Molecular Genetics and Metabolism 128 (2019) 84–91

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

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

Review article

# Pegvaliase: Immunological profile and recommendations for the clinical management of hypersensitivity reactions in patients with phenylketonuria treated with this enzyme substitution therapy

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ARTICLE INFO

*Keywords:*
Complement
Immune complex
Pegvaliase
Phenylalanine ammonia lyase
Phenylketonuria
Type III hypersensitivity

ABSTRACT

*Objective:* To provide recommendations for managing hypersensitivity adverse events (HAEs) to an injectable enzyme substitution therapy (pegvaliase, a PEGylated phenylalanine ammonia lyase enzyme) in adult patients with phenylketonuria (PKU).

*Methods:* Eight European academic immunology experts with a broad range of experience in hypersensitivity, anaphylaxis, and/or drug reactions, and two geneticists from the USA with pegvaliase experience convened for two advisory board meetings. Efficacy, safety, and immunological profile of pegvaliase were discussed with the objective of developing recommendations for the clinical management of HAEs associated with pegvaliase treatment.

*Results:* Based on available immunogenicity data, it was concluded that pegvaliase induces a Type III hypersensitivity reaction, causing HAEs with peak event rates during induction/titration and a decline over time during maintenance therapy. The decline in HAEs with longer duration of therapy was considered to likely be driven by anti-drug antibody affinity maturation, reduced immune complex formation, and decreased complement activation over time. Immunology and PKU experts unanimously supported that the use of an induction, titration, and maintenance dosing regimen and implementation of several risk mitigation strategies contributed to the improvement of tolerability over time. Key risk mitigation strategies utilized in the Phase 3 clinical trials such as premedication with H1-receptor antagonists, allowance for a longer titration period after an HAE, patient education, and requirement to carry auto-injectable adrenaline (epinephrine) should be continued in clinical practice. A tool for administration of auto-injectable adrenaline in patients using pegvaliase was suggested. It was added that after the occurrence of a severe HAE a temporary dose reduction is more likely to improve tolerability than treatment interruption.

*Conclusions:* Overall, it was agreed that pegvaliase has a generally tolerable safety profile in adults with PKU. Importantly, the risk mitigation strategies utilized in the clinical trials were considered to support the continued use of key strategies for management in the commercial setting, such as a slow induction/titration dosing paradigm and premedication with H1-receptor antagonists. However, physicians and patients need to be aware of the risk of HAEs associated with pegvaliase; presence of a trained observer during early treatment may be beneficial in certain circumstances, and a requirement to carry auto-injectable adrenaline is recommended. Because pegvaliase offers the possibility to normalize diet, while maintaining blood phenylalanine within the recommended therapeutic range, safe use of this medication in the clinical setting is important. Ongoing monitoring of long-term clinical safety of patients on pegvaliase treatment in the commercial setting was recommended.

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https://doi.org/10.1016/j.ymgme.2019.05.006
Received 14 March 2019; Received in revised form 13 May 2019
Available online 17 June 2019

## 1. Introduction

### 1.1. Objectives

The objectives of this publication are to provide recommendations from immunology experts and phenylketonuria (PKU) treating physicians regarding the clinical management of hypersensitivity adverse events (HAEs) to enzyme substitution therapy with pegvaliase (Palynziq®, BioMarin Pharmaceutical Inc., Novato, CA, USA), and safe re-administration of pegvaliase after HAEs, including acute systemic hypersensitivity reactions (ASHRs). In addition, the publication summarizes the opinion of the experts regarding the potential mechanisms behind HAEs related to the drug, potential risks of long-term pegvaliase use, and additional risk management measures to promote safe use of the drug in the clinical setting. Finally, a high-level summary of the disease and associated unmet medical need as well as the safety, efficacy, and immunogenicity of pegvaliase is included as background to provide context for the feedback provided in terms of the benefits of treatment as well as the risks.

### 1.2. Phenylketonuria (PKU)

PKU is an autosomal recessive disorder caused by a deficiency in the enzyme phenylalanine hydroxylase (PAH), which converts phenylalanine (Phe) to tyrosine in the liver [1]. The resulting high Phe concentrations in the blood and the brain negatively affect brain development and function. Untreated PKU is associated with neurological, cognitive, developmental, psychiatric, and behavioral problems [2]. Newborn screening programs and early treatment can prevent the development of the most severe symptoms in children with PKU [1,3]. Nevertheless, adults with PKU have a higher than expected prevalence of neuropsychiatric symptoms and deficits in executive function as compared to the general population, which have been linked to elevated blood Phe levels [4,5].

European guidelines for the management of PKU recommend life-long reduction of blood Phe to levels of 120–360 µmol/L in children up to 12 years of age and pregnant women, and to levels of 120–600 µmol/L in those ≥12 years [6,7]. US guidelines recommend life-long reduction of blood Phe to 120–360 µmol/L, regardless of age or pregnancy status [8]. To control blood Phe, both guidelines recommend a protein-restricted diet in combination with Phe-free medical foods [8,9]. Dietary treatment can be combined with sapropterin dihydrochloride (Kuvan®, BioMarin Pharmaceutical Inc., Novato, CA, USA), a synthetic form of tetrahydrobiopterin, the naturally occurring cofactor for PAH [6]. However, this therapy is only effective in patients with residual PAH activity, typically those with less severe phenotypes [10–12].

