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Two years of pegvaliase in Germany: Experiences and best practice recommendations

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ABSTRACT

Background: In 2019, pegvaliase was approved in Europe for the treatment of phenylketonuria (PKU) in patients aged 16 years and older with blood phenylalanine (Phe) concentrations above 600 μmol/L despite prior management with available treatment options. Since its European approval, German metabolic centres have gained valuable experience, which may be of benefit to other treatment centres managing patients on pegvaliase.
Methods: After a virtual meeting that was attended by nine German physicians, three German dietitians and one American physician, a follow-up discussion was held via an online platform to develop a set of recommendations on the use of pegvaliase in Germany. Eight German physicians contributed to the follow-up discussion and subsequent consensus voting, using a modified Delphi technique. The recommendations were supported by literature and retrospectively collected patient data.
Results: Consensus (≥75% agreement) was achieved on 25 recommendations, covering seven topics deemed relevant by the expert panel when considering pegvaliase an option for the treatment of patients with PKU. In addition to the recommendations, a retrospective chart review was conducted in seven of the centres and included 71 patients who initiated treatment with pegvaliase. Twenty-seven patients had been treated for at least 24 months and 23 (85.2%) had achieved blood Phe ≤600 μmol/L with some degree of diet normalisation. Of these patients, 14 had physiological blood Phe on a normalised diet.
Conclusion: The practical consensus recommendations provide guidance on the different steps along the pegvaliase journey from clinical site requirements to treatment goals and outcomes. The recommendations are intended to support less experienced European metabolic centres with the implementation of pegvaliase, emphasising that a core treatment team consisting of at least a dietitian and metabolic physician is sufficient to initiate pegvaliase and support patients during their treatment journey.

1. Introduction

As of May 2019, the European Medicines Agency (EMA) approved pegvaliase (Palynziq®) for the treatment of patients with phenylketonuria (PKU), an autosomal recessive inborn error of phenylalanine (Phe) metabolism [1,2]. Pegvaliase acts as a substitution therapy for the deficient phenylalanine hydroxylase (PAH) enzyme, converting blood Phe into trans-cinnamic acid and ammonia via the bacterially derived phenylalanine ammonia lyase (PAL) enzyme [3]. In Europe, patients aged

Abbreviations: ASHR, acute systemic hypersensitivity reaction; hypoPhe, hypophenylalaninaemia; EMA, European Medicines Agency; NSAIDs, non-steroidal anti-inflammatory drugs; PAH, phenylalanine hydroxylase; PAL, phenylalanine ammonia lyase; Phe, phenylalanine; PKU, phenylketonuria; PKU-QOL, phenylketonuria quality of life questionnaire; QoL, quality of life.

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16 years and older are eligible for pegvaliase provided they have blood Phe concentrations above the upper European guideline-recommended target (>600 μmol/L) despite prior management with available treatment options [1]. Currently, these alternative treatment options include medical nutrition therapy with or without the addition of sapropterin dihydrochloride (Kuvan®) [2]. Patients on medical nutrition therapy, especially those with a severe disease phenotype, should avoid most natural protein sources and compensate for the restriction of protein through supplementation with Phe-free synthetic amino acids or other medical foods, such as glycomacropeptide [4]. Following such a restrictive diet throughout life can be extremely difficult for patients, reflected through the deteriorating adherence to medical nutrition therapy from late childhood onwards [5–8]. For a subset of patients with residual PAH activity and a milder disease phenotype, Phe tolerance can be increased with sapropterin dihydrochloride, alleviating some of the burden of medical nutrition therapy [9–12]. Nevertheless, the reality remains that >50% of adult patients with PKU do not achieve lifelong metabolic control, having blood Phe concentrations that are consistently above 600 μmol/L [13]. These patients are at risk for developing a wide range of PKU-associated comorbidities, including deficits in selective domains of neurocognitive functioning (e.g. executive function, processing speed, motor skills and visuospatial skills) which remain sensitive to elevations in blood Phe in adult life [14–19]. Because of the negative association between blood Phe and neurocognitive, among other, PKU-related symptoms, guidelines recommend lifelong treatment to ensure continuous metabolic control [2,20]. However, many adult patients on medical nutrition therapy are not able to accomplish this treatment goal [5,6,8]. For those with poor metabolic control, pegvaliase can be considered an option, allowing most patients to achieve substantial blood Phe reduction in the long term, while increasing the intake of natural protein [3,21,22]. Although pegvaliase may reduce the dietary burden, treatment start can be challenging due to the titration schedule and the relatively high rate of adverse events during the first months of treatment. To help overcome these challenges, previous recommendations for the use of pegvaliase were published upon which clinical experience started to evolve [23–25]. After its approval in Europe, many German metabolic centres began offering pegvaliase to patients with PKU. Based on this two-year experience, pegvaliase best practice recommendations were developed, aiming to further support its implementation within metabolic centres in Germany and other European countries where pegvaliase is available.

