Interim Data from a Randomized, Placebo Controlled, Phase 1 Study of Givosiran (ALN-AS1), an Investigational RNAi Therapeutic for the Treatment of Acute Hepatic Porphyria

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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

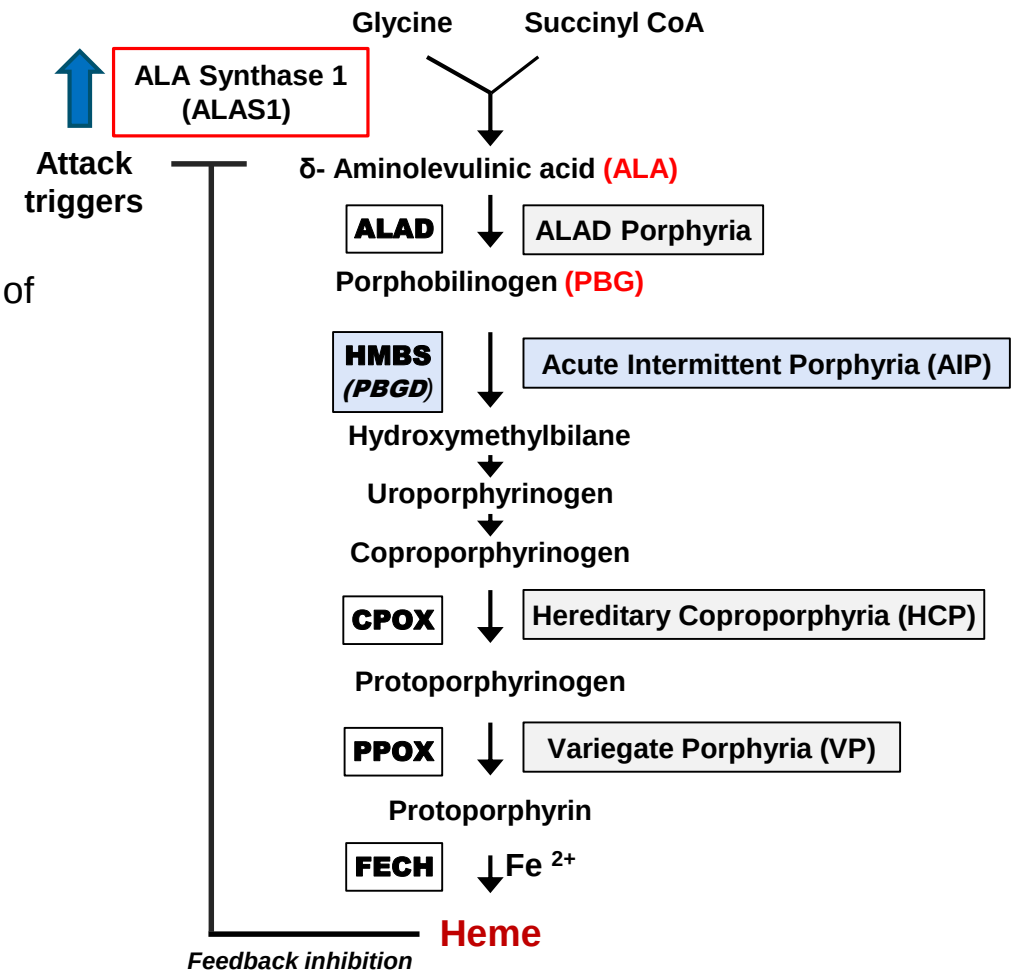
- Increased ALAS1 levels leads to accumulation of toxic heme intermediates ALA/PBG that cause acute attacks

