Molecular Genetics and Metabolism Reports 42 (2025) 101181

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Lessons learned from 5 years of pegvaliase in US clinics: A case series

Erin Cooney [a,*], Zineb Ammous [b], Tricia Bender [c], Gillian E. Clague [c], Marilyn Clifford [d], Angela Crutcher [e], Laura Davis-Keppen [f], Kirsten Havens [g], Melissa Lah [h], Stephanie Sacharow [i], Amarilis Sanchez-Valle [j], Erika Vucko [k], Bridget Wardley [c], Leah Wessenberg [l], Hans C. Andersson [m]

[a] University of Texas Medical Branch, Galveston, TX, USA
[b] The Community Health Clinic, Shipshewana, IN, USA
[c] BioMarin Pharmaceutical Inc., Novato, CA, USA
[d] Cooper University Health Care, Camden, NJ, USA
[e] Kentucky Children's Hospital, Lexington, KY, USA
[f] University of South Dakota, Sanford School of Medicine, Sioux Falls, SD, USA
[g] Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA
[h] Indiana University School of Medicine, Indianapolis, IN, USA
[i] Boston Children's Hospital, Boston, MA, USA
[j] University of South Florida Health, Tampa, FL, USA
[k] Ann & Robert H. Lurie Children's Hospital, Chicago, IL, USA
[l] OHSU Doernbecher Children's Hospital, Portland, OR, USA
[m] Hayward Genetics Center, Dept of Pediatrics, Tulane University Medical School, New Orleans, LA, USA

ARTICLE INFO

Keywords:
Phenylketonuria
PKU
Pegvaliase
Case series
Expert opinion
Treatment

ABSTRACT

Objective: To provide insights and strategies for pegvaliase management in challenging cases with phenylketonuria (PKU) based on the first 5 years of experience with pegvaliase in real-world clinical practice.
Methods: Twelve PKU experts gathered during a one-day, in-person meeting to discuss clinical cases illustrating important lessons from their experiences treating patients with pegvaliase in real-world clinical practice. Challenges with pegvaliase experienced prior to and during treatment and corresponding strategies to overcome them were discussed.
Results: Twelve cases of adults with PKU (eight females and four males, aged 18 to 68 years) receiving pegvaliase were reviewed and discussed. Challenges of the cases included medical or mental health comorbidities, executive function deficits, challenging social or socioeconomic situations, logistical or geographic barriers, or a combination of these; one was considering pregnancy. Despite challenges, pegvaliase was initiated successfully in most cases. Strategies to overcome barriers included individualized education, including side effect action plans, help from support organizations, collaboration with local providers, and use of telemedicine. Recommendations from the clinicians included that comorbid conditions should be monitored closely after treatment initiation and may require collaboration with other healthcare providers. A collaborative relationship with the clinic, ongoing education, and supportive relatives or friends can help individuals to remain adherent to pegvaliase. Suboptimal adherence may be addressed by a daily reminder system, telemedicine, in-home support, or a modified titration plan. Treated individuals with eating disorders require additional follow-up and support to achieve a healthy

Abbreviations: ADHD, Attention deficit hyperactivity disorder; AEs, adverse events; BMI, body mass index; EOD, every other day; HCPs, healthcare professionals; LNAA, large neutral amino acids; NSAIDs, non-steroidal anti-inflammatory drugs; PAH, phenylalanine hydroxylase; PCP, primary care provider; Phe, phenylalanine; PKU, phenylketonuria.

* Corresponding author at: University of Texas Medical Branch, University Blvd 301, Galveston, TX 77555, USA.
E-mail addresses: ercooney@utmb.edu (E. Cooney), zammous@indianachc.org (Z. Ammous), Tricia.Bender@bmrn.com (T. Bender), gillian.clague@bmrn.com (G.E. Clague), clifford-marilyn@CooperHealth.edu (M. Clifford), Angela.Crutcher@uky.edu (A. Crutcher), Laura.Davis-Keppen@SanfordHealth.org (L. Davis-Keppen), khavens@luriechildrens.org (K. Havens), mspurr@iu.edu (M. Lah), Stephanie.Sacharow@childrens.harvard.edu (S. Sacharow), asanche6@usf.edu (A. Sanchez-Valle), EVucko@luriechildrens.org (E. Vucko), bridget.wardley@bmrn.com (B. Wardley), bjornsko@ohsu.edu (L. Wessenberg), handers@tulane.edu (H.C. Andersson).

https://doi.org/10.1016/j.ymgmr.2024.101181
Received 31 October 2024; Received in revised form 17 December 2024; Accepted 17 December 2024

relationship with food. In most cases, including late-diagnosed individuals, reduced blood Phe levels resulted in improved PKU-related symptoms, including neurological issues.

Conclusion: Experience from the presented cases and 5 years of expert experience with pegvaliase in the real-world setting provide insight and guidance for healthcare professionals initiating and managing pegvaliase treatment in complex PKU cases. These cases demonstrate that, through comprehensive assessment and addressing barriers, pegvaliase treatment can be successful in adults with PKU, regardless of prior treatment success, age, socioeconomic, cognitive, or executive function challenges, as well as in those with comorbidities or considering pregnancy. Ongoing documentation of clinical experience is crucial for advancing the management of individuals receiving this treatment.

1. Introduction

Phenylketonuria (PKU) is a rare autosomal recessive metabolic disorder caused by a deficiency of the phenylalanine hydroxylase (PAH) enzyme that converts phenylalanine (Phe) to tyrosine [1]. The resulting elevated blood and brain Phe levels can affect neurodevelopment and manifest as neurocognitive, neurological, and neuropsychiatric symptoms [2–4].

To prevent severe comorbidities in individuals with PKU, guidelines of the American College of Medical Genetics and Genomics (ACMG) recommend early and lifelong maintenance of blood Phe levels ≤360 μmol/L [5]. European guidelines recommend maintaining blood Phe ≤360 μmol/L up to the age of 12 years and ≤600 μmol/L in older patients [6]. Blood Phe can be decreased by medical nutrition therapy, a Phe-restricted diet with medical food [5,6]. However, most patients with PKU are unsuccessful in following stringent dietary restrictions, particularly from early adolescence onwards resulting in deleterious blood Phe levels [3,7–9]. Treatment with sapropterin dihydrochloride is an option for individuals with residual PAH activity, but for most does not result in a reduction of blood Phe to target ranges and complete diet normalization [5,6,10,11].

Pegvaliase (Palynziq®, BioMarin Pharmaceutical Inc., Novato, CA, USA), a subcutaneously administered PEGylated recombinant phenylalanine ammonia lyase enzyme, was approved as a treatment for adults with PKU by the Food and Drug Administration in May 2018, and subsequently by the European Medicines Agency and in several other countries, including Canada, Australia, Japan, and Taiwan [12–17]. The final analysis of the phase 3 PRISM-1 (NCT01819727) and PRISM-2 (NCT01889862) clinical trials (N = 261), demonstrated a sustained Phe response of 85.5 % and 84.7 % at blood Phe thresholds ≤600 μmol/L and ≤360 μmol/L, respectively, over a mean of 36.6 months on pegvaliase; 78.1 % had a sustained Phe response ≤120 μmol/L, the upper limit of normal in unaffected individuals [18–20]. A recent comparative effectiveness study, using long-term data from the clinical trials and the Phenylketonuria Demographics, Outcomes and Safety Registry (PKUDOS; NCT00778206), showed lower median blood Phe levels and higher intact protein intake in individuals treated with pegvaliase than in those receiving medical nutrition therapy with or without sapropterin after 1, 2 and 3 years of treatment [11]. In addition, participants receiving pegvaliase more often achieved blood Phe targets of ≤360 μmol/L and ≤120 μmol/L. To mitigate the risk of hypersensitivity reactions, pegvaliase is administered through an induction, titration, and maintenance schedule, gradually increasing the dose from 2.5 mg weekly to an individualized maintenance dose of up to 60 mg once daily, as needed to achieve blood Phe reduction, [12,21,22].

