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ORIGINAL ARTICLE

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# A phase III, open-label clinical trial evaluating pegunigalsidase alfa administered every 4 weeks in adults with Fabry disease previously treated with other enzyme replacement therapies

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## Abstract

Pegunigalsidase alfa, a PEGylated α-galactosidase A enzyme replacement therapy (ERT) for Fabry disease, has a longer plasma half-life than other ERTs administered intravenously every 2 weeks (E2W). BRIGHT (NCT03180840) was a phase III, open-label study in adults with Fabry disease, previously treated with agalsidase alfa or beta E2W for ≥3 years, who switched to 2 mg/kg

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pegunigalsidase alfa every 4 weeks (E4W) for 52 weeks. Primary objective assessed safety, including number of treatment-emergent adverse events (TEAEs). Thirty patients were enrolled (24 males); 23 previously received agalsidase beta. Pegunigalsidase alfa plasma concentrations remained above the lower limit of quantification throughout the 4-week dosing interval. Thirty-three of 182 TEAEs (in 9 patients) were considered treatment-related; all were mild/moderate. No patients developed de novo anti-drug antibodies (ADAs). In the efficacy analysis ($n = 29$), median (inter-quartile range) eGFR change from baseline over 52 weeks was −1.9 (−5.9; 1.8) mL/min/1.73 $m^2$ ($n = 28$; males [$n = 22$]: −2.4 [−5.2; 3.2]; females [$n = 6$]: −0.7 [−9.2; 2.0]). Overall, median eGFR slope was −1.9 (−8.3; 1.9) mL/min/1.73 $m^2$/year (ADA-negative [$n = 20$]: −1.2 [−6.4; 2.6]; ADA-positive [$n = 9$]: −8.4 [−11.6; −1.0]). Lyso-Gb3 concentrations were low and stable in females, with a slight increase in males (9/24 ADA-positive). The BRIGHT study results suggest that 2 mg/kg pegunigalsidase alfa E4W is tolerated well in stable adult patients with Fabry disease. Due to the low number of patients in this study, more research is needed to demonstrate the effects of pegunigalsidase alfa given E4W. Further evidence, outside of this clinical trial, should be factored in for physicians to prolong the biweekly ERT intervals to E4W.

**Take-home message**

Treatment with 2 mg/kg pegunigalsidase alfa every 4 weeks could offer a new treatment option for patients with Fabry disease.

**KEYWORDS**

eGFR, enzyme replacement therapy, Fabry disease, lyso-Gb3, lysosomal storage disorders, pegunigalsidase alfa

## 1 | INTRODUCTION

Fabry disease (OMIM #301500) is a progressive lysosomal storage disorder estimated to affect between 1 in 1000–9000 people, based on estimates from newborn screening programs for all forms of the disease.[1,2] It is caused by an X-linked deficiency of the enzyme alpha-galactosidase A (α-Gal A), and can ultimately result in the development of life-threatening complications, such as cardiomyopathy, end-stage renal disease, and cerebrovascular disease.[1,3,4] Enzyme replacement therapy (ERT) with engineered α-Gal A delivers the functioning enzyme, which leads to clearance of the α-Gal A substrate, globotriaosylceramide (Gb3), its metabolite, globotriaosylsphingosine (lyso-Gb3), and other sphingolipids from the plasma and target tissues, resulting in improved renal, cardiac, and quality of life (QoL) outcomes.[5–8] Two ERTs, agalsidase alfa and agalsidase beta, have been available since the early 2000s and are administered by intravenous (IV) infusion every 2 weeks (E2W) at respective doses of either 0.2 or 1 mg/kg, with their accessibility varying by country.[9,10] Due to the limitations of these treatments, including short half-life, risk of development of anti-drug antibodies (ADAs), and infusion-related reactions,[5,9,10] there are remaining unmet treatment needs for patients with Fabry disease. A chaperone oral therapy (migalastat) is available and may address some of the limitations of ERTs,[11] but it is only suitable for a subgroup of patients with amenable α-Gal A gene (*GLA*) mutations.[5]

Pegunigalsidase alfa is a PEGylated (covalently conjugated with polyethylene glycol [PEG]), recombinant human α-Gal A expressed in plant cells, approved for the treatment of Fabry disease.[12–14] As a result of PEGylation, pegunigalsidase alfa exhibits *in vitro* stability in plasma and under lysosome-like conditions,[14] and prolonged plasma half-life in humans of approximately 80 hours, ranging between 53–121 h, compared with other commercially available ERTs with half-lives of ≤2 h.[12,15] Moreover, PEGylation may bring an additional benefit of epitope masking, resulting in lower affinity for pre-existing ADAs to pegunigalsidase alfa, reducing their inhibitory impact on the activity of the PEGylated enzyme and its cellular uptake, as suggested by *in vitro* experiments.[16]

Studies in ERT-naïve patients have shown clearance of tissue Gb3 deposits from the kidney following

treatment with pegunigalsidase alfa and indicated the potential for lower immunogenicity.[15,17] Pegunigalsidase alfa (1 mg/kg, E2W) has now been studied in over 110 patients with Fabry disease (both ERT-naïve and previously treated) in phase I/II and III trials, demonstrating benefits in biomarker and clinical outcomes,[12,13,15,17–19] and was recently approved by the European Medicines Agency (EMA) and the US Food and Drug Administration (FDA) for the treatment of adult patients with Fabry disease.[12,13]

The pharmacokinetics (PK) of pegunigalsidase alfa[15] could allow the interval between infusions to be extended from E2W to every 4 weeks (E4W), potentially decreasing the treatment burden and improving medication adherence in patients with Fabry disease.

Here, we report the results of BRIGHT (NCT03180840), a phase III, open-label, multinational, switchover study designed to evaluate the PK, safety, and efficacy of 2 mg/kg pegunigalsidase alfa administered E4W for 52 weeks in adult patients with Fabry disease previously treated with agalsidase alfa (0.2 mg/kg) or agalsidase beta (1 mg/kg) E2W. A plain language summary of this article is available in the Supplementary materials (Appendix S2).

## 2 | METHODS

### 2.1 | Study design

Patients with Fabry disease receiving 0.2 mg/kg agalsidase alfa or 1 mg/kg agalsidase beta E2W were switched to 2 mg/kg pegunigalsidase alfa administered by IV infusion E4W for 52 weeks (a total of 14 infusions). For any cases of recognized clinical deterioration, the protocol permitted a treatment modification to 1 mg/kg pegunigalsidase alfa E2W at the discretion of the investigator and medical monitor. After study completion, patients were invited to continue receiving pegunigalsidase alfa 2 mg/kg E4W in an extension study (NCT03614234).

Initial duration of infusion was 4.5 h for patients ≤100 kg and 6 h for patients >100 kg, with the intent to gradually reduce the infusion time to 2 and 3 h, respectively, if tolerated. The first infusions of pegunigalsidase alfa were administered under controlled conditions at the study site, and if the patient had been receiving premedication with their previous ERT, this was maintained for the first administration of pegunigalsidase alfa. A clinically stable infusion status was attained by sequentially reducing or eliminating premedications and reducing infusion durations, as tolerated. Home infusions were permitted depending on local regulations and if the investigator and medical monitor agreed it was safe to do so.

The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines at study sites in Belgium, Czech Republic, Denmark, Italy, Norway, United Kingdom, and the United States of America. Patients provided written informed consent, and the trial protocol was approved by an independent ethics committee or institutional review board as required according to local regulations.