2. Methodology

In October 2021, a virtual meeting was attended by nine German physicians and three German dietitians to gain insight into the two-year experience with pegvaliase in German treatment centres. In addition, one physician from the United States (US) with pegvaliase experience attended the meeting. After the virtual meeting, eight German physicians contributed to the follow-up discussions on an online platform to further inform the development of recommendations for the use of pegvaliase in Germany. By using a modified Delphi approach, the recommendations were discussed and rated with the aim of consensus generation. During the first round, participating experts anonymously rated each recommendation on a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree and 5 = strongly agree) along with providing feedback if not agreeing. Consensus was reached when at least 75% of the experts strongly agreed or agreed with a given recommendation (i.e. at least six experts needed to agree with each statement). Recommendations without agreement were revised based on the gathered feedback and anonymously revoted on in two consecutive rounds. The recommendations were supported by literature and through the retrospective collection of data on patients who initiated pegvaliase in seven of the participating German treatment centres prior to July 2022.

Table 1
Characteristics of pegvaliase-treated patients in seven German treatment centres.

	Centre 1	Centre 2	Centre 3	Centre 4	Centre 5	Centre 6	Centre 7
Number of patients, N	3	5	6	6	12	12	27
Male, %	67	60	84	50	58	80	41
Patients off diet, %	100	40	83	100	100	50	52
Mean age at treatment initiation, years (SD; range)	23 (5.7; 17–28)	39 (11.6; 26–51)	21 (9.7; 16–41)	35 (8.5; 17–42)	31 (8.5; 19–44)	27 (11.4; 16–50)	32 (11.0; 16–57)
Mean treatment duration, weeks (SD, range)	48 (64.7; 4–122)	70 (46.9; 17–139)	85 (49.3; 1–135)	36 (20.5; 8–62	72 (41.1; 1–112)	55 (54; 3–136)	106 (46.0; 15–161)
Mean blood Phe at treatment initiation, μmol/L (SD, range)	1261 (339.9; 1054–1653)	999 (411.7; 611–1671)	1097 (221.8 868–1457)	875 (224.8; 649–1382)	1403 (338.0; 860–2010)	1190 (370.0; 730–1608)	1165 (279.0; 647–1855)
Treatment discontinuation, N	1	0	0	0	2	1	6

3. Results

3.1. Two-year experience with pegvaliase in Germany

Table 1 provides a retrospective overview of patients who initiated pegvaliase in seven German treatment centres prior to July 2022. In total, 71 patients on pegvaliase, both male and female, were included in this review out of whom 10 patients (14.1%) discontinued treatment for reasons outlined in the sections below. Treatment was initiated as early as the age of 16 years and as late as the age of 57 years. Some patients started pegvaliase only recently, while others had been on pegvaliase for more than two years. Following the European product label [1], blood Phe concentrations at treatment initiation were above 600 μmol/L for all patients, mostly due to poor adherence to dietary management. In addition, two patients with an inadequate response to sapropterin were switched to pegvaliase. In these patients, sapropterin was discontinued for 4 weeks before initiating pegvaliase, though reinitiated in one patient to prevent the patient's neurocognitive performance from deteriorating, which occurred shortly after its discontinuation. Additional treatment outcomes are presented in Table 2.

3.2. Best practice recommendations

3.2.1. Clinical site requirements

Statement #1 In small treatment centres, pegvaliase can be implemented by the core multidisciplinary team consisting of at least a metabolic physician and dietitian, although, ideally, a field nurse and psychologist should be included in the care of patients receiving pegvaliase	**Consensus %** 88%
Statement #2 A patient support programme, offering practical tools, training and information through trained and certified field nurses, helps to support patients with the long-term course of PKU therapies, including pegvaliase	**Consensus %** 100%
Statement #3 For patients on pegvaliase, the field nurse can act as the first-line contact, providing rapid in-home support with the management of mild adverse events, prescription requests, communication of blood Phe test results, implementation of dose/dietary changes and potential difficulties with pegvaliase administration	**Consensus %** 88%
Statement #4 If available, an emergency phone or email address at the pegvaliase treatment centre can help with the management of adverse events, but in case of ASHRs, patients should defer to the emergency department of the nearest hospital	**Consensus %** 100%

Based on the German experience, implementation of pegvaliase should not be limited to large metabolic centres. In one of the smaller German treatment centres, a metabolic physician and dietitian are the sole members of the multidisciplinary team, although, ideally, at least two metabolic physicians should be present to guarantee continuous care. The main responsibilities of the metabolic physician include performing regular clinical examinations, training of patients and observers, determining and adjusting pegvaliase dosing, monitoring of adverse events, prescribing concomitant medications and evaluating blood Phe test results. Because relaxation of the Phe-restricted diet is one of the pegvaliase treatment goals [3,21,26,27], dietetic counselling is needed throughout the treatment course to gradually increase the intake of natural protein and reduce the intake of protein substitutes if consumed at treatment start. The dietitian can also be the first-line contact, responsible for communicating blood Phe test results.

