Patient Preference and Adherence

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ORIGINAL RESEARCH

Physician and Patient Preferences for Treatment of Anemia Associated with Chronic Kidney Disease in Japan: A Survey Including Best-Worst Scaling

Sari Mishina[1], Yuichiro Ito[1], Takumi Lee[1], Toshiaki Murofushi[2], Yoshiyuki Uetake[2], Tadao Akizawa[3]

[1]Astellas Pharma Inc, Tokyo, Japan; [2]INTAGE Healthcare Inc, Tokyo, Japan; [3]Division of Nephrology, Department of Medicine, Showa University School of Medicine, Tokyo, Japan

Correspondence: Sari Mishina, Astellas Pharma Inc, 2-5-1, Nihonbashi-Honcho, Chuo-ku, Tokyo, Japan, Tel +81-3-3244-0294, Email sari.mishina@astellas.com

Background: Several treatment options are available for anemia associated with chronic kidney disease (CKD); however, there remains a lack of awareness of physician and patient preferences regarding these treatments. We aimed to explore physicians' and patients' perceptions and preferences regarding the management of anemia of CKD in Japan.

Methods: A web-based survey, including best-worst scaling (BWS), was conducted with physicians who had treated ≥1 patient with anemia of CKD in the preceding year, and with patients with CKD who self-reported a clinical diagnosis of anemia of CKD or low hemoglobin levels. A three-step approach was used comprising cognitive interviews, a pilot survey, and a main survey. The BWS survey results were analyzed using multinomial logit and hierarchical Bayesian models.

Results: The survey was completed by 906 participants: 103 patients (average age 60.6 years; 77.7% male) and 803 physicians (166 nephrologists, 214 cardiologists, 137 diabetologists, and 286 general internists). Almost all (96.0%) physicians surveyed considered anemia of CKD to be an important condition to treat. Hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors had the highest treatment satisfaction among physicians, whereas patients had the highest satisfaction with both erythropoietin-stimulating agent therapy and HIF-PH inhibitors. Approximately one-third (35.9%) of patients surveyed indicated that they were receiving treatment. When comparing the relative importance of attributes and levels, physicians favored efficacy (particularly improvement in hemoglobin levels), whereas patients favored safety (particularly a lower rate of severe adverse events).

Conclusion: Although a majority of physicians consider treatment of CKD-related anemia important, differences in the perceptions and usage of medications exist between medical specialties. Preferences for the management of anemia of CKD vary between physicians and patients; therefore, patient involvement in treatment decisions may help optimize outcomes.

Keywords: anemia, best-worst scaling, chronic kidney disease, erythropoiesis-stimulating agents, hypoxia-inducible factor prolyl hydroxylase inhibitors, treatment preference

Introduction

Chronic kidney disease (CKD) is characterized by abnormalities of kidney structure or function that are present for over 3 months; the resultant damage is slowly progressive and, in most cases, irreversible.[1] In 2022, the prevalence of CKD in Japan was estimated to be 12.7% across all ages and stages.[2] CKD is associated with several complications that contribute to high morbidity and mortality and poor quality of life, one of which is anemia.[3] Patients with later stages of CKD have an increased prevalence of anemia.[4–7] Anemia of CKD is accompanied by several symptoms including fatigue, shortness of breath, insomnia, and headaches,[8] and is also associated with an increased risk of hospitalization, cardiovascular events, and all-cause mortality.[9–12]

Treatments available for anemia of CKD include iron therapy, erythropoietin-stimulating agents (ESAs), blood transfusions, and, most recently, hypoxia-inducible factor prolyl hydroxylase (HIF-PH) inhibitors.[7,9,13] Currently in Japan, the most commonly used treatments are oral iron therapy in the early stages of CKD and ESAs during the later stages.[14] Intravenous (IV) iron therapy is sparingly used across all CKD stages, and blood transfusion is given mostly to hospitalized patients.[15] However, each of these therapies has its limitations. Oral iron is affordable, readily available, and convenient to administer, but

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is associated with gastrointestinal adverse effects and variable absorption rates.[7] IV iron is more efficacious than oral iron, but requires IV access and is associated with infrequent but severe adverse events.[7] Moreover, although iron therapy is considerably cheaper than ESAs,[14] ESAs are required to address a second mechanism underlying anemia of CKD, namely deficiencies in endogenous erythropoietin production.[7,16] A notable disadvantage of ESAs is the requirement for either subcutaneous or IV administration, which can be painful and inconvenient for the patient, and/or necessitate hospital visits in the case of IV administration.[7] Lastly, blood transfusions, which are used infrequently, carry a greater risk of hyperkalemia, hemolytic reactions, and anaphylaxis, among other potential adverse events.[7]

Furthermore, a 2010 survey of 300 Japanese physicians, of whom 50% were nephrologists, revealed that ESAs were not being given to 50–60% of patients with CKD-related anemia – the reasons given included high drug cost, inadequate improvement of anemia, and short duration of effect.[17] An analysis of the Japan Chronic Kidney Disease Database (J-CKD-DB) also indicated that ESA utilization rates were low, with only 7.9% of patients with CKD stage G4 and 22.4% of patients with CKD stage G5 receiving this treatment.[4] Even among patients under the care of a nephrologist or diabetologist, it was found that fewer than half (43%) of those with anemia were treated with ESAs.[18]

Novel oral HIF-PH inhibitors are effective at correcting and maintaining hemoglobin (Hb) levels, may partially restore normal iron metabolism based on data from clinical trials, and are expected to address some of the challenges of ESA use.[13,19] However, there remains a lack of data on the current use of HIF-PH inhibitors in Japan. In addition, although previous studies conducted in Japan showed an increased satisfaction for the use of ESAs compared with other treatments,[17,20] physicians' and patients' preferences for treatment of anemia in CKD have not been fully explored. In our study, we explored physicians' perceptions of and attitudes to the management of anemia in non-dialysis-dependent (NDD)-CKD. We examined the differences in perception of treatment among different physicians' specialties, determined the similarities and differences in perceptions between physicians and patients, and sought to understand if perceptions for physicians and patients have changed as ESAs are well established as the standard of care.