The first expert recommendations for the use of pegvaliase, which were developed based on experience in the PRISM trials, indicated that pegvaliase should be considered for all adult patients with PKU able to give informed consent and to adhere to the treatment [23]. However, they cautioned against initiating pegvaliase in patients who have communication challenges, limited access to emergency services, self-injection issues, or severe mental health problems; in those who are unable to find a trained observer; or are pregnant or planning to become pregnant [23]. Since the initial recommendations were made, practice experiences have evolved with real-world experience and new recommendations and guidance to support clinicians [24–28].

Described herein are 12 complex clinical cases selected and discussed by US healthcare professionals (HCPs) with considerable experience in managing pegvaliase treatment. Experience from these cases, based on the first 5 years of pegvaliase use in the real-world setting, offers valuable new insights and guidance.

2. Methods

Twelve PKU experts gathered during a one-day in-person advisory board meeting in April 2023 to discuss their experiences treating adult patients with PKU on pegvaliase in real-world clinical practice. The multidisciplinary panel consisted of seven physicians and five nurse practitioners from 11 different treatment centers in the US. The participating HCPs had different levels of experience with pegvaliase; several participated in the clinical trials and all had treated in real-world clinical practice. They represented both rural and (sub)urban treatment settings.

During the in-person meeting, each expert presented one real-world clinical case with medical and/or psychosocial challenges. Challenges with pegvaliase prior to and during treatment were discussed along with corresponding mitigation strategies. In November 2023, the experts were asked to provide a brief update on their case.

All adults with PKU described in the case reports provided consent to include their treatment experience in this retrospective case series. No patient identification data are included.

3. Clinical case reports

3.1. Clinical case characteristics

Table 1 provides an overview of the demographics, baseline characteristics, concomitant conditions and details on induction/titration and maintenance of the 12 clinical cases described below. Specific details by case regarding pegvaliase dosing, blood Phe levels, prescribed diet, and adverse events (AEs) over time are available in Supplement 1 (Supplementary file 1). Information provided after the advisory board, in response to the request for case updates, has been added to the case reports where available and relevant.

3.2. Case 1: Referral to pegvaliase-experienced center due to psoriatic arthritis

This 19-year-old male college student with normal development and cognitive abilities was unable to achieve blood Phe control with diet management and sapropterin prior to pegvaliase initiation. Due to his medical history of psoriasis and psoriatic arthritis treated with secukinumab and meloxicam, his treating physician was uncomfortable with starting pegvaliase and referred him to a more experienced center. Pegvaliase was initiated after confirming that secukinumab was not pegylated.

Prior to starting pegvaliase, his blood Phe level was 988 μmol/L while on a Phe-restricted diet and sapropterin. Because of his medical

history, pegvaliase was titrated slower than the standard induction and titration schedule, and pre-medications (H1 and H2 antihistamines) were used to reduce the risk of pegvaliase-related arthralgia. During the first months of treatment, he experienced intermittent episodes of arthralgia (particularly at dose increases), which were managed with H1 antihistamine and non-steroidal anti-inflammatory drugs (NSAIDs) (Supplement 1). His pegvaliase dose was titrated up to 60 mg daily and after 9 months on this dose his blood Phe level decreased to <360 μmol/L; pre-medication (H2 antihistamine) and sapropterin were discontinued. When his blood Phe level decreased to <30 μmol/L, intact protein intake was increased and medical food was discontinued once consuming adequate intact protein; despite increased intact protein intake, his blood Phe levels remained low. Pegvaliase dose was decreased gradually to 40 mg daily and at the time of the advisory board (44 months of treatment) his blood Phe levels remained <30 μmol/L. Data provided after the advisory board showed that blood Phe remained low after 51 months of treatment and a further reduction of the pegvaliase dose was considered.

3.3. Case 2: Initiation of pegvaliase in an adult who does not tolerate PKU formula and desires a pregnancy

This 27-year-old female had a history of depression and fatigue and struggled to achieve blood Phe control with diet and sapropterin (870–1320 μmol/L in the 3 years prior to pegvaliase initiation). She had difficulty tolerating medical food due to irritable bowel syndrome. She expressed a desire to become pregnant, but also wanted to start pegvaliase to reduce her blood Phe levels. The clinic advised against pregnancy but agreed to start treatment, provided she signed a contract stating she understood the potential risks of pegvaliase in pregnancy and

Table 1
Case overview of demographics and baseline characteristics, and details on induction/titration, maintenance, and last follow-up.

Case	1	2	3	4	5	6	7	8	9	10	11	12
Demographics and baseline characteristics												
Age, years	19	27	18	26	33	29	22	44	50	68	48	53
Sex	M	F	M	F	F	F	F	F	M	F	F	M
BMI, kg/m^2	29	36	20	38	28	22	21	33	48	32	41	26
Actual intact protein, g/day[a]	19	60	5	40	8-10	10	6	20	40–50	50	55	Unrest.
Actual medical food protein, g/day[b]	121	29	53	30	45-60	40–50	50	75	80	15–60	0	0
Phe-restricted diet[c]	Y	N	Y	N	Y	Y	Y	N	N	N	N	N
Blood Phe, μmol/L	988	454	1114	818	777	1089	531	2100	1667	967	1914	1722
Sapropterin dihydrochloride at baseline[d]	Y	N	Y	Y	Y	N	N	N	Y	Y	N	N
Concomitant conditions[e]												
Medical comorbidities	**Y**	**Y**	–	**Y**	**Y**	–	–	**Y**	**Y**	**Y**	**Y**	**Y**
Mental health comorbidities	–	–	**Y**	**Y**	**Y**	**Y**	–	**Y**	**Y**	**Y**	**Y**	**Y**
Executive functioning deficits/ cognitive impairment	–	–	**Y**	**Y**	–	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Social/socioeconomic concerns	–	–	**Y**	**Y**	–	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**
Induction/titration												
Pre-medication	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1&H2	H1
Maintenance[f]												
Time to achieve blood Phe ≤360 μmol/L, months[g]	28.6	12.6	NA[h]	4.9	24.4	NA	6.6	6.9	27.3	NA	7.4	2.3
Pegvaliase dose at blood Phe ≤360 μmol/L, mg	60/day	40/day	NA[h]	20/day	40/day	NA	20/day	20/day	60/day	NA	20/day	20/day
Status at time advisory board												
On treatment, months	43.7	49.3	4.4	22.5	44.1	4.1	12.5	50.5	54.4	Discont.	44.7	13.6
Blood Phe, μmol/L	9	175	1186	376	886	1078	198	147	1193	1454	192	134
Pegvaliase dose, mg	40/day	10/day	40/day	20, 5×/wk	40/day	10, 2×/wk., 2.5, 1×/wk	20/day	10/day	40/day	Discont.	20/day	20, 3×/wk
Actual intact protein intake, g/day[a]	60–80	60	5	75	60	10–15	50–60	80–100	~73	50	65	Unrest.
Medical food intake, g/day[b]	0	0	68	0	0	40–50	0	0	0	60	0	0
Achievement of blood Phe ≤360 μmol/L by last follow-up[i]	Y	Y	Y	Y	Y	N	Y	Y	Y	N/A	Y	Y

BMI: body mass index; Discont.: Discontinued; F: female; M: male; NA: not achieved; N/A: not applicable; Phe: phenylalanine; dashes (–) indicate condition is not identified; H1 and H2 refer to H1 and H2 antihistamines.

