Evaluation of the safety and efficacy of givosiran in treating patients with acute hepatic porphyria and improving their quality of life: Clinical findings from the Expanded Access Protocol in Japan

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Abstract

Background

The givosiran Expanded Access Trial is an open-label, multicenter, single-arm study designed to provide access to investigational givosiran for patients with acute hepatic porphyria (AHP) who have limited or no available treatment options and for whom the treating physician believes the benefits outweigh the risks. The effects of givosiran were evaluated in an exploratory manner.

Results

Givosiran was administered to 10 patients: three patients who continued from the Phase III clinical study (the ENVISION study) and seven newly included patients from this study. Low aminolevulinic acid and porphobilinogen levels were maintained. Two porphyria attacks were reported by the patients; however, both were mild and did not require hemin or hospitalization. In the Givosiran Patient Experience Questionnaire, eight of the 10 patients reported symptom improvement. Adverse events occurred in eight cases, five of which were suspected to be causally associated with givosiran. All adverse events were non-serious, and there were no deaths; however, one patient discontinued treatment due to alopecia.

Conclusion

This study demonstrates that AHP patients on once-monthly administration of givosiran experienced clinical benefits, and there was an acceptable safety profile.

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Background

Acute hepatic porphyria (AHP) is a group of rare metabolic diseases caused by genetic mutations in the liver's enzymes involved in heme synthesis. AHP is characterized by potentially life-threatening acute attacks and, for some patients, chronic manifestations impacting daily functioning and quality of life (QOL). AHP attacks often require emergency medical care. The patients experiencing acute attacks have reported a reduced QOL due to feelings of isolation and an impact on personal relationships caused by the difficulty in adjusting to the disease's limitations [1)]. AHP has affected many facets of their daily living (e.g., altering sleep patterns, ability to work, walking abnormalities, dwindling finances, increased medical costs, and decreased socialization) [2,3)]. Even in patients with a low rate of acute attacks or long periods without attacks, AHP remains a chronically symptomatic disease that adversely affects health and QOL [1,4,5)]. To date, treatment options for all forms of AHP are limited, mainly because there is no prophylactic treatment available, and patients with AHP have been subjected to living in fear of attacks.

Givosiran (trade name: GIVLAARI® subcutaneous injection 189 mg; Alnylam Pharmaceuticals), a chemically synthesized double-stranded small interfering RNA (siRNA) targeting the mRNA of the 5'-aminolevulinic acid synthase 1 (ALAS1) gene in the liver, is a therapeutic agent for treating AHP. The drug was subcutaneously administered once a month and received manufacturing and marketing approval in Japan in June 2021.

Before the approval of this drug in Japan, this open-label, multicenter, single-arm, expanded access study was designed to provide access to investigational givosiran for AHP patients who have limited or no available treatment options and for whom the treating physician believes the benefits outweigh the risks. The effects of givosiran were evaluated with an exploratory manner in Japan.

Methods

The study population included patients diagnosed with acute intermittent porphyria (AIP), hereditary coproporphyria (HCP), variegate porphyria (VP), or ALA dehydratase-deficient porphyria (ADP) who met the following eligibility criteria, with few or no treatment options in Japan.

Eligibility Criteria

Inclusion Criteria

The inclusion criteria were: age > 12 years, documented diagnosis of AIP, HCP, VP, or ADP.

