	62	14	29

*Data transfer date: 07 Nov 2016

Interim Givosiran Phase 1 (Part C) Study Results*

Clinical Activity Data: Cohort 1, Givosiran – Patient 3



Period	Weeks	Attacks	Attacks Annualized	Max Attack-Free Interval (Days)	Hemin Doses	Hemin Doses Annualized
Run-In	12	8	35	10	11	44
Treatment	25	1	2	169	1	2

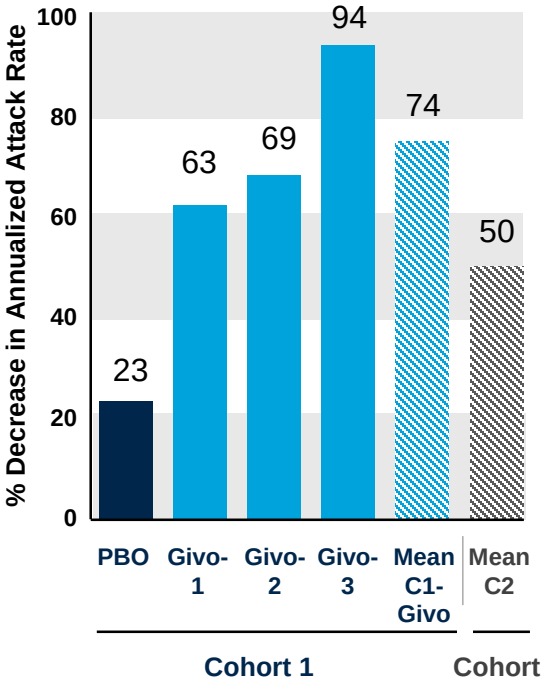
*Data transfer date: 07 Nov 2016

Interim Givosiran Phase 1 (Part C) Study Results*

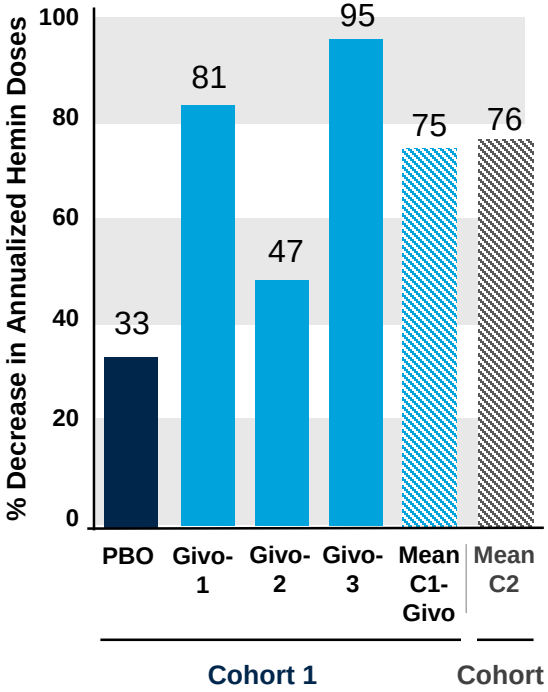
Summary of Clinical Activity Data Cohorts 1 and 2 in AIP Patients

Givosiran Treated Period Relative to Run-in

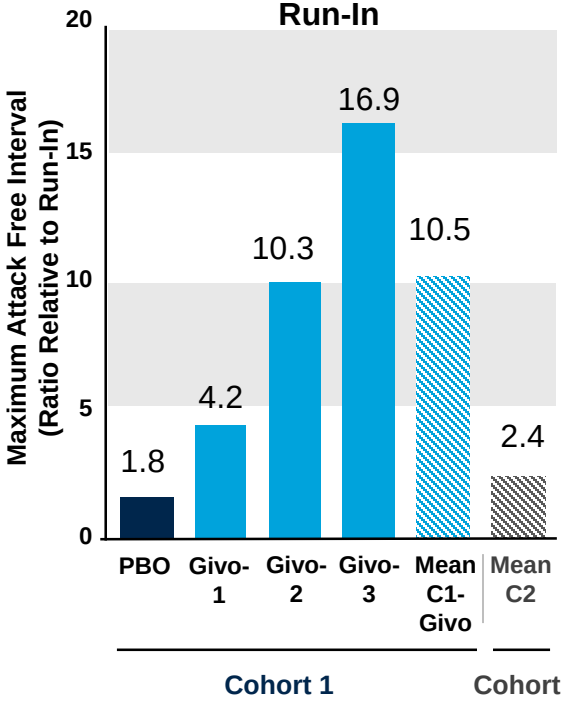
Cohort 1: Mean 74% Decrease in Annualized Attack Rate



Cohort 1: Mean 75% Decrease in Annualized Hemin Doses



Cohort 1: Maximum Attack Free Interval 10.5x Relative to Run-In



- Cohort 1 is through D168, Cohort 2 through D84 of the treatment phase
- Cohort 2 data is aggregated (including placebo) to protect blind

*Data transfer date: 07 Nov 2016

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Interim Givosiran Phase 1 (Part C) Study Results*
Cohorts 1 and 2 Summary and Next Steps

Givosiran safety and tolerability
- No drug-related SAEs or discontinuations due to AEs
- No dose-dependent AEs or clinically significant changes in vital signs, EKG, clinical laboratory parameters or physical examination
- Cohort 3: one unlikely related fatal SAE of acute pancreatitis complicated by a pulmonary embolism

Givosiran showed robust clinical activity in AIP patients with recurrent attacks
- Data suggest modest lowering, and/or blunting of further increases during attacks, of ALA/PBG may be sufficient for clinical activity
- Cohort 1 Data in Givosiran-treated patients:
  - 74% reduction in annualized attack rate compared to run-in
  - 75% reduction in annualized hemin usage compared to run-in
  - 10.5x maximum attack free interval (~82 days longer on average) compared to run-in
- Aggregated Cohort 2 Blinded Data:
  - Supportive data demonstrating reduction in attack rate and hemin usage compared to run-in

Next Steps
- Complete dosing of Cohorts 3 and 4
- Ongoing open label extension study for longer term safety and clinical activity data
- Initiate Phase 3 study in late 2017, subject to successful global regulatory interactions

*Data transfer date: 07 Nov 2016

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Q&A Session

Thank You!

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