### 2.2 | Patients

Male and female patients aged 18–60 years with a documented diagnosis of Fabry disease were considered for participation in the trial. The diagnostic criteria included one or more of the characteristic features of Fabry disease (neuropathic pain, cornea verticillata, and/or clustered angiokeratomas), accompanied by α-Gal A activity in either plasma or leukocytes below the lower limit of normal per laboratory reference range in male patients; and in female patients, historical genetic test results consistent with pathogenic *GLA* variants (or, in the case of novel mutations, a first-degree male relative with clinically manifest signs and symptoms of Fabry disease). Patients with a confirmed diagnosis were eligible for the study if they had been treated with agalsidase alfa or agalsidase beta for at least 3 years, with a stable dose (>80% labeled dose/kg, as recommended by the relevant approving bodies [EMA and FDA][9,10]) maintained for at least 6 months prior to enrollment, and if the investigator considered their clinical condition to be stable. All included patients were required to have an estimated glomerular filtration rate (eGFR) ≥30 mL/min/1.73 $m^2$ at screening, as calculated using the Chronic Kidney Disease – Epidemiology Collaboration (CKD-EPI) equation.[20] Patients with a linear eGFR slope more negative than −2 mL/min/1.73 $m^2$/year at screening (based on at least 4 serum creatinine values over approximately 2 years, including the screening value) were excluded. Additional exclusion criteria included a history of anaphylaxis or Type 1 hypersensitivity reaction to ERT; history of renal dialysis or transplantation; recent history of acute events (acute kidney injury, cardiac events [myocardial infarction, unstable angina], and cerebrovascular events [stroke, transient ischemic attack]); angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) therapy initiated or dose changed in the 4 weeks prior to screening; and urine protein to creatinine ratio (UPCR) >0.5 g/g at screening that was not treated with an ACEi or ARB (UPCR >0.5 g/g indicating severe proteinuria according to the Kidney Disease: Improving Global Outcomes [KDIGO] classification).[21]

### 2.3 | Endpoints and assessments

The primary endpoint was the number of treatment-emergent adverse events (TEAEs, assessed by Common

Terminology Criteria for Adverse Events [CTCAE][22]) that were considered to be related to treatment (possibly, probably, or definitely related). Other key safety endpoints included occurrence of infusion-related reactions and the development of ADAs directed against pegunigalsidase alfa. ADAs were assessed in a designated central laboratory at the screening visit, pre-infusion at baseline, and at pre-defined intervals throughout the trial. The bioanalytical methods used for evaluation of ADAs and neutralizing antibodies (nAbs) were based on solid-phase enzyme-linked immunosorbent assays for antibody detection and titer determination and *in vitro* enzymatic activity assay for assessment of neutralizing activity (Appendix S1), which were validated according to the FDA[23] and the EMA[24] guidelines.

Key efficacy endpoints of the BRIGHT trial included change in eGFR calculated using the CKD-EPI equation,[20] based on the serum creatinine values assessed using an enzymatic assay in designated central laboratories at screening and pre-infusion E4W during the 52 weeks of treatment. Pre-switch annualized eGFR slope was calculated using baseline values in addition to the historical and screening values. Post-switch, the slope was calculated for each patient based on baseline and all available post-baseline eGFR values using linear regression. Change in plasma concentrations of lyso-Gb3 over the trial period was also evaluated centrally, with blood samples collected at baseline and Weeks 12, 24, 40, and 52 prior to dosing. The samples were prepared by solid phase extraction using mixed-mode strong cation cartridges, separated by ultra-performance liquid chromatography, and analyzed for lyso-Gb3 concentration by tandem mass spectrometry. Disease severity according to the Mainz Severity Score Index (MSSI)[25,26] was evaluated and reported by the treating physician at baseline and Week 52. Patient-reported outcomes were recorded at baseline and Weeks 24 and 52 for the short form Brief Pain Inventory (BPI)[27] and QoL as assessed with the EuroQol 5 Dimensions 5 Levels Questionnaire (EQ-5D-5L).[28]

PK assessments were performed at a designated central laboratory for first infusion, infusions received at Week 24 or 40 (as per the protocol version with signed consent), and Week 52, with blood samples collected at 13 time points pre- and post-infusion within 28 days. Calculated plasma PK variables of pegunigalsidase alfa, including maximum observed concentration ($C_{max}$), area under the concentration–time curve from time zero to last measurable concentration ($AUC_{last}$), and terminal elimination half-life ($t_{½}$), were derived from individual plasma concentration versus time profiles.

## 2.4 | Statistical analysis

The following populations were defined for the analysis of this trial: the safety population included all patients who received at least one dose (partial or complete) of pegunigalsidase alfa; the efficacy population included all patients who received any dose of pegunigalsidase alfa 2 mg/kg and had at least one post-baseline visit with an efficacy evaluation; and the PK population included all patients who received at least one dose of pegunigalsidase alfa, who had no important protocol deviations affecting the PK variables, and for whom a sufficient number of evaluable samples were available to determine at least one PK variable. PK statistical comparisons were performed using analysis of variance (ANOVA).

For any cases of a treatment modification to 1 mg/kg pegunigalsidase alfa E2W due to clinical deterioration, only the data recorded prior to the change were included in the efficacy analysis presented here for the relevant patients. Subgroup analyses were conducted, with the study population stratified by sex, baseline ADA status (positive vs. negative), and eGFR values (≥120 mL/min/1.73 $m^2$ vs. ≤120 mL/min/1.73 $m^2$ [including 90≤ eGFR <120, 60≤ eGFR <90, and 30≤ eGFR <60]).

Due to the descriptive nature of this study and the relatively low numbers in some subgroups (e.g., female patients), descriptive statistics are presented here, including arithmetic mean, standard deviation (SD), standard error (SE), median, interquartile range (IQR; calculated using JMP PRO 17.2), and range. Furthermore, due to the differences in lyso-Gb3 levels between males and females, results for these two subgroups were analyzed separately and not combined.

# 3 | RESULTS

## 3.1 | Patients

A total of 52 patients, from 14 recruiting centers across 7 countries, were screened for participation in the study. Thirty (58%) patients met the inclusion criteria and received study treatment (24 [80%] male and 6 [20%] female; Figure 1); the main reason for screening failure among the remaining patients was the annual eGFR slope value more negative than −2 mL/min/1.73 $m^2$/year (19 [37%] patients). Twenty-nine patients completed the study, while one male patient who received the first infusion of pegunigalsidase alfa 2 mg/kg at baseline withdrew consent after this visit due to a road traffic accident. During the study, another male patient showed deterioration of kidney function (from an eGFR of 30.3 mL/min/1.73 $m^2$ at baseline to an eGFR of 24.0 mL/min/1.73 $m^2$ at Week 40). After receiving a total of 10 infusions of pegunigalsidase alfa 2 mg/kg E4W, the patient's regimen was modified to pegunigalsidase alfa 1 mg/kg E2W starting at Week 40, with 7 subsequent

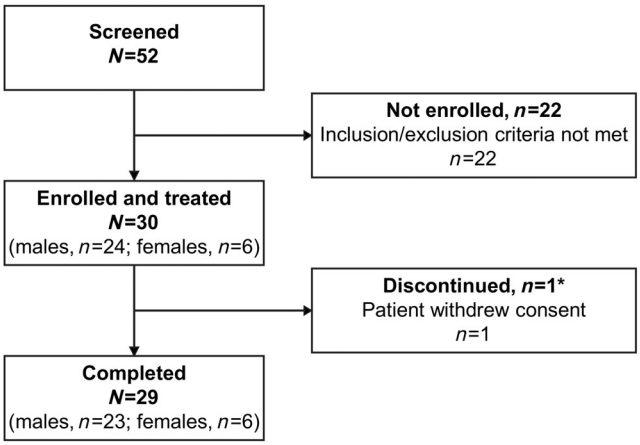


**FIGURE 1** Patient disposition. *One male patient who received the first infusion of pegunigalsidase alfa 2 mg/kg at baseline withdrew consent after this visit. Another male patient who completed the trial showed deterioration of kidney function, and after receiving a total of 10 infusions of pegunigalsidase alfa 2 mg/kg E4W, the patient's treatment regimen was modified to pegunigalsidase alfa 1 mg/kg E2W at Week 40, with 7 subsequent administrations. E2W, every 2 weeks; E4W, every 4 weeks.

administrations. The patient completed the trial and was subsequently enrolled in the NCT03614234 extension study, continuing on their modified administration regimen.