Exclusion criteria

The exclusion criteria were: Clinical Laboratory data at screening: ALT > 2' ULN, Total bilirubin level (TBL) > 1.5 'ULN or documented Gilbert's syndrome with a TBL < 2' ULN, estimated glomerular filtration rate < 15 mL/min/1.73 m^2 based on the Modification of Diet in Renal Disease Modification Formula or Schwartz Bedside Formula; Treatment history/concomitant treatment: current enrollment in a clinical trial of another medical device or drug or completion of a clinical trial of another medical device or drug but 30 days or five times the half-life of the drug (whichever is longer) have not passed or intake of any other investigational drug; Medical condition: active enrollment in the liver transplant waiting list, infection of active hepatitis B or C, according to previous serological tests, infection of the human immunodeficiency virus, history of multiple drug allergies or allergic reactions to oligonucleotides or N-acetylgalactosamine, history of intolerance to subcutaneous injections, conditions that may cause unsuitability for administration or may affect study compliance or patient safety, including medical concerns, alcohol or drug abuse, and significant active, uncontrolled (unstable) cardiovascular, neurological, gastrointestinal, endocrine, renal, or psychiatric disorders unrelated to porphyria, as identified by abnormal laboratory tests or medical history, scheduled to undergo major surgery during the first six months of the study, history of serious infection within one month before the screening, and evidence of malignant disease within two years before the screening, except for treated basal or squamous cell carcinoma of the skin, cervical carcinoma in situ, and breast ductal carcinoma; Pregnancy and lactation.

The study was a multicenter, single-arm, open-label study in which 2.5 mg/kg of givosiran was administered subcutaneously once a month to patients who gave written consent and met all the criteria for eligibility.

As an exploratory endpoint, we evaluated the efficacy of givosiran using the following parameters: urinary ALA level, urinary porphobilinogen (PBG) levels, the patient-reported incidence of porphyria attacks, hemin administration, patient-reported outcomes of givosiran-treated patients at the end of the study, as assessed using the Givosiran Patient Experience Questionnaire (GPEQ), and incidence of adverse events (AEs).

The sponsor may terminate the study at any time for any reason, including disapproval of givosiran. If givosiran had been approved in Japan, this expanded access study would have been terminated within 180 days of approval, and appropriate patients may have been transferred to commercial givosiran.

Statistical analysis was conducted primarily using descriptive statistics such as mean, standard deviation, median, minimum, and maximum values for continuous variables and frequencies and percentages for categorical and ordinal variables.

The clinical effects of givosiran were evaluated using the incidence of porphyria attacks and the number of days of hemin use as patient-reported outcomes. In addition, the pharmacodynamic analysis included the evaluation of changes in ALA and PBG levels.

The incidence of AEs was tabulated, and serious AEs (SAEs) and AEs that caused discontinuation of the study drug were also summarized.

Results

Givosiran was administered to 10 patients: three who continued from the multicenter, global Phase III clinical study (ENVISION study) and seven newly included patients from this study. The mean age of the three patients (two females and one male) included in the ENVISION study was 36 years. The AHP types were AIP (n = 2) and VP (n = 1), and all the patients had a history of hemin use. The mean age of the seven newly included patients was 43.9 years, and all were females. In addition, four of the seven patients had a history of hemin use, and the AHP types were AIP (n = 5) and HCP (n = 2). Other details regarding the patient background are shown in Table 1.

Table 1
Baseline Demographic and Clinical Characteristics (Safety Analysis Population)

	From ENVISION (N = 3)	Not from ENVISION (N = 7)	All patients (N = 10)
Ages (year)			
Mean (SD)	36.0 (14.1)	43.9 (12.5)	41.5 (12.8)
Median	34	45	43.5
Min, Max	23, 51	22, 61	22, 61
Sex, n (%)			
Male	1 (33.3)	0	1 (10.0)
Female	2 (66.7)	7 (100)	9 (90.0)
Weight (kg)			
Mean (SD)	58.8 (10.9)	57.8 (11.3)	58.1 (10.5)
Median	60.1	60.3	60.2
Min, Max	47.3, 69.0	41.6, 74.2	41.6, 74.2
Race, n (%)			
Asian	2 (66.7)	7 (100)	9 (90.0)
Mixed	1 (33.3)	0	1 (10.0)
History of hemin use, n (%)			
No	0	3 (42.9)	3 (30.0)
Yes	3 (100)	4 (57.1)	7 (70.0)
Type of AHP, n (%)			
AIP	2 (66.7)	5 (71.4)	7 (70.0)
VP	1 (33.3)	0	1 (10.0)
HCP	0	2 (28.6)	2 (20.0)
ADP	0	0	0

Abbreviations: ADP, aminolevulinic acid dehydratase-deficient porphyria; AHP, acute hepatic porphyria; AIP, acute intermittent porphyria; HCP, hereditary coproporphyria; Max, maximum; Min, minimum; n, number; SD, standard deviation; VP, variegate porphyria.

