Real-world treatment, dosing, and discontinuation patterns among patients treated with pegvaliase for phenylketonuria: Evidence from dispensing data

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ARTICLE INFO

ABSTRACT

Background: Phenylketonuria (PKU) is an inborn metabolic error characterized by a deficiency of the enzyme required for the metabolism of phenylalanine, an essential amino acid found in most protein-containing foods. Pegvaliase (Palynziq®) is an enzyme substitution therapy approved for adults with PKU who have inadequate blood phenylalanine control ($\geq$600 μmol/L) on existing management.

Objective: To characterize the treatment, discontinuation, and dosing patterns in patients treated with pegvaliase in real-world practice settings in the United States following commercial availability in 2018.

Study design: Retrospective cohort study using BioMarin's proprietary drug dispense database associated with the pegvaliase REMS program.

Methods: Sample construction identified all patients who properly initiated pegvaliase in real world settings ('full cohort') and a subset of patients ('extended follow-up cohort') with $\geq$12 months between first dispense of maximum dose and last pegvaliase dispense. Key outcomes were quantified across patients in both cohorts: maximum daily dose; time to maximum daily dose; maximum daily syringes; and dose escalation over time. The overall dose at discontinuation and time to discontinuation were calculated. Patients who subsequently reinitiated therapy were identified. For the extended follow-up cohort, 12-month changes in dose and syringes and dispensing gaps during the 12 months after maximum dose were quantified across all patients and were further stratified by maximum dose.

Results: Overall, 1596 patients associated with 33,814 dispenses were reflected in the pegvaliase dispense dataset during the study period from July 9, 2018, through December 31, 2021; 1280 patients associated with 25,973 dispenses met inclusion criteria for the full cohort, with 19.9 dispenses each on average. Of these patients, 483 patients associated with 15,149 dispenses also met the extended follow-up criteria, with an average of 31.4 dispenses.

Average treatment duration in the full cohort was 82.2 weeks, including 50.8 weeks after maximum daily dose was achieved. The average maximum daily dose was 30 mg with an average time to maximum dose of 31.8 weeks: 43.0% of patients had a maximum dose of 20 mg, 31.3% a maximum dose of 40 mg, and 12.0% a maximum dose of 60 mg. At data cut-off, 289 patients (22.6%) had discontinued; within this group, 126 patients (43.6%) discontinued within the first 6 months after reaching maximum dose.

The overall average treatment duration for patients in the extended follow up cohort at data cut off was 131.2 weeks, including 98.6 weeks after maximum dose was achieved. The average maximum daily dose across the cohort was 32.9 mg: 42.4% of patients had a maximum dose of 20 mg, 41.0% a maximum dose of 40 mg, and 11.2% a maximum dose of 60 mg. At 12 months after achieving maximum dose, 35% of patients had down-dosed, with a 46.8% decrease (on average) from their maximum dose.

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Conclusions: Real-world use of pegvaliase reflects longer titration periods than in the dosing schedule based on trial experience. Over time, a substantial number of patients are able to reduce their daily dose by titrating down from their maximum dose, a finding of great interest to clinicians and patients alike.

1. Introduction

Phenylketonuria (PKU) is an inborn error of metabolism characterized by a deficiency of the enzyme phenylalanine hydroxylase (PAH) which is required for the metabolism of phenylalanine (Phe), an essential amino acid found in most protein-containing foods [1]. There are approximately 450,000 people worldwide with PKU but prevalence varies regionally [2]. The overall incidence of PKU in the United States is approximately 1 in 15,000 [3].

Practice guidelines issued by the American College of Medical Genetics and Genomics (ACMG) outline the importance of initiating life-long management as early as possible for optimal outcomes. The accumulation of Phe is toxic and can result in a variety of complications including severe intellectual disability, seizures, tremors, behavioral problems and psychiatric symptoms in patients with PKU [4]. However, the mainstay of PKU treatment, a strict diet supplemented by low protein medical foods, is ineffective long-term as most adolescent and adult patients who receive Medical Nutrition Therapy (MNT) are unable to sustain blood Phe levels below the guideline recommended threshold of 360 μmol/L [5].

Pegvaliase (Palynziq®) is an enzyme substitution therapy approved for adults with PKU who have inadequate blood Phe control ($\geq$600 μmol/L) on existing management [6]. Pegvaliase is administered via a subcutaneous injection and is available in 2.5 mg/0.5 mL, 10 mg/0.5 mL, and 20 mg/mL single-dose syringes for patient auto injection. In October 2020, a maximum dose of 60 mg/day was approved in the United States, up from the original 2018 US label maximum of 40 mg per day [7,8].