Patients and Methods

Overall Study Design

This study included a physician perception survey, a patient perception survey, and a comparison of physician and patient preferences (Supplementary Figure 1).

Ethical Approval and Informed Consent

The study protocol and both the survey questionnaires were reviewed and approved by the Saga Memorial Hospital Institutional Review Board (IRB) between Jun 2021 and Mar 2022. This research was carried out in accordance with ethical principles outlined in the IRB and the Declaration of Helsinki (1964), and good clinical practice guidelines and applicable laws and regulations of Japan, such as the Ethical Guidelines for Life Science, Medical and Health Research for Human Subjects in Japan.[21] All participants provided informed consent prior to starting the surveys.

Cognitive Interviews

The physician and patient surveys were pre-tested via 60-minute web-based cognitive interviews and conducted in September 2021 with five physicians who had previously treated ≥1 patient with anemia of CKD in the last 12 months and with five patients with anemia of NDD-CKD. The interview findings were used to refine the definitions, instructions, and validity of items for use in best-worst scaling (BWS) in the main survey, hone the treatment plan schema, and confirm that patients understood the treatment-choice questions.

Pilot Survey

The questionnaire reflecting the results of the cognitive interviews was tested in a pilot survey in December 2021. This survey was conducted using a web-based platform that enrolled 50 patients and 50 physicians. The aim of the pilot survey was to ensure that the questions and BWS exercise were easy to understand; any necessary changes were then made before the main survey was conducted.

Main Survey

The physician survey covered medical background and experience; number of patients treated; comorbidities of patients with anemia of CKD; drug classes prescribed for anemia of CKD; purposes of treating or not treating anemia of CKD; treatment satisfaction; reasons for using particular drug classes; advantages of each drug class; importance of treating anemia of CKD with reasons; barriers to use of ESAs and HIF-PH inhibitors; and a BWS exercise (Supplementary Table 1). The patient survey covered patient demographics and medical history; diagnosis of CKD-related anemia and hemoglobin level, if known; symptoms experienced and symptoms that were burdensome; duration and location of treatments received for anemia of CKD; conditions treated other than anemia of CKD; treating specialist and treatments received for anemia of CKD; concerns about each drug class; important treatment characteristics; impact of treatment on daily life; burden of treatment; treatment satisfaction with each drug class; and a BWS exercise (Supplementary Table 2). The questions were provided in Japanese for self-completion. All assigned questions needed to be completed to allow data collection. Physicians' and patients' responses were recorded into an electronic database. In the event of a system error, missing values were not collected. The surveys were single-blinded, and participants were anonymized by assignment of a unique ID number.

Participants

Physicians (nephrologists, cardiologists, diabetologists, and general internists) who were registered as part of a panel of Japanese physicians maintained by PLAMED Inc.,[22] a platform for medical research which includes approximately 60,000 individuals, and had treated patients with anemia of CKD in the past year were invited to participate in this study. Eligible patients were adults (aged ≥18 years), had a self-reported diagnosis of CKD, had a self-reported diagnosis of anemia of CKD or low Hb levels according to the thresholds in the 2015 Japanese Society for Dialysis Therapy: Guidelines for Renal Anemia in CKD,[23] and were registered in the INTAGE Inc., Marketing Applications, Inc., or Rakuten Insight, Inc. panels. Patients receiving dialysis were excluded from the patient survey. Full inclusion and exclusion criteria for both physicians and patients are given in Supplementary Table 3.

Statistical Analyses

A web-based BWS exercise[24] was incorporated into the surveys to understand physicians' and patients' preferences for different treatment attributes (efficacy, safety, route of administration, usage, burden, and price); these attributes had previously been identified through a literature review. BWS is based on random utility theory, which estimates the contribution of each option to utility; a utility value for each option is generated based on the best and worst choices selected by participants. This study used the BWS profile case method, in which the level of each attribute is included in the options and the choice set has the structure of a single profile. The BWS questions included 20 options, with four options per task (Supplementary Table 4). The tasks were repeated 20 times. Options presented were randomly designated for each participant using Sawtooth Software SSI Web version 8.0 (Sawtooth Software, Provo, Utah, USA). Additionally, questions concerning treatment preferences and satisfaction for physicians and patients were answered using a Likert scale.

The results from the BWS questions were evaluated using multinomial logit and hierarchical Bayesian models using Sawtooth Software. A multinomial logit model relates the probability of choosing between two or more alternatives to the attribute-level characteristics that define those alternatives. Preferences were evaluated by utility score. The utility score of each item was estimated for each respondent as a relative importance using the hierarchical Bayesian model. Each preference was estimated for each individual using all data, including the unselected options from each question, obtained from the BWS survey.

