

Addressing global challenges in PKU

Welcome to the SSIEM 2024 congress review!

The 2024 Annual Symposium of the Society for the Study of Inborn Errors of Metabolism (SSIEM) took place in Porto, Portugal, from 3rd–6th September 2024. The meeting brought together leading experts to share expertise, learn from others, and contribute to the collective mission of improving the lives of those affected with inborn errors in metabolism (IEM).

As the field of phenylketonuria (PKU) management evolves, addressing the unmet needs of patients remains a critical focus. Despite advances in treatment options, many individuals with PKU continue to face difficulties with dietary adherence and maintaining optimal Phe levels. By highlighting recent developments and ongoing research, this congress review emphasises the importance of innovative solutions in bridging these gaps and enhancing the overall quality of treatments for PKU patients.

In this congress review, we have selected relevant presentations, symposia, abstracts, and posters with a focus on pegvaliase and sapropterin dihydrochloride treatment, diet, and protein sources, and other therapeutic approaches in PKU.

We hope that this congress review proves beneficial to you, offering insights into how the PKU community can contribute to addressing global challenges in PKU.

The PKU.expert Team

Sharing experience of pegvaliase in clinical practice

The BioMarin symposium drew on the experience of world-renowned experts as they gave practical advice for clinicians for implementing pegvaliase in clinical practice

Therapeutic advances in PKU

Explore cutting-edge strategies and technologies in development for PKU management

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Latest data on pegvaliase

Pegvaliase is a pegylated phenylalanine hydroxylase (PAH) enzyme substitution therapy that converts phenylalanine (Phe) to ammonia and trans-cinnamic acid, intended to provide a long-term treatment for patients with PKU.

Rovelli *et al.* investigated if pegvaliase for the treatment of PKU can trigger immune-mediated responses affecting blood Phe levels, leading to adverse events (AEs), and explored whether complement components C3 and C4 (C3/C4) levels could serve as indicators of immune response and guide adjustments in pegvaliase dosing. The study measured C3 and C4 antigen levels at baseline and then monthly throughout the induction, titration, and maintenance phases, continuing up to 1 year of treatment in 13 PKU patients.

During the early stages of treatment, C3 and C4 levels were at their lowest, with a mean of 0.44 g/L (standard deviation (SD) 0.8) and 0.07 g/L (SD 0.2) respectively. These levels peaked at around 3 months but began returning toward baseline as treatment progressed. Despite this trend, two patients still exhibited low C3/C4 levels after 23 months of treatment. Importantly, C3/C4 levels were found to correlate with adverse reactions when they occurred, suggesting their potential as markers for immune response.

C3/C4 markers provided valuable insights beyond Phe levels, helping clinicians adjust pegvaliase dosages and offering patients clearer feedback on their treatment progress, even when Phe levels remained unchanged. This approach could enhance personalised treatment strategies for PKU patients on pegvaliase therapy. [\[OC-047\]](#)

An evaluation of the effect of pegvaliase on Phe fluctuations was conducted by Schoen *et al.* in 14 adults with PKU (57% male) with a median age of 32.5 years. Phe concentrations were quantified by dried blood spots 1 year before and 1 year after achieving response to pegvaliase (defined as three consecutive plasma Phe concentrations $<360 \mu\text{mol/L}$ and intact protein intake $>60\%$ of the dietary reference intake). At least three Phe concentrations in both observation periods were required for inclusion.

Before achieving a response to pegvaliase, the average Phe concentration was $458.5 \mu\text{mol/L}$ (SD 147.8), with fluctuations (calculated as the SD of Phe) of $264 \mu\text{mol/L}$ (SD 96).

After 1 year of sustained pegvaliase therapy, average Phe levels dropped to $199.8 \mu\text{mol/L}$ (SD 132.9), and fluctuations decreased to $147.4 \mu\text{mol/L}$ (SD 93.8). This represented a significant reduction in both Phe concentrations with a mean decrease of $258 \mu\text{mol/L}$ (95% CI: $-377.5, -139.7$, $p=0.0004$) and mean decrease in variability of $116.6 \mu\text{mol/L}$ (95% CI: $-201.1, -32.1$, $p=0.01$).

Despite these improvements, some participants still experienced Phe levels above the recommended range, or hypophenylalanine (hypoPhe).