Pegvaliase is prescribed/administered in an induction/titration/maintenance (I/T/M) dosing regimen to improve patient tolerability of the immunogenic PAL enzyme, derived from the cyanobacteria *Anabaena variabilis* [9]. While this I/T/M dosing regimen is customizable, it is recommended that patients receive 2.5 mg once weekly for 4 weeks during the induction phase of therapy. The titration phase increases the weekly dose of pegvaliase, starting with 2.5 mg twice a week for one week, and then transitioning to the 10 mg syringe with the dosing frequency increasing each week from once weekly, to twice weekly, to four times weekly and finally daily. The maintenance phase of therapy begins when patients transition to a 20 mg daily dose. If there has not been an adequate blood Phe response by 24 weeks on 20 mg daily, it is recommended to increase the dose to 40 mg daily (2 × 20 mg syringes). Likewise, if there has not been an adequate blood Phe response by 16 weeks on 40 mg daily, it is recommended to increase the dose to 60 mg daily (3 × 20 mg syringes) for at least another 16 weeks.

Outside of the protocol-driven clinical trial experience, there has not yet been any long-term, real-world data reported on pegvaliase treatment trends and patterns. Pegvaliase is unique with regards to its pharmacokinetics, as clearance is determined by the body's immune response, which is time dependent but also varies from person to person [10]. The dose or time needed for substantial blood Phe lowering therefore also varies between patients and is not predictable at the start of therapy. In addition, due to the immunogenic nature of pegvaliase, there is an increased risk of hypersensitivity reactions, including immune-complex mediated anaphylaxis [6]. During the clinical trials, discontinuations were highest in the first six months of therapy, and were often associated with hypersensitivity reactions, though patients also cited reasons unrelated to tolerability for study discontinuation [11]. However, the employment of risk mitigation techniques partway into the PRISM-1 trial (including increased education surrounding treatment of hypersensitivity reactions, mandatory use of H1- and H2-

receptor antagonist medications, increased investigator flexibility to adjust the dosing schedule in the setting of any grade of hypersensitivity reactions, and a requirement to carry an auto-injectable epinephrine pen) were associated with a decreased rate of trial discontinuations, and particularly discontinuations associated with adverse events [9].

Several case series of pegvaliase use in the real world have documented use of alternative dosing regimens, and have noted that some patients appear to be able to require lower doses of pegvaliase than the dose at which they initially responded to maintain blood Phe levels in a desired treatment range [12–15]. These publications have also identified patients who have discontinued pegvaliase therapy at various points in the treatment journey, for reasons both related and unrelated to drug tolerability. These dosing patterns have yet to be captured on a larger scale and may be informative to both clinicians and patients in terms of time and dose needed for effective pegvaliase response.

Pegvaliase has a Risk Evaluation and Mitigation Strategy (REMS) program in the US. As such, all patients commercially treated with pegvaliase receive treatment management support and are monitored for potential safety concerns by BioMarin, and BioMarin maintains complete dispensing data as part of the REMS program. The dispensing data complemented with additional case management data collected via the REMS program offers a unique opportunity to study the entire patient population treated with pegvaliase (instead of a sample from selected clinics) in clinical practices over the longest follow up period possible and with minimal lag between events of interest and data capture.

The purpose of this study was to characterize the treatment, dosing, and discontinuation patterns in patients treated with pegvaliase in the United States following commercial availability in 2018. This study specifically aimed to examine in real-world practices: 1) I/T/M dosing regimens and the time between initiation and achieving a maximum daily dose, 2) change in dosing patterns (i.e., down-dosing) after achieving a maximum daily dose and 3) treatment discontinuation over time.

2. Methods

2.1. Data source and variable construction

This retrospective cohort study used data collected between July 9, 2018, and December 31, 2021, via BioMarin's proprietary drug dispense database associated with pegvaliase's REMS program. As no patient identifying information was available from the study dataset and all analyses were conducted in aggregate, ethics committee approval was not required for this study.

Each dispense record in the database included a unique, de-identified patient number (Case ID), the date of the dispense, the days' supply dispensed, and the number and sizes of syringes dispensed. The complete dispense history for each individual was created by aggregating all dispense records with the same Case ID. From these data elements, the daily dose and number of daily syringes of pegvaliase were calculated for each dispense. Number of daily syringes was examined separately from dose to capture patient burden associated with treatment administration. The dates of the first dispense of each standard dose (20 mg, 40 mg, and 60 mg) and the date that each patient first received their maximum dose were also identified. Patients' inventory of syringes over time were also reviewed. Dispensing gaps were quantified using the number of days in the 12 months post maximum dose where a patient would have experienced a gap in treatment (assuming perfect adherence to dosing schedule) because they had not been dispensed the next set of

syringes on schedule. Periods with dispensing gaps were identified to further understand down-dosing behaviors over time. Key variables are described in Table 1.

Patients were considered to have discontinued treatment if >90 days had elapsed beyond the expected next dispense date, and no resumption of treatment was observed during the study period. While the number of patients who resumed treatment after a >90 day gap was identified, dispenses associated with second and subsequent treatment intervals for these patients were excluded from average dose, average syringes and dispense gap analyses.