For adults with PKU, dietary therapy is difficult to maintain over the long term, resulting in suboptimal metabolic control and neuropsychological problems [1,13]. Moreover, adults often have persistently elevated blood Phe levels despite reporting compliance with dietary treatment [14].

### 1.3. Pegvaliase

#### 1.3.1. Background

Pegvaliase is a novel enzyme substitution therapy approved by the Food and Drug Administration (FDA) in May 2018 and by the European Medicines Agency (EMA) in May 2019 for the treatment of adult patients with PKU [15,16]. It is a PEGylated recombinant phenylalanine ammonia lyase (PAL) enzyme isolated from the cyanobacteria *Anabaena variabilis* [17]. PAL converts Phe to trans-cinnamic acid and ammonia, which are excreted in urine and metabolized in the liver, respectively. The active enzyme (in this case, PAL) is conjugated to polyethylene glycol (PEG) to increase the plasma half-life and decrease immune-mediated clearance, similar to other PEGylated drugs (Fig. 1) [18,19].

The efficacy and safety of pegvaliase have been studied over the past decade in multiple sequential clinical trials, including a Phase 1 study (NCT00634660) [17], three Phase 2 studies (NCT01560286, NCT00925054, NCT01212744) with their open-label extension PAL-003 (NCT00924703) [21], and two Phase 3 studies, i.e. PRISM-1 (NCT01819727) and the subsequent pivotal study PRISM-2 (NCT01889862) [22,23] with their open-label extension. The design and outcomes of PAL-003, PRISM-1, and PRISM-2 have been discussed in detail in previous publications [21–23].

#### 1.3.2. Efficacy of pegvaliase

Overall, the clinical trials demonstrated meaningful and sustained reductions in blood Phe concentration in subjects receiving pegvaliase, with 68.4%, 60.7%, and 51.2% of patients reaching therapeutic targets of ≤600 µmol/L, ≤360 µmol/L, and ≤ 120 µmol/L, respectively, within 24 months in the PRISM studies [21–23]. The PRISM studies also demonstrated changes in neuropsychiatric outcomes with long-term treatment, including improvements in inattention symptoms and mood, associated with reductions in blood Phe [23]. It should be noted that these effects were achieved in a study population where the majority of subjects were not on a Phe-restricted diet [23]. The effect of pegvaliase on blood Phe levels exceeds that of any other currently available treatment for adults with PKU. Unlike other treatments, pegvaliase offers the possibility to normalize diet, while maintaining blood Phe within a recommended range [24], potentially addressing one of the most common sources of poor compliance with treatment recommendations.

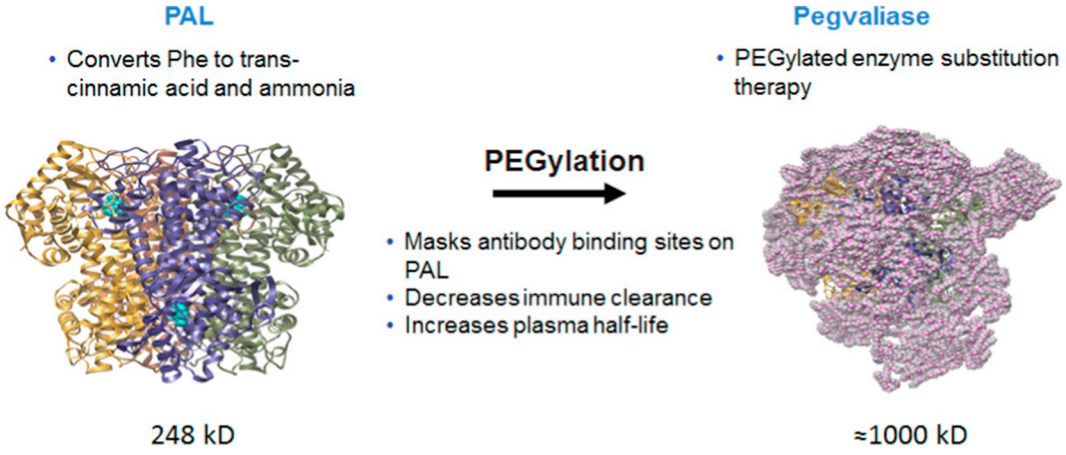


**Fig. 1.** Structure of pegvaliase: masking of phenylalanine ammonia lyase (PAL) epitopes by extensive PEGylation on the surface of the drug. Molecular weights are indicated below each compound [20].

*1.3.3. Immunogenicity of pegvaliase and impact on pharmacokinetics, safety, and efficacy*

All subjects treated with pegvaliase in the clinical trials developed anti-drug antibodies (Abs) against both the parent protein PAL and to PEG, which matured over time [25]. The early Ab response (during the first 6 months after treatment initiation) was comprised predominantly of anti-PEG IgM/IgG and anti-PAL IgM Abs (Fig. 2). In contrast, the immune response in late treatment (6 months after treatment initiation and beyond) was composed predominantly of anti-PAL IgG Abs, including drug-specific IgG4 Abs. Anti-drug Abs bound to drug in circulation give rise to circulating immune complexes (CIC). Mean CIC levels were highest during early treatment and then decreased over time. Peaking CIC levels in early treatment were associated with low C3 and C4 levels, indicating that complement activation was greatest in early treatment and decreased over time [25]. High levels of anti-PEG antibodies and anti-PAL IgM observed during early treatment are efficient activators of the classical complement pathway [25]. In contrast, the immune response in late treatment is composed predominately of anti-PAL IgG antibodies, which are less likely to bind to the drug product and fix complement due to the masking of PAL epitopes by extensive PEGylation on the surface of the drug. Additionally, the development of an IgG4 response in late treatment is consistent with the observed reduction in complement activation, as IgG4 does not activate complement and is associated with a mature immune response to a chronically administered protein.

