Givosiran: Timing of Dosing

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SUMMARY

- The recommended dose of givosiran is 2.5 mg/kg administered via subcutaneous injection once monthly; dosing is based on actual body weight.[1]
- The recommended dose and dosing frequency of givosiran is based on data from a 3-part multidose Phase 1 study that evaluated the safety, tolerability, pharmacokinetics, and pharmacodynamics of givosiran in patients with AIP.[2]
  - Patients with AIP who had recurrent attacks (n=17) were split into 5 cohorts and randomized to receive givosiran 2.5 mg/kg or 5 mg/kg at quarterly or monthly intervals or placebo.[2]
    - Patients who were treated with monthly givosiran (2.5 mg/kg or 5 mg/kg) had sustained ALA and PBG reductions as well as lower peak-to-trough fluctuations compared to patients treated with quarterly givosiran (2.5 mg/kg or 5 mg/kg).[2]
    - The largest reduction of mean AAR, an exploratory endpoint, was observed in patients treated with monthly givosiran 2.5 mg/kg or 5 mg/kg vs quarterly givosiran and placebo.[2]
  - Most AEs in the Phase 1 Study were mild or moderate, occurred at similar rates across the treatment groups, and had no clear relationship to givosiran dose. The most common AEs across all 3 parts of the study were abdominal pain, nausea, diarrhea, and nasopharyngitis.[2]

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GIVLAARI PRESCRIBING INFORMATION – RELEVANT CONTENT

For relevant labeling information, please refer to the following section(s) of the Prescribing Information:[1]

- DOSAGE AND ADMINISTRATION Section 2.1 Recommended Dosage

CLINICAL DATA

Study Design

The Phase 1 study of givosiran was a multicenter, randomized, placebo-controlled, 3-part study (n=23 in Parts A and B; n=17 in Part C) designed to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of givosiran. The clinical activity of givosiran was also explored in Part C. Parts A and B were single-blind trials of single ascending and multiple ascending dose phases, respectively, in patients

with AIP who were CHEs (defined as having a urinary porphobilinogen level >4 mmol/mol creatinine at screening and no attacks in the 6 months before baseline).[2]

Part C was a multidose, double-blind study in which patients with AIP were followed during a run-in period of 4 to 24 weeks. These patients had to have ≥1 attack prior to randomization, in addition to ≥2 attacks within the 6 months before the run-in period; or receive scheduled hemin prophylaxis at the start of the run-in period as needed. The 17 AIP patients were divided into 5 cohorts and were randomly assigned in a 3:1 ratio to receive givosiran (2.5 or 5.0 mg/kg) at quarterly or monthly intervals or placebo for 12 weeks (13 patients were assigned to receive givosiran and 4 to receive placebo). Patients were followed for an additional 12 weeks after the last injection.[2]

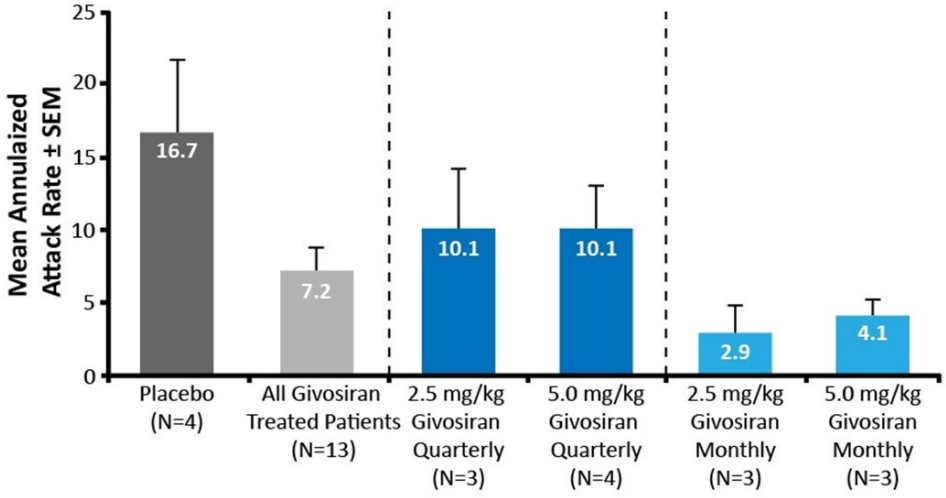
Pharmacodynamics

In Part C, in each of the four givosiran-treated cohorts (2.5 mg/kg quarterly for two doses, 2.5 mg/kg monthly for four doses, 5.0 mg/kg quarterly for two doses, or 5.0 mg/kg monthly for four doses), reduction of *ALAS1* mRNA from baseline was seen with maximal reductions of 49 (±3%), 67 (±3%), 53 (±7%), and 74 (±6%), respectively. Reduction in *ALAS1* mRNA was accompanied by a lowering of urinary ALA and PBG with a mean maximum reduction of >90% compared to baseline observed in both monthly doses. The monthly dosing regimens led to sustained urinary ALA and PBG reductions and lower peak-to-trough fluctuations when compared to the quarterly dosing regimen. There was no observed difference in reduction of urinary ALA or PBG with the increased monthly dose regimen (2.5 mg/kg versus 5.0 mg/kg).[2]