Results

Physician Survey

Physician Characteristics

In the group of 803 physicians surveyed, the specialties were nephrology (n = 166, 20.7%), cardiology (n = 214, 26.7%), diabetes (n = 137, 17.1%), and general internal medicine (n = 286, 35.6%). The primary workplace of most physicians (67.9%, 545/803) was a hospital with ≥20 beds. Within the past 5 years, 22.3% of physicians had treated ≥101 patients with anemia of CKD (Table 1). During this period, 100% of nephrologists, >80% of cardiologists and diabetologists, and >70% of general

Table 1 Number of Patients with Anemia of CKD Treated by the Participating Physicians Within the Past 5 Years

Number of Patients Treated	Physicians, n (%)
Total	803 (100)
1–10 patients	139 (17.3)
11–30 patients	204 (25.4)
31–50 patients	149 (18.6)
51–100 patients	132 (16.4)
≥101 patients	179 (22.3)

Abbreviation: CKD, chronic kidney disease.

internists saw ≥11 patients with anemia of CKD. On average, each surveyed physician had treated approximately 43 patients with anemia of CKD in the past year (Table 2).

Physicians' Attitudes to Management of Anemia of CKD

Almost all physicians (96.0%, 771/803) considered anemia of CKD to be "an important disease to treat", and the most commonly selected reason was "it's a disease that will affect life prognosis" (68.6%, 529/771) (Table 3). Among the 32 (4.0%) physicians who considered anemia of CKD to be "not that important or cannot say either way", the most selected reason was that it "has no effect on life prognosis" (31.3%, 10/32) (Table 4). Nephrologists most commonly selected "will lower patient quality of life" (70.4%, 112/159) as the reason for considering anemia of CKD as an important disease to be treated, whereas general internists most commonly selected "it's a disease that will affect life prognosis" (69.1%, 190/275) (Table 3). The latter reason was also the most common reason cited by cardiologists (65.7%, 138/210) and diabetologists (76.4%, 97/127) (Table 3).

Table 2 Number of Patients with Anemia of CKD Treated by the Participating Physicians in the Past Year, by CKD Stage

Patients with Anemia of CKD Treated in the Past Year	Mean (SD)	Median (Min–Max)
Total	42.5 (53.76)	21 (1–400)
By CKD stage[a]		
CKD G3a	6.1 (11.55)	2 (0–120)
CKD G3b	7.5 (9.48)	5 (0–100)
CKD G4	8.0 (9.79)	5 (0–65)
CKD G5	6.1 (11.01)	2 (0–108)
Dialysis dependent	14.6 (34.63)	1 (0–280)

Notes: Responses were received from a total of 803 participating physicians. [a]CKD was classified as per GFR (mL/min/1.73 m^2; term) category as follows: G3a (45–59; mildly to moderately decreased); G3b (30–44; moderately to severely decreased); G4 (15–29; severely decreased); and G5 (<15; kidney failure).[1]

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; Q, quartile; SD, standard deviation.

Table 3 Physicians' Reasons for Considering Anemia of CKD to Be an Important Disease to Treat

Reason, n (%)	All Physicians (N=771)	Nephrologists (N=159)	Cardiologists (N=210)	Diabetologists (N=127)	General Internists (N=275)
Will cause cardiovascular disease	495 (64.2)	105 (66.0)	159 (75.7)	75 (59.1)	156 (56.7)
Will affect renal prognosis	450 (58.4)	108 (67.9)	116 (55.2)	77 (60.6)	149 (54.2)
Will lower patient quality of life	470 (61.0)	112 (70.4)	115 (54.8)	78 (61.4)	165 (60.0)
It's a disease that will affect life prognosis	529 (68.6)	104 (65.4)	138 (65.7)	97 (76.4)	190 (69.1)
It's expected to prevent the progression of future complications, which will lead to reduction in treatment costs	317 (41.1)	74 (46.5)	75 (35.7)	58 (45.7)	110 (40.0)
Other	1 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
No particular reason	2 (0.3)	1 (0.6)	0 (0.0)	1 (0.8)	0 (0.0)

Abbreviation: CKD, chronic kidney disease.

Table 4 Physicians' Reasons for Considering Anemia of CKD Not to Be an Important Disease to Treat/Cannot Say Either Way

Reasons for considering anemia of CKD not to be an important disease to treat/cannot say either way (N=32)	Physicians, n (%)
Has no effect on life prognosis	10 (31.3)
Has no effect on patient quality of life	9 (28.1)
Should be determined by a specialist	8 (25.0)
There are only few applicable patients in clinical practice	7 (21.9)
Has no effect on cardiac/renal functions	6 (18.8)
Other	1 (3.1)
No particular reason	7 (21.9)

Abbreviation: CKD, chronic kidney disease.

Physicians' Rationale for Choosing a Particular Drug Class

The most popular reason among physicians for choosing a particular drug class for treatment of anemia of CKD was that the "effect of improving hemoglobin level is good." For this reason, ESA therapy had the highest score at 77.2% (541 responses from the 701 physicians who used ESAs) (Figure 1). Approximately one-third (33.8%, 143/423) of physicians considered HIF-PH inhibitors to reduce patients' hospital visits, compared with 7.2% (12/166) for IV iron, 12.9% (81/627) for oral iron, and 8.4% (59/701) for ESAs (Figure 1). HIF-PH inhibitors had the lowest percentage score among the drug classes for "familiar with its use" (46/423, 10.9%), while receiving the highest percentage score for "improvement in prognosis can be expected" (37.6%, 159/423), followed closely by ESAs (32.8%, 230/701) (Figure 1). Expectations of renoprotective and cardioprotective effects and improvements in patients' quality of life were higher for ESAs and HIF-PH inhibitors than for iron therapy (IV and oral) and highest for HIF-PH inhibitors overall. In terms of cost considerations, iron therapy (oral and IV) was the most commonly selected due to low drug price (Figure 1).