Ab titres for all Ab analytes, including neutralizing Abs, impacted efficacy of pegvaliase, likely through its impact on drug clearance from the plasma [25]. Subjects with higher titres for all Ab analytes had lower trough pegvaliase concentrations, due to increased immune-mediated clearance. Thus, subjects with higher Ab titres typically required two to three times higher doses than those with lower Ab titres, to overcome clearance and reach clinically meaningful blood Phe reduction. Subjects with higher Ab titres during early treatment (< 6 months), when Ab-mediated clearance was high and doses of pegvaliase were low, achieved less Phe reduction than subjects with low Ab titres [25]. With prolonged treatment beyond 6 months, and additional pegvaliase dose increase, blood Phe levels continued to decrease in most subjects, including those with higher Ab titres. Importantly, after the initial 6 months of treatment, Ab titres did not further increase in response to higher doses. Due to the high individual variability of the immune response across patients, no specific Ab titre was predictive of dose required to achieve response and consequently measurement of Ab levels will provide little to no clinical utility [23,25].

Overall, HAEs occurred most frequently during the first 6 months of treatment when the early immune response, comprised of PEG IgM, PEG IgG, and PAL IgM responses peaked, C3/C4 levels declined, and CIC levels were at their highest (Fig. 2) [23,25]. The frequency of HAEs decreased over time during long-term treatment as the incidence of these Abs decreased, CIC levels declined, and C3/C4 returned towards baseline. Most subjects developed an anti-pegvaliase IgG4 response over time, consistent with a humoral immune response against a chronically administered protein therapeutic [26]. All subjects who experienced ASHRs (reactions which an independent expert allergist/immunologist determined likely to meet NIAID/FAAN clinical diagnostic criteria for anaphylaxis) tested negative for drug-specific IgE (based on an ImmunoCAP technology, ThermoFisher Scientific) at or near the time of each event [25]. The IgE assay is not designed to detect antibodies developed against metabolites of the enzymatic reactions. The observed increases in CIC levels, in conjunction with C3/C4 complement consumption, lack of drug-specific IgE detection at the time of ASHRs, and ability to rechallenge the majority of patients with drug without recurrent reactions suggest that the predominant mechanism of HAEs in the pegvaliase clinical studies was Type III immune complex-mediated hypersensitivity [23,25]. It is known that immune complexes can activate the classical complement pathway leading to the production of anaphylatoxins and cause local inflammatory responses by acting directly on local blood vessels, stimulating an increase in blood flow and increased vascular permeability. Anaphylatoxins also activate mast cells to release mediators such as histamine and TNF-α that contribute to the inflammatory response. Together, these inflammatory reactions are called Type III hypersensitivity reactions and share many of the same signs/symptoms as the allergic reactions mediated by IgE. However, Type III events typically are less commonly described to lead to severe or life-threatening manifestations.

Published data suggest the change in immune response over time influences the dosing necessary to achieve efficacy. Thus, the guiding principles in developing an induction/titration dosing schedule necessary to achieve efficacious doses in later treatment while minimizing the occurrence of HAEs during early treatment, is based on the time course of anti-drug Ab maturation, IC formation, and complement activation [25]. Starting with a low, weekly dose, when the early Ab response, CIC levels, complement activation and frequency of HAEs is peaking and then increasing the dose and frequency when the Ab response has “matured”, and CIC levels and complement activation have declined, allows patients to achieve the expected clinical benefit, while minimizing the risk of