Although only available in two of the treatment centres taking part in this panel, patients on pegvaliase could benefit from psychological support to assess potential changes in neurocognitive and neuropsychological functioning and to support patients with any treatment-related psychological issues, such as difficulty with subcutaneous injections, occurrence of adverse events and impact of protein adjustments. In addition, one German treatment centre recommends consulting an allergist for the management of hypersensitivity reactions.

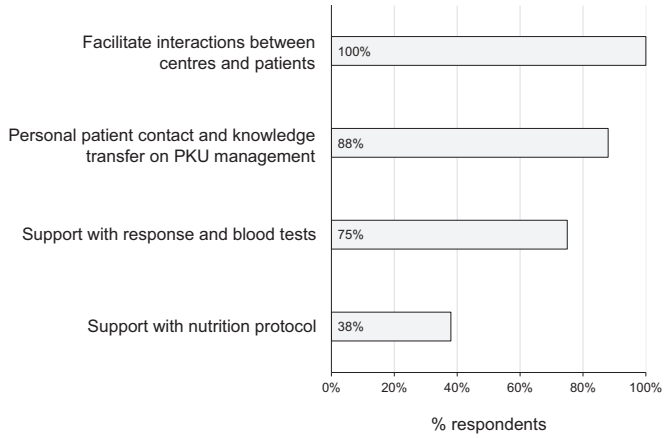

Fig. 1. General responsibilities of the field nurse. Percentages represent the responsibilities of the field nurse in eight German metabolic centres.

In Germany, all centres have access to a patient support programme through which a field nurse provides in-home support to all patients with PKU, irrespective of age or treatment regimen. In general, the patient support programme supplements the existing interactions between the patient and the treatment teams involved, counselling patients with PKU to adhere to treatment and maintain metabolic control. The responsibilities of the field nurses differ between German treatment centres, depending on the metabolic centres' needs (Fig. 1).

The patient support programme has greatly facilitated the implementation of pegvaliase in Germany. All, except one German treatment centre, consider the field nurse essential as short-notice contact for all questions related to pegvaliase. Within most German treatment centres, the field nurse provides first-line support during all treatment phases with the management of mild adverse events, rapidly communicating these with the metabolic clinic. Other tasks include coordination of prescription requests (pegvaliase and other medications), communication of blood Phe test results, consultation with the patient in case of dose changes and evaluation of injection hygiene (e.g. regular rotation of the injection site).

Besides the field nurse, a 24 h/7 days emergency phone or email address has proven to be helpful for the immediate reporting and management of adverse events. However, for severe adverse events, including acute systemic hypersensitivity reactions (ASHRs), patients should always defer to the nearest hospital. To help emergency physicians identify the possible trigger, it is recommended that patients carry an allergy card.

3.2.2. Patient selection

Statement #5 Besides age and blood Phe concentration, the availability of a reliable observer, burden of disease, prevention of PKU-associated comorbidities, living situation and motivation to start treatment should be considered when selecting patients for pegvaliase	**Consensus %** 100%
Statement #6 If patients are motivated to comply with the frequency of assessments and in-clinic visits, they should not be excluded from pegvaliase even though adherence to previous treatment options was suboptimal	**Consensus %** 100%
Statement #7 Patients with neurocognitive impairment, including those with a late diagnosis, can still benefit from pegvaliase, provided that patients	**Consensus %** 75%

(continued on next page)

have a reliable observer and the severity of symptoms do not hinder the patients' ability to follow the treatment recommendations, including the monitoring and management of adverse events. In addition, the metabolic team should, together with other healthcare providers, evaluate the patients' ability to consent with pegvaliase treatment	
Statement #8	**Consensus %**
From adolescence onwards (≥16 years of age), pegvaliase should be considered an option for all eligible patients, focussing on prevention rather than treatment of PKU-associated comorbidities, which often occur after childhood due to deteriorating adherence to dietary management	75%