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

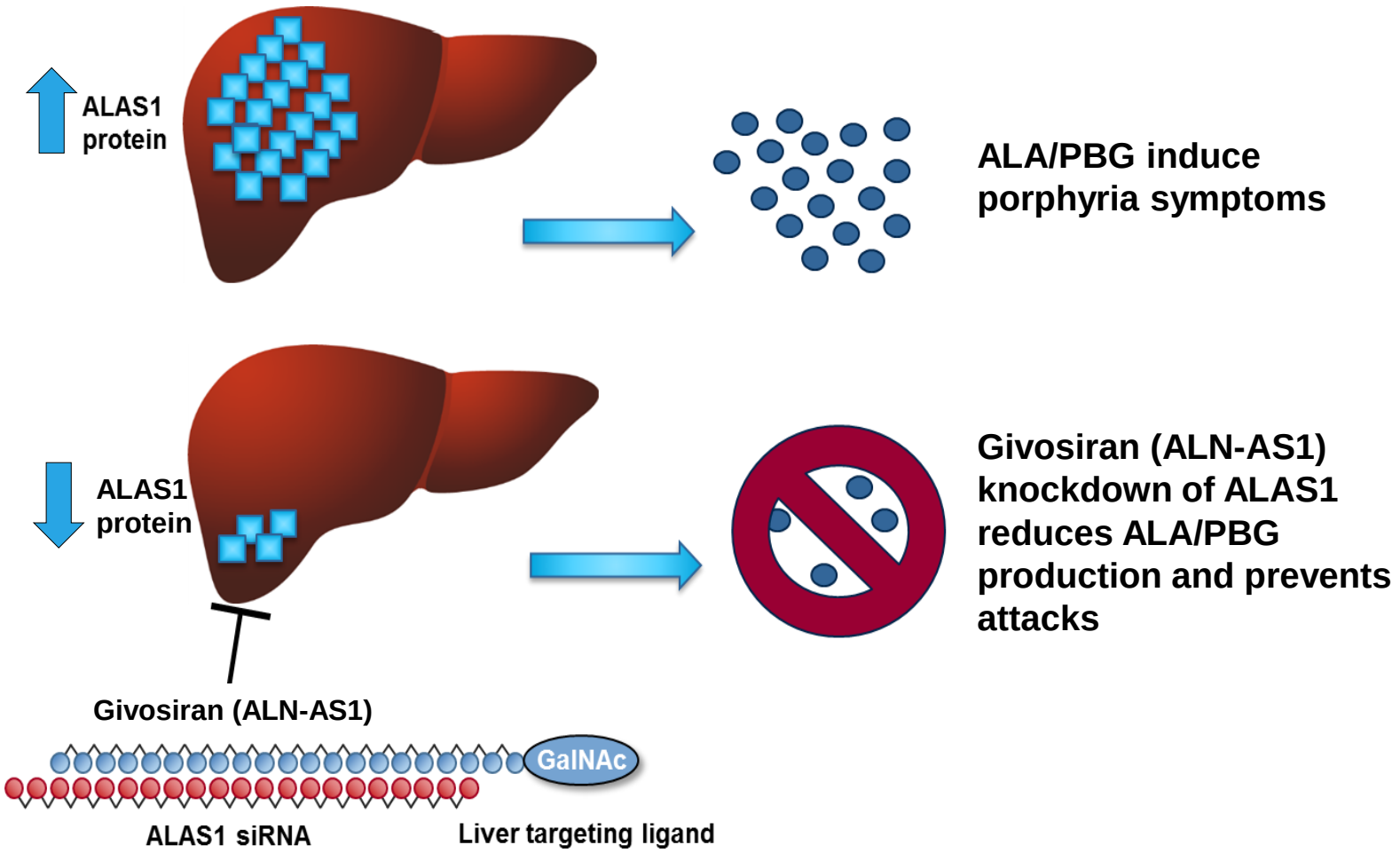
- Acute treatment and prophylaxis with human hemin (IV)
- Unmet need for more efficacious and safer therapies for prophylaxis



[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.