Physicians' Satisfaction with Drugs for Treatment of Anemia of CKD

HIF-PH inhibitors had the highest treatment satisfaction among physicians, with 82.5% (349/423) of all physicians selecting the highest satisfaction categories ("very satisfied" + "satisfied") (Figure 2). Among the different physicians'

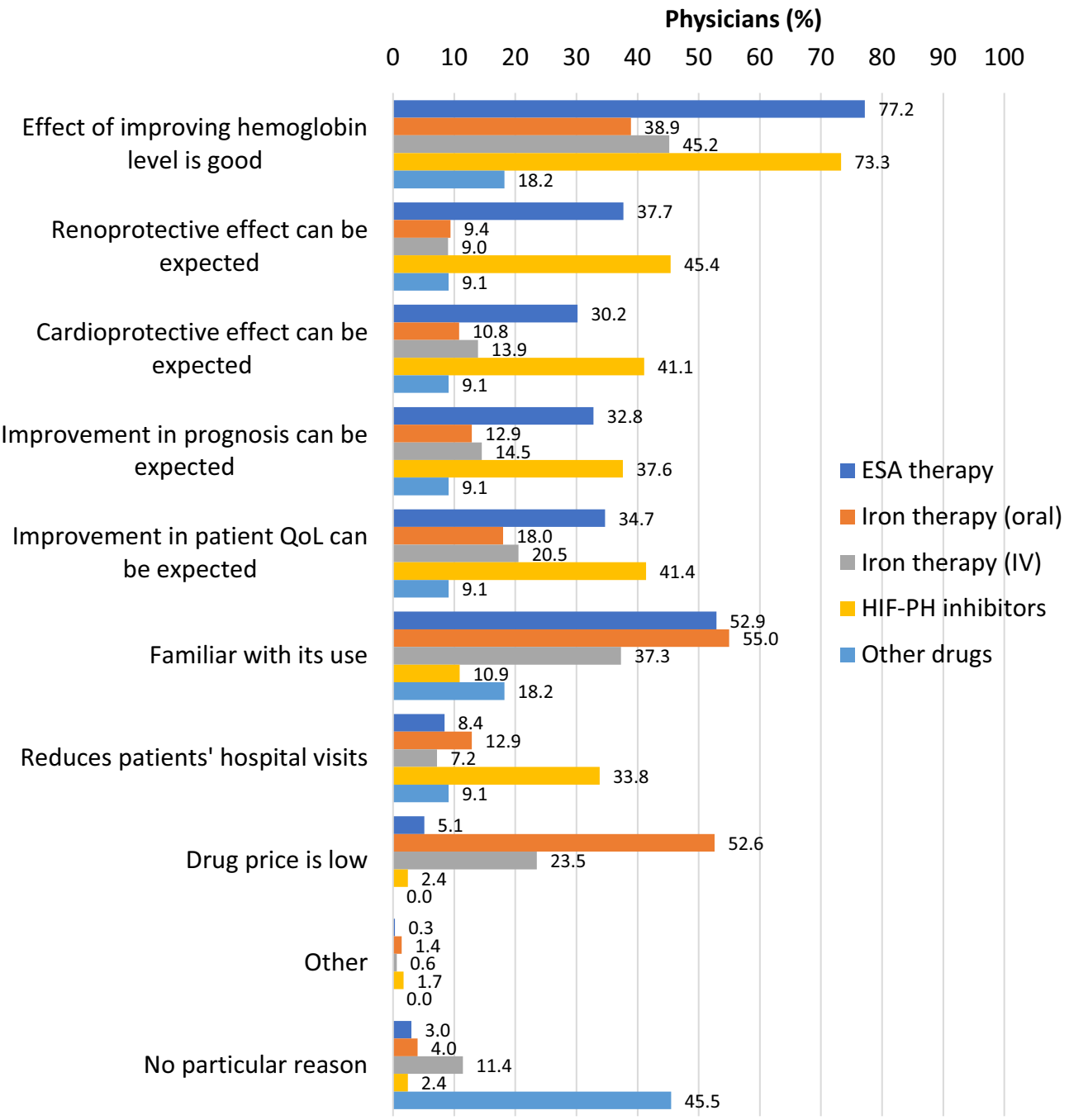

Figure 1 Physicians' reasons for selecting a particular drug class (N=803)[a].
Notes: [a]Of the total 803 physicians who responded, the number of physicians indicating use of each drug class was as follows: ESA therapy, 701; iron therapy (oral), 627; iron therapy (IV), 166; HIF-PH inhibitors, 423; and other drugs, 11.
Abbreviations: ESA, erythropoiesis-stimulating agent; HIF-PH, hypoxia-inducible factor prolyl hydroxylase; IV, intravenous; QoL, quality of life.

specialties, the satisfaction level with ESAs and HIF-PH inhibitors was similar (Figure 3A and D). Nephrologists had a greater satisfaction with iron therapies compared with other specialties (Figure 3A–D).

Physicians' Reasons for Not Prescribing a Specific Treatment

Among physicians who had not prescribed HIF-PH inhibitors to patients with CKD stage ≥3, the most common reason given was never having used HIF-PH inhibitors previously (48.9%, 174/356) (Table 5); this reason was provided by 25.5% (13/51), 47.1%