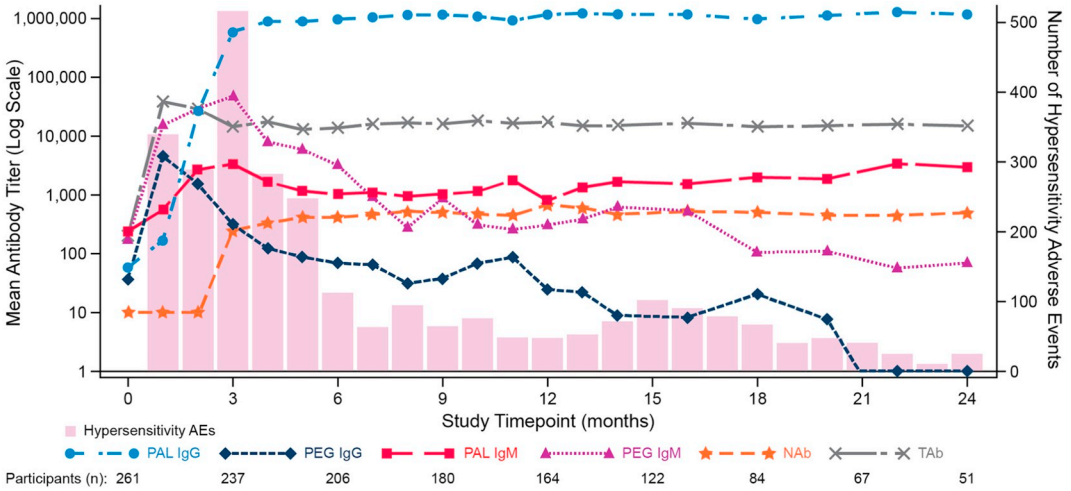


**Fig. 2.** Mean antibody titers over time and frequency of hypersensitivity adverse events (HAEs) in the pegvaliase Phase 3 clinical trials (PRISM). Reproduced from Thomas J et al. 2018 (doi: https://doi.org/10.1016/j.ymgme.2018.03.006) [23]; available under the terms of the Creative Commons Attribution License (CC BY: https://creativecommons.org/licenses/by/4.0/). IgG, immunoglobulin G; IgM, immunoglobulin M; PAL, phenylalanine ammonia lyase; PEG, polyethylene glycol; NAb, neutralizing antibodies; TAb, total antibody.

hypersensitivity.

Induction, titration, and maintenance (I/T/M) dosing was implemented in the Phase 2 program (165–205) and the Phase 3 PRISM studies [21]. The first two Phase 2 studies showed a manageable safety profile but poor efficacy with once-weekly dosing at 0.001 mg/kg to 0.1 mg/kg for 16 weeks (PAL-002), and a substantial reduction in blood Phe but poor tolerability with pegvaliase at 0.06 mg/kg to 0.4 mg/kg for 5 days/week (PAL-004) [21]. The Phase 3 studies involved treatment at a low dose of 2.5 mg/week for the first 4 weeks, a gradual increase in dose and dose frequency to the maintenance dose over at least 5 weeks (20 mg and 40 mg daily), and adjustment of the maintenance dose between 5 mg and 60 mg daily based on individual efficacy and safety [21,23]. Recently published consensus-based treatment recommendations for pegvaliase in adults with PKU recommend I/T/M dosing based on individual patient tolerability [24].

In addition, several risk mitigation strategies were implemented in the Phase 3 study to reduce the risk of severe outcomes of ASHR [22,23]. Risk mitigation strategies included the requirement for pre-medications, allowance of slower titration in subjects developing HAEs, requirement for all subjects to carry auto-injectable adrenaline (epinephrine) at all times, training of the subject and a responsible adult in the signs and symptoms of ASHRs, and the requirement to have the responsible adult present for at least the first 16 weeks of treatment [22,23]. Premedications used included a histamine H1-receptor antagonist, an H2-receptor antagonist, and, if tolerated, an antipyretic. It should be noted that H2-receptor antagonists have only weak or questionable benefits in the prevention of HAEs [27–29]. In animal studies, the elimination and systemic clearance rates of H1-receptor antagonists were significantly decreased during concomitant administration of H2-receptor antagonists [30]. This is thought to be the reason for the weak add-on effect of H2-receptor antagonists observed in clinical use.

Pegvaliase treatment using the I/T/M dosing regimen and risk mitigation strategies was associated with a manageable safety profile [22,23]. Table 1 provides a summary of AEs reported for all subjects who had I/T/M dosing in the Phase 2 and 3 clinical trials [21,23]. HAEs were mostly mild or moderate in severity, and the highest frequency of events occurred in the induction-titration phase, when pegvaliase doses were lowest. Most frequently reported HAEs were arthralgia and local injection site reactions. It should be noted that arthralgia was included in a broad definition of HAEs. The observed association between lower pegvaliase doses and higher event rates is likely due to the peaking early Ab response, peaking levels of CIC and complement activation during induction and titration, leading to HAEs. Since the doses were low and the HAEs were greatest during induction/titration, there appears to be an apparent association of higher HAE rates and lower doses. Assessment of complement data and AEs did not reveal an association between low complement levels and an increase in infection-related reports.

## 2. Methods

Eight European academic clinical allergists/immunologists with expertise in anaphylaxis, hypersensitivity, and/or adverse drug reactions and two geneticists from the USA, with extensive experience in managing PKU and who were involved in the pegvaliase clinical trials, gathered in Amsterdam on May 19, 2018 for a one-day meeting. The experts discussed the efficacy, safety, and immunological profile of pegvaliase, with focus on HAEs and how these were managed in the clinical trials, and agreed on the underlying mechanism of HAEs observed in the clinical trials and endorsed the mitigation measures used to manage these reactions in the clinical trials. Additionally, they offered recommendations for the real-world clinical management of drug-associated HAEs. The recommendations were further fine-tuned during a subsequent online “virtual” advisory board (June 27–July 22, 2018), during which the experts worked on a common document of questions.

The immunology experts were selected on the basis of a literature search with focus on drug allergy and immunological mechanisms of drug-related anaphylaxis, followed by suggestions from attendees of a European immunology congress from their scientific network. They had access to all published and summary data from the pegvaliase clinical trials. The data was provided prior to the advisory board meeting to allow for sufficient time to review. Additional data considered relevant for the purpose of the meeting, including individual patient data, was available to the panel on request. There was no data not permitted to the panel. Both the expert meeting and the virtual advisory board were coordinated and funded by BioMarin Pharmaceutical Inc.