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

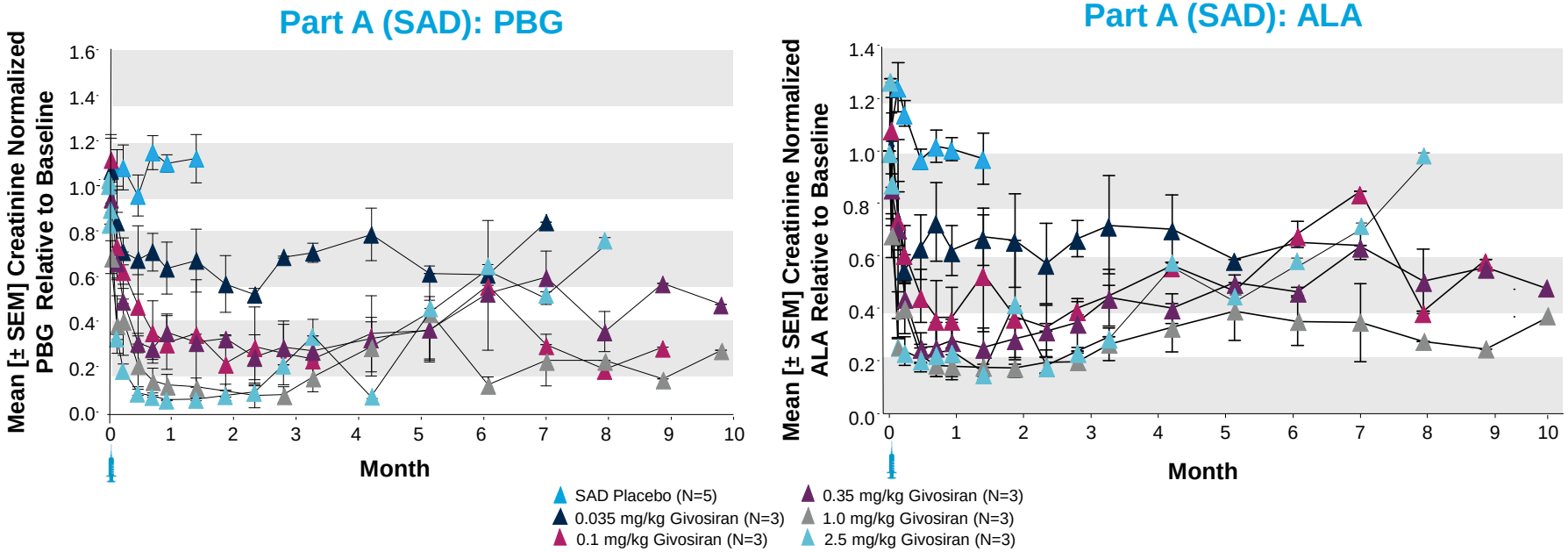
Part A and B Study Objectives:
- Primary: safety
- Secondary: PK and PD (ALA, PBG)
- Exploratory: ALAS1 mRNA by cERD