2.2. Sample selection and construction

This study included individuals with pegvaliase drug dispenses between July 5, 2018, and December 31, 2021. The following exclusion criteria were then used to exclude patients with incomplete real-world dispense histories: 1) clinical trial participants, 2) patients whose first dispense did not include 2.5 mg syringes; and 3) those who only had a single dispense recorded or otherwise did not successfully initiate treatment. Dispenses with a missing Case ID and dispenses with a Case ID that was not associated with a patient case history were also removed during the data cleaning step.

Two samples were then constructed. The 'full analytical sample' included data for all patients who properly initiated pegvaliase in real world settings. The 'extended follow-up sample' only includes patients with ≥12 months between first dispense of maximum prescribed dose and last pegvaliase dispense. The full analytical sample was used to understand treatment titration, dose-escalation, and discontinuation patterns. The extended follow-up sample was developed with the intent to meaningfully characterize down-dosing from maximum prescribed dose and long-term dose stability.

2.3. Study outcomes and statistical analyses

The following outcomes were quantified across patients in the full analytic sample and the extended follow-up sample: count and proportion of patients who reached maximum dose at <20 mg, 20 mg, >20 mg and <40 mg, 40 mg, >40 mg and <60 mg, 60 mg, and >60 mg; maximum average syringes; and time to maximum dose. Distributions of each characteristic across patients were summarized using mean,

median, and inter-quartile range (IQR).

For the initiation and titration period, dose escalation was mapped against the titration schedule presented in the US prescribing label, and the time to peak dose and time to each standard dose were assessed for both the full analytic sample and the extended follow-up sample. Twelve-month changes in dose and average number of syringes, as well as dispensing gaps during the 12 months after maximum dose were quantified across all patients in the extended follow-up cohort and for the subsets of patients whose maximum dose was 20 mg, 40 mg, and 60 mg to understand patterns of down dosing. Specifically, the 12-month changes in daily dose and number of syringes were quantified to assess dosage maintenance or decrease from maximum dose.

The number and proportion of patients with a dispensing gap of >90 days were identified. Subsets of patients who subsequently resumed therapy, whose dose at the gap was lower than their maximum dose, and who discontinued treatment were also identified. Among patients who discontinued treatment, the mean (SD) and median (IQR) overall dose at discontinuation were calculated. Patients who discontinued were categorized by the time between treatment initiation and treatment discontinuation (<6 months, 6–12 months, 12–18 months, 18–24 months, and >24 months).

Among patients in the extended follow-up cohort, dispensing gaps that occurred during the first 9 months after maximum dose were examined to determine how frequently down-dosing occurred after a dispensing gap. The following measures were quantified: number of patients with any dispensing gap >15 consecutive days, number of dispensing gaps >15 days, number of dispensing gaps >15 days followed by down-dosing within 3 months, and number of dispensing gaps that resulted in down-dosing at a later dispense. These measures were quantified across all patients in the extended follow-up cohort, as well as the subsets of patients whose maximum dose was 20 mg, 40 mg, and 60 mg.

3. Results

3.1. Sample description

Overall, 1596 patients associated with 33,814 dispenses were reflected in the pegvaliase dispense dataset during the study period from July 9, 2018, through December 31, 2021, after data cleaning activities to remove dispenses that were either duplicates, same day supply and dispenses, commercial bridging, or dose combinations of 10 mg and 2.5 mg which excluded 4000 dispense entries (Fig. 1). Of these, 205 patients were excluded as they had been enrolled in pegvaliase clinical trials, 29 patients were excluded because they did not initiate treatment with 2.5 mg syringes, and 81 patients were excluded because they did not meet treatment history criteria (i.e., they only had a single dispense on file). The total number of patients who met inclusion criteria for the full dataset was 1280 patients associated with 25,973 dispenses. Of these patients, 483 patients associated with 15,149 dispenses also met the extended follow-up criteria.
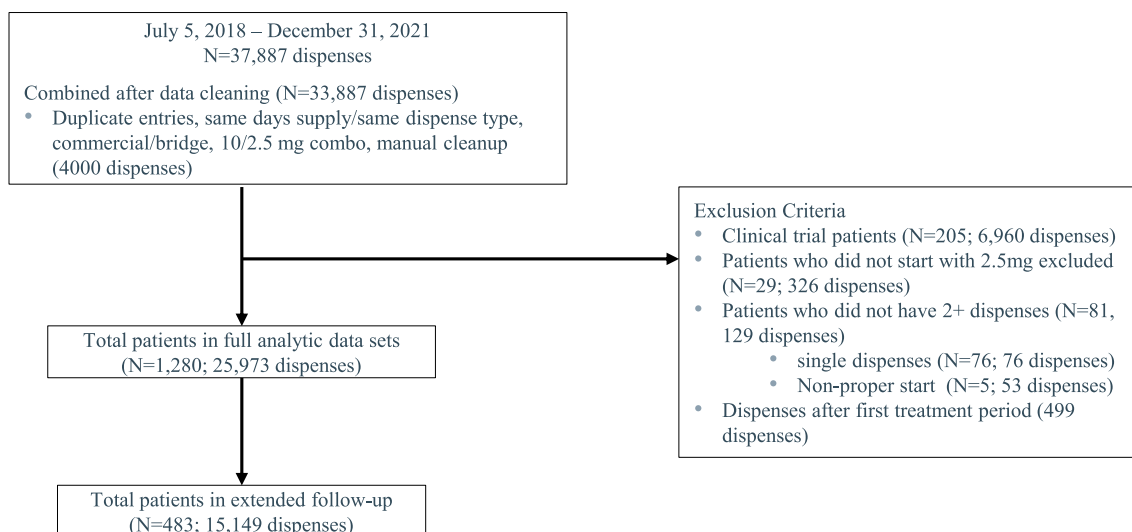
3.2. Full analytical sample