Givosiran was administered for at least 7–11 months.The endpoints of this study are as follows.

Changes in urinary ALA and PBG levels are shown in Fig. 1. For the three patients who continued from the ENVISION study, their urinary ALA and PBG levels were low at baseline and remained low throughout the study period. For the seven newly included patients with elevated urinary ALA and PBG levels at baseline, these levels decreased and remained low, after treatment using givosiran.

Regarding the patient-reported incidence of porphyria attacks and hemin administration, two of the three patients who continued from the ENVISION study reported porphyria attacks during the study period. Furthermore, the VP patient had seven attacks during the study period, five of which were treated at home. One patient with AIP experienced one attack and recovered with home care. The attacks were mild and did not require hemin administration or hospitalization. No acute attacks were reported in the seven newly included patients.

Table 2 shows patients' overall evaluation of givosiran according to the GPEQ compiled at the end of the clinical study. Eight (80%) of the 10 patients reported some improvement, with three reporting very much-improved symptoms, four reporting much-improved symptoms, and one reporting minimally improved symptoms. The degree of improvement in quality of life (QOL), including specific clinical symptoms, is summarized in Tables 3 and 4.

Table 2
GPEQ Change in Overall Status as a Result of Treatment with Givosiran (Safety Analysis Population)

	From ENVISION (N = 3)	Not from ENVISION (N = 7)	All patients (N = 10)
	n (%)	n (%)	n (%)
Since the start of the study, my overall status is:			
Very much improved	1 (33.3)	2 (28.6)	3 (30.0)
Much improved	1 (33.3)	3 (42.9)	4 (40.0)
Minimally improved	1 (33.3)	0	1 (10.0)
No change	0	1 (14.3)	1 (10.0)
Minimally worse	0	1 (14.3)	1 (10.0)
Much worse	0	0	0
Very much worse	0	0	0
Abbreviations: GPEQ, givosiran patient experience questionnaire; n, number			

Table 3
Quality of life improvements (symptoms and physical problems)

	Pain	Fatigue	Constipation	Diarrhea	Appetite loss	Concentration problems	Numbness	Tingling	Muscle weakness	Insomnia
A lot better	3	1	0	0	1	0	0	0	0	0
Better	2	2	0	0	1	1	1	2	2	3
No change	4	5	6	6	5	5	3	4	5	4
Worse	0	1	1	0	0	0	1	0	0	1
A lot worse	0	0	0	0	0	0	0	0	0	1
Does not apply	1	0	3	4	3	4	5	4	3	1

Table 4
Quality of life improvements (emotional and social impacts)

	Depression	Anxiety	Traveling for work or pleasure	Planning ahead (schedules, appointments, etc.)	Ability to meet friends or family outside of the house	Ability to do the things you enjoy doing	Ability to do things independently	Feeling like you are a burden to your family	Ability to work
A lot better	0	2	2	1	2	1	1	2	1
Better	2	2	1	1	1	3	3	2	3
No change	2	3	5	5	4	3	3	4	4
Worse	0	0	1	0	1	0	0	0	0
A lot worse	1	1	0	1	0	1	1	1	1
Does not apply	5	2	1	2	2	2	2	1	1

Regarding AEs, at least one treatment-emergent AE (TEAE) occurred in eight of the 10 patients. Five had AEs suspected to be causally related to the study drug. All AEs were non-serious and mild or moderate in severity; however, one patient discontinued treatment due to an AE, mild alopecia, that was considered to be associated with the study drug. No death occurred. Table 5 summarizes the AEs suspected to be causally related to the study drug.