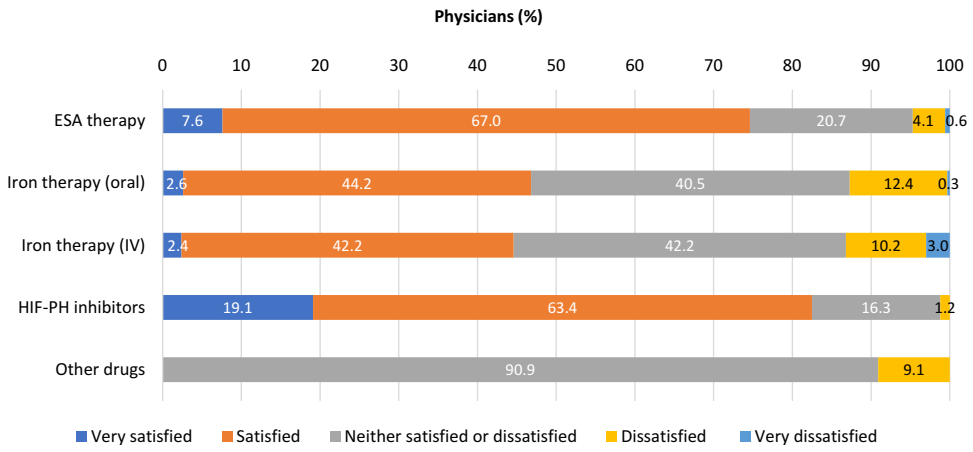

Figure 2 Physicians' satisfaction with drug classes (N=803)[a].
Notes: [a]Of the total 803 physicians who responded, the number of physicians indicating use of each drug class was as follows: ESA therapy, 701; iron therapy (oral), 627; iron therapy (IV), 166; HIF-PH inhibitors, 423; and other drugs, 11.
Abbreviations: ESA, erythropoiesis-stimulating agent; HIF-PH, hypoxia-inducible factor prolyl hydroxylase; IV, intravenous.

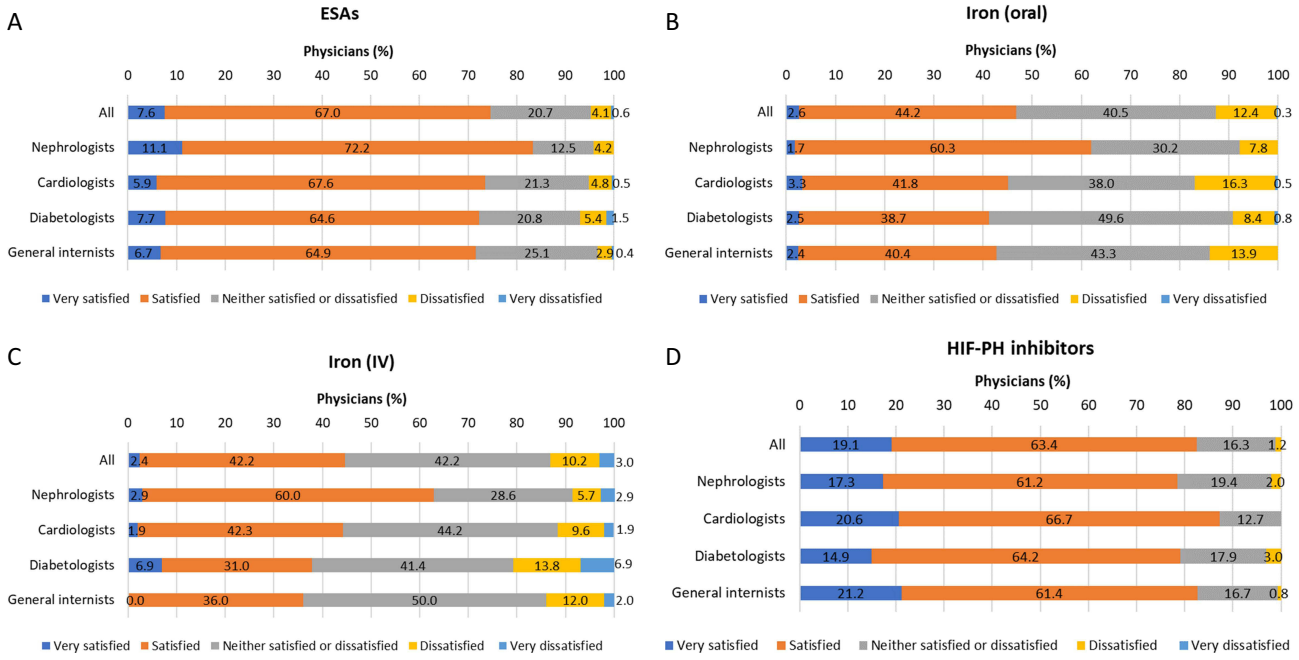

Figure 3 Physicians' satisfaction with drug classes, by specialty: (**A**) ESAs, (**B**) iron (oral), (**C**) iron (IV), and (**D**) HIF-PH inhibitors (N=803)[a].
Notes: [a]Of the total 803 physicians who responded, the number of physicians indicating use of each drug class was as follows: ESA therapy, 701; iron therapy (oral), 627; iron therapy (IV), 166; HIF-PH inhibitors, 423; and other drugs, 11.
Abbreviations: ESA, erythropoiesis-stimulating agent; HIF-PH, hypoxia-inducible factor prolyl hydroxylase; IV, intravenous.

(33/70), 59.3% (51/86) and 51.7% (77/149) of nephrologists, diabetologists, cardiologists, and general internists, respectively. Across all specialties, the most common reasons for not prescribing ESAs to patients with CKD stage ≥3 were the high financial burden on patients (44.9%, 35/78) and complicated usage/dosage (34.6%, 27/78) (Table 5). An insufficient effect on anemia was the most commonly reported reason for not prescribing iron to patients with CKD stage ≥3 (30.3%, 37/122) (Table 5); in particular, this reason was highlighted by 55.0% (11/20) of cardiologists, but the most common reason cited by nephrologists for not prescribing iron was side effects (31.0% [9/29]). Further challenges faced by physicians when prescribing treatment are presented in Supplementary Table 5.