Sustained pegvaliase therapy reduced Phe variability in adults with PKU, suggesting improved stability in Phe control. Future research should investigate the long-term effects of Phe fluctuations on neurocognitive outcomes, beyond the initial year of treatment. [\[PO-597\]](#)

Latest data on sapropterin dihydrochloride

Sapropterin dihydrochloride, a synthetic form of tetrahydrobiopterin, enhances the activity of PAH in PKU patients, allowing for improved metabolic control and dietary flexibility.

An observational, longitudinal study, conducted by Gama *et al.*, in 17 children (mean age 10.8 years, SD 4.2) treated with sapropterin aimed to assess changes in food quality, mental health, and burden of care. Questionnaires on food frequency, anxiety and depression, impact on family and burden of care were completed by parents at baseline, 3 months, 6 months, and 12 months. Data on growth, nutritional intake, and metabolic control were collected at all timepoints. Two children discontinued sapropterin due to poor drug adherence.

After 12 months, there were significant increases in natural protein ($p < 0.001$) and a decrease in protein substitute dose ($p = 0.001$). Increase in natural protein food sources, including milk ($p = 0.002$), meat/fish/eggs ($p = 0.006$), bread ($p = 0.009$) and pasta ($p < 0.001$) was observed, whilst low-protein foods decreased. There was a decrease in anxiety ($p = 0.012$) and depression ($p = 0.015$) in caregivers, familial-social impact ($p < 0.001$) and caregiver personal strain ($p < 0.001$). Weight z-score increased in both children aged ≤ 10 years ($p < 0.001$) and > 10 years ($p = 0.001$) but body mass index (BMI) z-scores remained unchanged ($p = 0.145$ and $p = 0.448$, respectively). Caregivers spent less time on PKU tasks, the majority ate out more regularly and fewer caregivers denied their children food choices.

Gama *et al.* concluded sapropterin treatment led to improvements in food patterns, behaviours, and caregiver burden. It was highlighted that changing eating patterns takes time, it is important to manage family expectations, and to consider all environmental factors e.g., stress, family dynamics and burden of care when introducing new treatments in PKU. [\[PO-082\]](#)

A quality assurance activity to understand the level of adherence to sapropterin therapy following a sapropterin responsiveness test, among individuals with PKU in Queensland, Australia was presented by Inwood *et al.*

Of the 97 individuals (74 children and 23 adults) tested, 77 were found to have a tetrahydrobiopterin (BH_4)-responsive form of PKU. Medical records were audited to evaluate long-term adherence, considering factors such as patient age, responsiveness percentage, reduction in blood Phe levels, adherence to ongoing therapy, number of prescriptions filled over the past 2 years, and reasons for discontinuation among those who ceased treatment. The study revealed that 12% of children and 38% of adults had discontinued sapropterin therapy, with a higher discontinuation rate among those showing a 30–45% response. Of those with less than 45% responsiveness, 55% discontinued therapy, with many taking longer than 3 days to respond during the 7-day load test. It was noted that the results may be skewed due to the small number of males choosing to undergo a BH_4 responsive test. For the ten adults who discontinued therapy, two opted to take sapropterin only in pregnancy and one did not start therapy after completing the load test.

Individuals with PKU showing less than 45% responsiveness to sapropterin often perceive limited benefits, leading to discontinuation. Reported reasons for discontinuation included limited perceived benefit, adherence to a protein restricted diet and needing a Phe-free or glycomacropeptide (GMP) formula, no difference in quality of life (QoL), and burden of high number of daily pills/sachets. These findings highlight the need for more effective treatments to enhance protein tolerance, improve metabolic control, and promote better adherence to therapy. [\[OC-056\]](#)

Protein sources and dietary interventions

Management of PKU primarily involves a strict low-Phe diet to prevent the accumulation of Phe in the brain, which can lead to severe neurological damage. This section includes data on recent research into protein sources and dietary interventions for individuals with PKU.

The comparison of the kinetic profile of three different protein sources: Phe-free L-amino acids (L-AA), low Phe casein glycomacropeptide (cGMP), and casein, in healthy adults, was conducted by Daly *et al.* to assess how these properties can help determine the most effective protein substitute for patients with PKU.

In this three-way randomised, controlled crossover study, 20 healthy adult participants (11 females), median age 43 years (range 23–49), consumed 0.4 g/kg of protein equivalent from either low Phe cGMP, L-AA, or casein on separate occasions under controlled conditions. Blood samples were collected at baseline (fasting) and at intervals up to 240 minutes post-ingestion. Key metrics including area under curve (AUC), peak concentration (C_{max}), and time to maximum (T_{max}) were measured for insulin, urea, glucose, total amino acids (TAA), essential amino acids (EAA), large neutral amino acids (LNAA), and branch chain amino acids (BCAA).