The safety population included the 30 patients who received at least one dose of treatment, with the efficacy and PK populations comprising 29 and 30 patients, respectively. Patient demographics and baseline characteristics in the safety population, overall and stratified by sex and ADA status, are presented in Table 1.

A total of 23 (77%) patients (19 males and 4 females) had been previously treated with agalsidase beta, with the remaining 7 (23%) patients (5 males and 2 females) switched from agalsidase alfa. Eleven (48%, all male) of the patients previously treated with agalsidase beta were positive for ADAs, whereas none of the patients switched from agalsidase alfa had ADAs at baseline. Overall, pre-existing ADAs that cross-reacted with pegunigalsidase alfa were detected in 10 (33%) patients at baseline, all of whom were male and had been previously treated with agalsidase beta. A comprehensive overview of *GLA* pathogenic variants in the study population is presented in Table S1.

## 3.2 | Safety

### 3.2.1 | Adverse events

Overall, 33 (18%) out of a total of 182 TEAEs, reported in 9 (30%) patients in the safety population, were considered treatment-related (Table 2), and the majority of patients (7/9) with treatment-related TEAEs were male. All treatment-related events were mild or moderate in severity, and there were no TEAEs leading to study withdrawal or death.

A total of 3 TEAEs in 2 (7%) patients (both male) were severe and were not considered treatment-related. In one patient, these included events of both pyrexia and infusion-related reaction (the infusion-related reaction was defined according to the preferred terms of CTCAE and manifested as generalized pain upon infusion initiation; however, the event was adjudicated as unlikely to be related to the study drug by the investigator). The second patient was involved in a road traffic accident. Two serious TEAEs occurred in the same 2 (7%) patients described above: an accidental overdose of carbamazepine in the patient with pyrexia and an infusion-related reaction; and road traffic accident in the second patient.

### 3.2.2 | Infusion-related reactions

Overall, there were 27 infusion-related reactions reported in 5 (17%) patients, all of whom were male (Tables 3 and S1). Of these 5 patients, 4 had previously received agalsidase beta and had pre-existing ADAs at baseline, and remained ADA-positive while receiving pegunigalsidase alfa treatment. The 5th patient who experienced an infusion-related reaction had previously been treated with agalsidase alfa and was negative for ADAs at all time points. Infusion-related reactions were more common in the first 2 months after the switch to pegunigalsidase alfa treatment (9 [33%]) than in subsequent months. All infusion-related reactions occurred during the infusion or within 2 h post-infusion and were mild (17 events in 3 [10%] patients) or moderate (10 events in 5 [17%] patients) in severity, and all resolved.

### 3.2.3 | Duration of infusion

Initial mean (SE) duration of infusion was 4.5 (0.03) h for patients weighing up to 100 kg ($n = 25$) and 6.1 (0.01) h for the remaining 5 patients weighing over 100 kg (Figure S1). The infusion duration gradually decreased (in line with the protocol) and, by Week 52, reached target lengths of 2 h (mean [SE]: 2.1 [0.1] h) and 3 h (3.0 [0.2] h) for patients weighing up to or more than 100 kg, respectively.

When possible and desired by the patient, infusions were administered in a home care setting, based on the investigator's recommendation and local regulations. Due to the necessity of controlled administration of initial

**TABLE 1** Patient demographics and baseline characteristics (safety population).

| Characteristic | Male ($n = 24$) | Female ($n = 6$) | ADA-negative ($n = 20$) | ADA-positive ($n = 10$) | Overall ($N = 30$) |
|---|---|---|---|---|---|
| Age, years | | | | | |
| Mean (SD) | 39.3 (12.2) | 45.2 (5.3) | 44.1 (10.5) | 33.2 (9.6) | 40.5 (11.3) |
| Median (range) | 39.0 (19; 58) | 46.5 (37; 52) | 46.5 (19; 58) | 32.5 (20; 48) | 40.5 (19; 58) |
| Age at ERT start, years | | | | | |
| Mean (SD) | 29.9 (13.6) | 38.5 (4.0) | 36.1 (11.5) | 22.7 (10.3) | 31.6 (12.7) |
| Median (range) | 30.5 (7; 51) | 38.5 (33; 45) | 36.5 (7; 51) | 21.0 (10; 41) | 34.5 (7; 51) |
| Previous ERT, *n* (%) | | | | | |
| Agalsidase alfa | 5 (20.8) | 2 (33.3) | 7 (35.0) | 0 (0.0) | 7 (23.3) |
| Agalsidase beta | 19 (79.2) | 4 (66.7) | 13 (65.0) | 10 (100.0) | 23 (76.7) |
| eGFR, mL/min/1.73 $m^2$[a] | | | | | |
| *n* | 24 | 6 | 20 | 10 | 30 |
| Mean (SD) | 101.2 (23.4) | 94.7 (16.6) | 96.2 (17.3) | 107.3 (29.1) | 99.9 (22.1) |
| Median (IQR) | 103.7 (87.7; 118.0) | 100.4 (87.4; 104.3) | 97.8 (86.2; 106.1) | 116.2 (101.9; 123.7) | 102.2 (90.3; 113.0) |
| Range | 30.3; 135.9 | 61.7; 106.1 | 58.5; 135.9 | 30.3; 132.2 | 30.3; 135.9 |
| Annualized eGFR slope, mL/min/1.73 $m^2$/year | | | | | |
| *n* | 24 | 6 | 20 | 10 | 30 |
| Mean (SD) | −1.2 (3.2) | −4.2 (4.7) | −2.3 (4.2) | −0.9 (2.2) | −1.8 (3.7) |
| Median (IQR) | −0.8 (−2.7; 0.4) | −3.1 (−6.2; −1.2) | −1.7 (−3.6; 0.3) | −0.9 (−2.4; 0.4) | −1.2 (−3.2; 0.2) |
| Range | −10.5; 3.6 | −13.6; −0.5 | −13.6; 3.6 | −4.3; 3.3 | −13.6; 3.6 |
| Plasma lyso-Gb3, nM | | | | | |
| *n* | 23 | 6 | 20 | 9 | 29 |
| Mean (SD) | 23.3 (18.3) | 4.4 (2.5) | 12.3 (10.8) | 35.1 (21.4) | 19.4 (18.1) |
| Median (IQR) | 17.2 (12.1; 32.8) | 4.4 (2.4; 6.4) | 9.3 (4.6; 16.6) | 29.0 (17.0; 54.2) | 14.5 (6.1; 26.2) |
| Range | 0.5; 75.1 | 0.7; 7.8 | 0.5; 39.0 | 13.8; 75.1 | 0.5; 75.1 |
| Presence of severe proteinuria[b] | | | | | |
| *n* | 24 | 6 | 20 | 10 | 30 |
| Yes, *n* (%) | 2 (8.3) | 0 (0.0) | 0 (0.0) | 2 (20.0) | 2 (6.7) |
| No, *n* (%) | 22 (91.7) | 6 (100.0) | 20 (100.0) | 8 (80.0) | 28 (93.3) |