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

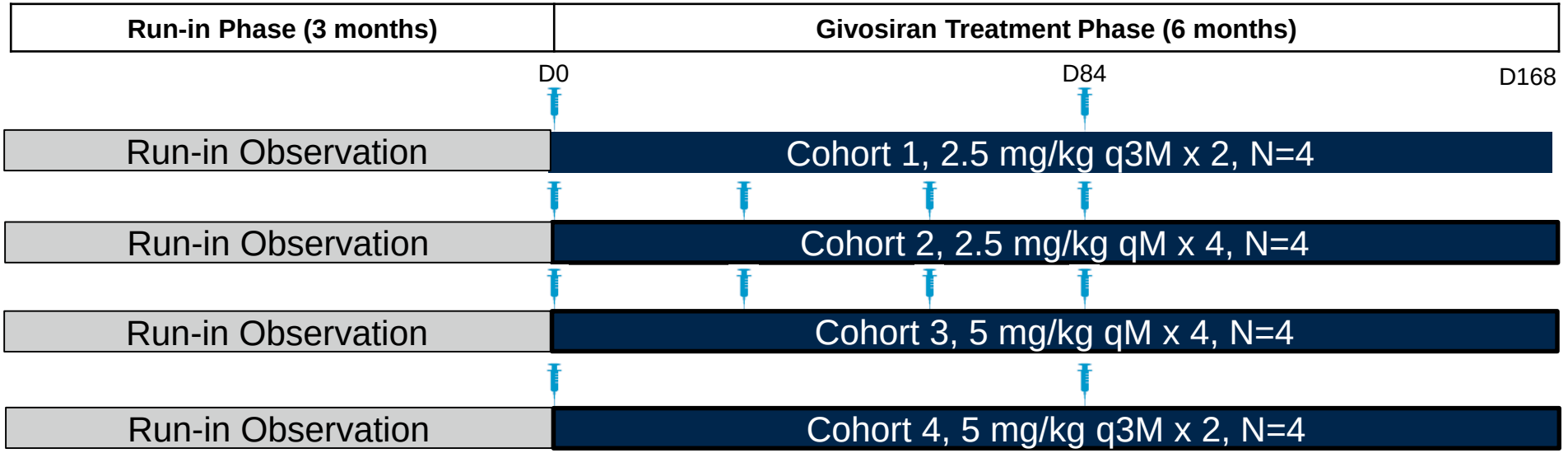
Results

- 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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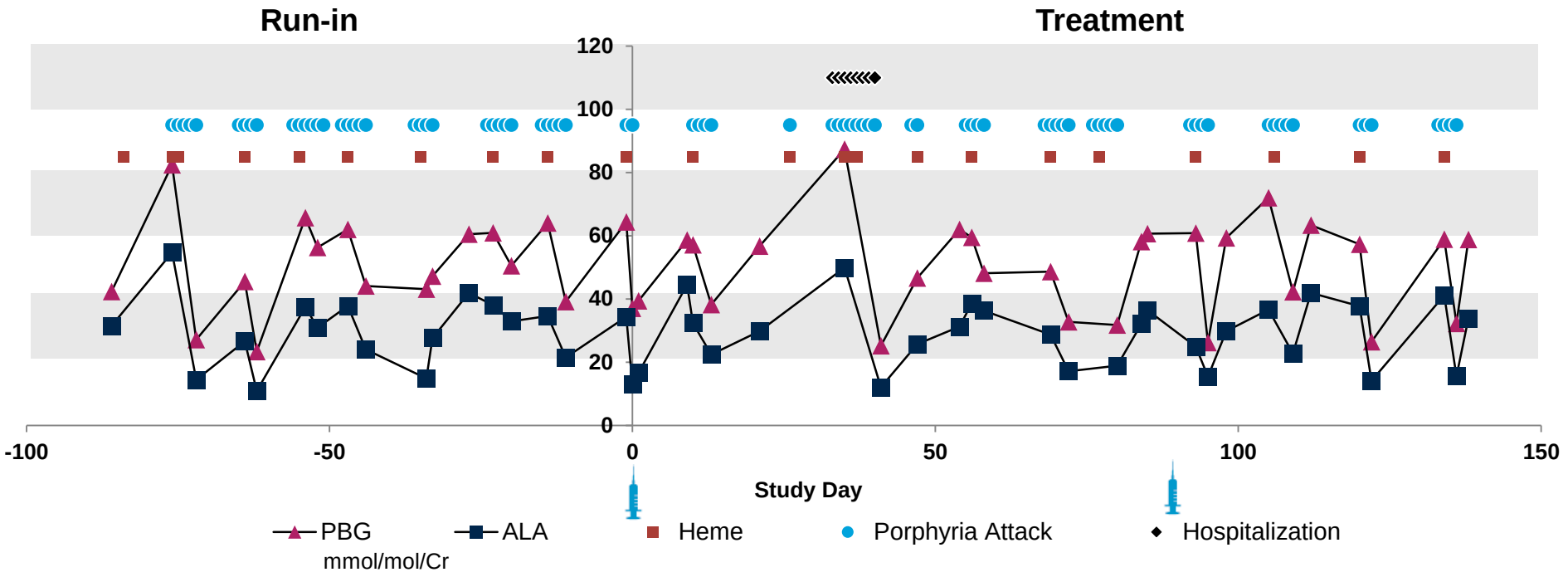
Interim Givosiran Phase 1 (Part C) Study Results*