The average treatment duration of the patients in the full analytic sample at data cut-off was 82.2 weeks including 50.8 weeks after maximum dose was achieved (Table 2).

3.2.1. I/T/M dosing patterns and time to maximum daily dose

The average maximum daily dose was 30 mg, which reflects 550 patients (43.0%) with a maximum dose of 20 mg, 400 patients (31.3%) with a maximum dose of 40 mg, and 154 patients (12.0%) with a maximum dose of 60 mg (Table 2). The average number of syringes per day 12 months after treatment initiation was 1.5 syringes.

The recommended titration schedule and the observed time to an average dose of 20 mg, 40 mg, and 60 mg for the full analytical sample

Table 1
Key variable descriptions.

Variable	Description
Daily dose	'Daily dose' was computed for each dispense by dividing the total amount of medication across all syringes dispensed (i.e., total dose) by the number of days' supply. On days with >1 dispense, the total dose for each syringe size was calculated and then summed across dispenses.
Number of syringes per day	This variable reflects the average number of syringes used each day and is calculated by dividing the number of total dispensed syringes by the number of days' supply. It is calculated for each dispense.
Dispensing gaps	Dispensing gaps were quantified using the number of days in the 12 months post maximum dose where a patient would have experienced a gap in treatment because they had not received the next set of syringes on schedule (assuming perfect adherence to dosing schedule and assuming unused syringes from prior dispenses are available from later use). Dispensing gaps were further classified by the number and proportion of patients with dispensing gaps of >15 consecutive days.
Treatment discontinuation	Patients were considered to have discontinued treatment if >90 days had elapsed beyond the expected next dispense date, where the expected next dispense date is calculate as the number of days' supply after the last dispense. The date of discontinuation was defined as last dispense prior to discontinuation plus the days' supply associated with that dispense.

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┌─────────────────────────────────────────────────┐
│         July 5, 2018 – December 31, 2021         │
│              N=37,887 dispenses                  │
│                                                  │
│   Combined after data cleaning (N=33,887 dispenses) │
│   • Duplicate entries, same days supply/same dispense type, │
│     commercial/bridge, 10/2.5 mg combo, manual cleanup │
│     (4000 dispenses)                             │
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┌──┐
│ Exclusion Criteria   │
│ • Clinical trial patients (N=205; 6,960 dispenses) │
│ • Patients who did not start with 2.5mg excluded   │
│   (N=29; 326 dispenses)   │
│ • Patients who did not have 2+ dispenses (N=81,   │
│   129 dispenses)   │
│   • single dispenses (N=76; 76 dispenses)   │
│   • Non-proper start (N=5; 53 dispenses)   │
│ • Dispenses after first treatment period (499   │
│   dispenses)   │
└──┘

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┌─────────────────────────────────────┐
│  Total patients in full analytic data sets │
│       (N=1,280; 25,973 dispenses)   │
└─────────────────────────────────────┘

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│  Total patients in extended follow-up │
│       (N=483; 15,149 dispenses)     │
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Fig. 1. Analytical sample construction.

Note: The following exclusion criteria were used at the dispense level to identify and exclude unsuccessful attempts at treatment initiation. The first dispense was considered a false start if it was followed by a dispensing gap of ≥ 90 days beyond the days' supply. In this scenario, the second dispense was considered as the timepoint of treatment initiation. This second dispense would also be considered as a non-proper start if any other dose but 2.5 mg syringes were being dispensed. Of the patients who were flagged as having false start, only those who restarted with a 2.5 mg syringe at the subsequent dispense were included in the analytical samples.

Table 2
Patient characteristics.