The C_{max} for TAA, BCAA, LNAA, and EAA was highest for cGMP, followed by L-AA and casein, with statistically significant differences ($p < 0.05$) observed for TAA, BCAA, LNAA, and EAA between the various protein sources. The T_{max} was longer for L-AA compared to cGMP and casein, with significant differences ($p < 0.05$) noted for TAA, BCAA, and EAA, while insulin T_{max} showed a significant difference ($p < 0.05$) only between cGMP and casein. The AUC was highest for L-AA, followed by cGMP and casein, with significant differences ($p < 0.05$) for TAA and BCAA.

This study demonstrates that cGMP and L-AA are absorbed more rapidly than casein, with L-AA showing an improved kinetic profile over cGMP for certain parameters. The results suggest that cGMP does not offer a kinetic advantage over L-AA in terms of absorption. These findings highlight the importance of individualised treatment plans based on absorption kinetics and patient needs. [\[OC-013\]](#)

The effect of slow-released protein substitute (PS) on gut microbiota composition was investigated by Verduci *et al.* in 13 children with PKU, with a mean age of 16 years (13 males, 7 females). From baseline to 4 months, no significant changes were observed in BMI or BMI z-score, however, there were notable biochemical changes: mean blood glucose levels decreased from 84 to 79 mg/dL ($p = 0.104$); insulin levels from 9.5 to 7.2 $\mu\text{U}/\text{mL}$ ($p = 0.019$); homeostasis model assessment insulin resistance (HOMA-IR) from 2.0 to 1.4 ($p = 0.009$), and Quantitative Insulin Sensitivity Check Index (QUICKI) improved from 0.646 to 0.698 ($p = 0.040$). Additionally, the gut microbiota showed an increase in *Anaerobutyricum* (*Eubacterium hallii*), which is associated with improved insulin sensitivity, from 0.7% to 2.5% ($p = 0.031$).

There were also non-significant trends of increased *Bifidobacterium* and *Blautia* genera and a decrease in *Bacteroides* and *Escherichia*.

The findings suggest that slow-release Phe-free PS can influence gut microbiota composition, particularly increasing the presence of beneficial microbes such as *Anaerobutyricum*, which may contribute to improved insulin sensitivity. Given the rising incidence of non-communicable diseases among individuals with PKU, the impact of slow-release PS on gut microbiota and metabolic health warrants further investigation in larger studies. [\[OC-014\]](#)

Pinto *et al.* investigated if GMP, containing residual Phe, benefits satiety, oxidative stress, renal function, inflammation, and gastrointestinal (GI) tolerance due to its prebiotic properties. GMP significantly improved several GI symptoms compared to AAs, including reductions in stomach pain ($p = 0.003$), heartburn/reflux ($p = 0.04$), wind/bloating ($p = 0.02$), and nausea ($p = 0.02$). There was also a trend toward reduced constipation ($p = 0.068$) and discomfort with eating ($p = 0.07$). No significant differences

were found for markers of renal function, oxidative stress, inflammation, or measures of satiety. Plasma AA analysis showed that levels of isoleucine ($p=0.03$), leucine ($p=0.01$), and valine ($p<0.001$) were lower with GMP, while threonine was higher ($p<0.001$), though all remained within normal ranges. Notably, mean blood Phe levels were $114 \mu\text{mol/L}$ higher with GMP compared to AAs ($p<0.001$), with no differences observed in tyrosine levels.

GMP-based PS significantly improved GI symptoms in children with PKU, offering potential benefits over traditional AA-based PS. However, the residual Phe in GMP poses challenges, particularly for children with minimal Phe tolerance, as indicated by the higher blood Phe levels. While GMP may enhance GI tolerance, its Phe content must be carefully managed in the dietary treatment of PKU. Further research is needed. [\[OC-015\]](#)

Comparison of 34 early and continuously treated adults with PKU (ETAwPKU) adults (16 females; mean age 28 years; SD 9) with 34 age- and sex-matched controls regarding nutrient status, dietary intake, and cognitive wellbeing was conducted by Couce *et al.* All participants were on a PS, but adherence to a Phe-restricted diet varied.