Clinical Activity Data: Cohort 1, Placebo Patient

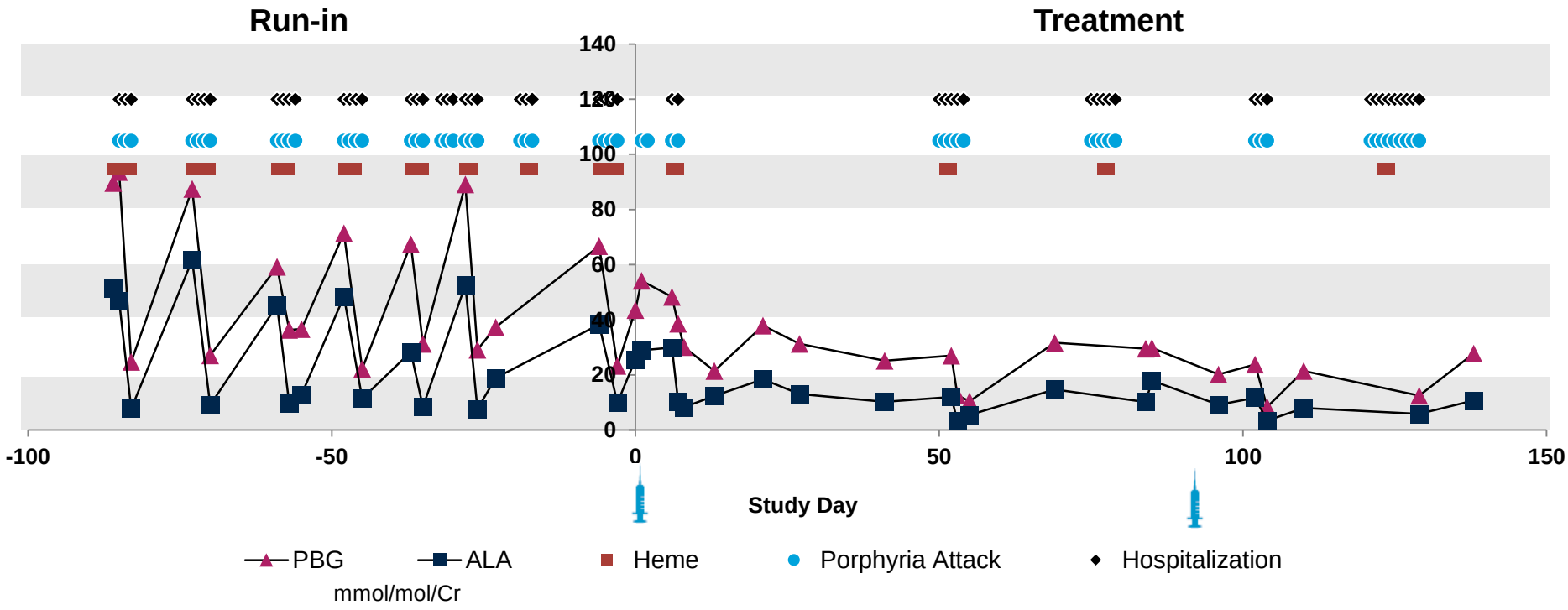


Period	Weeks	Attacks	Attacks Annualized	Max Attack-Free Interval (Days)	Hemin Doses	Hemin Doses Annualized
Run-In	12	8	34	9	10	43
Treatment	22	11	26	16	12	29