[a] Actual protein intake was derived from diet records and may deviate from prescribed intake. When intact protein provided in mg Phe, 50 mg Phe was considered equivalent to 1 g of intact protein.

[b] Actual medical food intake was derived from diet records and may deviate from prescribed intake.

[c] >75 % of protein from medical food.

[d] N = either never tried or non-responder to sapropterin.

[e] Case 2 had a pregnancy after initiating pegvaliase.

[f] Case 10 discontinued treatment due to poor compliance related to adverse events, family issues and psychological problems.

[g] First time blood Phe ≤360 μmol/L (see Supplement for more details).

[h] Case 3 had not yet achieved maintenance phase at the time of the advisory board. He first achieved blood Phe ≤360 μmol/L 12 months after initiating pegvaliase, at a dose of 60 mg/day.

[i] Based on data collected after the advisory board (~6 months). Further details on changes in blood Phe levels, diet and dose are available in Supplementary file 1.

agreed to obtaining regular blood Phe levels.

Prior to starting pegvaliase, her blood Phe level was 454 μmol/L. Pegvaliase was initiated using the standard induction and titration schedule, with H1 and H2 antihistamines as pre-medications. AEs during induction and titration were managed with NSAIDs (Supplement 1). She stopped taking medical food after 3 months of treatment due to stomach pain. After 8 months of treatment, her pegvaliase dose was increased to 40 mg daily, and blood Phe levels decreased to <100 μmol/L; dietary intact protein was increased. When she stopped birth control, she started sending blood Phe levels to the clinic twice weekly. She became pregnant at month 19 of treatment on 20 mg pegvaliase daily. During her pregnancy, pegvaliase dose and diet adjustments were made according to gestational age and in response to blood Phe level changes (Supplement 1). Her average blood Phe level during pregnancy was 200 μmol/L. She gave birth to a healthy baby at 39 weeks of gestation while on pegvaliase 10 mg every other day (EOD). She struggled to consume adequate amounts of protein, particularly after giving birth, but with the support of a dietitian achieved a consistent adequate intake. She reported fatigue when blood Phe levels were >240 μmol/L, while levels <30 μmol/L resulted in headaches, an upset stomach and hair loss. At the time of the advisory board, her blood Phe level was within the ACMG target range while on pegvaliase 10 mg daily, and she reported feeling happier, being less irritable, sleeping better, and having more energy. She has remained on pegvaliase and subsequently had a second pregnancy with no complications and a healthy full-term baby. Data provided after the advisory board shows that she initially continued pegvaliase 10 mg daily after her second pregnancy, but the dose was later increased to alternating 10 and 20 mg EOD.

3.4. Case 3: Initiation of pegvaliase in an adult with poor social support

This 18-year-old male was unemployed with housing instability, poor social support, and no daily routine. As a child he had poor adherence to diet, challenging social circumstances, and was placed in foster care and then adopted at a young age. Despite having some response to sapropterin, his blood Phe levels remained well above ACMG target range. His motivation for starting pegvaliase was to consume a regular diet and discontinue sapropterin. The clinic was supportive of this despite the challenging social situation.

Prior to starting pegvaliase, his blood Phe level was 1114 μmol/L. Pegvaliase was initiated using the standard induction and titration schedule, with H1 and H2 antihistamines as pre-medications. His first injection was given at home and witnessed by the clinic utilizing telemedicine with the support of the BioMarin Clinical Coordinator. Throughout induction and titration, he reported no AEs despite irregular intake of pre-medications. After 4 months of treatment with both pegvaliase and sapropterin, blood Phe levels remained high (>1000 μmol/L); his pegvaliase dose was increased to 40 mg daily ahead of schedule due to no reported AEs. His blood Phe was still high (>1000 μmol/L) at the time of the advisory board, at 4.4 months of treatment. After the advisory board, at around 10 months of treatment, his dose was increased to 60 mg daily. At 12 months, his blood Phe dropped to 180 μmol/L. His social situation remained challenging, access to healthy food was limited, and he did not always attend (virtual) follow-up visits. At month 13 of treatment, his blood Phe level was undetectable. Medical food protein was discontinued, he was advised to eat a normal diet, and his dose was reduced to 40 mg daily.

3.5. Case 4: Initiation of pegvaliase in an adult with anxiety

This 26-year-old female lived independently in a rural setting over 2 h away from clinic, distant from family, and had a history of anxiety, seasonal allergies, and palpitations when taking cetirizine. She had discontinued diet and was lost to care around age 13. At age 21 she returned to clinic to learn about new treatments and started sapropterin; however, her blood Phe levels remained elevated. Her motivation for starting pegvaliase was to continue consuming a regular diet and take control of her PKU.

Prior to starting pegvaliase, her blood Phe level was 818 μmol/L. She was started on pegvaliase with pre-medications (H1 and H2 antihistamines) and continued on sapropterin. Initiation of pegvaliase was complicated by anxiety and panic attacks requiring treatment with escitalopram and hydroxyzine leading to an interruption of pegvaliase for 2 months. Once anxiety symptoms were controlled, pre-medications were started 1 week prior to restarting pegvaliase, and pegvaliase was reintroduced using the standard induction and titration schedule. Due to continued palpitations and anxiety, H1 antihistamine was discontinued during titration and on-demand hydroxyzine was prescribed. The clinic worked closely with her local primary care provider (PCP) to manage AEs and anxiety. She experienced mild to moderate AEs throughout treatment, some unlikely related to pegvaliase, which resolved spontaneously or were managed by symptomatic treatment (Supplement 1). In month 8 of treatment, blood Phe levels dropped to <30 μmol/L. Sapropterin was discontinued, and dietary intact protein was increased. At month 13, her blood Phe levels remained low, and she reported experiencing fatigue. The pegvaliase dose was reduced to 20 mg 5×/week, with a subsequent increase in blood Phe levels to within the ACMG-recommended target range, resolving the fatigue. At the time of the advisory board, she was on 20 mg 5×/week pegvaliase, consuming an unrestricted diet, taking escitalopram with rare use of hydroxyzine for anxiety, was not taking pre-medications, and was generally doing well. She was diagnosed with attention deficit hyperactivity disorder (ADHD) for which she is taking medication and participates in weekly therapy sessions to address her anxiety and ADHD symptoms. Since the advisory board, she had one additional Phe level >360 μmol/L which was attributed to consistently injecting at the same location, but blood Phe levels returned to ACMG target range with rotation of injection sites.

3.6. Case 5: Initiation of pegvaliase in an adult with depression and an eating disorder

This 33-year-old college-educated female struggled with diet and was unable to achieve adequate Phe control with sapropterin. She received psychiatric care for an unspecified eating disorder but remained anxious about her weight and food; in addition, she was being treated for depression with duloxetine. After a break in PKU care, she returned to clinic with sporadic follow-up but was reluctant to get blood tests as elevated Phe levels increased her depression. Her motivation for starting pegvaliase was to decrease her blood Phe levels and stop weighing and measuring food. The clinic was supportive, believing pegvaliase would allow her to normalize her diet and improve her mental health.