Exploratory Clinical Outcomes

The mean AAR was evaluated in Part C as an exploratory endpoint and is shown in **Figure 1**. Attacks were defined as those leading to hospitalization, urgent healthcare visits, or the use of intravenous hemin at home. The mean AAR during the treatment period of Part C was 7.2 for all givosiran-treated groups, compared to 16.7 in the placebo group (a 57% difference). The mean AAR was further reduced when only the 2.5 and 5.0 mg/kg monthly givosiran dosing groups were compared to placebo (83% and 75% reduction, respectively). Though a statistical analysis was not conducted, patients who received monthly givosiran at either dose had a lower mean AAR than patients who received either quarterly givosiran dose (**Figure 1**).[2]

Figure 1. Mean AAR.[2]

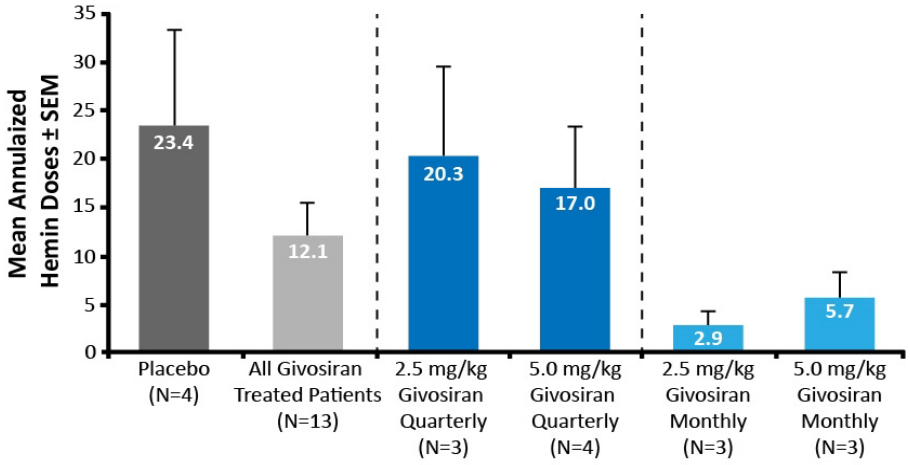


From Sardh et al[2]
Abbreviations: SEM = standard error of the mean.

The annualized number of hemin doses was also evaluated between treatment groups in Part C and is shown in **Figure 2**. Patients treated with givosiran across all groups in Part C had a mean annualized number of

hemin doses of 12.1 versus 23.4 for the placebo group (a 48% reduction). When comparing the run-in period to the treatment period, givosiran treatment reduced the annualized hemin doses by a mean of 64% across all groups as compared to a 34% mean reduction in the placebo group. Though a statistical analysis was not conducted, patients who received monthly givosiran at either dose had lower mean annualized number of hemin doses than patients who received either quarterly givosiran dose (**Figure 2**).[2]

Figure 2. Mean Annualized Number of Hemin Doses.[2]



From Sardh et al[2]
Abbreviations: SEM = standard error of the mean.

Safety

Most AEs in the Phase 1 Study were mild or moderate, occurred at similar rates across the treatment groups, and had no clear relationship to givosiran dosing. The most common AEs across all 3 parts of the study were abdominal pain, nausea, diarrhea, and nasopharyngitis. Injection-site reactions were reported in 6 patients who received givosiran (18%) and in no patients who received placebo.[2] Eight SAEs occurred in 6 patients who received givosiran and none who received placebo, including abdominal pain (2 patients) and spontaneous abortion, influenza A infection, functional gastrointestinal disorder, staphylococcal bacteremia, auditory hallucination, and fatal hemorrhagic pancreatitis (1 patient each). All SAEs were assessed as unlikely to be related to givosiran treatment by the investigating physician.[2,3]

ABBREVIATIONS

AAR = annualized attack rate; AE = adverse event; AIP = acute intermittent porphyria; ALA = aminolevulinic acid; ALAS1 = aminolevulinic acid synthase 1; CHE = chronic high excreter; PBG = porphobilinogen; SAE = serious adverse event.

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REFERENCES

1. GIVLAARI (givosiran) Prescribing Information. Cambridge, MA: Alnylam Pharmaceuticals, Inc.
2. Sardh E, Harper P, Balwani M, et al. Phase 1 trial of an RNA interference therapy for acute intermittent porphyria. *N Engl J Med*. 2019;380(6):549-558. doi:10.1056/NEJMoa1807838
3. Supplement to: Sardh E, Harper P, Balwani M, et al. Phase 1 trial of an RNA interference therapy for acute intermittent Porphyria. *N Engl J Med*. 2019;380(6):549-558. doi:10.1056/NEJMoa1807838