TABLE 1 (Continued)

| Characteristic | Male ($n = 24$) | Female ($n = 6$) | ADA-negative ($n = 20$) | ADA-positive ($n = 10$) | Overall ($N = 30$) |
|---|---|---|---|---|---|
| Treatment with ACEi or ARB | | | | | |
| *n* | 24 | 6 | 20 | 10 | 30 |
| Yes, *n* (%) | 9 (37.5) | 1 (16.7) | 7 (35.0) | 3 (30.0) | 10 (33.3) |
| No, *n* (%) | 15 (62.5) | 5 (83.3) | 13 (65.0) | 7 (70.0) | 20 (66.7) |
| Use of pre-medication for ERT infusion prior to enrollment | | | | | |
| *n* | 24 | 6 | 20 | 10 | 30 |
| Yes, *n* (%) | 7 (29.2) | 2 (33.3) | 5 (25.0) | 4 (40.0) | 9 (30.0) |
| No, *n* (%) | 17 (70.8) | 4 (66.7) | 15 (75.0) | 6 (60.0) | 21 (70.0) |
| ADA status for pegunigalsidase alfa[c] | | | | | |
| *n* | 24 | 6 | 20 | 10 | 30 |
| Positive, *n* (%) | 10 (41.7) | 0 (0.0) | 0 (0.0) | 10 (100.0) | 10 (33.3) |
| Negative, *n* (%) | 14 (58.3) | 6 (100.0) | 20 (100.0) | 0 (0.0) | 20 (66.7) |
| ADA status for agalsidase alfa[c] | | | | | |
| *n* | 5 | 2 | 7 | 0 | 7 |
| Positive, *n* (%) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) | 0 (0.0) |
| Negative, *n* (%) | 5 (100.0) | 2 (100.0) | 7 (100.0) | 0 (0.0) | 7 (100.0) |
| ADA status for agalsidase beta[c] | | | | | |
| *n* | 19 | 4 | 13 | 10 | 23 |
| Positive, *n* (%) | 11 (57.9) | 0 (0.0) | 1 (7.7) | 10 (100.0) | 11 (47.8) |
| Negative, *n* (%) | 8 (42.1) | 4 (100.0) | 12 (92.3) | 0 (0.0) | 12 (52.2) |

*Note*: All patients enrolled in the study were White.

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ADA, anti-drug antibody; ARB, angiotensin receptor blocker; CKD-EPI, Chronic Kidney Disease – Epidemiology Collaboration; eGFR, estimated glomerular filtration rate; ERT, enzyme replacement therapy; IgG, immunoglobulin G; IQR, interquartile range; KDIGO, Kidney Disease: Improving Global Outcomes; lyso-Gb3, globotriaosylsphingosine; SD, standard deviation; UPCR, urine protein to creatinine ratio.

[a]Estimated using the CKD-EPI equation. The higher mean and median values of eGFR in ADA-positive versus ADA-negative patients were due to a higher proportion of patients with eGFR ≥120 mL/min/1.73 $m^2$ in this subgroup.

[b]Severe proteinuria defined as a UPCR >0.5 g/g according to the KDIGO classification.

[c]ADA status for pegunigalsidase alfa based on the results of the IgG for pegunigalsidase alfa at baseline; ADA status for agalsidase alfa based on the results of the IgG for agalsidase alfa at baseline among patients who were treated with agalsidase alfa prior to the switch; ADA status for agalsidase beta based on the results of the IgG for agalsidase beta at baseline among patients who were treated with agalsidase beta prior to the switch.

infusions as well as those accompanying multiple study visit procedures, most infusions (partial or complete) were administered on site (mean [SE] of 11.2 [0.6] infusions per patient) and 4.6 [0.5] infusions per patient were given at home.

#### 3.2.4 | Anti-drug antibodies

No patients developed *de novo* ADAs following the switch to pegunigalsidase alfa treatment, and only patients with pre-existing immunoglobulin G (IgG) antibodies were positive for anti-pegunigalsidase alfa antibodies. Eleven (37%) male patients had pre-existing ADAs to agalsidase beta, 10 of whom had ADAs cross-reacting with pegunigalsidase alfa at baseline. Of these, 6 remained ADA-positive until the end of the study, 2 became ADA-negative during the study, 1 was ADA-negative at all subsequent time points after the baseline visit, and 1 withdrew consent after the first infusion. At most time points where ADAs were observed, these were neutralizing and targeting the enzyme moiety. All patients tested negative for antibodies to the plant glycans or PEG moieties of pegunigalsidase alfa throughout the duration of the study. Figure 2 illustrates changes in ADA status over time in individual patients and the overall safety population.

### 3.3 | Efficacy

#### 3.3.1 | Renal function: glomerular filtration rate

During the 52-week treatment period, absolute eGFR values remained stable in the efficacy population, with a median (IQR) change from baseline of −1.9 (−5.9; 1.8, $n = 28$) mL/min/1.73 m$^2$ (Table S2). At most timepoints, absolute eGFR values were slightly higher in males compared with females, with the respective median (IQR) changes from baseline to Week 52 of −2.4 (−5.2; 3.2, $n = 22$) and −0.7 (−9.2; 2.0, $n = 6$) mL/min/1.73 m$^2$ (Figure 3A, Table S3). At baseline, 5/29 patients in the efficacy population (all male, 4/5 ADA-positive, Table S2) presented with eGFR values >120 mL/min/1.73 m$^2$. This subgroup of patients had a median (IQR) change of −3.7 (−10.2; −3.2) mL/min/1.73 m$^2$ over 52 weeks, with the remaining 23 patients (baseline eGFR ≤120 mL/min/1.73 m$^2$) having a median (IQR) change of −0.7 (−4.5; 2.5) mL/min/1.73 m$^2$ over 52 weeks (Figure 3B, Table S2). The patient whose dosing regimen was modified to pegunigalsidase alfa 1 mg/kg E2W at Week 40 due to deterioration in kidney function had the lowest eGFR values throughout the study (30.3 and 24.0 mL/min/1.73 m$^2$ at baseline and Week 40, respectively; Figure 3C).

The median (IQR) eGFR annualized slope was −1.9 (−8.3; 1.9) mL/min/1.73 m$^2$/year for the efficacy population. In male patients ($n = 23$), the median (IQR) annualized eGFR slope over 52 weeks was −1.5 (−8.4; 1.7) mL/min/1.73 m$^2$/year, whereas in females ($n = 6$), the corresponding value was −4.3 (−6.9; 3.3) mL/min/1.73 m$^2$/year (Figure S2A, Table S4). When stratified by ADA status, median (IQR) annualized eGFR slope was −1.2 (−6.4; 2.6) mL/min/1.73 m$^2$/year in the ADA-negative subgroup ($n = 20$), and −8.4 (−11.6; −1.0) mL/min/1.73 m$^2$/year in the ADA-positive subgroup ($n = 9$, comprising male patients previously treated with agalsidase beta, 4 of whom had baseline eGFR >120 mL/min/1.73 m$^2$; Figure S2B, Table S4). The median (IQR) annualized eGFR slope in all patients with baseline eGFR >120 mL/min/1.73 m$^2$ ($n = 5$) was −1.9 (−13.0; 0.5) mL/min/1.73 m$^2$/year compared with −2.1 (−8.1; 2.5) mL/min/1.73 m$^2$/year in patients with baseline eGFR ≤120 mL/min/1.73 m$^2$ ($n = 24$); the corresponding mean (SE) values were −5.4 (3.2) and −2.4 (1.1) mL/min/1.73 m$^2$/year, respectively (Figure S2C, Table S4). A summary of eGFR slope data by baseline eGFR status (eGFR ≥120, 90≤ eGFR <120, 60≤ eGFR <90, and 30≤ eGFR <60 mL/min/1.73 m$^2$) is shown in Table S5.

#### 3.3.2 | Fabry disease biomarkers: plasma lyso-Gb3

In males, the median (IQR) change in plasma lyso-Gb3 concentration was 5.1 (0.3; 7.9) nM over 52 weeks ($n = 22$; Figure 4A, Table S6), with the individual data for these patients (Figure 4B) showing variability both at baseline and over the course of the study. The two male patients with the highest plasma lyso-Gb3 concentrations during the course of the study were ADA-positive at baseline and throughout the trial. Plasma lyso-Gb3 concentrations in the male subgroup additionally stratified according to ADA status at baseline are presented in Table S6. In female patients (who were all ADA-negative), plasma lyso-Gb3 concentrations remained low and relatively stable (Figure 4A).