Prior to starting pegvaliase, her blood Phe level was 777 μmol/L. Pegvaliase was initiated using a slightly modified induction and titration schedule (see figure Case 5 in Supplement 1). H1 and H2 antihistamines were used as pre-medications. During titration, blood Phe levels started to decline while on 10 mg daily pegvaliase and sapropterin was discontinued. During the first months of treatment, she experienced a localized reaction and an episode of shortness of breath (Supplement 1). Her busy lifestyle, managing two jobs, resulted in suboptimal adherence to pegvaliase, leading to blood Phe levels consistently >360 μmol/L. Due to her reluctance to administer multiple daily injections, introducing a 40 mg dose was delayed until 22 months of treatment. Blood Phe levels declined to ≤120 μmol/L on 40 mg pegvaliase daily. Intact protein intake was increased, and medical food was discontinued at month 28. She experienced hair thinning that resolved with a vitamin B complex supplement. Her blood Phe levels remained low except for a single level >600 μmol/L due to missing several pegvaliase doses. Hair loss returned at month 38, and she was recommended to further increase intact protein intake to 60 g/day. She struggled to eat this level of protein and was advised to consume protein shakes or bars, which proved to be helpful. After 42 months on treatment, she reported feeling

healthier, having improved interactions with family and friends, and enjoying food offered at family gatherings. Her most recent Phe levels collected after the advisory board were 30–36 μmol/L, and she was advised to decrease dosing to alternating doses of 20 mg 3×/week and 40 mg 4×/week.

3.7. Case 6: Initiation of pegvaliase in an adult with significant executive functioning deficits

This 29-year-old female with a history of poor Phe control, executive functioning deficits, attention problems, anxiety, and depression was motivated to get her blood Phe levels under control to start a family. She had been lost to care for several years and current access was limited due to living more than six hours from clinic. Upon re-establishing care, she was prescribed sapropterin and a Phe-restricted diet but struggled to adhere with blood Phe levels consistently >1000 μmol/L. The clinic revisited treatment options and strongly recommended getting her established on pegvaliase and demonstrating maintenance of Phe levels <360 μmol/L prior to conception.

Prior to starting pegvaliase, her blood Phe level was 1089 μmol/L. Pre-medications (H1 and H2 antihistamines) were started two weeks before initiating pegvaliase. Due to her distance from clinic and executive function deficits, she was offered extensive support including regular check-ins and education sessions via telemedicine visual information sheets including a patient specific "Side Effect Action Plan" detailing different potential side effects at increasing levels of severity and their specific management (Supplementary files 2 and 3); and in-home consultations where she was asked to teach back what she had learned about pegvaliase. All pre- and on-demand medications were prescribed in advance and affixed with detailed, custom labels on their use which were color coded to match her "Side Effect Action Plan." Her first injection was at home under supervision of an HCP; the BioMarin Clinical Coordinator was present at the first 3 injections. A simplified and prolonged titration schedule was followed to minimize the risk of AEs (see figure Case 6 in Supplement 1). Two weeks after initiation, she experienced a rash on both arms and abdomen as well as mild arthralgia, which self-resolved (Supplement 1). She reported no further AEs, but her lack of abstract reasoning made it difficult to assess tolerability, and her executive functioning deficits impacted her ability to manage her titration schedule and to adhere to her prescribed diet and Phe monitoring. The clinic adapted by increasing check-ins to weekly and asking her more specific and concrete questions. The more frequent check-ins were coordinated between the clinic team and BioMarin Clinical Coordinator. Blood Phe levels remained consistently >1000 μmol/L; however, this was after 4 months on a conservative titration schedule, and she had not yet reached optimal dosing. Following the advisory board, she gradually transitioned to a 10 mg daily dose. Although her blood Phe levels continue to be high, she is motivated to reduce them, and the clinic plans to increase her dose to 20 mg daily.

3.8. Case 7: Pegvaliase in an adult with late diagnosis and intellectual disabilities

This 22-year-old female was diagnosed with PKU at 15 years of age (blood Phe >1000 μmol/L) and started on a Phe-restricted diet and medical food. She had intellectual disabilities, was reluctant to speak, and had difficulties with diet due to limitations in social support. After being admitted to the hospital, her blood Phe levels were lowered to <600 μmol/L and it was noted that she became more talkative and engaged. However, after discharge she no longer remained on treatment, and her blood Phe levels increased. Her non-English speaking mother reached out to the clinic for help as her daughter was not able to take care of herself. The clinic was supportive of starting pegvaliase because of the previous positive impact of reducing Phe levels. Several visits were scheduled to discuss the treatment plan and provide education on possible AEs before starting pegvaliase.

Immediately prior to starting pegvaliase, her blood Phe level was 531 μmol/L, although earlier levels had been averaging around 700 μmol/L. Pegvaliase was initiated together with H1 and H2 antihistamines as pre-medications, but a prolonged induction and titration schedule was used due to an AE (knee pain) experienced after 1 month of dosing (see figure Case 7 in Supplement 1). After 6 months of pegvaliase treatment, her blood Phe levels declined to <360 μmol/L on 20 mg daily. Her Phe-restricted diet was gradually liberalized. At the time of the advisory board, blood Phe levels remained in the ACMG-recommended target range on 20 mg pegvaliase daily, she was eating an unrestricted diet with no medical food and had not reported any AEs. She was noted to be more talkative and able to take care of herself (e.g. attending a community college). After the advisory board, her pegvaliase dose was reduced to 20 mg 3×/week while maintaining low blood Phe levels (188 μmol/L after 19 months).

3.9. Case 8: Pegvaliase management in an adult with cancer in addition to psychiatric and social challenges

This 44-year-old female was unable to maintain employment because of cognitive and executive functioning deficits and mental health issues. She lived with her husband, and two children who both have maternal PKU syndrome. She was unresponsive to sapropterin, had poor adherence to a Phe-restricted diet and high blood Phe levels (500–2000 μmol/L) throughout life. She was diagnosed with cervical cancer, and following treatment a joint decision was made with the clinic team to improve PKU care by commencing treatment with pegvaliase.

Prior to starting pegvaliase, her blood Phe level was 2100 μmol/L. Pegvaliase was initiated using the standard induction and titration schedule, with H1 and H2 antihistamines as pre-medications. A daily phone alert was established to remind her on the day of injections. During induction and titration, she experienced minor injection site reactions and arthralgia (Supplement 1). After 7 months of treatment, blood Phe levels dropped to ≤360 μmol/L on pegvaliase 20 mg daily and then to <100 μmol/L. Pegvaliase dose was adjusted in response to episodes of low blood Phe (<30 μmol/L) and hair loss; pre-medications and medical food were discontinued at month 9. The reduced blood Phe levels had a positive impact on her employment status, family relations, and self-awareness. The altered treatment schedule (EOD dosing), and a recurrence of her cancer impacted her adherence to pegvaliase treatment, and blood Phe levels increased to >600 μmol/L. Pegvaliase dose was adjusted to 10 mg daily to improve treatment adherence and resulted in lowering blood Phe levels to within the ACMG target range. Since the advisory board, blood Phe levels remained <360 μmol/L on pegvaliase 10 mg daily, while consuming 80–100 g intact protein.

3.10. Case 9: Initiation of pegvaliase in an adult with social stressors

This 50-year-old male had not been on a Phe-restricted diet since he was 5 years of age and had impaired neurocognitive function, mood swings, depression, and several medical comorbidities, including type 2 diabetes, asthma, hypertension, and obesity. He returned to clinic at 37 years of age with blood Phe levels >1500 μmol/L and struggled to follow a Phe-restricted diet and adhere to sapropterin treatment. He wanted to start pegvaliase to improve his PKU-related symptoms and eliminate current treatments. The clinic supported this decision because of the long-standing history of poor blood Phe control and the financial stress experienced in trying to maintain the low-Phe diet.