In Europe, patients aged 16 years and older with inadequate blood Phe control (>600 μmol/L) despite prior management with available treatment options are eligible for pegvaliase [1]. As a precaution for the potential of ASHRs, each self-injection should be supervised by an observer for 60 min during at least the first 6 months of treatment [1]. However, finding a reliable observer has proven to be difficult, especially for older adult patients who are living alone. Besides these mandatory requirements, upcoming life events should be considered, preferring patients with a stable living situation at least during the first year of treatment. In addition to the practical considerations, success of treatment highly depends on the patient's intrinsic motivation to start treatment and overcome obstacles that may present along the treatment course, such as daily injections, adverse events and variable time to efficacy. The motivation to start pegvaliase often ties together with the burden experienced by previous treatments and willingness to prevent any PKU-associated comorbidities, such as deterioration of neurocognitive functioning. As a result, preferred patients are those experiencing a significant diet burden and/or deficits in daily life activities (e.g. work, education, relationship) due to inadequate metabolic control. Paradoxically, patients with a history of suboptimal adherence to previous treatment options often have the highest motivation to start pegvaliase. For those patients, the burden of daily injections and potential for adverse events seem easier to accept than following a severely restricted diet for life, as has been confirmed by a survey conducted with patients living in the US [28]. However, it should be considered that patients not adhering to previous treatments can in some cases be less compliant with in-clinic visits and assessments, requiring more active follow-up.

Because studies have shown that PKU-related symptoms can at least be partially reversed upon blood Phe reduction [29–32], the majority of the expert panel does not exclude patients with neurocognitive impairment from pegvaliase. For these patients, adhering to the complex dietary regimen can be particularly difficult, though it should be acknowledged that implementation of pegvaliase is not free of burden and poses new challenges, especially during the first 6 months of treatment. Nevertheless, most of these challenges can be overcome by support from the metabolic team, field nurse and observer. When considering pegvaliase for patients with neurocognitive impairment, the severity of symptoms should, however, not preclude patients of providing consent and understanding the treatment recommendations.

In Europe, pegvaliase can be initiated as early as adolescence, a period characterised by declining adherence to the dietary restrictions and resulting increases in blood Phe concentrations [5,8]. As of July 2022, eight adolescent patients (aged between 16 and 17 years) were being treated with pegvaliase in four of the German treatment centres included in this panel. By controlling blood Phe concentrations before they start to increase, pegvaliase may prevent rather than treat symptoms of neurodegeneration and neurocognitive impairment that can occur due to the deterioration of metabolic control after childhood [33]. Adolescent patients who already lost metabolic control in childhood should also be considered candidates for pegvaliase to both treat and halt progressive worsening of PKU-related symptoms if present.

3.2.3. Patient information and education

Statement #9	**Consensus %**
Initiation of pegvaliase should be preceded by a minimum of two extensive consultations. During the first visit, patients and their caregiver(s) or relative(s) should be provided with all basic information, preferably followed by an in-home consultation with the field nurse. The second visit is intended to provide further information and training. If patients are still considered eligible and willing to start, pegvaliase can be administered during the second or third in-clinic visit upon which the patient must remain in observation for approximately 1-4 hours based on each centres' protocol/-preference	88%
Statement #10	**Consensus %**
After treatment initiation, education should be provided on an individual basis during every in-clinic and in-home visit	100%

Prior to treatment start, patients and their relatives or caregivers should be well-informed about pegvaliase during a 30–60 min session, providing all basic information and setting realistic expectations on the application of the subcutaneous injections, importance of adherence, frequency and type of adverse events, need for a trained observer, time-to-efficacy, variability in treatment response and willingness to maintain a stable diet until efficacy is reached. If interested to start pegvaliase, patients should be given information in a written format either immediately after the first visit or later on by the field nurse at the home of the patient. The field nurse should repeat the implications of initiating pegvaliase, especially to patients who are not well-controlled as they may find it difficult to understand the provided information if experiencing deficits in neurocognitive functioning. One German treatment centre also offers patients the possibility to share experiences with other patients on pegvaliase prior to treatment start. The second consultation is intended to answer questions concerning treatment, adverse events and emergency medication and bring the patient in contact with the field nurse if available and an in-home visit has not taken place. During this consultation or an additional one, further information is provided, the use of the syringe is practiced, the titration plan is explained and the observer(s) is (are) trained. If the patient is still considered a good candidate, the first injection is administered in-clinic followed by an observation period of 1-4 hours. Subsequent self-injections can be performed at home, although one German treatment centre requires patients to perform the first three injections in the hospital. After treatment start, education should be continued on an individual basis at every visit and, preferably, during in-home consultations with the field nurse, answering all remaining questions and considering that an open and honest communication with the patient is vital for successful treatment.

3.2.4. Baseline assessments and treatment initiation

Statement #11	**Consensus %**
Prior to pegvaliase initiation, a physical examination and routine blood chemistry should be performed. Other baseline assessments (e.g. QoL and neurocognitive testing) are optional but will help to evaluate long-term treatment outcomes	100%
Statement #12	**Consensus %**
During the induction/titration phase, blood Phe should be assessed at least monthly, while patients should attend in-clinic visits every month or 2 months. The frequency of blood Phe testing can be increased to weekly or biweekly, depending on the patient's need (e.g. hypoPhe, adverse events) and facilities of the clinic	88%

Besides physical examination and routine blood chemistry, no other specific examinations are needed prior to the initiation of pegvaliase. In addition to these, four of the German treatment centres participating in this panel evaluate the patients' quality of life (QoL) (e.g. Inventar zur Erfassung der Lebensqualität or PKU-QOL), two centres conduct neurocognitive testing and one centre performs magnetic resonance imaging

before starting pegvaliase (and one year after reaching efficacy). Although additional baseline assessments will help to evaluate treatment outcomes, they should not exclude patients from pegvaliase if unavailable.