ETAwPKU participants had significantly lower blood nutrient concentration of 12/19 AAs, while Phe ($p\leq 0.0001$) and glycine ($p<0.05$) levels were higher. Vitamins D ($p\leq 0.0001$), B12 ($p\leq 0.0001$), B6 ($p\leq 0.0001$) and folic acid ($p\leq 0.0001$) were significantly higher in ETAwPKU, whereas vitamin E was lower ($p<0.05$). No differences were found in docosahexaenoic acid (DHA), calcium, ferritin, transferrin, or zinc, except selenium (lower in ETAwPKU) and magnesium (higher in ETAwPKU). Dietary intake of minerals and vitamins was higher in ETAwPKU, with no significant differences in energy, fibre, and protein intake.

Blood DHA and micronutrient status of ETAwPKU who take PS were adequate, except for selenium. Patients relied heavily on PS to meet nutritional needs, and further research is needed to understand the clinical implications of these findings. [\[PO-590\]](#)

At the SSIEM Dietitian Group meeting, Dr Alex Pinto presented the results from a longitudinal study on the natural protein intake and dietary management of patients with PKU in Europe and Turkey, with the aim of understanding how natural protein tolerance varies with age and Phe levels. Data from 1,323 patients aged between 1–57 years were collected retrospectively from nine centres between 2012 and 2018, and dietary intake, Phe tolerance, and the impact of PKU severity on protein requirements analysed.

The study found that natural protein intake increases with age in PKU patients, starting at approximately 7 g/day in children under 2 years and peaking at 31 g/day in adults aged 19–30 years. Patients with mild PKU tolerated approximately 50% more natural protein compared to those with more severe forms, with no significant differences in protein intake between males and females. Phe tolerance was highest in childhood at 1.3 g/kg of body weight, decreasing to 0.6 g/kg per day after age 31, and some patients no longer required protein substitutes as they aged.

Dr Pinto concluded that natural protein intake steadily increases through childhood, peaking in young adulthood, with mild PKU patients tolerating higher protein levels than those with severe PKU. There is a need for further research on other food sources and specific protein requirements based on factors such as growth, age, and PKU severity. The authors emphasised the importance of individualised dietary management for PKU patients and called for future guidelines to account for variations in protein tolerance.

[\[SSIEM Dietitian Group meeting\]](#)

Therapeutic approaches in metabolic disorders

This section explores cutting-edge strategies and technologies being developed to treat a variety of IEM, with data highlighting approaches to pave the way for more effective and personalised treatments.

Exploring how incorporating freely available fruits and vegetables, which contain low levels of Phe, into patients' diets affects their Phe tolerance and metabolic control compared to classical medical nutrition therapy (MNT) was presented by Akbulut *et al.*

A total of 28 patients (median age 7 years old) receiving classical MNT were informed which fruits and vegetables they could consume freely, how other natural protein sources should be portioned, and current treatment regimens changed. Data were collected over two periods, 6 months before and 6 months after the dietary change. During the 6-month period before the study, the mean AA mixture intake increased from 1.5 g/kg/day (SD 0.4) to 1.6 g/kg/day (SD 0.4) in the 6 months after the study. The average Phe intake increased from 265 mg/day (SD 144) before the study to 458 mg/day (SD 154) in the 6 months after the study. Blood Phe levels remained stable, indicating that metabolic control was not compromised, with mean blood Phe levels of 257 $\mu\text{mol/L}$ (SD 181) before the study and 263 $\mu\text{mol/L}$ (SD 170) after; within recommended range.

This study demonstrated that incorporating freely available fruit and vegetables into PKU diets can increase Phe tolerance without negatively impacting metabolic control, suggesting that such dietary modifications may offer greater flexibility and dietary variety, improving overall QoL while maintaining necessary restrictions to control PKU. [\[PO-599\]](#)

Safety, tolerability, and efficacy findings from a Phase 1/2 clinical trial investigating JNT-517, a novel SLC6A19 inhibitor, designed to lower plasma Phe levels in patients with PKU were presented by Harding *et al.* JNT-517 offers a potential new therapeutic approach by blocking the reabsorption of Phe in the intestines and kidneys, thereby reducing its concentration in the bloodstream.