Prior to starting pegvaliase, his blood Phe level was 1667 μmol/L, and he was taking sapropterin and large neutral amino acids (LNAA). Pegvaliase was initiated using a prolonged induction and titration schedule, with H1 and H2 antihistamines as pre-medications. In the first months of treatment, he experienced an injection site reaction, rash, and anaphylaxis, all of which resolved with symptomatic treatment (Supplement 1) and a short pegvaliase dose reduction. Blood Phe levels

declined to <30 μmol/L at month 27 on 60 mg daily. Sapropterin was discontinued after 28 months and LNAA after 29 months. Blood Phe control was sustained for around 10 months during which time the pegvaliase dose was gradually reduced to 20 and 40 mg EOD. He reported feeling more focused, less irritable, and less tired and had improved quality of life due to diet normalization. However, family issues and financial problems emerging during the treatment course impacted his adherence to pegvaliase, resulting in blood Phe levels >800 μmol/L from month 39 onwards. At month 46, he and his wife became homeless, and while he made every effort to continue treatment and kept in contact with the clinic, he struggled to maintain blood Phe control and levels increased to >1000 μmol/L. He tried to regain control of his blood Phe level, being aware of the positive impact on his neurocognitive symptoms. At the time of the advisory board, he was prescribed pegvaliase 40 mg daily, although he admitted not consistently adhering to the daily injections. Following the advisory board, he was consistently injecting pegvaliase 40 mg daily, resulting in a blood Phe level of 98 μmol/L after 61 months of treatment.

3.11. Case 10: Initiation of pegvaliase in a late-diagnosed adult with comorbidities and limited social support

This 68-year-old female was diagnosed with PKU at 5 years of age and remained untreated until she was in her 30s. She was unemployed, had two children with maternal PKU syndrome, and lived with her mother who was homebound and has memory lapses. She had many medical comorbidities, including hypothyroidism, hypertension, hypercholesterolemia, migraines, balance issues, arthritis, allergies (e.g., to prednisone, bee venom), asthma, and chest pain. Her treatment consisted of a Phe-restricted diet, medical food, and sapropterin, but adherence was poor and high blood Phe levels affected her daily life. Despite concerns about lacking an adult observer, she was motivated to start pegvaliase to escape dietary restrictions, stop sapropterin and achieve metabolic control. The clinic was hopeful that this would result in her being able to better take care of herself and her family.

Prior to starting pegvaliase, her blood Phe level was 967 μmol/L. The induction and titration schedule was prolonged due to AEs (see figure case 10 in Supplement 1), with H1 and H2 antihistamines used as premedications. After 1 month of treatment with pegvaliase, she reported feeling better and having more energy although her blood Phe level was still >900 μmol/L. Blood Phe levels declined to 360 μmol/L after 3 months, shortly after increasing pegvaliase to 20 mg daily. However, she did not adhere to her prescribed diet and occasionally self-adjusted pegvaliase dosing as she perceived her symptoms to be related to pegvaliase. As a result, blood Phe levels rose to >600 μmol/L and remained high. To manage continuing AEs, she was advised to increase her H1 antihistamine dose to 10 mg 2×/day; she did not follow this recommendation. At month 12, pegvaliase dose was increased to 40 mg daily, but reduced again shortly thereafter to 20 mg daily due to a hypersensitivity reaction, after which she stopped taking pegvaliase for 2 months. During this treatment interruption, she reported sleepiness and feeling disoriented, possibly due to her elevated blood Phe levels. Shortly after resuming pegvaliase 10 mg daily and experiencing swelling of her knees and feet, she discontinued pegvaliase. Since then, her blood Phe levels have been >800 μmol/L for the last 20 months. At the time of the advisory board, her blood Phe level was 1454 μmol/L. She was having several family issues and depression and had no interest in resuming pegvaliase treatment.

3.12. Case 11: Managing pegvaliase in a psychologically and socially complex adult with communication barriers

This 48-year-old female had been on a Phe-restricted diet throughout childhood but was primarily off treatment since adulthood and was unresponsive to sapropterin. She was a single mother to a teenage daughter born with maternal PKU syndrome. Neurocognitive testing revealed executive functioning deficits and psychiatric distress. Additional barriers to care included her financial situation and a busy work schedule, limiting communication with the clinic. Her motivations for starting pegvaliase were diet liberalization and self-reported concerns about her executive function and mood instability.

Prior to starting pegvaliase, her blood Phe level was 1914 μmol/L. Pegvaliase was initiated using the standard induction and titration schedule, with H1 and H2 antihistamines as pre-medications. During induction and titration, she experienced AEs which resolved with symptomatic treatment (Supplement 1). Blood Phe levels declined to <360 μmol/L at 7 months of treatment on pegvaliase 20 mg daily, with most in the normal range (<120 μmol/L) and some dropping <30 μmol/L through 22 months of treatment. Despite limited communication with the clinic due to her work schedule, she maintained adherence to pegvaliase treatment but struggled to achieve her prescribed diet. At 23 months, she reduced her dose to 20 mg EOD in response to low blood Phe levels without informing the treatment team and she remained at this dose for more than a year. At the time of the advisory board, she was receiving pegvaliase 20 mg daily and consuming intact protein 65 g/day. She noted improvements in her neurocognition and mental health and found herself to be a better parent. Communication with the clinic has remained difficult.

3.13. Case 12: Pegvaliase management in an adult with intellectual disability living independently

This 53-year-old male had borderline intellectual functioning (IQ 78, impaired reading and writing), many medical comorbidities (esophageal reflux, arthritis, gout, lumbar spine pain, hyperlipidemia, hypertension), and was a tobacco user. While he reportedly maintained a Phe-restricted diet throughout his childhood, some of his developmental issues were felt to be caused by PKU. He had been off diet since adulthood, was unresponsive to sapropterin, and had been absent from care for the 6 years prior to pegvaliase initiation. His intolerable symptoms associated with high blood Phe levels (memory loss, significant tremor, mood issues, anger, irritability and frustration) motivated him to request pegvaliase. He lived with his wife who also had learning disabilities, and they had a child who was in foster care but with whom they had regular contact. Because of the complexity of his social and medical situation, frequent check-ins (including telemedicine, phone calls and in-person visits) were established to build relationship and trust and ensure good communication with the clinic team.

Prior to starting pegvaliase, his blood Phe level was 1722 μmol/L on an unrestricted diet. Pegvaliase was initiated using the standard induction and titration schedule, with H1 antihistamines as pre-medication. He reported no AEs during induction and titration. In month 2 of treatment, soon after receiving pegvaliase 20 mg daily, his blood Phe level declined to <30 μmol/L. As blood Phe levels remained very low at month 4, the dose was reduced to 20 mg 3×/week. At month 6 of treatment, he experienced leg numbness, which resolved after referral to his PCP (Supplement 1). Since then, his blood Phe levels have remained <360 μmol/L. He expressed relief from his PKU-related symptoms and reported having an improved level of independence and a better relationship with his spouse because he was less irritable. Additionally, he was eating a healthier diet and had become more physically active, resulting in weight loss.

4. Discussion: Key learnings of the case series

Pegvaliase was approved in the US for the treatment of adults with PKU in 2018 and US HCPs managing patients with PKU had more than 5 years of experience with its use in real-world clinical practice at the time the cases were initially presented [12]. A previously published case series, based on observations over the 2 years following approval, described key learnings from the initial experiences of US HCPs [25]. The case series presented here builds on these earlier findings and

highlights approaches to the management of more complex PKU cases, where treatment with pegvaliase might not initially have been considered feasible.

