# A Silent Crisis: A Pediatric MOGAD-ADEM Case to Remember

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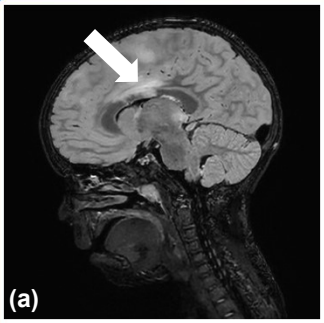
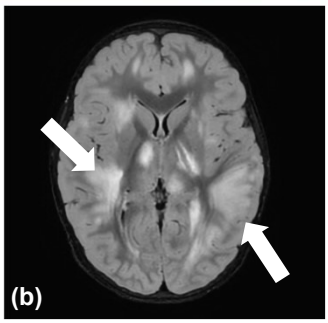
## Background

- **M**yelin **O**ligodendrocyte **G**lycoprotein **A**ntibody-associated **D**isease (MOGAD)
  - ➢ Rare autoimmune demyelinating condition of the central nervous system
  - ➢ Antibodies against the MOG protein → CNS demyelination
- **Epidemiology**: Global prevalence 2/100'000, ♂ = ♀, typical 0-40 years



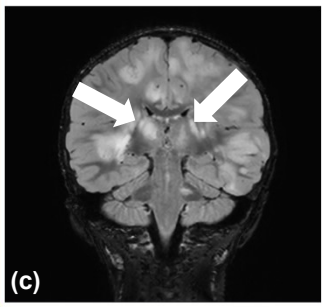




**Figure 1:** MRI on day 3 showing multiple T2 hyperintense white matter lesions (white arrows): (a) sagittal view, involvement of the corpus callosum, (b) axial view with "fluffy" hemispheric lesions involving the grey matter and cortical thickening, and (c) coronal view demonstrating bilateral thalami involvement.

- **Symptoms**
  - **ADEM (41%):** acute disseminated encephalomyelitis
  - **Optic neuritis (ON, 41%)**: mono- or bilateral, severe visual deficits
  - **Transverse Myelitis (12%)**: often severe with paraparesis
  - **Cerebral cortical encephalitis (5%)**: aphasia, focal seizures

  frequency ↑
  - ➢ Children more frequently with ADEM, adults more often optic neuritis
- **Diagnostics**
  - **Cerebrospinal fluid (CSF):** Mild pleocytosis (50-100/µl), Anti-MOG-IgG
  - **MRI**: usually heterogeneous and longitudinally extensive
    - Optic nerves: long lesions, mainly anterior segments
    - Spinal cord: generally >1 lesion, H-sign axially
    - Brain: fluffy lesions in white and deep grey matter, extensive involvement of cerebellar peduncles
- **Treatment**: High-dose steroids, intravenous immunoglobulin (IVIG), plasma exchange (PLEX) / immunoadsorption (IA) in severe cases
- **Prognosis:** Most cases with (near) complete recovery
  - Up to 30% relapse, mostly monophasic, rarely progressive
  - The risk of relapse correlates with serum MOG-IgG titers
  - Maintenance therapy may be required in cases of severe residual deficits or relapsing episodes.

## Case Presentation

| Treatment | Diagnostics | Day | Symptoms |
|---|---|---|---|
| | | -2 | **dysphagia** slurred **speech** motor weakness |
| High-dose **steroids** and **IVIG** | MRI: White matter lesions<br>Blood test unremarkable<br>CSF mild pleocytosis | 0<br>Transfer to ICU | somnolence meningism **aphasia** |
| **Anticonvulsants** | MRI: Progression of white matter lesions | 3 | focal and generalized **seizures** |
| **PLEX** | **Anti-MOG antibody** titer (**1:320**, ref: <1:10) | 6 | |
| **Delirium** treatment | Normalized EEG | 10 | coherent speech + hyperactive delirium |
| Steroid tapering | | 17<br>Discharge | **full neurological recovery** |
| | Anti-MOG antibody titer decline **(1:32)** | **5 month follow-up** | complete recovery **no relapses** |
| | Anti-MOG antibody titer normalized **(1:10)** | **12 month follow-up** | |

## Key points

- MOGAD is a rare, antibody-mediated demyelinating CNS disease. ADEM and ON are the most common presentation in children.
- Diagnosis is supported by typical MRI findings, and elevated anti-MOG antibodies in the serum.
- Multimodal immunotherapy (steroids, IVIG, PLEX) can lead to full neurological recovery, even in severe cases.

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# A Case Report : Complete Trisomy 5p

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## --- Background ---

Complete 5p trisomy is among the rarest autosomal trisomies, with fewer than 20 cases reported worldwide (1-4). Its phenotypic spectrum - marked by craniofacial dysmorphism, profound hypotonia, congenital heart defects, and life-threatening respiratory failure - remains incompletely defined despite prenatal diagnostic advances, posing substantial challenges for counselling and management.
Herein, we present a novel case of trisomy 5p, resulting from a mirror duplication.