#### 3.3.3 | Disease severity index and patient-reported outcomes

Evaluation of disease severity and patient-reported outcomes in the efficacy population is summarized in

**TABLE 2** Summary of treatment-emergent adverse events (safety population).

| | Male ($n = 24$) | | Female ($n = 6$) | | Overall ($N = 30$) | |
|---|---|---|---|---|---|---|
| | Patients, *n* (%) | Events, *n* | Patients, *n* (%) | Events, *n* | Patients, *n* (%) | Events, *n* |
| At least 1 TEAE | 22 (91.7) | 164 | 5 (83.3) | 18 | 27 (90.0) | 182 |
| At least 1 mild or moderate TEAE | 21 (87.5) | 161 | 5 (83.3) | 18 | 26 (86.7) | 179 |
| At least 1 severe TEAE[a] | 2 (8.3) | 3 | 0 (0.0) | 0 | 2 (6.7) | 3 |
| At least 1 serious TEAE | 2 (8.3) | 2 | 0 (0.0) | 0 | 2 (6.7) | 2 |
| At least 1 related TEAE[b] | 7 (29.2) | 30 | 2 (33.3) | 3 | 9 (30.0) | 33 |
| At least 1 related mild or moderate TEAE[b] | 7 (29.2) | 30 | 2 (33.3) | 3 | 9 (30.0) | 33 |
| At least 1 related severe TEAE[a,b] | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 |
| At least 1 related serious TEAE[b] | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 |
| At least 1 TEAE leading to study withdrawal | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 |
| At least 1 TEAE leading to death | 0 (0.0) | 0 | 0 (0.0) | 0 | 0 (0.0) | 0 |

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
[a]The "severe" category also included events classified as "very severe" (Grade 4) or fatal (Grade 5) according to CTCAE.
[b]Related TEAEs included events that were possibly, probably, or definitely related to study treatment.

**TABLE 3** Summary of infusion-related reactions (safety population).

| | Overall ($N = 30$) | | |
|---|---|---|---|
| | Patients, *n* (%) | Events, *n* | Infusions, *n*[a] |
| At least 1 infusion-related reaction[b] | 5 (16.7) | 27 | 22 |
| At least 1 mild or moderate infusion-related reaction | 5 (16.7) | 27 | 22 |
| At least 1 serious or severe infusion-related reaction[c] | 0 (0.0) | 0 | 0 |
| At least 1 non-serious infusion-related reaction | 5 (16.7) | 27 | 22 |
| At least 1 infusion-related reaction leading to study withdrawal | 0 (0.0) | 0 | 0 |
| At least 1 infusion-related reaction leading to death | 0 (0.0) | 0 | 0 |

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; TEAE, treatment-emergent adverse event.
[a]The number of infusions associated with at least 1 infusion-related reaction for each category.
[b]Infusion-related reactions were defined as TEAEs occurring during the infusion or within 2 h after the completion of the infusion that were reported as related to study treatment (excluding TEAEs defined as injection site reactions).
[c]The "severe" category also included events classified as "very severe" (Grade 4) or fatal (Grade 5) according to CTCAE.

Table S7. The MSSI and EQ-5D-5L overall health scores, as well as BPI pain severity results remained stable throughout the study.

## 3.4 | Pharmacokinetics

Over the course of the study, the median (IQR) plasma $C_{max}$ of pegunigalsidase alfa ranged from 35.6 (29.6; 42.1, $n = 30$) to 45.4 (35.5; 51.9, $n = 28$) μg/mL, with median (IQR) $AUC_{last}$ ranging from 1818.0 (1344.6; 2280.8, $n = 30$) to 2015.2 (1552.6; 2670.7, $n = 28$) μg*h/mL, and median (IQR) $t_{½}$ ranging from 112.4 (46.8; 141.0, $n = 30$) to 142.5 (118.4; 166.3, $n = 26$) h (Table S8), from the first to the last infusion. These observations were consistent with the outcome of the modeling projections for the dosing regimen of 2 mg/kg E4W and supported by previously published data from patients enrolled in a phase I/II dose-ranging study of pegunigalsidase alfa.[15] Mean pegunigalsidase alfa concentrations at the end of each analyzed 4-week dosing interval in the PK population were above the lower limit of quantification (LLoQ, 0.020 μg/mL) and ranged from 0.167 to 0.302 μg/mL (Figure 5). There was no noticeable difference in PK parameters between male and female patients (data not shown). Patients with pre-existing ADAs that cross-reacted with pegunigalsidase alfa at baseline (before the first dose) had significantly lower $AUC_{last}$ and shorter $t_{½}$

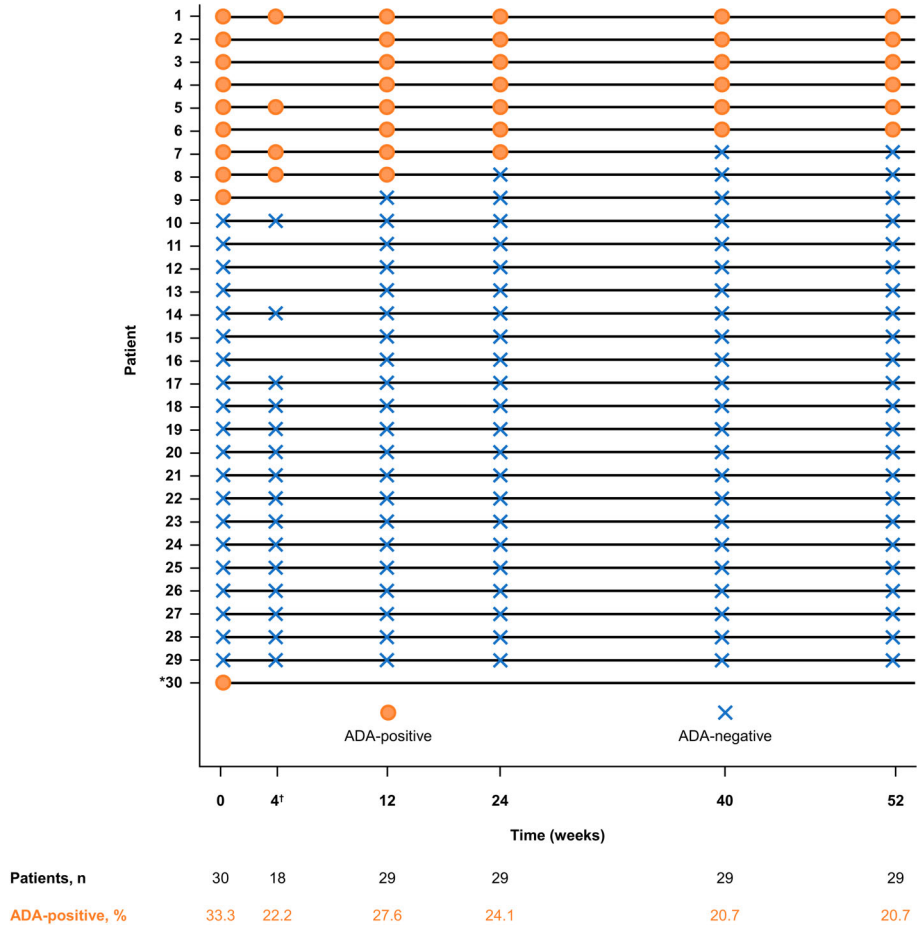


**FIGURE 2** Anti-drug antibody status in individual patients and overall safety population over 52 weeks. *One patient who was ADA-positive at baseline withdrew consent after the first infusion, therefore no ADA data were available for this patient post pegunigalsidase alfa treatment. †The sampling at Week 4 was added as a protocol amendment and therefore was not taken from all patients. ADA, anti-drug antibody.

after the first infusion and throughout the study compared with the ADA-negative patients (Table S8).