While the cases described in this report are highly diverse, they are representative of the range of complex individual situations that might be seen within a PKU clinic population. Age at initiation of pegvaliase treatment ranged from 18 to 68 years and baseline blood Phe levels ranged from 454 to 2100 μmol/L. Patients presented with a variety of medical and/or mental health comorbidities, some with varying degrees of cognitive disability, executive function deficits, and challenging social or socioeconomic situations. Several individuals would not have met the strict eligibility criteria of the pegvaliase phase 3 clinical trial, which excluded subjects with blood Phe levels <600 μmol/L, those concomitantly using sapropterin or LNAA, and those planning to become pregnant [29], or the initial selection criteria detailed by Longo et al. [23].

4.1. Strategies for the management of complex cases

Key learnings from the presented cases are summarized in Table 2.

4.1.1. Evaluation and management of medical comorbidities

In patients with multiple or complex medical comorbidities, characterization of symptoms of underlying disease prior to treatment initiation is critical to ensure that possible pegvaliase-related AEs can be differentiated from those that are unrelated once treatment is initiated [27]. Additionally, concomitant medications should be evaluated for potential interactions with pegvaliase. If a clinic is uncomfortable with initiating pegvaliase in an individual due to their medical history or concomitant medications, referral to a more experienced clinic may be considered. Following pegvaliase initiation, ongoing monitoring of preexisting and emergent comorbidities is necessary and may require coordination with other HCPs involved in management.

Table 2
Key learnings from the case series prior to and after initiating pegvaliase.

Before initiating pegvaliase
Considerations for starting pegvaliase
• Medical or mental health issues, intellectual disability, executive function deficits, social or socioeconomic complexities, older age, or concomitant medications should not prevent individuals from being offered pegvaliase [25,27]. • Women contemplating pregnancy should be informed about the known risks of maternal PKU syndrome and potential risks of continuing pegvaliase while trying to become pregnant/during pregnancy. Providers can share published case reports to assist individuals with decision-making, but should clarify that pegvaliase has not been formally tested or received regulatory approval for use during pregnancy [28,30]. • Identifying and setting up additional support such as regular telemedicine or local provider visits (PCP) or connecting with a local support organization ahead of starting pegvaliase can be reassuring and help overcome logistical issues.
Education of candidates for pegvaliase treatment
• Individualization of education is especially important for those with more complex backgrounds (e.g. impaired cognitive function or communication difficulties). • In cases of impaired executive or cognitive function, the teach-back method or clear, simple written resources with images, such as side effect and medication action sheets, and emergency protocols can help confirm and support learning. • Set realistic expectations regarding time to efficacy, number of injections, and possibility of modifying the dosing schedule [25].
After initiating pegvaliase
Managing adverse events
• Individualization of dosing is important for those with complex medical and/or psychosocial challenges. The induction and titration phase can be modified in an attempt to reduce the risk of AEs, particularly in case of comorbid conditions that may make attribution of AE's more challenging. A prolonged and/or simplified induction and titration schedule can also help address executive function and psychosocial issues. • Start pre-medication prior to pegvaliase to maximize AE prevention and to distinguish between pre-medication- and pegvaliase-related AEs [27]. • Comorbid conditions should be monitored closely during pegvaliase treatment and may require collaboration with HCPs involved in managing underlying comorbid conditions.
Managing treatment adherence
• A collaborative relationship with the clinic, ongoing education, and supportive relatives or friends can help individuals to remain adherent while utilizing pegvaliase. • Supporting adherence may be addressed by a daily reminder system, telemedicine, in-home support, or a simplified or shortened treatment plan. • In the absence of a dedicated support person, in-home support, social workers, and/or support organizations may ensure access to medications and continued connection with the treatment team. • Increased touch points with individuals and tailoring pegvaliase management to mitigate social determinants of health can allow for successful management even after a treatment interruption.
Adjusting diet and pegvaliase dosing during maintenance
• Additional dietetic support and education on how to transition to a nutritionally balanced and healthy diet may be required, particularly in those with disordered eating or who struggle to eat higher protein foods [31]. • Some individuals may require a reduction in the dose and number of daily injections since the requisite dose for efficacy often decreases over time. A dose reduction should also be considered in case of blood Phe levels <30 μmol/L once intact protein intake is optimized if these low levels are associated with symptoms such as hair loss, headaches, or fatigue [31].
Managing pegvaliase during pregnancy
• Use of pegvaliase during pregnancy has not been studied and requires a benefit/risk discussion and assessment [30]. A surveillance program (https://palomino-study.com) is ongoing and evidence continues to emerge [28]. • If the decision is made to continue pegvaliase during pregnancy, it is preferable that a stable dose and efficacy have been achieved prior to conception. Blood Phe levels should be monitored frequently prior to and during pregnancy to maintain blood Phe within the treatment range [28].

AEs: adverse events; HCPs: healthcare professionals; PCP: primary care provider; Phe: phenylalanine; PKU: phenylketonuria.

4.1.2. Tailored education and support prior to initiation of pegvaliase

Provision of education on expected AEs; use of pre-medications, side-effect medications and emergency medications; proper injection technique; expectations around time to efficacy; and dietary changes are essential for all patients starting pegvaliase treatment [25], but complex cases may require a more tailored approach. For instance, pretreatment education should be specifically tailored to meet the needs of patients with impaired cognitive function or communication difficulties. Patients may benefit from using the teach-back method, which requires individuals to repeat information they receive in their own words [32]. This approach can be used to assess individuals' level of comprehension and to support their self-confidence [33,34]. If there are ongoing concerns regarding level of comprehension, further support can be provided by a dedicated and well-trained observer.

Potential barriers to treatment success should be identified and, wherever possible, addressed proactively prior to treatment initiation. For example, in the case of patients facing social and/or socioeconomic barriers, referral to general or PKU-specific support organizations may provide help to overcome logistical issues by offering transport to the clinic or providing other resources to support the use of telemedicine. Patient anxiety around pegvaliase and the treatment journey should be assessed before starting treatment and addressed if interfering with decision-making or ability to function [27].

4.1.3. Targeted strategies to manage AEs

Patients who are at increased risk of developing AEs, as well as those with cognitive impairment or social challenges that make management of AEs difficult, may benefit from a prolonged or simplified induction/titration phase to potentially reduce the risk/severity of AEs. Prescription of on-demand medications can ensure that the patient is prepared to manage AEs, however careful education is needed to support appropriate utilization. Patients with impaired cognitive or executive function may benefit from visual information aids: for example, an AE "Action Plan" including pictures of common manifestations of side effects and/or simple instructions on steps to address them, along with custom labels for both pre- and on-demand medications. Similar approaches have been used successfully in the management of hypersensitivity/allergic reactions and conditions like chronic asthma [35–37]. Other strategies to support management of AEs include scheduling of follow-up visits to coincide with the time that AEs might be expected and initiation of pre-medications 1–2 weeks prior to starting treatment to ensure that pegvaliase-related AEs can be easily distinguished from those related to the medication.

4.1.4. Strategies to promote adherence to pegvaliase treatment

Follow-up visits were generally planned before the first injection and could be in-person or virtual, depending on the physician's and patient's preference. Social circumstances, cognitive impairment, or executive functioning deficits can impact an individual's ability to adhere to the treatment schedule in the long term but should not preclude treatment. Regular follow-up visits are critical to support adherence and leveraging telemedicine or PCP support may be necessary, particularly where there are logistic challenges, or the patient lives a long distance from the clinic. In cases where there are communication difficulties, a BioMarin Clinical Coordinator (in the US), social workers, and/or support organizations can help to maintain the connection with the treatment team. Additional strategies that may help to promote adherence include use of daily reminder systems (e.g., phone calls or text messages) coordinated by the clinic and simplified dosing schedules. If tolerability allows, pegvaliase maintenance doses may be increased earlier than planned to shorten the time to efficacy, supporting continued patient adherence. All adults on pegvaliase need individualized support and counselling to optimize nutritional status and achieve a healthy diet and relationship with food [31]. Those with disordered eating and greater degree of food neophobia may need additional counselling support to help adjust to a healthy diet and previously forbidden foods [26].