Table 5 Physicians' Reasons for Not Prescribing HIF-PH Inhibitors, ESAs, or Iron

Reasons for Not Prescribing Treatment, n (%)	HIF-PH Inhibitors (N=356)	ESAs (N=78)	Iron (N=122)
Usage/dosage is complicated	61 (17.1)	27 (34.6)	9 (7.4)
Anemia improvement effect is insufficient	21 (5.9)	5 (6.4)	37 (30.3)
There are many side effects	42 (11.8)	7 (9.0)	26 (21.3)
Heavy financial burden on patients	106 (29.8)	35 (44.9)	3 (2.5)
Difficulty to increase/decrease dosage	11 (3.1)	4 (5.1)	1 (0.8)
Have never used it	174 (48.9)	8 (10.3)	2 (1.6)
Require frequent patient visits	22 (6.2)	25 (32.1)	1 (0.8)
Other	19 (5.3)	7 (9.0)	15 (12.3)
No particular reason	37 (10.4)	6 (7.7)	43 (35.2)

Notes: Responses were received from a total of 556 participating physicians who had not prescribed HIF-PH inhibitors, ESAs, or iron therapy for patients with CKD stage ≥3. Physicians could select multiple answers to this question.
Abbreviations: ESA, erythropoiesis-stimulating agent; HIF-PH, hypoxia-inducible factor prolyl hydroxylase.

Patient Survey

Patient Characteristics

A total of 103 patients were included; 80 (77.7%) were male and the average age was 60.6 years. Overall, 47/103 (45.6%) patients reported a diagnosis of anemia of NDD-CKD, 53/103 (51.5%) patients said they were undiagnosed, and 3/103 (2.9%) patients did not know if they had been diagnosed. The mean ± SD Hb level of the 85/103 patients with information available was 12.3 ± 3.2 g/dL. A total of 23 patients had Hb <11.0 g/dL; the mean ± SD Hb in this group was 7.9 ± 2.1 (g/dL). The most common symptom experienced was getting tired easily (58.3%, 60/103), followed by dizziness and lightheadedness (45.6%, 47/103) (Supplementary Figure 2). Getting tired easily was most commonly selected as a burdensome symptom in daily life by patients (39.8%, 41/103), and also the most frequently classed as "the most" burdensome in daily life (28.2%, 29/103) (Supplementary Figures 3 and 4).

Of all surveyed patients, 37 (35.9%) were currently receiving treatment for anemia of NDD-CKD, of whom 23 (62.2%) had received treatment for 1 or more years. Sixty (58.3%) patients were not receiving treatment, while the remaining six (5.8%) were unsure. Of participants with Hb <11.0 g/dL, treatment was not being received by 34.8% (8/23) patients. Over half (51.4%, 19/37) of patients receiving treatment for anemia of NDD-CKD were being seen by nephrologists, followed by general internists (18.9%, 7/37), cardiologists (10.8%, 4/37), diabetologists (10.8%, 4/37), and others (8.1%, 3/37) (Supplementary Figure 5). Of the specified options, the most common treatment prescribed to patients with anemia of NDD-CKD was iron therapy (37.8%, 14/37), followed by HIF-PH inhibitors (16.2%, 6/37).

Patients' Satisfaction with Treatments for Anemia of NDD-CKD

The patient survey aimed to understand their preferences on their current method of treatment. Highest treatment satisfaction was seen among patients for ESA therapy ("injection drugs") and HIF-PH inhibitors ("oral drugs besides iron agents"): 66.6% of patients (2/3 of those receiving ESA therapies and 4/6 of those receiving HIF-PH inhibitors) selected "very satisfied" or "satisfied" for both drug classes (Supplementary Figure 6).

The main patient concern for all treatments was being unable to feel the effects (iron therapy [35.7%, 5/14]; ESAs [33.3%, 1/3]; HIF-PH inhibitors [16.7%, 1/6]) (Supplementary Figure 7). Among patients receiving iron therapy, 28.6% (4/14) felt that there were "many side effects" (Supplementary Figure 7). The three treatment attributes most commonly selected by patients as being the most important were "can feel the effect" (59.5%, 22/37), "few side effects" (48.6%, 18/37) and "can be treated with one drug" (29.7%, 11/37) (Supplementary Figure 8).

Most of the patients receiving treatment for anemia of CKD (67.6%, 25/37) responded that it had no impact on their daily life (Supplementary Figure 9A). Of those who stated that treatment did impact their daily life, the impacts included making it easier to move (37.5%, 3/8) and having more opportunity to go out (25.0%, 2/8) (Supplementary Figure 9B). Of the five patients who provided a response regarding perceived treatment burden, two patients felt no burden; "cannot feel the effect", "do not know the timing and amount of usage or dosage/it's complicated", and "have to continue taking the drug for a long period of time" each received one response.

Relative Importance of Attributes and Levels in Terms of Utility Value: Physicians and Patients

In the BWS exercise, physicians considered the following treatment attributes and levels to be the most important: improvement in Hb level (relative importance 10.95); improvement in mobility, such as walking and climbing stairs (9.95); improvement in palpitations and shortness of breath (9.76); and improvement in malaise (8.71) (Figure 4). In contrast, of greatest importance to patients was the occurrence of severe adverse events, which had a relative importance of 10.29 among patients versus 8.48 among physicians (Figure 4). The second, third, fourth, and fifth most important attributes and levels to patients were improvement in Hb level (8.85), improvement in vitality (8.16), improvement in malaise (8.03), and occurrence of moderate adverse events (8.00) (Figure 4).