## 4 | DISCUSSION

In previous studies, pegunigalsidase alfa demonstrated a favorable safety profile, was well-tolerated, and either maintained stability or stabilized kidney function in patients with Fabry disease when administered 1 mg/kg E2W.[12,13,15,17–19] The results of this study suggest that an E4W administration following a switch from other ERTs administered E2W preserves disease stability in most patients. As ERT is a lifelong therapy, currently requiring intravenous administration E2W,[5] the possibility to increase the interval between infusions of pegunigalsidase alfa could help to reduce treatment burden for patients with Fabry disease and their caregivers, for example, by alleviating stress associated with frequent hospital treatment visits[29] and reducing the amount of absences from school or work as a result of receiving ERT.[30]

Pegunigalsidase alfa has a distinct pharmacokinetic profile, including prolonged circulatory half-life compared with other available ERTs.[9,10,14] The previously described key PK parameters for pegunigalsidase alfa administered at 1 mg/kg vs. 2 mg/kg E2W, $C_{max}$ and $AUC_{0-\infty}$, demonstrated consistent dose-related increases, whereas $t_{½}$ did not systematically change with the higher dose but did exhibit variability between the two doses.[15] Pegunigalsidase alfa plasma concentrations at the end of each 4-week dosing interval in this study were substantially and consistently above the LLoQ, corroborating the extended availability of the PEGylated recombinant enzyme and supporting the potential use of an E4W administration regimen.

Safety and tolerability profiles of the E4W dosing regimen were favorable and consistent with previous studies,[15,17–19] with no severe or serious treatment-related TEAEs and all infusion-related reactions being mild or moderate in severity. No hypersensitivity reactions or withdrawals due to safety reasons were reported, and a reduction in infusion duration was achieved in all patients, further supporting the tolerability of this regimen.

In this study, switching to treatment with pegunigalsidase alfa E4W did not induce *de novo* ADA development in any patients, even though its dose per infusion

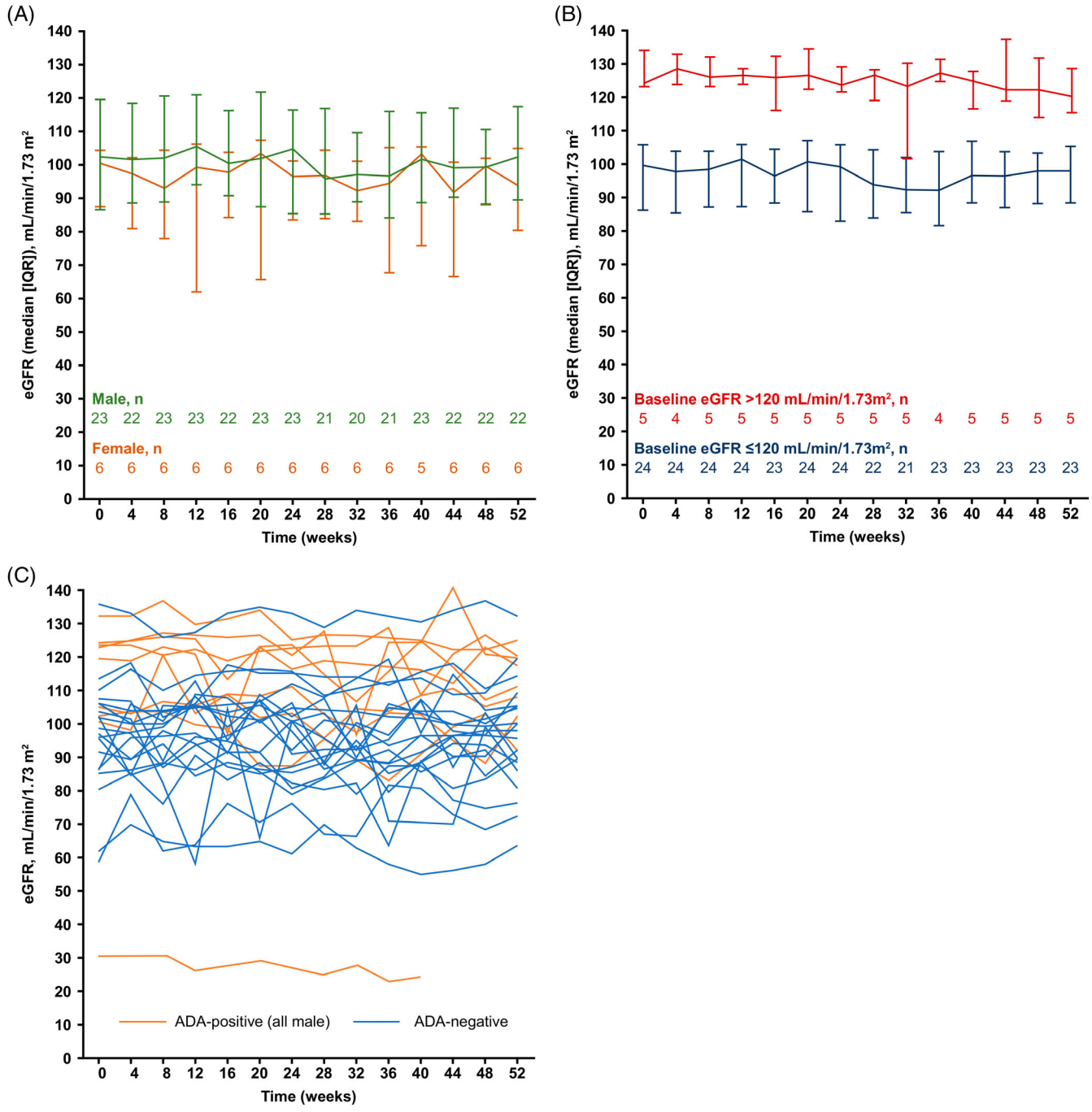


**FIGURE 3** eGFR profiles over 52 weeks (A) in male and female patients (median [IQR]), (B) stratified by baseline kidney function (eGFR >120 mL/min/1.73 $m^2$ vs. ≤120 mL/min/1.73 $m^2$; median [IQR]), and (C) in individual patients according to ADA status at baseline (efficacy population). ADA, anti-drug antibody; eGFR, estimated glomerular filtration rate; IQR, interquartile range.

was double to that specified in the approved regimen. An increased risk of ADA development following ERT with agalsidase beta vs. agalsidase alfa was previously reported.[31,32] In this study, only males previously treated with agalsidase beta with pre-existing ADAs had cross-reactive ADAs to pegunigalsidase alfa. Baseline ADA reactivity to pegunigalsidase alfa is due to recognition of the enzyme components of the shared amino acid sequence between pegunigalsidase alfa and agalsidase beta.[16] The ADAs of most of these patients were neutralizing, as manifested by decreased *in vitro* enzymatic activity of the study drug determined using a validated assay. However, the current lack of a standard definition of nAbs[33] and the use of diverse ADA assays limit comparison with other studies. ADA-binding of the recombinant α-Gal A reduces the amount of the free drug in plasma,