The double-blind, placebo-controlled trial involved adults aged 18–65 years who were able to maintain a stable Phe diet during the trial, and who had a baseline plasma Phe level $>600 \mu\text{mol/L}$. Participants received either 75 mg or 150 mg of JNT-517 two times a day (BID) or placebo for 28 days. Significant reductions in plasma Phe were observed as early as Day 7, with substantial decreases by Day 28 (75 mg, $p=0.0019$; 150 mg, $p=0.0002$). In the 75 mg and 150 mg BID groups 37.5% and 81.8% of patients had Phe levels below $600 \mu\text{mol/L}$, respectively. Additionally, JNT-517 selectively reduced Phe levels without affecting other AAs in the blood, and reduction in plasma Phe levels was closely linked to increase in Phe excretion in urine, which peaked early in the treatment and then stabilised.

JNT-517 was well-tolerated, with no serious adverse events (SAEs) reported. Mild to moderate gastrointestinal side effects such as nausea and diarrhoea were the most common, but were manageable and did not lead to discontinuation of treatment.

JNT-517 significantly lowered Phe levels with good tolerability and minimal side effects. These results support further exploration of JNT-517 as a therapeutic option in patients with PKU. [\[PO-566\]](#)

Morotti *et al.* provided an update on the Phenylalanine Families and Researchers Exploring Evidence (PHEFREE) Consortium's study, a group of eight academic centres and the National PKU Alliance (NPKUA) that focuses on understanding the health, cognitive, behavioural, psychiatric, and QoL impacts of PAH deficiency, bipterin synthesis/recycling disorders, and DNAJC12 deficiency. The study investigated the impact of hyperphenylalanine (hyperPhe) through collecting medical, dietary, laboratory, and patient-reported outcome measures annually from individuals with hyperPhe identified through newborn screening (NBS).

As of August 2024, 138 participants (66 with PAH deficiency) aged 3 months–60 years were enrolled, with 47 completing the first annual follow-up. The cohort is racially diverse, with 84% identifying as White, 10% as Hispanic/Latino, and 3% as Asian. Baseline assessments reveal that despite early therapy, individuals with PAH deficiency demonstrate persistent deficits in fluid cognition, specifically in areas such as attention and cognitive flexibility. These cognitive issues were evaluated using the NIH Toolbox and the Connors continuous performance test-3 (CPT-3), with a notable proportion of participants also experiencing anxiety, depression, or both.

Preliminary data from 73 participants suggest that these cognitive deficits persist across age groups, highlighting the need for ongoing longitudinal assessments to determine their clinical significance. Future plans for the study include recruiting individuals with disorders involving bipterin synthesis or recycling (such as DNAJC12 deficiency), and efforts to further diversify the cohort in terms of racial and ethnic representation. The ongoing research will enhance the understanding of how hyperPhe affects cognitive development and mental health, and in guiding treatment strategies. [\[PO-584\]](#)

Barroso *et al.* presented findings from a study investigating sepiapterin's dual action in treating PKU, with the hypothesis that it functions not only as a precursor to BH₄ but also as a pharmacological chaperone.

Through molecular modelling and laboratory analyses, sepiapterin was compared with BH₄ on both wild-type PAH and common BH₄-unresponsive variants. Sepiapterin demonstrated enhanced PAH stabilization and enzyme activity across tested variants (R68S, R261Q, Y417H), with docking studies revealing it binds within the PAH enzyme's BH₄ pocket, forming additional stabilizing bonds. Laboratory assays further confirmed that sepiapterin, more so than BH₄, dose-dependently increased stability and activity of mutant PAH, supporting its chaperone effect.

The dual action of sepiapterin, serving as both a BH₄ precursor and a PAH stabilizer, offers therapeutic promise for PKU patients with some residual PAH function, particularly those with BH₄-unresponsive variants. [\[PO-565\]](#)

Symposia and panel discussions

Industry-sponsored symposia and panel discussions brought together experts to explore the evolving landscape of PKU management. These sessions addressed a wide range of topics, from the dietary challenges faced by patients with PKU to emerging therapeutic options.

Satellite Symposium (BioMarin)

PKU management in evolution: Discussion on the changing soundscape

Presenters:

Professor Ania Muntau, Dr Johannes Krämer, Professor Júlio César Rocha

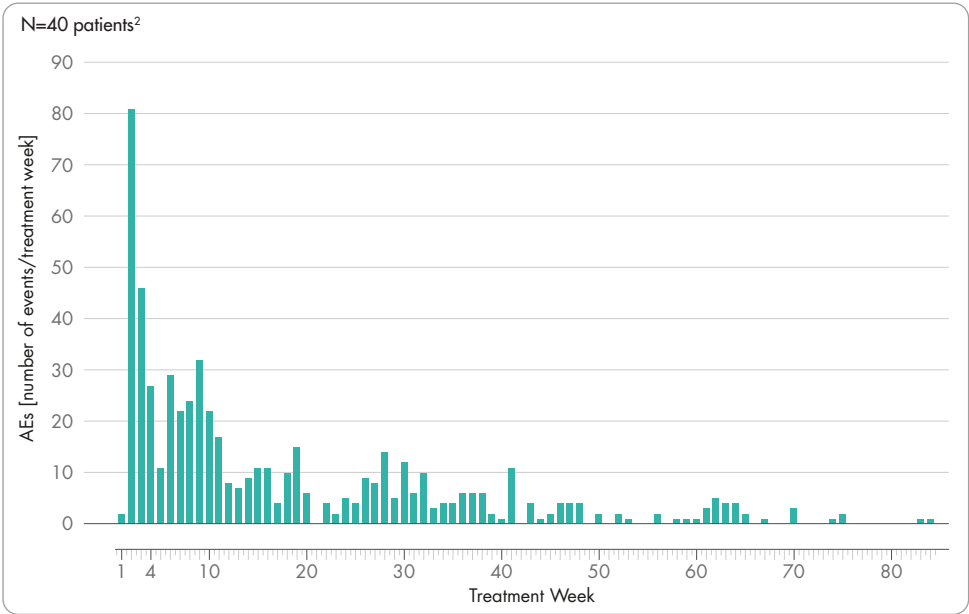
Professor Ania Muntau was joined by Dr Johannes Krämer and Professor Júlio César Rocha as they discussed the latest developments in PKU treatment, with focus on current challenges in managing PKU and the emerging role of pegvaliase as a treatment option.

The symposium began with a discussion on the pathophysiology of PKU, highlighting the practical challenges faced by adults with untreated or sub-optimally treated PKU, such as employment difficulties and adherence to strict dietary restrictions. Professor Rocha noted that while adherence to the PKU diet is crucial for controlling Phe levels, it becomes increasingly difficult with age due to rising social and practical barriers. Although sapropterin dihydrochloride offers an alternative to dietary management, it is effective only for a subset of patients, underscoring the need for additional treatment options.

Pegvaliase, an enzyme substitution therapy, offers a therapeutic option for patients with PKU aged 16 years and older who have inadequate blood phenylalanine control despite prior management with available treatment options, and allows patients to metabolise Phe and achieve physiological blood Phe levels without the same degree of dietary restriction. Professor Muntau presented data from clinical trials which showed that by 48 months of treatment, 93% of patients in clinical trials had achieved blood Phe levels $\leq 600 \mu\text{mol/L}$, and 86.2% had reached physiological levels.

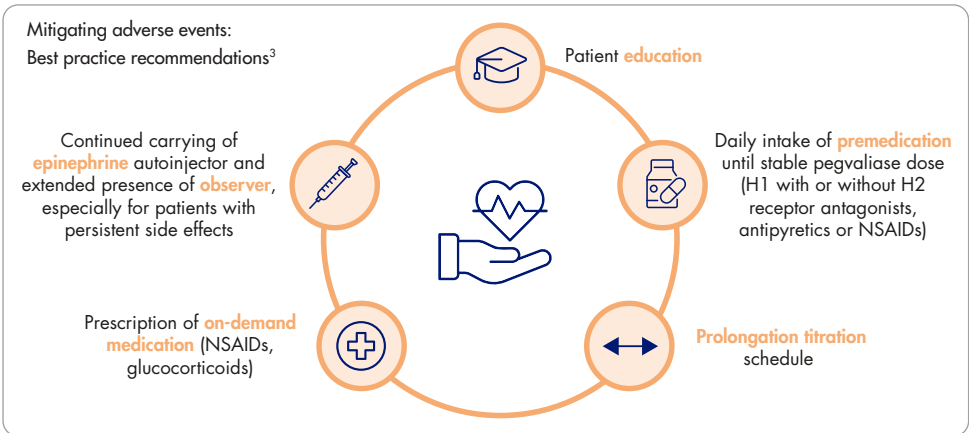
Professor Muntau highlighted that she has treated 40 patients with pegvaliase in her clinic, who have shown improvements in patients by stabilising blood Phe levels, improving neurological function and QoL. Professor Muntau shared real-world case studies, which included a 48-year-old patient who regained partial mobility and vision after years of severe PKU symptoms and another who, after struggling with dietary compliance, achieved substantial reductions in blood Phe levels and improved cognitive function with pegvaliase. These case studies highlighted the therapeutic potential of pegvaliase in managing long-term complications of PKU, particularly for patients who had struggled to adhere to traditional dietary treatments.