Characteristic	Full analytic sample ($N = 1280$)	Extended follow-up cohort[a] ($n = 483$)
Total dispenses (N)	25,474	15,149
Time from first dispense to discontinuation[b]/ censoring (weeks), mean (IQR) [median]	82.2 (35.1, 129.2) [77.3]	131.2 (111.7, 152.6) [134.3]
Time from maximum daily dose to discontinuation/censoring (weeks), mean (IQR) [median]	50.8 (13.4, 84.0) [38.9]	98.6 (73.5, 118.6) [99.0]
Number of observed dispenses per patient, mean (IQR) [median]	19.9 (8.0, 31.0) [18.0]	31.4 (25.0, 37.0) [32.0]
Maximum daily dose		
Mean dose (IQR) [median]	30.0 (20.0, 40.0) [20.0]	32.9 (20.0, 40.0) [40.0]
<20 mg, n (%)	146 (11.4)	10 (2.1)
20 mg, n (%)	550 (43.0)	205 (42.4)
>20 mg and < 40 mg, n (%)	24 (1.9)	15 (3.1)
40 mg, n (%)	400 (31.3)	198 (41.0)
>40 mg and < 60 mg, n (%)	2 (0.2)	0 (0)
60 mg, n (%)	154 (12.0)	54 (11.2)
>60 mg, n (%)	4 (0.3)	1 (0.2)
Number of syringes per day at 12 months after initiation[c], mean (IQR) [median]	1.5 (1.0, 2.0) [2.0]	1.4 (1.0, 2.0) [1.0]
Number of syringes per day at 12 months after maximum dose	NR	1.5 (1.0, 2.0) [1.0]

Abbreviations: IQR, interquartile range; mg, milligrams.

Notes

[a] Patients with ≥ 12 months between first dispense of maximum prescribed dose and discontinuation or last dispense as of the data cut-off date (December 31, 2021).

[b] Discontinuation is defined as at least a 90-day dispensing gap or no dispenses in the 90 days plus last days' supply preceding the data cut-off date (December 31, 2021) without resumption of therapy during the study period. Censoring occurs at the earlier of a patient's first 90-day dispensing gap or at the last dispense plus day's supply prior to data cut-off.

[c] Sample size for Number of syringes 12 months after initiation in the full analytic sample was $N = 774$.

are compared in Fig. 2. The average time to maximum dose for the overall sample was 31.8 weeks (Supplementary Table 1), with patients requiring an average of 11.8 weeks to reach 20 mg, 44.1 weeks to reach 40 mg, and 80.7 weeks to reach 60 mg. The mean time to each maximum dose does not differ significantly from the time to intermediate dose among patients who then continue to a higher dose.

3.2.2. Discontinuation patterns

Within the full cohort, 289 patients (22.6%) discontinued treatment during the study period. Of these patients, 126 (43.6%) discontinued within 6 months of treatment initiation, 76 (26.3%) discontinued between 6 and 12 months, 49 (17.0%) discontinued between 12 and 18 months, 24 (8.3%) discontinued between 18 and 24 months, and 14 (4.8%) discontinued after 24 months. The average daily dose at discontinuation was 19.4 mg. Including patients who discontinued treatment, 350 (27.3%) patients had a long dispensing gap of >90 days. Sixty-one (4.8%) patients resumed therapy after a long dispensing gap and, for 97 patients (7.6%), the dose at the first long dispensing gap was lower than their maximum dose (See Table 4).

3.3. Extended follow-up sample

The extended follow-up sample includes 483 patients with ≥ 12 months between first dispense of maximum prescribed dose and last dispense. The overall average treatment duration of these patients at data cut-off was 131.2 weeks (Table 2), including 98.6 weeks after maximum dose was achieved. The average maximum daily dose across the cohort was 32.9 mg, reflecting 205 patients (42.4%) with a maximum dose of 20 mg, 198 patients (41.0%) with a maximum dose of 40 mg, and 54 patients (11.2%) with a maximum dose of 60 mg. The average number of syringes per day 12 months after maximum dose was 1.5 syringes.

Changes between maximum daily dose and average daily dose 12 months after the maximum dose are presented in Table 3. Across the sample, 65% of patients had maintained their dose; 35% had down-dosed, with a 46.8% decrease (on average) from their maximum dose. Among patients whose maximum daily dose was 20 mg ($n = 205$), 42.0% down-dosed, with a 51.8% decrease from their maximum dose (on average). Among patients whose maximum daily dose was 40 mg (n
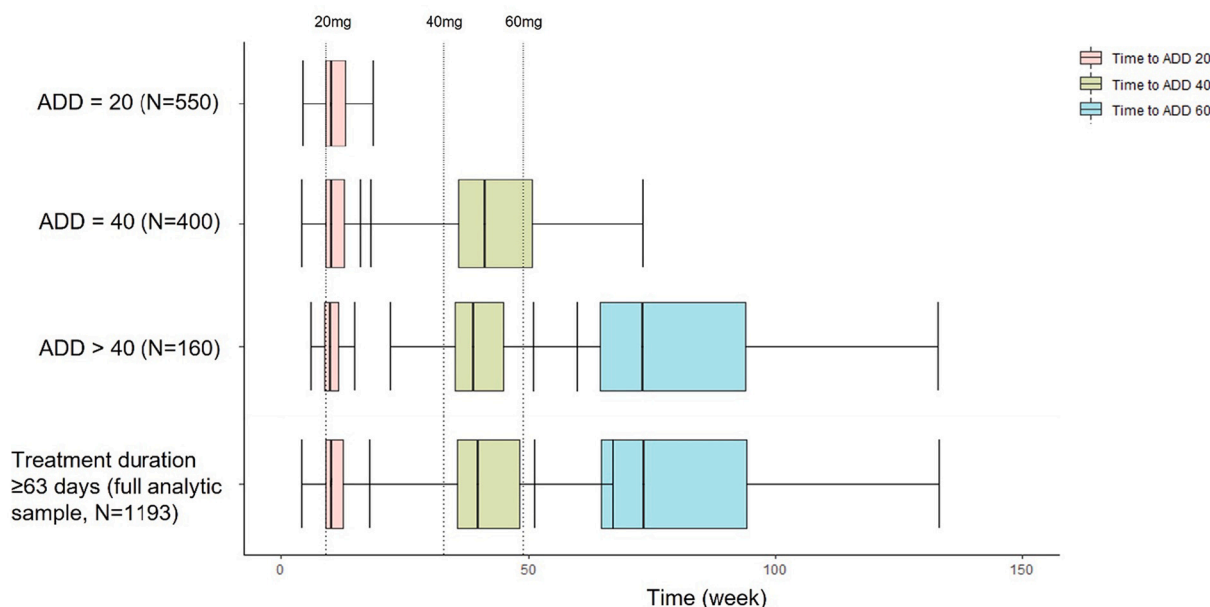
Fig. 2. Dose escalation against titration schedule and time to average dose of 20 mg, 40 mg, and 60 mg, full analytic sample.
Note: The minimum time (in weeks) to achieve an average dose of 20 mg, 40 mg, and 60 mg per US prescribing label is indicated via the dotted vertical line.