The attribute-level with the greatest difference in score between physicians and patients was the occurrence of mild adverse events, which had a relative importance of 2.99 among physicians and 6.47 among patients (Figure 4). Of all attributes and levels, cost per month had the greatest similarity in relative importance between physicians and patients (Figure 4). Other attributes and levels with close similarity in relative importance were improvement in vitality (8.28 and 8.16 for physicians and patients, respectively), improvement in malaise (8.71 and 8.03), and improvement in dizziness (5.89 and 6.73) (Figure 4).

Discussion

This survey of physician and patient opinions of treatments for anemia of NDD-CKD addresses a knowledge gap and provides an update in this area, as a previous Japanese study was conducted prior to the introduction of HIF-PH inhibitors.[17] Most physicians surveyed considered anemia of NDD-CKD to be an important condition to treat due to its effect on the patient's prognosis and quality of life. However, over half of patient participants self-reported as not having a diagnosis of anemia of NDD-CKD, suggesting a potential lack of awareness or recognition of the condition among patients. Overall, the preferred treatments for both physicians and patients were ESAs and HIF-PH inhibitors. Although physicians considered the efficacy of ESAs and HIF-PH inhibitors to be similar, there was less familiarity with HIF-PH inhibitors and a lack of clinical evidence was identified as a barrier to HIF-PH inhibitor prescription. These perceptions could be due to the relatively recent launch of HIF-PH inhibitors and physicians having less experience and evidence to prescribe this treatment, particularly diabetologists, cardiologists, and general internists. The lack of guidelines for the use of HIF-PH inhibitors may also be a contributing factor. Nephrologists had a higher level of satisfaction with iron therapies compared with other specialties or general internists, which may reflect a recognition of the effectiveness of using iron concomitantly with ESAs, rather than iron alone.

Findings from the present survey indicate that, overall, 60% of patients with anemia of NDD-CKD were not receiving any treatment, including 35% of those with an Hb level <11.0 g/dL. These results are similar to those from the previous 2010 survey of Japanese physicians, which showed that 50–60% of patients with anemia of CKD were not receiving ESAs.[17] Even among patients with serum creatinine ≥2 mg/dL and Hb level <10 g/dL, just over half (53.7%) were receiving EPO preparations.[17] Our findings are also confirmed by a database study using records from the JMDC Claims Database, which reported that only 15% of patients with anemia of NDD-CKD (defined using Japanese Society for Dialysis Therapy guidelines) were treated for anemia.[14] Similarly, a study of records from the Japan Chronic Kidney Disease Database showed that over three-quarters of patients with CKD stages G4 or G5 and Hb level ≤11.0 g/dL were not receiving ESA treatment.[4] However, a paper by Okamoto et al indicates that ESA treatment may differ widely by