The presenters emphasised that traditional dietary management often imposes a heavy burden on both patients and their families, limiting their social interactions, food choices, and autonomy. The National PKU Alliance (NPKUA) survey identified that in 463 participants the most desired outcomes when considering new treatments were reductions in blood Phe levels (87.5%), improved attention and ability to focus (65.7%), enhanced executive functioning (61.6%), and improved mood (55.1%).¹

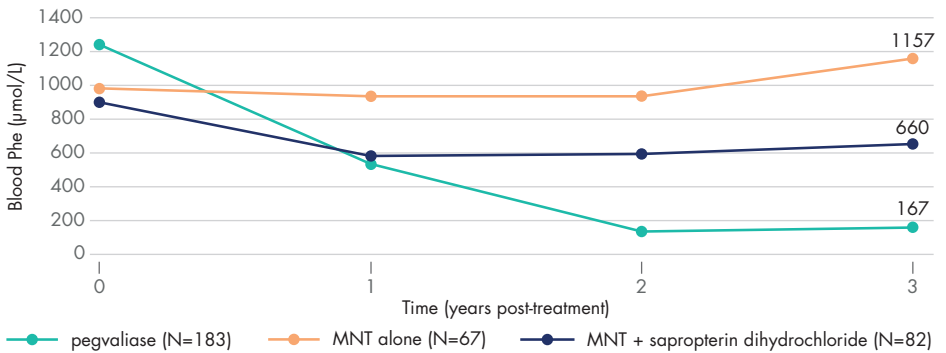


The presenters also discussed the management of AEs associated with pegvaliase. Hypersensitivity reactions, including anaphylaxis, were a key concern. The data showed that AEs were most common during the induction and titration phases of treatment, with hypersensitivity reactions subsiding in most cases over time. Dr Krämer presented key

strategies for mitigating these effects, including close monitoring during treatment initiation, dose adjustments, and supportive therapies. Dr Krämer also emphasised the importance of educating patients on the potential immune-related side effects and providing clear communication about the signs to watch for.



Median blood Phe levels observed in PRISM and PKDOS studies⁴



*These studies have different study designs, populations and endpoints and are not meant for direct comparison.

Exploratory analysis of 3-year PRISM and PKUDOS* data of adults with blood Phe >600 µmol/L showed that pegvaliase reduced blood Phe levels and enabled a higher intact protein intake compared to MNT with or without sapropterin dihydrochloride. It was highlighted that the potential of sustained reduction achieved with pegvaliase may improve the long-term outcomes and overall QoL in individuals with PKU. The symposium highlighted the significant advancements made in the management of PKU, including the introduction of pegvaliase. Presenters emphasised the importance of understanding the patient needs, setting expectations, providing patient and caregiver education, and being able to adapt treatment plans for individuals. Attendees were polled on their likelihood of adopting pegvaliase as part of their clinical practice at the beginning and at the end of the symposium; there was a 14% increase (from 23% to 37%) who would treat their patients with pegvaliase if it were available in their country.

While traditional methods of managing PKU, such as diet and sapropterin remain valuable, pegvaliase presents a promising option, particularly for patients who are seeking alternatives to lifelong dietary restrictions. The symposium underscored the importance of continued research, patient-centred care, and the integration of new therapies into clinical practice to improve the lives of individuals living with PKU.

Satellite Symposium (Jnana Therapeutics)

Harnessing Hartnup as a potential treatment approach for PKU and related amino acid disorders

Presenters:

Dr John Throup, Professor Nicola Longo, Professor Cary Harding, Professor Ania Muntau

The session, moderated by Dr John Throup of Jnana Therapeutics, featured three key presentations, outlining the origins of current research, updates on clinical trials of JNT-517, and future therapeutic possibilities.

Professor Longo discussed Hartnup disorder, a rare genetic condition resulting from mutations in the SLC6A19 gene, which encodes a transporter responsible for reabsorbing neutral AAs such as tryptophan (Trp), Phe, and leucine (Leu) in the kidneys and intestines. A defect in this transporter leads to excessive loss of AAs in the urine, manifesting as photosensitivity, neurological problems, and skin issues due to Trp and niacin deficiency. The knowledge gained from studying the mechanisms of transport inhibition laid the groundwork for targeting AA transporters, such as SLC6A19, in conditions such as PKU.