## 3. Results

### 3.1. Potential mechanism of HAEs observed with pegvaliase

During the meeting the potential immunologic mechanism of HAEs observed with pegvaliase in the clinical trials were discussed. There was agreement that pegvaliase most likely induces a Type III immune-complex mediated reaction based on the available data [25]. An important factor is the lack of drug-specific IgE detected at or near the time of HAEs, including ASHRs, using PAL and pegvaliase as antigens in an established highly sensitive routine serological test. The temporal association between the frequency of HAEs and peaking CIC levels, sharply dropping C3/C4 levels, and peaking anti-PEG Abs also supports this mechanism (see Section 1.3.3) [25]. The HAEs associated with pegvaliase also had a different clinical presentation and nature than typical IgE-mediated Type I events [31]. For example, subjects treated with pegvaliase frequently developed arthralgia, which is not a clinical manifestations of Type I reactions, but more common in Type III reactions [32]. In addition, subjects who experienced an ASHR could be redosed, with 75% remaining on therapy, and had a less severe clinical presentation than what would be expected for an IgE mediated event. Of the 21 ASHRs in the I/T/M population, none required advanced measures including intubation or vasopressor support, seven were self-limiting and required no treatment or dose change, and all were of short

**Table 1**
Exposure-adjusted adverse events (AEs) rates reported for the induction-titration (I/T) and maintenance (M) phases in the I/T/M population of the pegvaliase Phase 2 165–205 and Phase 3 clinical trials as of May 6, 2017. Total exposure was 135.4 person-years for the I/T phase and 444.1 person-years for the M phase.

| Event rate per person-year (number of events) | I/T phase ($N$ = 285) | M phase ($N$ = 223) |
|---|---|---|
| AEs | | |
| Any AE | 52.40 (7095) | 19.01 (8443) |
| Treatment-related AEs | 43.06 (5830) | 9.15 (4062) |
| AEs leading to dose reduction | 1.12 (152) | 0.26 (115) |
| AEs leading to dose interruption | 1.57 (212) | 0.22 (99) |
| AEs leading to study drug discontinuation[a] | 10.5% (30) | 4.9% (11) |
| SAEs | | |
| Any SAE | 0.24 (32) | 0.10 (46) |
| Treatment-related SAEs | 0.17 (23) | 0.03 (15) |
| AEs of special interest | | |
| HAEs[b] | 15.14 (2050) | 4.00 (1776) |
| Acute systemic hypersensitivity reactions[c] | 0.08 (11) | 0.02 (10) |
| Injection site reactions | 21.89 (2964) | 3.95 (1754) |
| Arthralgia | 6.05 (819) | 0.95 (422) |

The table includes all enrolled subjects who received at least one dose of pegvaliase in Study 165–205 or Study PRISM-1. Maintenance phase is defined as a stable dosing period of at least 8 weeks. HAE: hypersensitivity AE; SAE: serious AE.

[a] Subject incidence only.

[b] Hypersensitivity AEs by broad Standard MedDRA Queries.

[c] Events confirmed by an independent allergist/immunologist to be consistent with clinical anaphylaxis criteria defined by National Institute of Allergy and Infectious Diseases/Food Allergy and Anaphylaxis Network.

duration and resolved without sequelae. Moreover, the next administration of pegvaliase following an ASHR did not immediately lead to another event, as would be expected of a classical IgE-mediated anaphylaxis reaction. Typically, IgE-mediated Type I reactions are triggered by very small doses of the antigen and become increasingly severe with subsequent increased doses. It remains to be established whether cofactors established in IgE-mediated anaphylaxis (e.g. intake of non-steroidal anti-inflammatory drugs (NSAIDs), and/or infections, physical exercise, and alcohol) also increase the risk of ASHRs to pegvaliase [33–35].

It was agreed that the longitudinal immunological and safety data of pegvaliase indicate that there was a change in the frequency and pattern of HAEs of pegvaliase over time. The experts further endorsed that this change is likely driven by the change from a predominant anti-PEG and/or PAL IgM response during early treatment to a predominantly anti-PAL IgG and IgG4 response during late treatment [26]. Reduction in anti-PEG Abs reduces CIC formation due to inefficient binding of anti-PAL Abs on drug where the PAL epitopes are masked due to extensive PEGylation. In addition, the development of an IgG4 response over time may be suggestive of a state of clinical "tolerance" induction, as defined by a state of clinical non-responsiveness through constant antigen exposure as has been demonstrated for antigen-specific immunotherapy [36]. It has been reported that IgG4 activate complement less efficiently than IgG1 both *in vitro* and *in vivo* [37], but there is currently no evidence that IgG4 is associated with the development of tolerance in Type III reactions.

### 3.2. Clinical management of HAEs of pegvaliase

#### 3.2.1. Endorsement of the measures used for clinical management of HAEs and additional recommendations

Overall, there was general agreement about the measures utilized to manage HAEs in the clinical trials. The best practice recommendations outlined below to further improve tolerability to pegvaliase, particularly during initial treatment, were provided (Table 2).