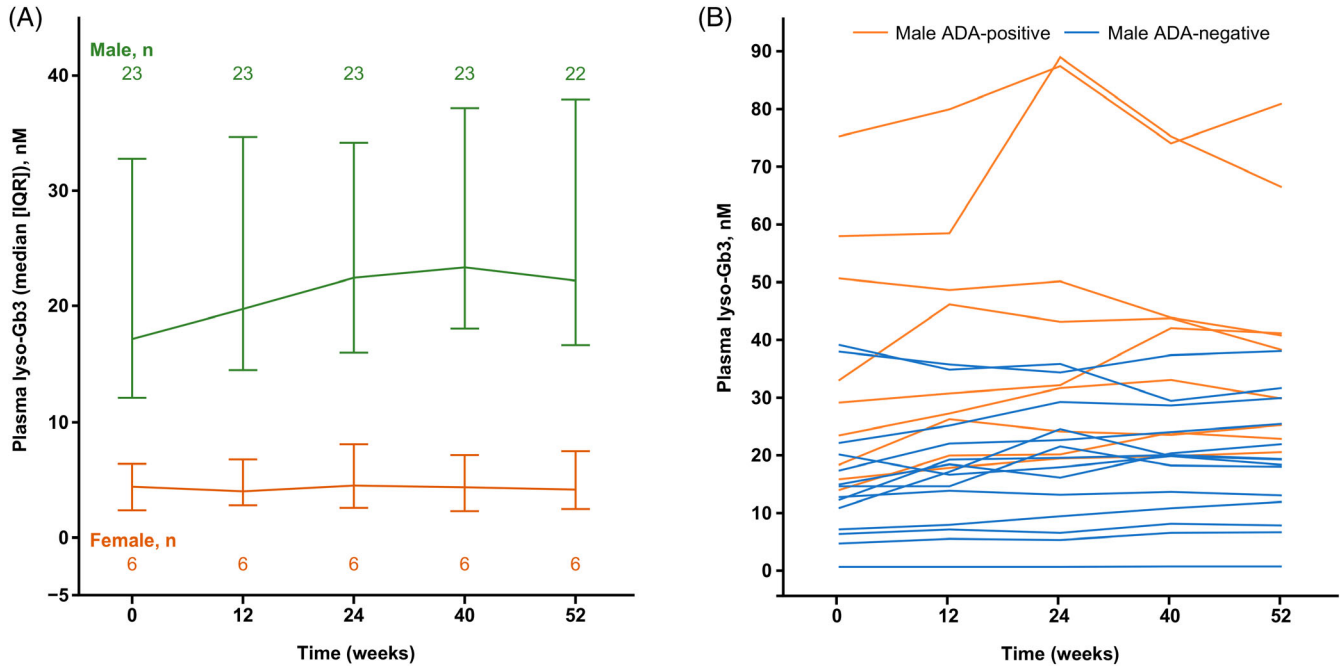


**FIGURE 4** Plasma lyso-Gb3 concentrations over 52 weeks (A) stratified by sex (median [IQR]) and (B) in individual male patients according to ADA status at baseline (efficacy population). ADA, anti-drug antibody; lyso-Gb3, globotriaosylsphingosine; IQR, interquartile range.

and recognition and uptake of ADA-drug complexes by cells of the immune system, such as macrophages, leads to increased drug clearance.[16,34,35] This may have contributed to the lower exposure observed in patients with pre-existing ADAs compared with patients who were ADA-negative at baseline. Furthermore, even if internalized, ADA-drug complexes are unlikely to dissociate within the lysosomes,[34] affecting both clinical and biomarker parameters of Fabry disease, and may have a negative impact on therapeutic efficacy and, ultimately, disease progression. Over the course of the BRIGHT trial, three patients who had ADAs at baseline became ADA-negative. The study results suggest that the subgroup of patients with pre-existing ADAs may require more careful clinical monitoring if they were to receive the E4W treatment regimen (e.g., regular follow-up visits to monitor eGFR, ADA status, etc.), and additionally that there may be some patients for whom this administration schedule may not offer benefits over alternative E2W regimens.

Observations of the change in eGFR over the course of the trial and the annualized eGFR slope suggested that kidney function remained relatively stable in the overall study population. Although it is not possible to draw any definitive conclusions regarding the influence of sex on annualized eGFR slope outcomes due to the small sample size in this study, the numerically lower median values noted in female patients compared with males may have stemmed from discrepancies between the subgroups at study baseline. Patients in the female subgroup started ERT treatment at a later age, were all ADA-negative, and had lower eGFR and more negative annualized eGFR slope values. In line with the observations of absolute eGFR values and with previous studies with other ERTs,[36] a more negative mean annualized eGFR slope was noted in patients with baseline eGFR >120 mL/min/1.73 $m^2$ compared with the remaining efficacy population; concurrently, the calculated median slope values were less negative in patients with eGFR >120 mL/min/1.73 $m^2$ at baseline. Similarly, a more negative mean eGFR slope was seen in patients with baseline eGFR ≥120 mL/min/1.73 $m^2$ compared with patients in the other eGFR categories <120 mL/min/1.73 $m^2$, while the median eGFR slope in patients with baseline eGFR ≥120 mL/min/1.73 $m^2$ was less negative than in patients with 60≤ eGFR <90 but more negative than in patients with 90≤ eGFR <120 and 30≤ eGFR <60 mL/min/1.73 $m^2$. However, the patient numbers in these subgroups were low, making it difficult to draw conclusions from these results. As the group with a higher baseline eGFR accounted for a reasonable proportion of the overall population (5/29 patients), the variability of data among those patients may have impacted the overall population results. Moreover, the calculation of the pre-switch annualized eGFR slope using baseline values in addition to the screening and historical values, which

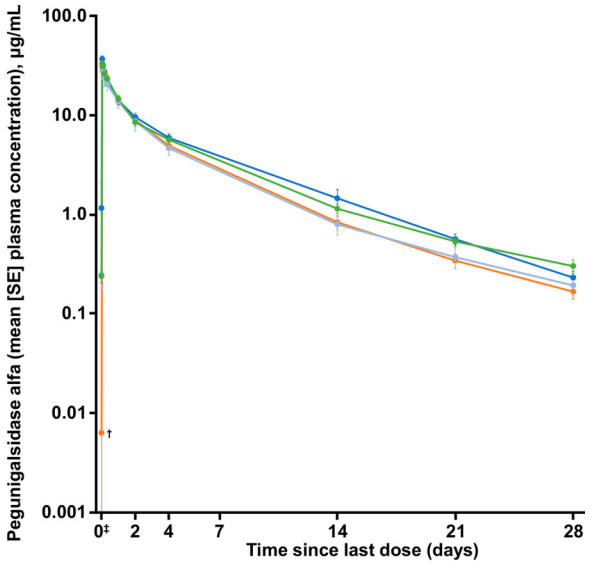


**FIGURE 5** Mean plasma concentration–time profiles of pegunigalsidase alfa (2 mg/kg) administered E4W: Semi-log scale (PK population*). *The number of patients with available data varied at each time point (minimum $n = 9$). †Prior to dosing of the first infusion, all but one patient had pegunigalsidase alfa concentration values lower than the LLoQ (set as "0" for the analysis). Due to unknown reasons, one patient had a detectable value of 191 ng/mL. Therefore, the calculated mean concentration value of the pre-dose time point at baseline was below the LLoQ (0.02 µg/mL). ‡Pre-dose sampling. At Weeks 24, 40, and 52, most patients had residual measurable plasma levels of pegunigalsidase alfa at the time of pre-dose sampling due to the long half-life of the drug (Table S8). E4W, every 4 weeks; LLoQ, lower limit of quantification; PK, pharmacokinetics; SE, standard error.

were not obtained in central laboratories, may be a limitation of this study. Nonetheless, the change in mean annualized eGFR slope was lower than established values observed in patients with progressive renal deterioration (annual declines in eGFR >3 mL/min/1.73 $m^2$/year), as defined by Wanner et al.[4]

Although there are some potential limitations to the use of lyso-Gb3 as a biomarker for Fabry disease progression,[37] the inclusion of this endpoint in clinical trials has been shown to be useful with regards to treatment monitoring.[18,19,38,39] Plasma lyso-Gb3 concentrations remained stable throughout the study. As expected, and in line with previous observations,[40,41] lyso-Gb3 concentrations tended to be higher and more variable in males. Primarily driven by few individual male patients, median plasma lyso-Gb3 concentrations increased slightly over the study period, although this increase was small, with biomarker concentrations remaining stable in female patients. The male patients with increased plasma lyso-Gb3 concentrations recorded during the course of the trial were ADA-positive throughout the study period, which may reinforce the need for careful monitoring and possible treatment modification in cases of a significant change in biomarker concentrations or associated signs of clinical deterioration in this patient subgroup. Other than baseline readings, historical lyso-Gb3 concentrations were not assessed in this study, and so it is not possible to define whether lyso-Gb3 concentrations had been increasing in these patients prior to their enrollment.