Table 3
Change in daily dose and number of syringes per day at 12 months after reaching maximum dose, extended follow-up cohort[a,b].

Variable	Overall[c] (N = 483)	Maximum dose of 20 mg (n = 205)	Maximum dose of 40 mg (n = 198)	Maximum dose of 60 mg (n = 54)
Daily dose 12 months after maximum dose				
Maximum dose maintained, n (%)	314 (65.0)	119 (58.0)	133 (67.2)	48 (88.9)
Lower daily dose, n (%)	169 (35.0)	86 (42.0)	65 (32.8)	6 (11.1)
Magnitude of decrease from maximum dose (%), mean (IQR) [median]	46.8 (28.6, 50.0) [50.0]	51.8 (42.9, 69.7) [50.0]	43.3 (25.0, 50.0) [50.0]	38.4 (33.3, 40.0) [33.3]
Number of syringes per day 12 months after maximum dose				
Increased number of syringes per day, n (%)	2 (0.4)	2 (1.0)	0 (0)	0 (0)
Number of syringes per day maintained, n (%)	357 (73.9)	151 (73.7)	143 (72.2)	48 (88.9)
Lower number of syringes per day, n (%)	124 (25.7)	52 (25.4)	55 (27.8)	6 (11.1)

Abbreviations: mg, milligram.
Notes
[a] Patients in the extended follow-up cohort are those with ≥12 months between first dispense of maximum prescribed dose and discontinuation or last dispense as of the data cut-off date (December 31, 2021).
[b] Outcomes measured at the first dispense at least 12-months after the maximum dose.
[c] Dosing categories were only used for maximum dose analyses. While all patients were included in the overall counts, patients whose maximum dose was <20 mg, >20 mg and <40 mg, >40 mg and <60 mg, and >60 mg were excluded from the breakouts.

= 198), 32.8% down-dosed, with a 43.3% decrease from their maximum dose (on average). Among patients whose maximum daily dose was 60 mg (n = 54), 11.1% down-dosed, with a mean 38.4% decrease from their dose. Data on down-dosing behavior at 3 months, 6 months, 9 months, and 12 months after achieving maximum daily dose are presented in Fig. 3 and Table 5.

Dispensing gaps during the 9 months after maximum dose were assessed for evidence of subsequent dose reduction within 3 months of the gap (Supplementary Table 2). Dispensing gaps are common: 184 patients (38.1%) collectively had 300 dispensing gaps of over 15 consecutive days at some point. Of these 300 dispensing gaps, 76 (25.3%) resulted in down-dosing within 3 months of the gap and 143 (47.7%) resulted in down-dosing in later dispenses.

4. Discussion

This study is the first attempt to describe long-term dosing patterns in a very large cohort of nearly all patients receiving pegvaliase in clinical practices in the US. By leveraging pharmaceutical dispensing data to understand real-world use of treatments, especially treatments with REMS programs in place, this study presents novel use of secondary data sources for outcomes research. The dispense level dataset collected as part of the REMS program provides a unique opportunity to understand real-world pegvaliase dosing patterns among US patients.

In the full sample, the average maximum daily dose across the full analytical sample was 30 mg, which reflects 550 patients (43.0%) with a maximum dose of 20 mg and 400 patients (31.3%) with a maximum dose of 40 mg, consistent with FDA-approved dosing regimens.

Notably, it appears that it takes patients longer to titrate to higher doses than indicated in the prescribing label. The average time to maximum daily dose for the overall sample was 31.8 weeks (Supplementary Table 1), with patients requiring an average of 11.8 weeks to reach 20 mg, 44.1 weeks to reach 40 mg, and 80.7 weeks to reach 60 mg (compared to the 9, 33, and 49 weeks specified in the prescribing label, respectively). Fewer patients recorded a maximum dose of 60 mg (12.0%), though the label expansion may have occurred too recently (October 2020) to observe the population titrating to this higher dose in the dispense data.