The fact that most subjects in the clinical trials wanted to continue taking pegvaliase despite HAEs during early treatment suggests that the advantages of the drug outweigh its safety and tolerability issues. Treatment reduces blood Phe to the recommended target concentration in most patients, which is otherwise very difficult to maintain long-term, particularly for those with great difficulty adhering to the Phe-restricted diet. Further improvements in tolerability by the risk minimization measures outlined in Table 2 can make it easier for patients to get through the difficult initial treatment period, when HAEs are most frequent, and to fully realize the benefits of treatment.

#### 3.2.2. Induction, titration, and maintenance dosing schedule

It was agreed that based on the clinical trial data, the risk of HAEs during initial treatment can be minimized by using the I/T/M dosing protocol included in the pegvaliase prescribing information, starting with a low weekly dose, and slow titration in dose and frequency towards a maintenance dose [20]. This schedule may be refined further based on the results of future research.

#### 3.2.3. Risk mitigation strategies

It was agreed that the risk mitigation precautions utilized during the clinical trials helped to improve safety of home treatment with pegvaliase, including premedications, presence of a trained observer, availability of auto-injectable adrenaline, and allowance of slower titration in the event of tolerability issues. These risk mitigation strategies were implemented as a whole in the clinical trials in May 2014 as an amendment during the Phase 3 program. Their introduction reduced the incidence and severity of HAEs. The incidence of AEs leading to study drug discontinuation decreased from 0.91 episodes/person/year before ($N$ = 143) to 0.42 episodes/person/year after the implementation ($N$ = 170), HAEs based on broad preferred term search decreased from 0.18 to 0.10 episodes/person/year, and adjudicated anaphylaxis events meeting Brown's severe criteria decreased from 0.04 to 0 episodes/person/year (Supplementary Table 1).

Of all the premedications utilized in the pegvaliase clinical trials, the H1-receptor antagonists were considered likely to be most effective due to their mechanism of action as well as the data in the literature showing effectiveness in reducing symptoms of allergy [27,28]. In Type III hypersensitivity reactions, immune complexes activate the classical complement pathway leading to release of anaphylatoxins, which can then activate mast cells leading to cell degranulation and release of histamine (and other chemical mediators) from the mast cell or basophil. Once released, histamine can react with local or widespread tissues through histamine receptors. Histamine, acting on H1-receptors, then causes various local inflammatory and allergic symptoms. H1-receptor antagonists block binding of histamine to H1 receptors.

It was also agreed that the initial dose of pegvaliase should be administered under the supervision of a healthcare professional until the patient and a trained observer can demonstrate competency in dosing and recognition of HAEs.

There was unanimous agreement that, as a precaution for ASHRs, all patients receiving pegvaliase should have auto-injectable adrenaline available at all times. Before starting pegvaliase, patients should be able to recognize signs and symptoms of ASHRs, and should be counseled when to administer adrenaline, how to inject, and who to contact. Existing training programs or instructions for patients on how and when to apply auto-injectable adrenaline available in hospitals/clinics should also be used to instruct patients receiving pegvaliase [38]. Use of videos and (online) structured patient/physician education programs to recognize and manage anaphylaxis/ASHRs should also be considered [38,39]. In addition, regular training with a trainer auto-injector is recommended. Patients may also be provided an emergency treatment plan and play one fictive episode under observation. Adrenaline should be given without delay at the first sign of anaphylactic symptoms. These management approaches for anaphylaxis have been established in the setting of IgE-mediated acute anaphylaxis, such as hymenoptera venom and food allergy [38–40].

Patients with a history of anaphylaxis or severe allergic reactions to other PEGylated drugs should be referred to an allergist/immunologist before starting pegvaliase to see if certain precautions, avoidance measures, or therapies should be taken. If the patient had previous reactions to other drugs, e.g. to other PEG-containing drugs, it is recommended to check reactivity to excipients in the pegvaliase formulation. Allergic

**Table 2**
Best practice recommendations for the clinical management of HAEs of pegvaliase.

- The risk of HAEs during initial treatment with pegvaliase can be minimized by starting with a low weekly dose, and slow titration in dose and frequency towards a maintenance dose
- Premedication, allowance for a longer titration period after an HAE, training and education of patients and/or caregivers if needed, and availability of auto-injectable adrenaline at all times, can improve safety of home treatment with pegvaliase
- To prevent injection site reactions, patients should be encouraged to rotate injection sites between doses. Injection site reactions can be treated with an H1-receptor antagonist, topical steroids, or cold compresses
- Recommended treatments for arthralgia are NSAIDs (if the patient has no renal dysfunction or other contraindications to NSAIDs), acetaminophen/paracetamol, or low dose steroids for a maximum of 6 weeks
- Acute systemic hypersensitivity reactions to pegvaliase should be treated with auto-injectable adrenaline as early as possible after the onset of signs/symptoms
- After the occurrence of a severe HAE, a temporary dose reduction is more likely to improve tolerability than treatment interruption
- Patients who previously demonstrated tolerance to pegvaliase can be redosed after a long interruption, starting at a lower dose than the last tolerated dose and applying a modified, accelerated I/T/M schedule
- Patients who previously demonstrated tolerance to pegvaliase can be redosed after a long interruption, starting at a lower dose than the last tolerated dose and applying a modified, accelerated I/T/M schedule

I/T/M: induction, titration, and maintenance; NSAIDs: non-steroidal anti-inflammatory drugs.

diseases should be treated adequately and should be stable and under control before initiating pegvaliase.