Table 5
TEAEs associated with the study treatment based on SOC and PT (Safety Analysis Population)

SOC **PT**	**Safety Analysis Population** **(N = 10)** **n (%)**
Number of patients reporting at least one TEAE associated with study treatment	5 (50)
General disorders and administration site conditions	1 (10)
Infusion site erythema	1 (10)
Edema	1 (10)
Investigations	2 (20)
Alanine aminotransferase increased	1 (10)
Aspartate aminotransferase increased	1 (10)
Blood alkaline phosphatase increased	1 (10)
Blood homocysteine increased	1 (10)
Gamma-glutamyltransferase increased	1 (10)
Liver function test increased	1 (10)
Metabolism and nutrition disorders	1 (10)
Hyperhomocysteinaemia	1 (10)
Renal and urinary disorders	1 (10)
Renal impairment	1 (10)
Skin and subcutaneous tissue disorders	2 (20)
Alopecia	2 (20)
Abbreviations: n, number; PT, preferred term; SOC, system organ class; TEAEs,	
treatment-emergent adverse events	

Note: TEAE was defined as any AEs that started after exposure to the study drug

or worsened in severity after dosing.

Discussion

The details of this study are shown in Table 6. A total of 10 patients participated in the study, including three who continued from the ENVISION study. In the ENVISION study, a composite attack was defined as an attack requiring hospitalization, urgent care, or a home infusion of hemin.[6)]. When the study was evaluated considering this definition, only one patient who continued from the ENVISION study was considered to have a composite attack, with two emergency room visits during the treatment period of approximately 9 months. The other two patients who continued from the ENVISION study did not have an attack that met the definition. The average frequency of attacks in these three patients was approximately 0.5, which seemed low compared with that in the entire study drug group for AIP in the ENVISION study (3.2 per year (95% confidence interval: 2.3–4.6). No attacks were observed in any of the seven newly included patients. Since this study did not restrict participation based on a history of composite attacks or hemin use within six months like ENVISION study, even patients with a relatively mild disease could participate in the study, it is possible that the newly included patients were milder disease severity compared to the from ENVISION study group.

Table 6
Details of the patients' assessment

ID	Participation to ENVISION	Type	Age	Sex	Hemin usage	Remarks	Overall status
1	Yes	AIP	23	Female	Yes	1 attack during the dose period	Very much improved
2	Yes	AIP	51	Male	Yes		Much improved
3	Yes	VP	34	Female	Yes	7 attacks during the dose period(2 urgent health cares)	Minimally improved
4	No	AIP	45	Female	Yes	Discontinued due to onset of alopecia (mild)	Very much improved
5	No	HCP	22	Female	No		Very much improved
6	No	HCP	61	Female	Yes		Much improved
7	No	AIP	42	Female	Yes		Much improved
8	No	AIP	53	Female	No		Much improved
9	No	AIP	36	Female	Yes	Doses were missed several times due to liver dysfunction	No change
10	No	AIP	48	Female	No	Feel stressed with scheduled clinical visits	Minimally worse

Patient satisfaction ratings tended to be higher among continuing patients. Even the patient (ID = 3) who had seven attacks after givosiran administration, who before receiving givosiran experienced immediate hospitalization often, improved the patient's lives and could receive home healthcare. Moreover, the numbness in her limbs causing her difficulty walking improved to the extent that she could walk to the hospital. The patient (ID = 4) who discontinued treatment due to mild alopecia was a newly included patient. She felt that the treatment was effective; however, the treatment was discontinued because of the importance of her appearance. Despite the resolution of alopecia symptoms after discontinuing the drug, the patient was hesitant to resume the medication because of concerns about the recurrence of alopecia. The patient (ID = 10) with the lowest overall rating indicated that regular visits were painful, thus suggesting that in this case the original AHP symptoms were mild, and the treatment burden outweighed the benefits.