4.1.5. Managing pegvaliase treatment during pregnancy

In one case presented, the patient became pregnant after initiating pegvaliase and reaching efficacy; treatment was maintained, and the patient gave birth to a healthy infant. Although experience of pegvaliase use in pregnancy remains limited, individuals are preferably on a stable dose and have achieved efficacy prior to pregnancy [28]. Frequent Phe monitoring (e.g., twice weekly), is recommended prior to and during pregnancy to maintain blood Phe levels consistently $\leq$360 μmol/L while addressing low blood Phe levels and ensuring adequate nutritional intake. Adjusting pegvaliase dose and/or dietary protein and Phe intake is needed to maintain blood Phe levels within the target range [12].

5. Conclusion

The cases presented demonstrate that with comprehensive assessment and targeted strategies to address potential barriers, pegvaliase treatment can be successful in many adults with PKU and should be considered regardless of prior treatment, age, socioeconomic, cognitive, or executive function challenges, as well as in those with comorbidities or considering pregnancy. Because of their challenges, none of the presented cases would have met the selection criteria for initiating pegvaliase in the clinical trials or those initially specified by Longo et al. in 2019 [23,29]. Nevertheless, the majority achieved blood Phe lowering and improvements in diet while on a stable pegvaliase dose. Persistent treatment and further refinements of the dosing regimen and/or diet resulted in improved blood Phe levels and quality of life of several individuals after the advisory board. Ongoing documentation of clinical experience is crucial for advancing the management of individuals receiving this treatment. For example, another area that deserves further exploration is the impact of cultural differences on interactions between clinics and patients, as these may influence treatment outcomes. Additionally, while reimbursement for clinical services was beyond the scope of this report, it is a critical issue that warrants further consideration, particularly in resource-constrained settings.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgmr.2024.101181.

Funding

The in-person meeting leading up to this manuscript, as well as assistance in development of the current manuscript, were funded by BioMarin Pharmaceutical Inc.

CRediT authorship contribution statement

Erin Cooney: Writing – review & editing, Validation. **Zineb Ammous:** Writing – review & editing, Validation. **Tricia Bender:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Gillian E. Clague:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Marilyn Clifford:** Writing – review & editing, Validation. **Angela Crutcher:** Writing – review & editing, Validation. **Laura Davis-Keppen:** Writing – review & editing, Validation. **Kirsten Havens:** Writing – review & editing, Validation. **Melissa Lah:** Writing – review & editing, Validation. **Stephanie Sacharow:** Writing – review & editing, Validation. **Amarilis Sanchez-Valle:** Writing – review & editing, Validation. **Erika Vucko:** Writing – review & editing, Validation. **Bridget Wardley:** Writing – review & editing, Project administration, Methodology, Conceptualization. **Leah Wessenberg:** Writing – review & editing, Validation. **Hans C. Andersson:** Writing – review & editing, Validation.

Declaration of competing interest

The expert panel was compensated for their participation in the in-person advisory board.

Erin Cooney received compensation from BioMarin for attending an advisory board related to this manuscript.

Zineb Ammous is a consultant for Mirum pharmaceuticals and had attended advisory board meetings for Moderna.

Marilyn Clifford received compensation from BioMarin for attending an advisory board related to this manuscript.

Angela Crutcher received compensation for attending advisory boards, institutional payments, and travel support from BioMarin.

Laura Davis-Keppen received compensation from BioMarin for attending meetings from BioMarin.

Kirsten Havens received support for attending meetings from BioMarin, consulting fees from Zevra Therapeutics, and participated in advisory boards of BioMarin and Zevra Therapeutics.

Melissa Lah received payments for attending advisory boards from BioMarin, PTC Therapeutics and Travere Therapeutics and is a Principal Investigator on clinical trials for BioMarin and PTC Therapeutics.

Stephanie Sacharow has been an investigator and/or advisor for BioMarin, PTC Therapeutics, Jnana Therapeutics, and Synlogic. She has not personally accepted payment from BioMarin advisory activities since 2018.

Amarilis Sanchez-Valle is Principal Investigator for clinical trials of Alexion, BioMarin, Jnana, Homology, Recordati, and Ultragenyx and received payments for lectures and advisory boards from Amgen, Acer, Applied Therapeutics, BioMarin, Jnana, Sanofi and Ultragenyx.

Erika Vucko received consulting fees and payments for lectures, attending meetings and/or advisory boards from BioMarin, PTC Therapeutics, and Horizon.

Leah Wessenberg received payments for participating in advisory boards from BioMarin and Javygtor.

Hans C. Andersson is Co-Principal Investigator in ongoing BioMarin clinical studies.

Tricia Bender, Gillian E. Clague, and Bridget Wardley are employees and stockholders of BioMarin.

Acknowledgments

The authors are grateful to Ismar Healthcare NV who provided medical writing assistance on behalf of BioMarin Pharmaceutical Inc., and to Kristin Lindstrom and Kaleigh Whitehall from BioMarin for reviewing and editing the manuscript.

Data availability

No data was used for the research described in the article.