The small amount of extra time spent during induction and titration before reaching the 20 mg dose (average of 11.8 weeks, compared with
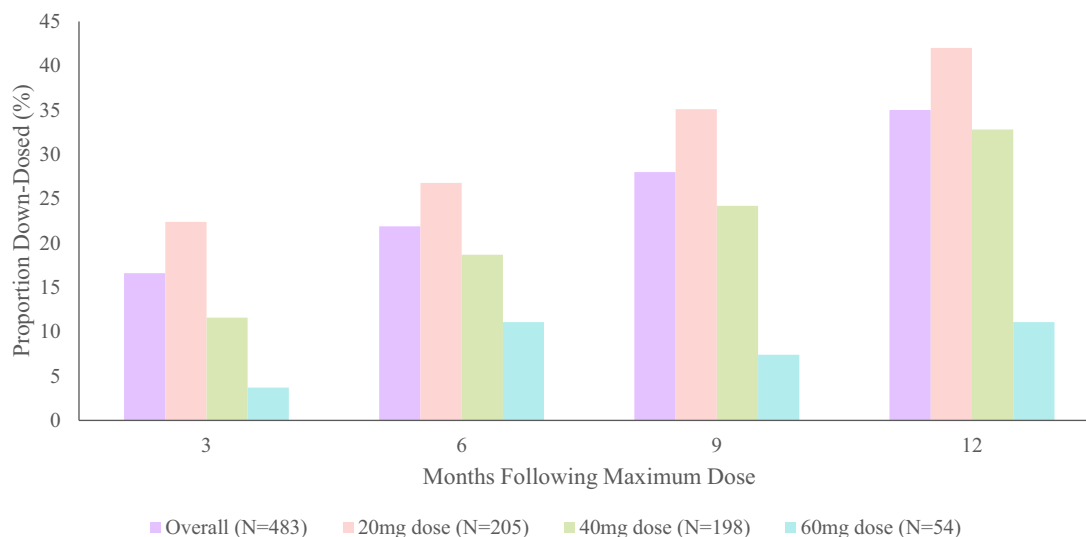
Fig. 3. Proportion of patients who down-dosed after maximum average dose, extended follow-up cohort.

Table 4

Long treatment gaps, discontinuation and time to discontinuation, full analytical sample.

Variable	Full Analytic Sample (N = 1280)
>90 day treatment gap within study period, n (%)	350 (27.3)
Resumption within study period, n (%)	61 (4.8)
Dose at gap lower than maximum dose, n (%)	97 (7.6)
Discontinuations [a], n (%)	289 (22.6)
Dose at discontinuation (mg)	
Mean (SD)	19.4 (15.3)
Median (IQR)	20.0 (5.3, 20.0)
Time to discontinuation[b]	
Number of patients who discontinued <6 months from treatment initiation, n (%)	126 (43.6)
Number of patients who discontinued 6–12 months from treatment initiation, n (%)	76 (26.3)
Number of patients who discontinued 12–18 months from treatment initiation, n (%)	49 (17.0)
Number of patients who discontinued 18–24 months from treatment initiation, n (%)	24 (8.3)
Number of patients who discontinued >24 months from treatment initiation, n (%)	14 (4.8)

Abbreviations: IQR, interquartile range; mg, milligrams; SD, standard deviation.
Notes
[a] Discontinuation is defined as at least a 90-day in dispensing gap or no dispenses in the 90 days plus last days' supply preceding the data cut-off date (December 31, 2021) without resumption of therapy within the study period.
[b] Date of discontinuation is defined as last dispense prior to discontinuation plus days' supply.

9 weeks recommended in the label) is not surprising given that adverse events tend to occur more frequently early in treatment due to the significant variability in drug tolerability while the immune response to pegvaliase is still maturing. The larger gap between the observed amount of time to reach the 40 mg dose (average of 44.1 weeks, compared to 33 weeks recommended in the label) is likely due to prolonged time (>24 weeks) spent on the 20 mg dose. This may occur for several reasons, including patient hesitation to increase to 2 injections/day, timing of patient appointments, delays in obtaining blood Phe levels to determine if the 40 mg dose is needed, delays in insurance approval, and potentially an assumption of increased risk of adverse events with escalating maintenance dose, though this was not supported in clinical trial data. As stated in the prescribing information: "The types and rate of adverse reactions reported during the maintenance phase in

Table 5

Down-dosing after achieving maximum dose, extended follow-up cohort.