*Data transfer date: 07 Nov 2016

Interim Givosiran Phase 1 (Part C) Study Results*

Clinical Activity Data: Cohort 1, Givosiran – Patient 1

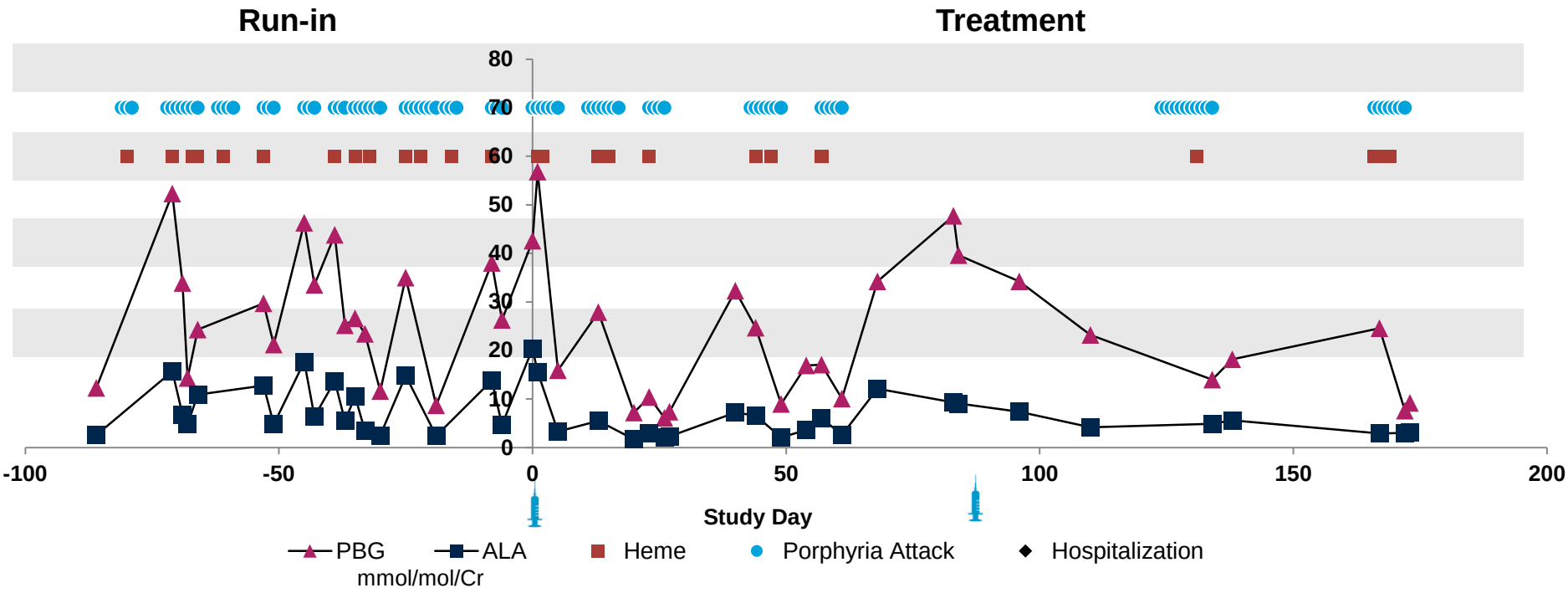


Period	Weeks	Attacks	Attacks Annualized	Max Attack-Free Interval (Days)	Hemin Doses	Hemin Doses Annualized
Run-In	12	9	38	10	24	102
Treatment	22	6	14	42	8	19

*Data transfer date: 07 Nov 2016

Interim Givosiran Phase 1 (Part C) Study Results*

Clinical Activity Data: Cohort 1, Givosiran – Patient 2

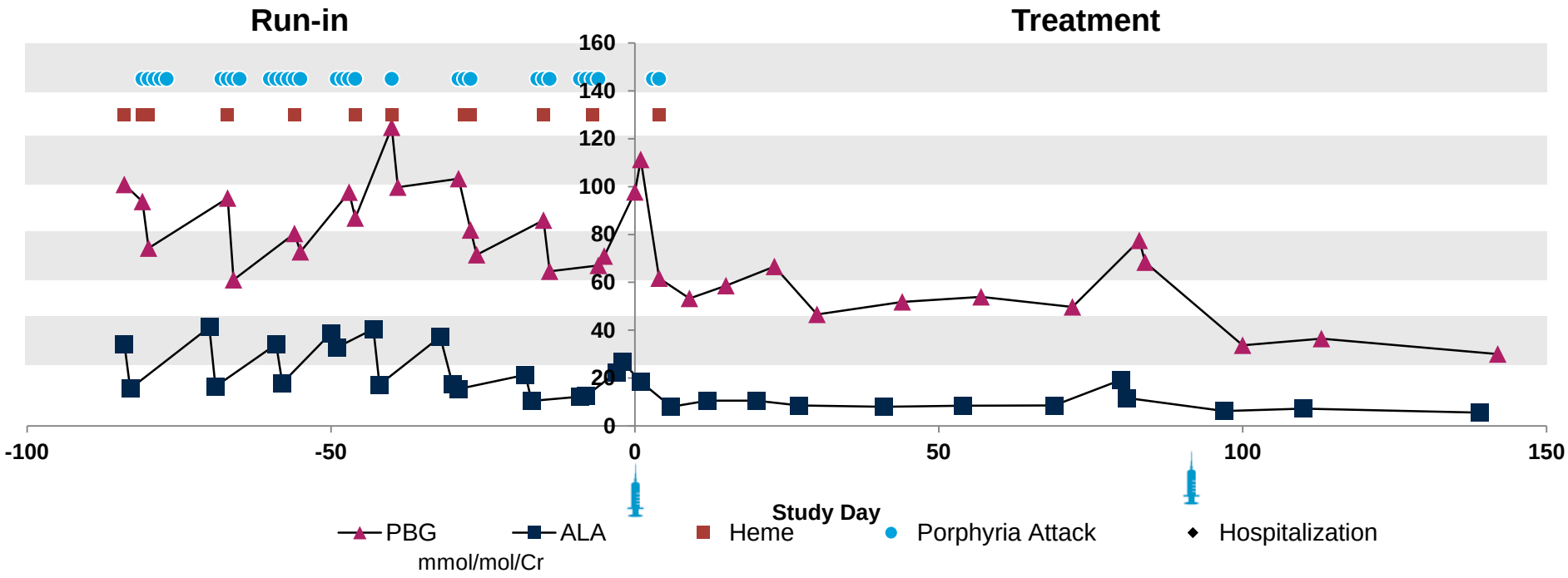


Period	Weeks	Attacks	Attacks Annualized	Max Attack-Free Interval (Days)	Hemin Doses	Hemin Doses Annualized
Run-In	12	11	47	6	13	55
Treatment	25	7	15	62	14	29