During the induction and titration phase, blood Phe should be assessed at least monthly, although most German treatment centres prefer to monitor blood Phe every two weeks or even (bi)weekly using dried blood spots. If needed, daily blood Phe measurements can also be considered. Generally, the frequency of assessments will have to be determined on an individual basis depending on the patient's needs. Patients should, furthermore, be willing to attend in-clinic appointments every month or two months, though more regular in-home support can be provided by the field nurse at the patient's request. For smaller treatment centres with limited staff, the frequency of in-clinic visits can be reduced to every three to six months provided that patients receive regular short-term feedback on two weekly or (bi)weekly blood Phe test results. Throughout the induction and titration phase, the dietitian should regularly monitor the intake of natural and synthetic protein via diet diaries, ensuring patients follow the centre's nutrition protocol and maintain a stable diet until efficacy is reached. A panel of European dietitians previously developed a dietitian road map, providing further guidance on the nutritional management of patients with PKU on pegvaliase [25].

3.2.5. Management of adverse events

Statement #13 During the induction and titration, daily intake of premedication (H1-receptor antagonists with or without H2-receptor antagonists, antipyretics or NSAIDs) is recommended to reduce the risk of hypersensitivity reactions	**Consensus %** 88%
Statement #14 Injection site reactions (including erythema), arthralgia, headache and fever are common adverse events during the induction and titration phase. In some patients, injection site reactions and arthralgia persist in the maintenance phase, requiring long-term use of pre- and on-demand medication, often for 6–12 months or longer, until all adverse events resolve and pegvaliase dosing is stable	**Consensus %** 75%
Statement #15 For managing injection site reactions (including erythema), it is recommended to increase the dose of antihistaminic medication and/or NSAIDs, apply cooling, administer topical antihistaminic medications and/or glucocorticoids and if needed prescribe short-term use of oral glucocorticoids	**Consensus %** 100%
Statement #16 For managing arthralgia, it is recommended to prescribe NSAIDs and short-term use of oral glucocorticoids	**Consensus %** 100%
Statement #17 To manage adverse events that frequently occur during the first 2–-3 months of treatment, the titration of pegvaliase can be prolonged by administering, for an extended period, the dose during which no adverse events occurred, avoiding use of oral glucocorticoids	**Consensus %** 100%
Statement #18 If adverse events persist in the maintenance phase, it is recommended to evaluate compliance to the prescribed pre- and on-demand medications and assess the rotation of the injection site	**Consensus %** 100%
Statement #19 Because ASHRs can occur in the maintenance phase, presence of an observer and carrying an epinephrine autoinjector remain recommended, especially for patients who continue to experience severe adverse events after the first 6 months of treatment	**Consensus %** 88%

In agreement with previous guidance, antihistamines and antipyretics are recommended premedications to reduce the risk of hypersensitivity reactions [23,24]. Six of the participating German treatment centres prescribe an H1-receptor antagonist (cetirizine 10 mg/day or loratadine 10 mg/day), while two centres prescribe both an H1- and H2-receptor antagonist (loratadine 10 mg/day or fexofenadine 120 mg/day together with famotidine 20–40 mg/day). According to the expert panel, antihistamines should be taken daily throughout the induction and titration phase, including on days without pegvaliase administration. Three of the participating German treatment centres also routinely prescribe antipyretics and nonsteroidal anti-inflammatory drugs (NSAIDs) (paracetamol 500 mg/day and ibuprofen 600 mg/day) as premedication. After the induction and titration phase, the use of premedication should be re-evaluated. For patients who continue to experience adverse events during the maintenance phase, premedication remains recommended but also compliance to pre- and on-demand medications and rotation of the injection site should be evaluated.

Despite these risk mitigation strategies, hypersensitivity reactions can still occur along the treatment course [3,24]. Based on the clinical trial and German experience, local injection site reactions and arthralgia are the most frequently reported hypersensitivity reactions [3,24]. For the management of injection site reactions (including erythema), the dose of oral antihistamines and/or NSAIDs (e.g. ibuprofen) can be increased or an additional oral antihistamine can be added. Cooling and application of topical antihistamines may further help to alleviate discomfort. In case of arthralgia, NSAIDs (e.g. ibuprofen 400 mg; 2–3 times/day) are recommended. If these on-demand medications fail to resolve the hypersensitivity reactions, short-term use of oral glucocorticoids (e.g. prednisone 10–40 mg for 2 to 5 days or prednisolone 25 mg for 3 days) can be considered, though extending the period on the last well-tolerated dose is often the preferred alternative.