### 3.2.4. Management of injection site reactions

In the pegvaliase clinical trials, injection site reactions were treated with oral antihistamines, corticosteroids, steroid injections, or discontinuation of pegvaliase [20]. To prevent injection site reactions, patients should be encouraged to rotate injection sites between doses (i.e. upper arm, thigh, buttocks, or abdomen) as described [20,22]. Injection site reactions can be treated with an H1-receptor antagonist, topical steroids or cold compresses. Treatment with an H2-receptor antagonist is not recommended. Controlled up-dosing of the H1-receptor antagonist, as done in chronic urticaria, is recommended over combination therapy with H1- and H2-receptor antagonists, as H2-receptor antagonists have only weak or questionable benefits in the prevention of HAEs [27–29]. For the treatment of urticaria (and anaphylaxis), H1-receptor antagonists are sometimes given in doses up to four times exceeding the normal recommended daily dose [27]. However, for prophylaxis by premedication, generally only the standard daily dose of an antihistamine has been given in several studies and should also be used before giving pegvaliase [28,41–43].

### 3.2.5. Management of arthralgia

In the pegvaliase clinical trials, arthralgia episodes were managed with medications (NSAIDs, glucocorticoids, acetaminophen), or by pegvaliase dosage reduction, interruption, or withdrawal [20]. These measures were considered appropriate.

Following the clinical trial experience, it was recommended to treat arthralgia with acetaminophen/paracetamol (preferred) or NSAIDs, if the patient has no renal dysfunction or other contraindications to NSAIDs, or low dose steroids for a maximum of 6 weeks. It was speculated that antihistamines likely have no impact on arthralgia.

### 3.2.6. Management of ASHRs

There was general agreement that ASHRs to pegvaliase should be treated with adrenaline as early as possible after the onset of signs/symptoms. According to current guidelines, adrenaline is the medication of choice for anaphylaxis regardless of its mechanism [44]. Although most experience on the efficacy of adrenaline comes from IgE-mediated reactions, it has also been successfully used in immune complex Type III reactions, e.g. dextrane reactions [45]. To train patients in the commercial setting, it was suggested to use a simple “red, yellow, green” patient training tool to guide them. Similar tools have successfully been used in other therapies (e.g. asthma: http://www.aafa.org/page/programs-for-patients-and-caregivers.aspx). Patients should seek medical attention right away after the first onset of symptoms (Fig. 3).

It was agreed that patients who had a previous ASHR may be rechallenged, if the patient consents after receiving all information regarding the risks and benefits of rechallenging. With severe ASHRs, a prior allergy work-up in collaboration with an allergologist experienced in drug hypersensitivity is recommended, e.g. measurement of baseline tryptase in serum, and in-depth search for alternative allergens or explanations for the reaction observed. Skin-prick testing is not recommended as a screening criterion for pegvaliase due to negative results (using pegvaliase at a dilution of 1:100) obtained from a subset of patients in a Phase 2 trial with pegvaliase (BioMarin, data on file).

Redosing should occur in a controlled environment with rescue medication and equipment available (in clinic) for the first injection, and starting at a lower dose: one or two steps back in the titration schedule, with the dose depending on the severity of the event. Steroids can potentially be used in addition to an H1-receptor antagonist as premedication. Rechallenging with pegvaliase is not recommended if the patient is not motivated or in the case of a very severe/life threatening reaction (meeting Brown's severe criteria such as hypotension, dyspnoea with hypoxia, syncope [46]), in patients unable to deal with HAEs (e.g. very scared, or not able to reliably administer auto-injectable adrenaline without proper support), or in patients with recurrent ASHRs.

### 3.2.7. Treatment interruption after a HAE

Halting treatment after a HAE was generally considered to be less favorable, as opposed to a dose reduction, so as not to interrupt the “desensitizing” effect of continued antigen exposure and getting the patient through induction-titration where the risk of HAEs is greatest [40]. Temporary reduction of the pegvaliase dose after a reaction during the titration phase may be required to prevent further events, with the dose (one or two steps back in the dosing regimen) depending on the severity of the event. This approach is also common practice in allergen immunotherapy [40]. The I/T/M dosing regimen may also be