The treatment effect was mainly the reduction of pain associated with symptoms. This was experienced by half of the total respondents. In addition, the QOL evaluation indicated that patients' anxieties, enjoyment of their hobbies, sense of independence, feeling of indebtedness to family members, and job performance improved.

This study had some limitations. First is the lack of interviews on the occurrence/severity of AHP symptoms and attacks before givosiran administration. Second is the lack of a unified assessment of other factors affecting symptoms and QOL during givosiran treatment. Finally, this study was conducted from an expanded access perspective, making a rigorous evaluation difficult; however, the GPEQ results suggest that many continuing and new patients showed improvement in health status after receiving the drug.

Conclusions

While treatment options for AHP have been limited and have focused on supportive care to date, this study demonstrates the benefits and acceptable safety profile of administering givosiran once a month in AHP patients.

Abbreviations

AHP, acute hepatic porphyria; ALA, aminolevulinic acid; AIP, acute intermittent porphyria; HCP, hereditary coproporphyria; VP, variegate porphyria; ADP, aminolevulinic acid dehydratase-deficient porphyria; TBL, total bilirubin level; PBG, porphobilinogen; GPEQ, Givosiran Patient Experience Questionnaire; AEs, adverse events; QOL, quality of life

Declarations

Ethics approval and consent to participate:

The study with protocol was approved by Iizuka Hospital ethic committee.

All patients have provided written informed consent prior to inclusion.

.*Consent for publication:*

Not applicable.

Availability of data and materials:

The data that support the findings of this study are either included in the article or available from the corresponding author on reasonable request.

Competing interests:

N.F. and T.O. are employees of Alnylam Japan K.K.. K.F. is an employee, and M.J.F. is a former employee of Alnylam Pharmaceuticals Inc. The other authors declare no conflicts of interest. The writing of this article was supported by the Multiplex Limited Liability Company and funded by Alnylam Japan K.K.

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Authors' contributions:

All authors have made great contribution to this work; MJF and NF in the conception and design of this study, NO, YG, TO KF and TA in the acquisition of the data. All authors are contributors to the data analysis and the interpretation of data and have read, revised manuscript, and approved the submission of this final one.

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Figures

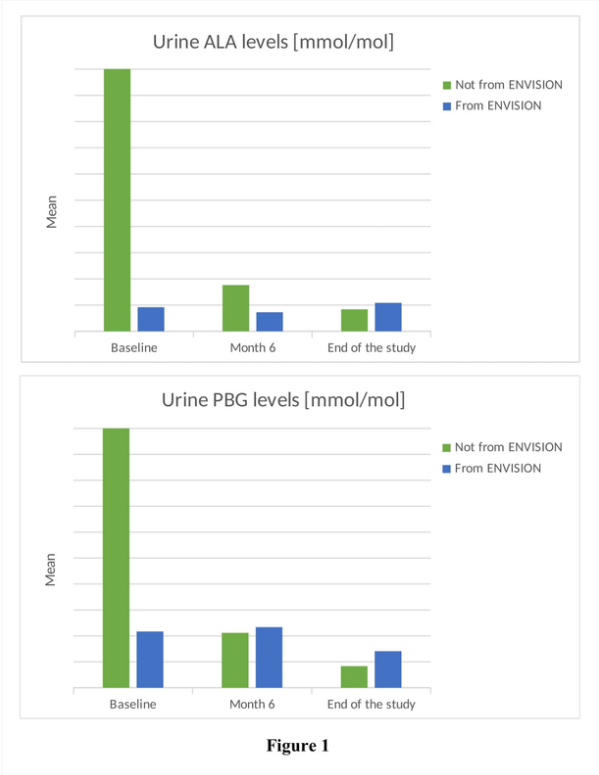

Figure 1

Figure 1

Urine ALA and PBG levels.