Out of the 71 patients initiating pegvaliase in seven of the German treatment centres participating in this panel, 5.6% (4/71) experienced an ASHR, a percentage similar to the one reported in the phase 2 and phase 3 clinical trials (4.4% [21/481]) [24]. For three of these patients, the ASHR occurred during the first 14 weeks of treatment leading to discontinuation of pegvaliase in two patients. The other patient was admitted to the emergency department for a suspected ASHR because of experiencing shortness of breath a few minutes after injection of a daily 20 mg dose. In the hospital, pegvaliase was re-introduced under close observation at the same day and dose without any further adverse events. It should be noted that patients on pegvaliase can be prone to experience symptoms of anxiety or even panic attacks that can be hard to distinguish from ASHRs; however, when in doubt, risk mitigation strategies should be followed [34]. Another patient experienced severe adverse events (generalised rash, swelling of lips and hands, thoracic pain and tachycardia) throughout the maintenance phase and discontinued pegvaliase following an ASHR with hypotonia, tachycardia and dyspnoea at week 43 of treatment. Hence, the recommendation to continue to carry the epinephrine autoinjector and extend the presence of the observer beyond the first 6 months of treatment, especially for patients with persisting adverse events.

3.2.6. Treatment maintenance and follow-up

Statement #20 During the maintenance phase, blood Phe should be assessed monthly. In addition, the patient should attend quarterly in-clinic appointments, although the frequency of in-clinic visits can be reduced depending on the patient's need and through support of the field nurse	**Consensus %** 88%
Statement #21 In case of hypoPhe, protein intake should be increased. For patients on a normalised diet or for those not able to increase the intake of natural protein, the pegvaliase dose should be adjusted, preferring daily dose reductions over intermittent injections to maintain tolerability and prevent increases in blood Phe concentrations	**Consensus %** 75%
Statement #22 Pegvaliase administration should be continued during travelling, although it can be considered to temporarily interrupt dosing in case of severe adverse events and resume the same dose upon returning	**Consensus %** 75%

During the maintenance phase, monthly assessment of blood Phe should be continued but the frequency of in-clinics visits can be reduced to quarterly or half-yearly, depending on the patient's need and clinic's capacity. If needed, the field nurse can provide more regular in-home support. Regarding dietary management, the German treatment centres

follow the previously published European recommendations [25]. Briefly, patients should maintain a consistent diet during the induction and titration to determine treatment response. After a drop in blood Phe, protein intake can be gradually adjusted, aiming for diet normalisation.

In total, 22 patients (31.0%) experienced episodes of hypophenylalaninaemia (hypoPhe). For patients not yet consuming a normalised diet, natural protein intake should be increased first under dietary counselling. For patients on a normalised diet or for those not able to increase the intake of natural protein, the pegvaliase dose should be reduced. Most experts prefer to lower the dose of daily injections to prevent sudden increases in blood Phe and maintain the patient's tolerability, avoiding adverse events from dose interruption. In some cases, reducing the dose on only one day may be sufficient to raise blood Phe concentrations above 30 μmol/L, illustrating that subtle dose adjustments can be adequate to manage hypoPhe. However, one expert favours alternating daily injections with higher doses. As patients may start to experience injection fatigue, reducing the number of weekly dose injections can be preferred, provided that blood Phe remains controlled and adverse events do not recur.

For patients on pegvaliase who plan to travel, the dosing schedule should, generally, be maintained. However, when severe adverse events are experienced, a temporary dose interruption or reduction can be considered. Following this recommendation, the induction was interrupted in one patient, though, it is preferred that patients limit travelling during the induction and titration phase.

3.2.7. Treatment goals and outcomes

Statement #23	**Consensus %**
The ultimate goal of pegvaliase is to achieve lifelong blood Phe concentrations within the physiological range (31–120 μmol/L) while avoiding prolonged periods of hypoPhe. In addition, patients should, ideally, be able to consume a normal amount of natural protein without the need for supplementation with protein substitutes	75%
Statement #24	**Consensus %**
An acceptable treatment outcome to continue pegvaliase is achievement of blood Phe concentrations below the European guideline-recommended target range (<600 μmol/L) with a significant increase in the intake of natural protein for patients on a Phe-restricted diet	100%
Statement #25	**Consensus %**
Patients should be treated for at least 18 months to determine treatment response, considering dosing, injection hygiene (fatigue and rotation) and the intake of natural protein in case of limited efficacy	75%

Overall, the experts agreed that pegvaliase treatment should aim for blood Phe concentrations within the physiological range along with diet normalisation. Because aiming for physiological blood Phe increases the risk of hypoPhe, two experts recommend targeting slightly higher blood Phe concentrations with a lower limit of 60 μmol/L. For patients not achieving the ultimate treatment goal, pegvaliase can be continued if blood Phe concentrations are below the European guideline-recommended target range (<600 μmol/L), though the increase in natural protein intake should be significant to ensure a positive benefit-risk ratio. It should furthermore be noted that three experts were not convinced about the benefits that can be gained with physiological blood Phe due to the lack of published evidence and, therefore, aim for higher blood Phe concentrations between 240 and 600 μmol/L.