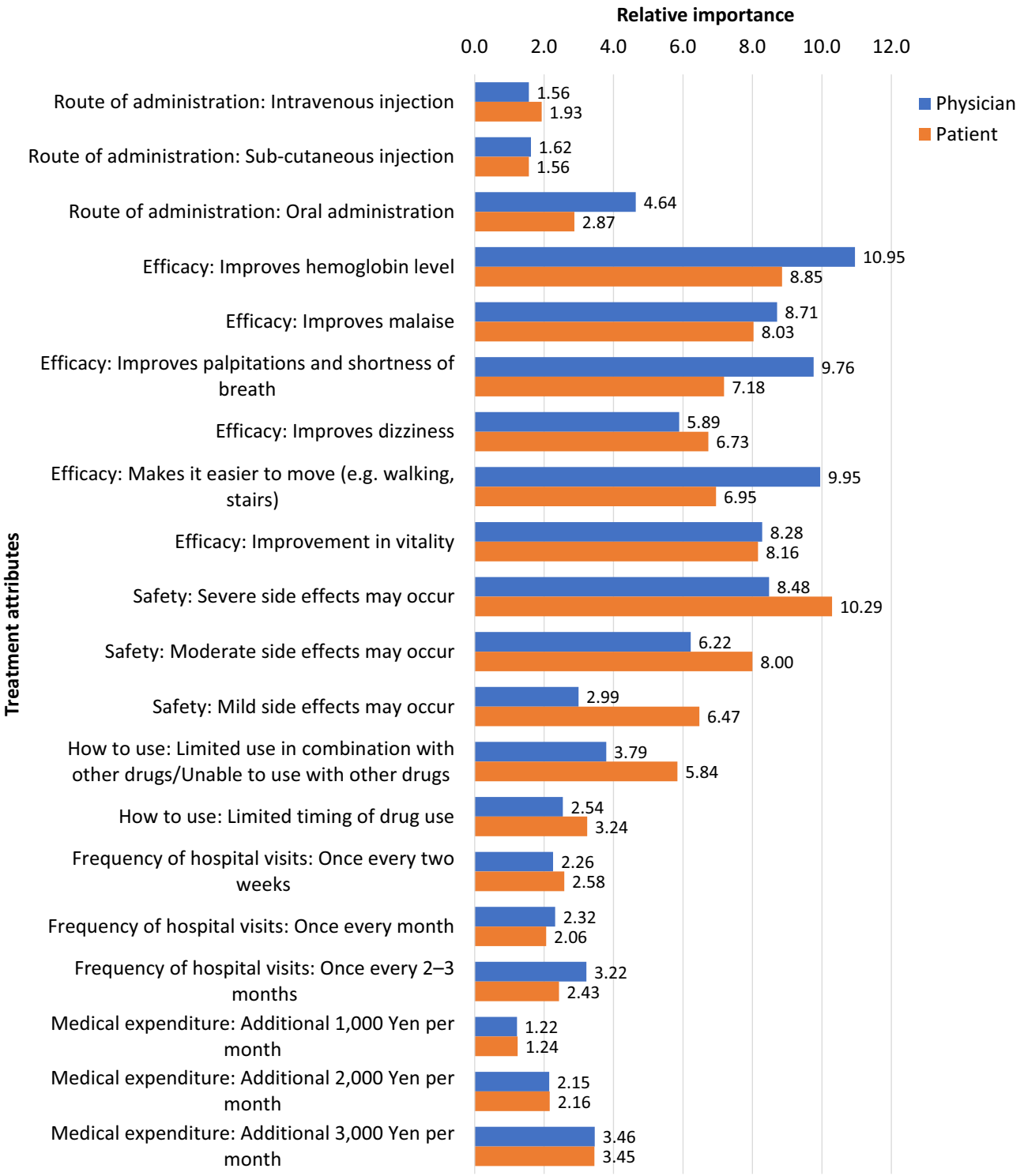

Figure 4 Relative importance of treatment attributes and levels in terms of utility value between physicians and patients[a,b].
Notes: [a]Rescaled scores (0 to 100 scaling). [b]Data for one patient and one physician were missing from the best-worst scaling exercise, so the number of respondents was 102 and 802, respectively.

specialty: 77.3% of patients with anemia of CKD (Hb level ≤11.0 g/dL) and under the care of a nephrologist were prescribed ESAs, but less than one-third of patients with anemia of CKD in other clinical departments were prescribed ESAs.[25] Such disparity may indicate variation in the level of awareness of anemia of CKD between specialties.

When considering the most important attributes and levels of treatment for anemia of CKD, physicians and patients had differing opinions. For physicians, the most important attribute-level was improvement in Hb levels, whereas patients considered the occurrence of severe adverse events to be of the greatest importance. These results are consistent with earlier research: for example, of 45 studies comparing the preferences of physicians and patients, a majority identified disparity between the two groups.[26] On the other hand, the cost of treatment emerged as an important consideration both for physicians and patients. Furthermore, a previous study conducted in Europe and Japan found that the mode and frequency of administration was considered by NDD patients to be an important aspect of their treatment, with a preference for oral administration over subcutaneous administration.[27] The same study also found that patients with anemia of NDD-CKD were willing to tolerate some increases in side effects in exchange for more energy or a more convenient mode of treatment administration.[27]

The advantages and disadvantages of therapies for CKD-related anemia (including iron formulations, ESAs and HIF-PH inhibitors) were discussed at the KDIGO conference in December 2021.[28] Although ESA treatments have the data to support long-term use, disadvantages include the need for regular clinic visits due to their injectable formulation, as well as the issue of resistance in chronic inflammatory states.[28] HIF-PH inhibitors, administered orally once daily or three times weekly, offer increased convenience but sufficient long-term safety data are still lacking.[28] Physicians need to explain to their patients the benefits and risks of each treatment option. Compared with physicians, patients place greater importance on treatment safety, underscoring the importance of shared decision-making between both parties. Furthermore, the substantial proportion of patients who reported not being diagnosed, despite experiencing anemia of CKD, highlights the value of increasing patient awareness of their condition to facilitate appropriate treatment.

Strengths of this study included the enrollment of physicians from different specialties, to represent the range of clinical fields involved in the management of anemia of CKD. Another strength was the use of questions and topics encompassing several factors that impact patients with anemia of NDD-CKD, such as the route of administration and frequency of hospital visits. Limitations included the small patient group; in particular, only approximately one-third of patients indicated that they were receiving drug treatment. The low proportion of treated patients could be due to a lack of physician or patient awareness of anemia of CKD or a lack of consistency in how this comorbidity is communicated.[26] Additionally, there was no method of cross-verification of the patient responses, so results may be affected by recall bias. Furthermore, the patient respondents in this study were younger than the average patient with anemia of CKD – from a nationwide cohort study of patients registered in the J-CKD-DB, the median age of Japanese patients with anemia of NDD-CKD was 72 years.[4] This age difference may be due to our survey being only web-based, as previous research has shown participation in web-based surveys to be dependent on the age and education level of the respondents: in particular, younger patients were more likely to prefer an online platform over telephone or mail.[29] Furthermore, participants for our study were recruited solely from the PLAMED Inc. panel (physicians), or the INTAGE Inc., Marketing Applications, Inc., or Rakuten Insight, Inc. panels (patients). Thus, our results may not be generalizable to all patients with anemia of NDD-CKD or their physicians. The physicians' responses may have been dependent on their level of experience in treating patients with CKD-related anemia; additionally, the specialties of the physicians surveyed were differently distributed to the specialties of the physicians attending to the patients surveyed, which may have contributed to the differences in treatment preferences. To address these various potential influences and provide a more comprehensive understanding, further research should be conducted, especially studies involving physicians and those patients concurrently within their care, to verify and expand upon our findings.

Conclusions

In conclusion, although an overwhelming majority of physicians acknowledge the importance of treating anemia of CKD, differences in the perceptions and usage of medications exist between medical specialties. Furthermore, treatment preferences for the management of CKD-related anemia differ between physicians and patients: HIF-PH inhibitors have the highest treatment satisfaction among physicians, whereas patients have the highest satisfaction with both ESA therapy and HIF-PH inhibitors. Additionally, the treatment attributes that are considered important differ between physicians and patients. The involvement of patients in treatment decisions, coupled with physicians thoroughly explaining the advantages and disadvantages of various treatment options, is crucial to broaden patients' awareness of their condition and optimize outcomes and treatment satisfaction for patients.

Data Sharing Statement

Researchers may request access to anonymized participant-level data, trial-level data, and protocols from Astellas-sponsored clinical trials at www.clinicalstudydatarequest.com. For the Astellas criteria on data sharing see: https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Astellas.aspx.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

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