References

[1] N. Blau, F.J. van Spronsen, H.L. Levy, Phenylketonuria, Lancet 376 (9750) (2010) 1417–1427.
[2] G.M. Enns, R. Koch, V. Brumm, E. Blakely, R. Suter, E. Jurecki, Suboptimal outcomes in patients with PKU treated early with diet alone: revisiting the evidence, Mol. Genet. Metab. 101 (2–3) (2010) 99–109.
[3] C. Romani, L. Palermo, A. MacDonald, E. Limback, S.K. Hall, T. Geberhiwot, The impact of phenylalanine levels on cognitive outcomes in adults with phenylketonuria: effects across tasks and developmental stages, Neuropsychology 31 (3) (2017) 242–254.
[4] K. Ashe, W. Kelso, S. Farrand, J. Panetta, T. Fazio, G. De Jong, et al., Psychiatric and cognitive aspects of phenylketonuria: the limitations of diet and promise of new treatments, Front. Psych. 10 (2019) 561.
[5] J. Vockley, H.C. Andersson, K.M. Antshel, N.E. Braverman, B.K. Burton, D. M. Frazier, et al., Phenylalanine hydroxylase deficiency: diagnosis and management guideline, Genet. Med. 16 (2) (2014) 188–200.
[6] A.M.J. van Wegberg, A. MacDonald, K. Ahring, A. Belanger-Quintana, N. Blau, A. M. Bosch, et al., The complete European guidelines on phenylketonuria: diagnosis and treatment, Orphanet J. Rare Dis. 12 (1) (2017) 162.
[7] F. Nardecchia, F. Manti, F. Chiarotti, C. Carducci, C. Carducci, V. Leuzzi, Neurocognitive and neuroimaging outcome of early treated young adult PKU patients: a longitudinal study, Mol. Genet. Metab. 115 (2–3) (2015) 84–90.
[8] L. Palermo, T. Geberhiwot, A. MacDonald, E. Limback, S.K. Hall, C. Romani, Cognitive outcomes in early-treated adults with phenylketonuria (PKU): a comprehensive picture across domains, Neuropsychology 31 (3) (2017) 255–267.
[9] E.R. Jurecki, S. Cederbaum, J. Kopesky, K. Perry, F. Rohr, A. Sanchez-Valle, et al., Adherence to clinic recommendations among patients with phenylketonuria in the United States, Mol. Genet. Metab. 120 (3) (2017) 190–197.
[10] KUVAN (Sapropterin Dihydrochloride) Tablets, for Oral Use; KUVAN (Sapropterin Dihydrochloride) Powder for Oral Solution; Highlights of Prescribing Information, Accessed 30 July 2024, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/022181s020,205065s006lbl.pdf, 2019.
[11] B.K. Burton, G.E. Clague, C.O. Harding, E. Kucuksayrac, D.G. Levy, K. Lindstrom, et al., Long-term comparative effectiveness of pegvaliase versus medical nutrition therapy with and without sapropterin in adults with phenylketonuria, Mol. Genet. Metab. 141 (1) (2024) 108114.
[12] PALYNZIQ (pegvaliase-pqpz) injection, for subcutaneous use; Highlights of prescribing information, Accessed 18 December 2023, https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761079s005lbl.pdf, 2018.
[13] PALYNZIQ (Pegvaliase-pqpz) Injection, for Subcutaneous Use; Summary of Product Characteristics, Accessed 18 December 2023, https://www.ema.europa.eu/en/documents/product-information/palynziq-epar-product-information_en.pdf, 2019.
[14] Product Monograph PALYNZIQ (Pegvaliase Injection) (Product Monograph Canada), Accessed 18 December 2023, https://www.biomarin.ca/pdf/Palynziq-Product-Monograph-English-IFU.pdf, 2024.
[15] Australian Product Information, PALYNZIQ (Pegvaliase), Accessed 18 December 2023, https://www.biomarin.com/en-au/wp-content/uploads/sites/2/2022/01/palynziq-pegvaliase-pqpz-product-information-australia.pdf, 2024.
[16] Pegvaliase (Genetic Recombinant) Preparation (Package Insert Japan), Accessed 18 December 2023, https://www.bmrn.co.jp/cms/wp-content/themes/biomarin/pdf/physicians/bmrn_palynziq_01.pdf, 2024.
[17] Palynziq® Solution for Injection 2.5 mg MOHW Rare Disease Biologic (Package Leaflet Taiwan), 2024.
[18] J. Thomas, H. Levy, S. Amato, J. Vockley, R. Zori, D. Dimmock, et al., Pegvaliase for the treatment of phenylketonuria: results of a long-term phase 3 clinical trial program (PRISM), Mol. Genet. Metab. 124 (1) (2018) 27–38.
[19] K. Viau, A. Wessel, L. Martell, S. Sacharow, F. Rohr, Nutrition status of adults with phenylketonuria treated with pegvaliase, Mol. Genet. Metab. 133 (4) (2021) 345–351.
[20] C.O. Harding, N. Longo, H. Northrup, S. Sacharow, R. Singh, J.A. Thomas, et al., Pegvaliase for the treatment of phenylketonuria: final results of a long-term phase 3 clinical trial program, Mol. Genet. Metab. Rep. 39 (2024) 1–10.
[21] O. Hausmann, M. Daha, N. Longo, E. Knol, I. Müller, H. Northrup, et al., Pegvaliase: immunological profile and recommendations for the clinical management of hypersensitivity reactions in patients with phenylketonuria treated with this enzyme substitution therapy, Mol. Genet. Metab. 128 (2019) 84–91.
[22] S. Gupta, K. Lau, C.O. Harding, G. Shepherd, R. Boyer, J.P. Atkinson, et al., Association of immune response with efficacy and safety outcomes in adults with phenylketonuria administered pegvaliase in phase 3 clinical trials, EBioMedicine 37 (2018) 366–373.
[23] N. Longo, D. Dimmock, H. Levy, K. Viau, H. Bausell, D.A. Bilder, et al., Evidence- and consensus-based recommendations for the use of pegvaliase in adults with phenylketonuria, Genet. Med. 21 (8) (2019) 1851–1867.
[24] J. Krämer, C. Baerwald, C. Heimbold, C. Kamrath, K.G. Parhofer, A. Reichert, et al., Two years of pegvaliase in Germany: experiences and best practice recommendations, Mol. Genet. Metab. 139 (1) (2023) 107564.
[25] D. Adams, H.C. Andersson, H. Bausell, K. Crivelly, C. Eggerding, M. Lah, et al., Use of pegvaliase in the management of phenylketonuria: case series of early experience in US clinics, Mol. Genet. Metab. Rep. 28 (2021) 100790.
[26] A. Cunningham, F. Rohr, P. Splett, S. Mofidi, H. Bausell, A. Stembridge, et al., Nutrition management of PKU with pegvaliase therapy: update of the web-based PKU nutrition management guideline recommendations, Orphanet J. Rare Dis. 18 (1) (2023) 155.
[27] K.J. Bjoraker, C. Eggerding, E. Ellenberg, S. Hollander, B.M. Holmes, K. Lindstrom, et al., Best practice recommendations for the management of anxiety during the pegvaliase journey, Mol. Genet. Metab. 141 (1) (2024) 107737.
[28] C. Bier, K. Dickey, B. Bibb, A. Crutcher, R. Sponberg, R. Chang, et al., Outcomes in 14 live births resulting from Pegvaliase-treated pregnancies in PKU-affected females, Mol. Genet. Metab. 141 (3) (2024) 108152.
[29] C.O. Harding, R.S. Amato, M. Stuy, N. Longo, B.K. Burton, J. Posner, et al., Pegvaliase for the treatment of phenylketonuria: a pivotal, double-blind randomized discontinuation phase 3 clinical trial, Mol. Genet. Metab. 124 (2018) 20–26.

[30] F. Rohr, A. Wessel, C.O. Harding, S.E. Waisbren, K. Viau, A. Kritzer, Reinstitution of pegvaliase therapy during lactation, Mol. Genet. Metab. Rep. 33 (2022) 100938.
[31] F. Rohr, B. Burton, A. Dee, C.O. Harding, J. Lilienstein, K. Lindstrom, et al., Evaluating change in diet with pegvaliase treatment in adults with phenylketonuria: analysis of phase 3 clinical trial data, Mol. Genet. Metab. 141 (3) (2024) 108122.
[32] Health Literacy Universal Precautions Toolkit, Use the Teach-Back Method: Tool 5, 3rd edition, 2024. Accessed 8 March 2024, https://www.ahrq.gov/health-literacy/improve/precautions/tool5.html.
[33] P.H. Yen, A.R. Leasure, Use and effectiveness of the teach-back method in patient education and health outcomes, Fed. Pract. 36 (6) (2019) 284–289.
[34] J.C. Rocha, H. Bausell, A. Belanger-Quintana, L. Bernstein, H. Gokmen-Ozel, A. Jung, et al., Development of a practical dietitian road map for the nutritional management of phenylketonuria (PKU) patients on pegvaliase, Mol. Genet. Metab. Rep. 28 (2021) 100771.
[35] American Academy of Pediatrics, Allergy and Anaphylaxis Emergency Plan, Accessed 25 May 2025, https://downloads.aap.org/HC/AAP_Allergy_and_Anaphylaxis_Emergency_Plan.pdf, 2024.
[36] Anaphylaxis UK, Adult Allergy Action Plan, Accessed 25 May 2024, https://www.anaphylaxis.org.uk/wp-content/uploads/2022/11/ADULT-ALLERGY-ACTION-PLAN.pdf, 2024.
[37] NIH National Heart, Lung, and Blood Institute, UK, Asthma Action Plan, Accessed 25 may 2024, https://www.nhlbi.nih.gov/resources/asthma-action-plan-2020, 2024.