*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

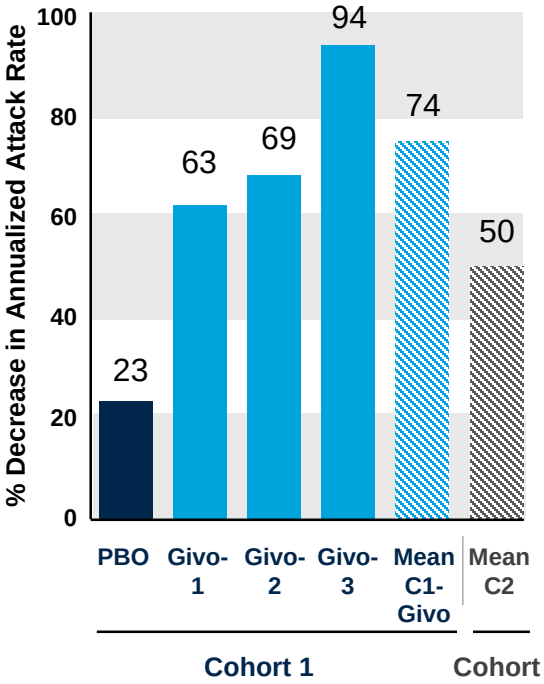
*Data transfer date: 07 Nov 2016

Interim Givosiran Phase 1 (Part C) Study Results*

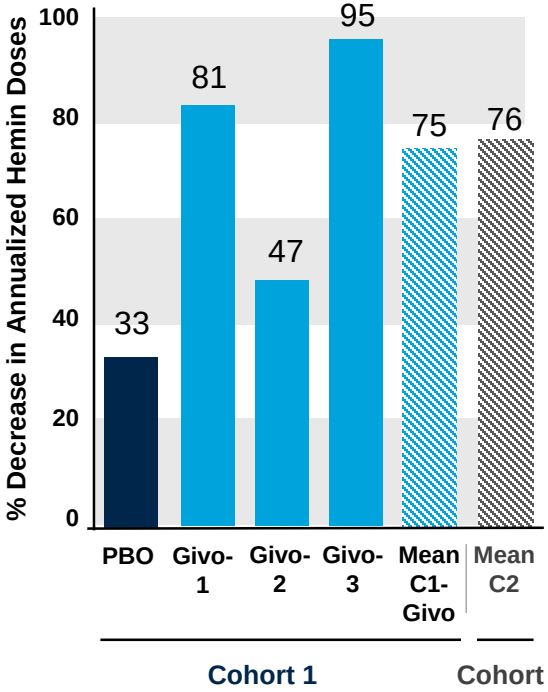
Summary of Clinical Activity Data Cohorts 1 and 2 in AIP Patients

Givosiran Treated Period Relative to Run-in

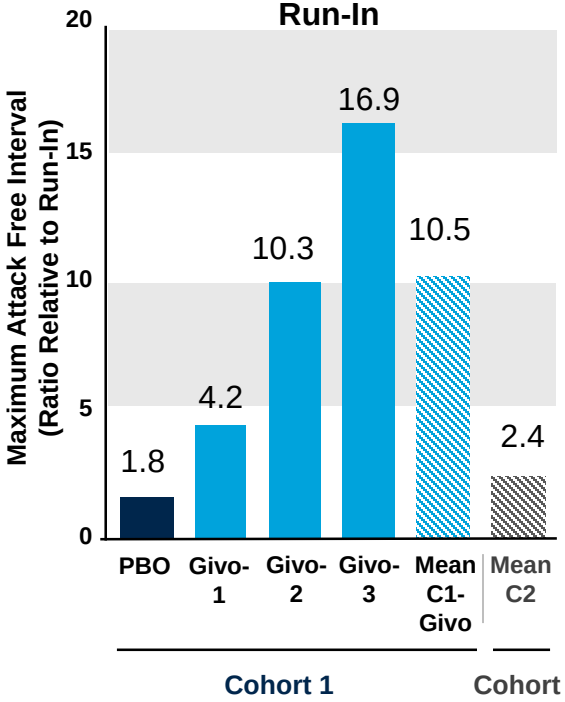
Cohort 1: Mean 74% Decrease in Annualized Attack Rate



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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