Generally, pegvaliase must be administered for 12–18 months to evaluate the treatment response, although in some patients it can take up to 24 months to reach full efficacy. Dosing should be personalised with some patients requiring dose escalation up to the maximum dose (60 mg/daily). In case of lack of efficacy, it is recommended to evaluate compliance to the self-injections and rotation of the injection site. In addition, time-to-efficacy can be prolonged if patients prematurely normalise their diet.

Out of the 27 patients who were treated for >24 months, 23 (85.2%) reached efficacy by 24 months defined as blood Phe ≤600 μmol/L with some degree of diet normalisation at pegvaliase doses ranging between 3 doses of 10 mg/week to 60 mg daily. In addition, 14 of these patients had physiological blood Phe on a normalised diet. Pegvaliase was discontinued in only one of the patients who did not achieve efficacy by 24 months of treatment. The other three patients showed some treatment benefit that justified treatment continuation or did not yet achieve the maximum pegvaliase dose. Of the additional 44 patients who initiated pegvaliase, nine discontinued treatment. One patient was unwilling to increase the pegvaliase dose after the first 6 months of treatment despite experiencing no relevant adverse events. Three other patients discontinued pegvaliase due to (i) fear of potential adverse events, (ii) challenges with organisation, neurocognition and diet stability and (iii) pregnancy planning. The remaining five treatment discontinuations were due to ASHRs or other adverse events that affected work and private life.

Based on the German experience, the benefits of pegvaliase were believed to be related to the ability of patients to achieve metabolic control. Patients reported that they felt more energetic, had fewer mood swings, experienced reduced irritability, aggression, depression and anxiety, noticed improvements in neurocognition (e.g. concentration and processing speed), had the ability for professional reorientation and experienced fewer headaches and sleep disturbances. In addition, patients reported feeling happier with diet normalisation and noted their QoL was improved by reducing the diet-related burden and costs. Improvements were also observed in patients with neurocognitive deficits, although experience remains limited. So far, the reported benefits remain based on anecdotal experiences with a need for future studies to evaluate long-term patient-related outcomes.

4. Discussion

Since the approval of pegvaliase, several recommendations on its use have been published [23–25]. These recommendations are mainly

Table 2
Patient outcomes after 24 months of pegvaliase treatment.

	Centre 1	Centre 2	Centre 3	Centre 5	Centre 6	Centre 7
Number of patients being treated for ≥ 24 months, N	1	2	3	3	3	15
Median daily pegvaliase dose at 24 months, mg (range)	60	30 (20–40)	20 (4–40)	47 (20–60)	60 (20–60)	40 (10–60)
Number of patients with blood Phe < 600 μmol/L with some degree of diet normalisation at 24 months, N	1	2	3	2	2	13
Median daily pegvaliase dose, mg (range)	60	30 (20–40)	20 (4–40)*	47 (20–60)	40 (20–60)	40 (10–60)
Number of patients with blood Phe between 31 and 120 μmol/L on a normalised diet at 24 months, N	0	2	1	2	1	8
Median daily pegvaliase dose, mg (range)	–	30 (20–40)	4	47 (20–60)	20	20 (10–40)

Centre 4 was excluded from the table because no patients had follow-up beyond 24 months of treatment.
* One of the patients in Centre 3 was receiving pegvaliase 3 times weekly at 10 mg.