Variable	Sample at Time 0 (N)	Patients down-dosed at 3 mos post maximum dose (%)	Patients down-dosed at 6 mos post maximum dose (%)	Patients down-dosed at 9 mos post maximum dose (%)	Patients down-dosed at 12 mos post maximum dose (%)
Overall	483	80 (16.6)	106 (21.9)	135 (28.0)	169 (35.0)
Maximum dose <20 mg	10	5 (50.0)	5 (50.0)	5 (50.0)	5 (50.0)
Maximum dose = 20 mg	205	46 (22.4)	55 (26.8)	72 (35.1)	86 (42.0)
Maximum dose >20 mg & <40 mg	15	4 (26.7)	3 (20.0)	5 (33.3)	7 (46.7)
Maximum dose = 40 mg	198	23 (11.6)	37 (18.7)	48 (24.2)	65 (32.8)
Maximum dose = 60 mg	54	2 (3.7)	6 (11.1)	4 (7.4)	6 (11.1)

Abbreviations: mos, months.
Notes
[a] Patients in the extended follow-up cohort are those with ≥12 months between first dispense of maximum prescribed dose and discontinuation or last dispense as of the data cut-off date (December 31, 2021).
[b] While all patients were included in the overall count, 1 patient whose maximum dose was >60 mg was excluded from the breakout.

patients who received 20 mg once daily, 40 mg once daily, and 60 mg once daily were similar" [6]. The length of the gap observed to reach the 60 mg dose (average of 80.7 weeks, compared to 49 weeks recommended in the label) may also be due in part to hesitancy to increase to 3 injections/day, insurance delays, an (incorrect) assumption of increased adverse event risk, and the 60 mg dose not being added to the label until 2.5 years after initial FDA approval, giving fewer patients timely access to this dose. Strategies to support patients during the initiation and titration phases to achieve an effective dose in a prompt manner is likely to be of interest to clinicians and an area of future research.

The analyses of the extended follow-up cohort show that many patients are able to successfully reduce their dose after titration is

complete. While the average maximum daily dose was 32.9 mg across the extended follow-up cohort (indicative of a mixture of 20 mg and 40 mg doses), many of these patients were able to lower their dose over time. After each 3-month interval, progressively more patients managed to down-dose from the maximum dose, with 40.6% of patients having down-dosed from their maximum dose at 12 months after first reaching their maximum dose. Specifically, almost half (42.0%) of the patients whose maximum dose was 20 mg and a third (32.8%) of the patients whose maximum dose was 40 mg managed to reduce their dose by 1 year after reaching maximum dose.

In a cross-section of pegvaliase patients, the average number of syringes used would depend on how many patients were in each treatment phase and how many had stabilized at each dose level. The average number of syringes for the full analytic sample was 1.5 syringes (IQR 1–2) twelve months after treatment initiation, consistent with either 20 mg (1 syringe) or 40 mg (2 syringes) dosing schedules. Most patients in the extended follow-up cohort were either able to maintain (73.9%) or reduce their average number of syringes as they continued pegvaliase treatment, with 25.7% of patients reducing their number of syringes by 1 year after reaching maximum dose. At 12 months after initiation, the average number of daily syringes was 1.4 [IQR 1.0–2.0].

Experiencing gaps between dispenses was also fairly common (38.1% of patients experienced at least 1 gap >15 days in the 9 months after reaching their maximum dose). Some of these gaps are followed by a reduction in prescribed dose, suggesting that prescribed dose might only be reduced after a patient stabilizes on a lower dose rather than when down-dosing is first attempted. Gaps in dispenses may also be due to temporary suspension of treatment due to adverse events, insurance delays, or using previously stockpiled syringes (e.g., from an unsuccessful down-dosing attempt or treatment holiday).

5. Conclusion

Real-world use of pegvaliase reflects longer titration periods than in the dosing schedule based on trial experience. This discrepancy between the I/T/M dosing schedule specified in the prescribing label and the time to titration to stable dose levels in real world settings is likely to be of interest to clinical stakeholders. Moreover, the possibility that patients are likely to be able to decrease their treatment dose over time and, therefore, need fewer injections every month is likely of great value to improving patient experience and adherence to treatment. Titration timeline and treatment behavior change over time in relation to treatment tolerability, adherence, and the ability to maintain Phe levels below a threshold over time are promising areas for further research.

6. Limitations

The combination of case management and dispensing data available for this study provided sufficient patient-level information on patient demographics, treatment history, new treatment initiation, and dispensing records for every prescription to allow for meaningful analysis of real-world dosing patterns. However, it is important to acknowledge that our analyses were based on secondary analysis of case management and business transaction data not collected for clinical research purpose, which limits clinical interpretation of treatment patterns observed. For instance,

- The number of syringes dispensed do not necessarily equal the number of syringes taken by patients as the dispensing timeframe is distinct from the usage timeframe.
- Potential stockpiling behavior affects interpretation of dispensing gaps and down-dosing.
- Discontinuation and planned treatment gaps of longer than 90 days, such as may occur for female patients managing a pregnancy, may be conflated in this study if treatment resumption

occurred after the end of the study period. Additionally, the proportion of long treatment gaps associated with pregnancy could not be determined, due to inconsistent documentation of women's health data.

Data availability

The authors do not have permission to share data.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2022.100918.

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