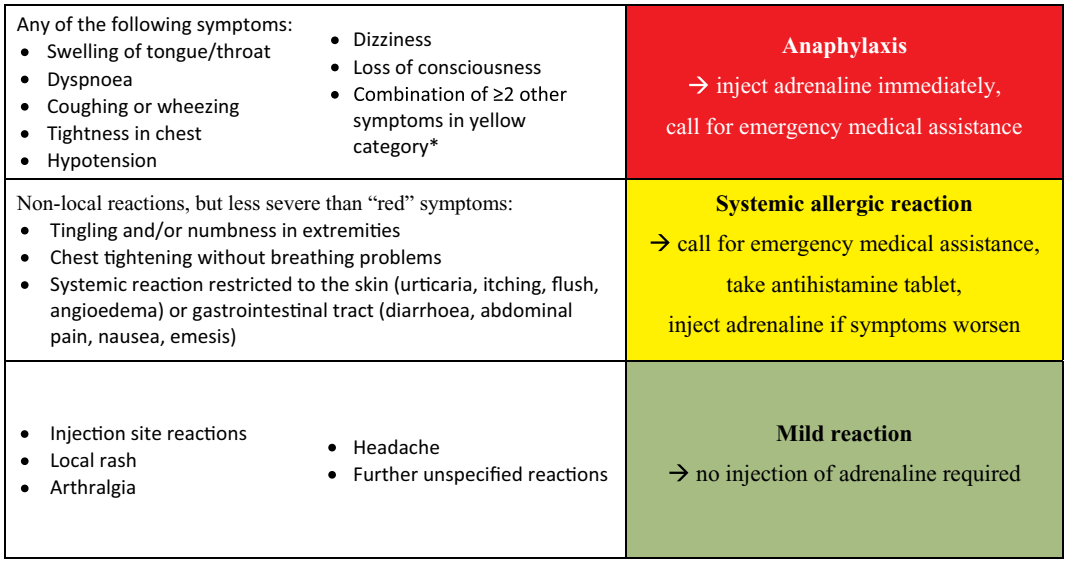


**Fig. 3.** Tool for administration of auto-injectable adrenaline in patients using pegvaliase.
*e.g. urticaria or angioedema plus gastrointestinal symptoms, such as sudden diarrhoea or abdominal pain.

revised after a severe or very severe reaction (i.e. slower titration) [47]. The subject's ability to tolerate and manage the HAE (i.e. pain tolerance, support network, and emotional stability) should also be considered when deciding on the best approach.

#### 3.2.8. Redosing pegvaliase after a long interruption

Patients who were previously on maintenance dosing to pegvaliase can be redosed after a long interruption due to e.g. pregnancy, starting at a lower dose than the last administered dose and applying a modified I/T/M schedule. This recommendation is based on the finding that patients who stopped treatment during the randomized discontinuation trial in PRISM-2 could resume treatment rapidly after 8 weeks without adverse reactions [23]. Dosing in these patients should be resumed in the clinic, using the same premedication as before the interruption.

#### 3.2.9. Safety of pegvaliase with long-term use

It was agreed that based on the clinical trials, there was no overt evidence of IC-mediated end organ damage caused by pegvaliase [21,23,25]. An extensive review of the clinical safety data with 401.3 patient-years identified no AEs suggesting pegvaliase-associated IC-mediated end organ damage such as renal failure, haemolytic anaemia, serositis, central nervous system manifestations, or myocardial ischemic events related to pegvaliase. Arthralgia events mostly occur during early treatment, can be resolved with standard NSAID treatment, and do not recur afterwards in the majority of patients.

A sustained hepatic function is important for IC clearance. Red blood cells may bind C3b-coated immune complexes and transport them to phagocytes, mostly in liver and spleen. Immune complexes can also be deposited in different organs, including the kidney. Monitoring in ongoing clinical studies (e.g. urine assessment for microalbuminuria and liver function tests) and in the post marketing setting (e.g. enhanced pharmacovigilance) is being done to confirm IC-mediated end-organ damage is not occurring with pegvaliase with longer term dosing.

## 4. Conclusions and future directions

Overall, it was agreed that the clinical trials have shown that pegvaliase is effective in lowering blood Phe concentration to guideline-based treatment targets, while allowing diet relaxation, in adult patients with PKU [17,21–23]. Because of the difficulty to adhere to a Phe-restricted diet, and the significant morbidity associated with high blood Phe levels, pegvaliase treatment can be life-changing for patients. However, physicians and patients need to be aware of the risk of HAEs associated with pegvaliase, particularly during early treatment, and of the time needed to reach full efficacy due to low drug doses and immune-mediated drug clearance during the first 6 months of treatment [25]. The immunogenicity of pegvaliase and its impact on safety and efficacy were considered to be well characterized. There was overall agreement that currently available immunological data from the pegvaliase clinical trials suggest a Type III IC-mediated hypersensitivity response to pegvaliase, which provides a rationale for the risk mitigation approaches recommended. The authors also agreed with and contributed to the list of recommendations in this publication, including implementation of the I/T/M dosing regimen and risk mitigation strategies, as well as proposing treatment strategies to improve safety outcomes of pegvaliase. Continued monitoring is required to confirm the long-term safety of pegvaliase and to assess risk of CIC accumulation in organs.

## Financial disclosures

The content of this manuscript was based on presentations and discussions during an expert meeting and a virtual advisory board that were coordinated and funded by BioMarin Pharmaceutical Inc. All authors or their institutions received an honorarium and travel support from BioMarin to participate in at least one or both meetings.

In addition, Dr. Hausmann has been a consultant for BioMarin Pharmaceutical Inc. to optimize study protocols of the Phase 2/3 clinical trials. Drs. Northrup and Longo have received grant funding from BioMarin Pharmaceutical Inc. for drug trials on the medication Palynziq®, and honoraria for participation in advisory boards from BioMarin Pharmaceutical Inc. Dr. Northrup also received payment from Symbiotix for participating as a speaker in the Speakers Bureau for Palynziq.

## Acknowledgments

The authors are grateful to Ismar Healthcare NV for their assistance in the writing of this manuscript, which was funded by BioMarin Pharmaceutical Inc. The expert meeting in Amsterdam and the virtual advisory board were also coordinated by Ismar Healthcare NV and sponsored by BioMarin Pharmaceutical Inc.

## Funding

This work was supported by BioMarin Pharmaceutical, Inc., Novato, CA, USA.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ymgme.2019.05.006.

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