based on pegvaliase clinical trial experience, which may differ from experiences that are gathered in a real-world setting. In Europe, most experience with pegvaliase has been acquired in Germany. Based on these two years of experience, eight clinicians from German treatment centres developed 25 practical consensus recommendations that can be used to support the implementation of pegvaliase in less experienced treatment centres within or outside of Germany. The recommendations provide guidance on seven topics deemed relevant by the experts to ensure optimal treatment outcomes. Regarding the impact of pegvaliase on patient-related outcomes, studies have been limited to the assessment of inattention and mood symptoms [3,35]. Although improvements have been observed, more studies are needed to evaluate the impact of pegvaliase on neurocognitive and neuropsychological functioning in the long term. Until then, evidence remains limited to case series, anecdotal experiences (as shared in the current manuscript) and studies outside of pegvaliase that show reversibility of PKU-related symptoms upon blood Phe reduction [29–32,34,36]. Measurement of patient-related outcomes remains, however, an important shortcoming of PKU care. On one hand, available assessment tools lack specificity to capture outcomes relevant in PKU [37]. On the other hand, many European metabolic centres do not have paediatric-to-adult care transition programmes, resulting in poor access to adult resources [38]. Also, in one of the participating German treatment centres, QoL and neurocognitive tests are only available to patients under the age of 18 with waiting times of approximately 6 months. Although these assessments are not considered a prerequisite for starting pegvaliase, they will help to generate evidence on the treatment benefits that can presumably be achieved by the maintenance of blood Phe within the physiological range on a normalised diet. Areas of interest are improvements in QoL and social life (e.g. eating out), preservation or amelioration of cognitive performance and prevention or reversal of neurological and/or neuropsychological comorbidities. Following the assumption that all or most PKU-related comorbidities can be prevented by maintaining physiological Phe, one German treatment centre currently gives priority to early- and well-treated adolescents and young adults with PKU.

The retrospective chart review showed that nearly all patients with ≥24 months of treatment (23/27, 85.2%) reached the acceptable treatment outcome of blood Phe reduction to guideline thresholds with some degree of diet normalisation. Approximately half of these patients achieved physiological blood Phe while on a normalised diet. Three of these patients continued treatment despite not reaching this definition of efficacy because blood Phe was substantially lower than before pegvaliase, a significant treatment benefit was experienced, or because the maximum pegvaliase dose was not yet achieved. According to a recent case report, some patients will require a pegvaliase dose as high as 80 mg daily to achieve significant blood Phe reductions [39]. Although this dose surpasses the maximum dose approved in the product label [1], the safety profile was similar to that of lower maintenance doses [39]. To achieve such a high dose, patients will have to administer four injections daily, a burden that may not be generally accepted. Nevertheless, the dose needed to maintain an adequate response appears to decrease over time, likely allowing dose reductions and fewer injections upon re-evaluation of the maintenance dose, though more evidence is needed to justify any of these alternative dosing regimens [40,41]. Patients who discontinued treatment for reasons other than not achieving clinical efficacy or in response to experiencing adverse events were mostly driven by personal motivations, including pregnancy planning. None of the experts managed pregnant patients on pegvaliase, which, per product label, is not recommended, unless the clinical condition of the women requires treatment with pegvaliase and alternative strategies to control Phe levels have been exhausted [1]. So far, published information on the continuation of pegvaliase during pregnancy is limited to one case report [42], warranting further real-life experience to increase confidence on using pegvaliase in pregnant women.

Although pegvaliase can be considered highly effective, a number of practical considerations will determine a patient's eligibility. In Germany, the patient support programme has greatly facilitated the implementation of pegvaliase. The field nurse can be seen as an extended arm of the treatment team, providing feedback to both the patient and metabolic team on the use of pegvaliase and its adverse events. Despite premedication, hypersensitivity reactions are frequently experienced with rare cases of ASHRs. The clinical trial data demonstrated that the relatively high frequency of hypersensitivity reactions corresponds to the peak in antibody responses against the pegylated PAL enzyme [24,43]. However, after the first 6 months of treatment, the antibody response matures and the patient's tolerability improves. In most cases, hypersensitivity reactions can be managed by slowing down the titration until all adverse events are resolved or diminished to an acceptable level to continue the dose escalation. A recent study using real-world dispensing data showed that the higher the maintenance dose, the longer the titration phase, which usually takes more time than indicated in the product label [41]. Besides hypersensitivity reactions, 31.0% of patients had episodes during which blood Phe concentrations dropped below 30 μmol/L, which seems to occur in patients with lower antibody-mediated clearance and subsequently higher pegvaliase trough plasma concentrations [43]. Although prolonged periods of hypoPhe should be avoided, it should be noted that, so far, no serious adverse events have been reported. The only side effect that is hypothesised to be related to pegvaliase is alopecia [23]. The underlying mechanism is not yet understood but alopecia was shown to improve when restoring the suboptimal intake of total protein, supporting the recommendation to first increase the intake of natural protein in the event of hypoPhe [36].

Because the recommendations are derived from expert consensus, they reflect the personal experiences of a panel of eight experts with varying and sometimes limited pegvaliase experience, though generated through applying a modified Delphi approach with all recommendations having at least 75% agreement. Nevertheless, the recommendations are largely in line with the ones published based on clinical trial experience [23,24]. In addition, they are supported by patient data and evidence when available.

In conclusion, eight German experts developed 25 practical consensus recommendations for the use of pegvaliase covering seven topics going from clinical site requirements to treatment goals and outcomes. The recommendations can be a starting point for other metabolic centres within Germany or Europe that plan to start offering pegvaliase to patients with PKU aged 16 years and older.

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Author contributions

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Data availability

Data will be made available on request.

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