The short form BPI results regarding pain severity remained low and stable throughout the course of the study, which indicated no major changes in pain perception over the treatment period with pegunigalsidase alfa administered E4W, compared with the pre-switch E2W treatment with agalsidase alfa or agalsidase beta. Mean BPI score was in the mild range at baseline and remained so after 52 weeks of treatment with pegunigalsidase alfa. These results support the sustained, long-term improvements in pain scores that have been observed previously with other ERTs,[7,42–44] as well as with pegunigalsidase alfa in ERT-naïve patients.[15,17] However, the 52-week span of the BRIGHT study may have been of insufficient duration to observe any significant changes in BPI. No notable changes were observed in the EQ-5D-5L descriptive results, or overall health score as assessed by MSSI, indicating stable QoL with no negative impact of the longer interval between treatment infusions. Improvements in QoL as a result of reduced infusion frequency were not observed in this study, potentially due to the limitations associated with the measurement tools used to assess QoL in patients with Fabry disease. The key constraints of the EQ-5D-5L questionnaires have been addressed in a recent review article,[45] and include inability to capture actual rather than subjective changes in patient health state,[42] and challenges in method validation due to consistently low numbers of patients with this ultra-rare disorder (e.g., necessity to pool questionnaires in different languages to obtain sufficiently large samples).[46]

The low number of participants inherent to the rarity of Fabry disease (especially the under-representation in the female cohort), along with the heterogeneity of clinical manifestations of this disorder, is a general limitation of this trial. The results of the subgroup analyses should therefore be interpreted with caution. An additional limitation is the treatment duration, which was relatively short. Data from the ongoing open-label extension trial may offer further longer-term insights into the efficacy and safety of this treatment regimen.

## 5 | CONCLUSIONS

The BRIGHT study results suggest that 2 mg/kg pegunigalsidase alfa administered E4W is tolerated well in adult patients with Fabry disease previously treated with other ERTs. Switching from agalsidase alfa or agalsidase beta to pegunigalsidase alfa at this dosing regimen showed no new safety signals while maintaining disease stability for the majority of patients. As some patients with pre-existing ADAs experienced greater decline in kidney function compared with those without ADAs prior to treatment start, follow-up ADA testing and monitoring for proteinuria and eGFR decline is recommended for all patients with pre-existing ADAs, regardless of their ERT dosing schedule. Additional evidence is required to confirm the long-term effectiveness of this administration schedule. In conclusion, the increased interval between infusions of 2 mg/kg pegunigalsidase alfa E4W presents a promising option to reduce treatment burden for some patients with Fabry disease and may improve adherence to treatment.

### AUTHOR CONTRIBUTIONS

JAB, MH, AS, RR, EBA, SA, and RC contributed to the conception and design of the study. All authors provided substantial contributions to the acquisition, analysis, and interpretation of the data. All authors contributed to the drafting, revising, or reviewing of the manuscript, and provided their approval of the final version.

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### CONFLICT OF INTEREST STATEMENT

AL has received speaker's honoraria and/or consulting fees from Amicus Therapeutics, Chiesi, Protalix Biotherapeutics, Sanofi, and Takeda. AP has received grants and travel support from Amicus, Genzyme/Sanofi, Chiesi, Protalix Biotherapeutics, and Shire. AS was a paid consultant for Chiesi and Protalix Biotherapeutics. CT has received speaker's honoraria and/or consulting fees for advisory board meetings from Acelink, Amicus, Chiesi, Freeline, Sangamo, and Sanofi. DGW has no conflicts of interest to report. DH has received speaker's honoraria and/or consulting fees for advisory board meetings from Amicus, Chiesi, Protalix Biotherapeutics, Freeline, Sangamo, Sanofi, and Takeda. EW has been involved in clinical trials with Spark Therapeutics, Idorsia, Sanofi Genzyme, Protalix Biotherapeutics, and Chiesi. He is also a consultant for Amicus, Chiesi, Protalix Biotherapeutics, Sanofi, and Walking Fish; and has received a research grant from Sanofi. FE has received speaker's fees or honoraria for lectures, presentations, or educational events from Amicus, Sanofi, and Takeda; has received meeting attendance and/or travel support from Recordati, Sanofi, and Takeda; and has been involved in advisory board meetings with Chiesi, Protalix Biotherapeutics, Sanofi, and Ultragenyx. JAB receives research support from Avrobio, BioMarin Pharmaceutical, Chiesi Farmaceutici, Idorsia Pharmaceuticals, Pfizer, Protalix Biotherapeutics, Sangamo Therapeutics, Sanofi, Takeda, and Travere Therapeutics; has received a speaker's honorarium from the Fabry Support and Information Group; and has been involved in advisory board meetings with Chiesi USA, Sanofi, and Takeda. MH was a principal or co-investigator on the initial phase I–III pegunigalsidase alfa trials. He has also received speaker's honoraria from Chiesi and Protalix Biotherapeutics, and has participated in advisory boards with Sanofi and Amicus. NL has been involved in clinical trials with Aeglea, Amicus, Audentes/Astellas, BioMarin, Chiesi, Protalix Biotherapeutics, Genzyme/Sanofi, Hemoshear, Homology, Horizon Pharma, Moderna, Pfizer, PTC Therapeutics, Reneo, Synlogic, Takeda, Travere Therapeutics, and Ultragenyx; and his Institution has received consulting fees for advisory board meetings from Alnylam, Amicus, Audentes/Astellas, BioMarin, BridgeBio/CoA Therapeutics, Chiesi, Genzyme/Sanofi, Hemoshear, Horizon Pharma, Jaguar Gene Therapy, Jnana, Leadiant Biosciences, Moderna, Nestle' Pharma, PTC Therapeutics, Recordati, Reneo,

Synlogic, Takeda, and Ultragenyx. OGA has received grant support and consultancy fees from Chiesi. PD received institutional support for expenses incurred during the conduct of this trial from Protalix Biotherapeutics, and travel support from Chiesi. SW was a paid consultant for Chiesi and Protalix Biotherapeutics. UFR has received speaker's honoraria and/or consulting fees for advisory board meetings from Amicus, Chiesi, Protalix Biotherapeutics, Freeline, Recordati, Sanofi, and Takeda. UFR's research salary was sponsored by a grant from Kirsten and Freddy Johansen's Fund. WRW has been a consultant for Chiesi, Sanofi Genzyme, Amicus, Takeda, Spark, and UniQure; has been involved in clinical trials with Chiesi, Protalix Biotherapeutics, Sanofi Genzyme, Takeda, Amicus, 4D Molecular Therapeutics, and Sangamo; and has received research grants from Amicus and Takeda. RR is an employee of Chiesi Farmaceutici S.p.A. EBA and RC were full-time employees of Protalix Biotherapeutics at the time of study conduct and analysis, and are now consultants to Protalix Biotherapeutics. SA is a full-time employee of Protalix Biotherapeutics.

## DATA AVAILABILITY STATEMENT

Any data requests received from external parties will be reviewed on a case-by-case basis. Chiesi reserves the right to deny requests for any and all legally appropriate reasons. Data requests that risk sharing participant-level data or proprietary information will not be approved.

## INFORMED CONSENT

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study. The trial was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines at study sites in Belgium, Czech Republic, Denmark, Italy, Norway, United Kingdom, and the United States of America.

## ANIMAL RIGHTS

This article does not contain any studies with animal subjects performed by any of the authors.

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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