Professor Harding provided an update on the ongoing clinical trials of JNT-517, an investigational drug being developed by Jnana Therapeutics to treat PKU. JNT-517 is a first-in-class, orally bioavailable inhibitor of the SLC6A19 transporter. By blocking this

transporter, JNT-517 promotes increased urinary excretion of Phe, potentially reducing plasma Phe levels in individuals with PKU.

Professor Harding presented data from Phase 1/2 clinical trials, which showed that JNT-517 achieved significant reductions in plasma Phe levels in patients with PKU. Specifically, the 150 mg BID dose demonstrated a 60% mean reduction in plasma Phe, with most patients achieving clinically relevant reductions of over 30%. Importantly, JNT-517 was well-tolerated, with no significant AEs or disruptions in the levels of other AAs, such as tyrosine (Tyr) and Trp. The oral administration and favourable safety profile distinguishes JNT-517 from other PKU therapies, making it an alternative option for a broad range of patients, including those who may not tolerate or respond to current therapies.

Professor Muntau concluded by discussing the future potential of JNT-517 and its applicability beyond PKU to other AA metabolism disorders, such as Maple Syrup Urine disease (MSUD) and Urea Cycle disorders (UCD). There is a need for continued research into the role of AA transporters in metabolic disorders, as inhibiting transporters such as SLC6A19 could offer a new approach to treating a range of conditions that currently rely on restrictive diets and other burdensome management strategies. Future clinical trials for JNT-517, including a planned Phase 3 trial, will be critical in confirming these findings and expanding the therapeutic options for patients with PKU and other related conditions.

SDG Academy Review

Addressing dietetic challenges: Phenylketonuria, panel, and audience Q&A discussion

Professor Anita MacDonald

The SSIEM-DG Academy session on PKU offered crucial insights for healthcare professionals, focusing on the development and regulation of PS. Professor MacDonald emphasised the role of clinical dietitians and nutritionists in formulating PS with appropriate AA ratios, vital for managing PKU through MINT. While AA-based formulations are generally consistent, cGMP formulations meet minimal regulatory standards but lack uniformity in AA content and energy balance, which may lead to weight gain. EU regulations on foods for special medical purposes vary by country, affecting the approval and reimbursement of PS. Clinical benefits of cGMP include reduced blood Phe variability, improved growth, and lower fat mass, though mixed outcomes were noted for microbiota and bone mineral density.

The session also discussed challenges in accessing special low-protein foods due to supply chain issues and the rise of pharmaceutical treatments, leading to the discontinuation of many products in the UK. A study involving 12 PKU patients reported reduced gastrointestinal symptoms with cGMP formulations. The session concluded with a panel stressing the importance of product quality over quantity, better monitoring of AAs, and the need for balanced nutrition in PKU diets. International collaboration in PS regulation was encouraged, alongside greater involvement of dietitians and nutritionists in the development process, with a caution against over-regulation.

Abbreviations

AA	amino acid	Leu	leucine
AEs	adverse events	LNAA	large neutral amino acids
AUC	area under curve	MNT	medical nutrition therapy
BCAA	branch chain amino acids	MSUD	Maple Syrup Urine Disease
BH ₄	tetrahydrobiopterin	NBS	newborn screening
BID	two times a day	NPKUA	National PKU Alliance
BMI	body mass index	NSAIDs	non-steroidal anti-inflammatory drug
cGMP	casein glycomacropeptide	PAH	phenylalanine hydroxylase
C _{max}	peak concentration	Phe	phenylalanine
CPT-3	Connors continuous performance test-3	PHEFREE	Phenylalanine families and researchers exploring evidence
DHA	docosahexaenoic acid	PKU	phenylketonuria
EAA	essential amino acids	PS	protein substitutes
ETAwPKU	early and continuously treated adults with PKU	QoL	quality of life
GI	gastrointestinal	QUICKI	quantitative insulin sensitivity check index
GMP	glycomacropeptide	SAEs	serious adverse events
HOMA-IR	homeostasis model assessment insulin resistance	SD	standard deviation
HyperPhe	hyperphenylalanine	TAA	total amino acids
HypoPhe	hypophenylalanine	T _{max}	time to maximum
IEM	inborn errors of metabolism	Trp	tryptophan
L-AA	L-amino acids	Tyr	tyrosine
		UCD	Urea cycle disorders

References

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