## --- Case Timeline ---

### Prenatal

- Female infant diagnosed *in utero* with complete trisomy 5p
- Cytogenetic analysis identified a supernumerary derivative chromosome 5 with mirror duplication of the entire short arm (**Fig 1**)
- Pregnancy complicated by severe polyhydramnios
- Pathological CTG

### Perinatal

- Profound hypotonia and birth asphyxia upon delivery
- Severe respiratory distress requiring:
  - Immediate resuscitation
  - Prolonged ventilatory support
- APGAR score of 1/3/6/8
- Umbilical cord arterial pH of 7.15 and arterial lactate of 7.8 mmol/l

### Postnatal

- Multisystem involvement documented (Summarised in **Fig 2**), most noteably:
  - Congenital heart defects, CNS malformations, and hydrocephalus
  - Acute on chronic respiratory insufficiency
  - Dysmorphic features (**Fig 3**)
- Differing with past case reports (1), we observed:
  - Absence of epilepsy
  - Severe diaphragmatic hernia
- Alive at 13 months of age
- Severe prognosis discussed with family through shared decision-making:
  - Palliative-oriented care approach
  - Decision not to intubate

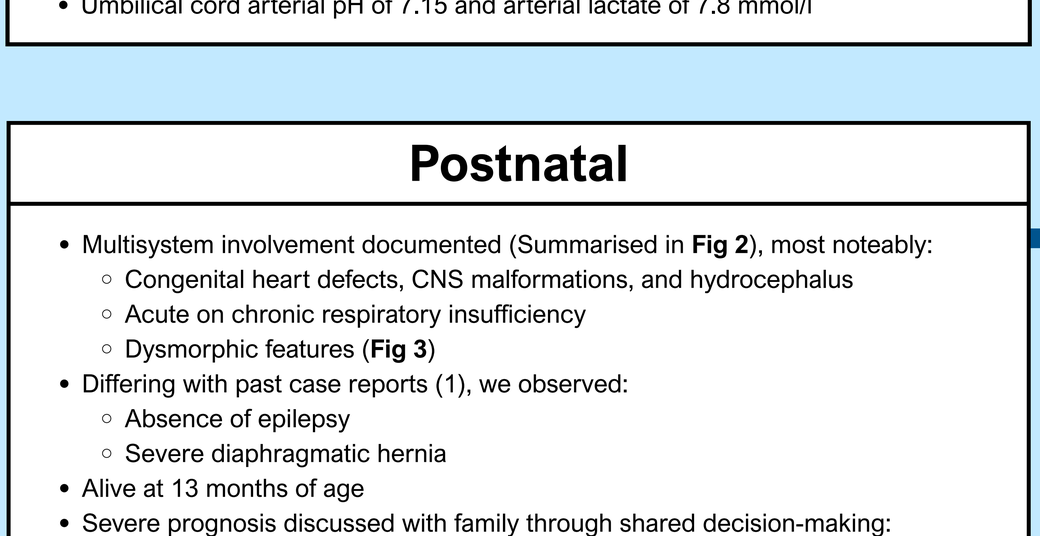

**Fig 3.** Images of the individual's phenotype showing facial dysmorphism and macrocephaly due to hydrocephalus.

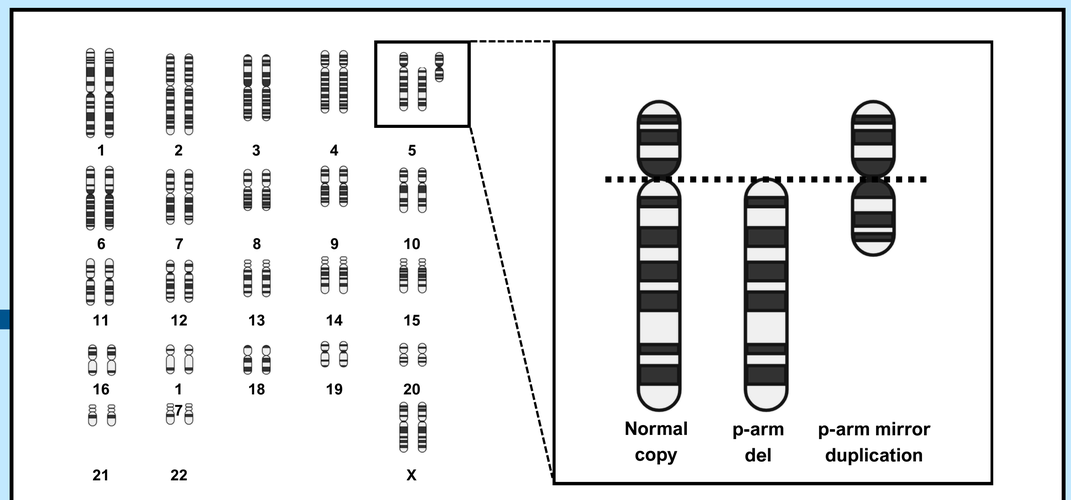


**Fig 1.** Schematic representation of the pathological karyotype of the patient with the structural anomaly highlighted with three copies of the short arm of chromosome 5.

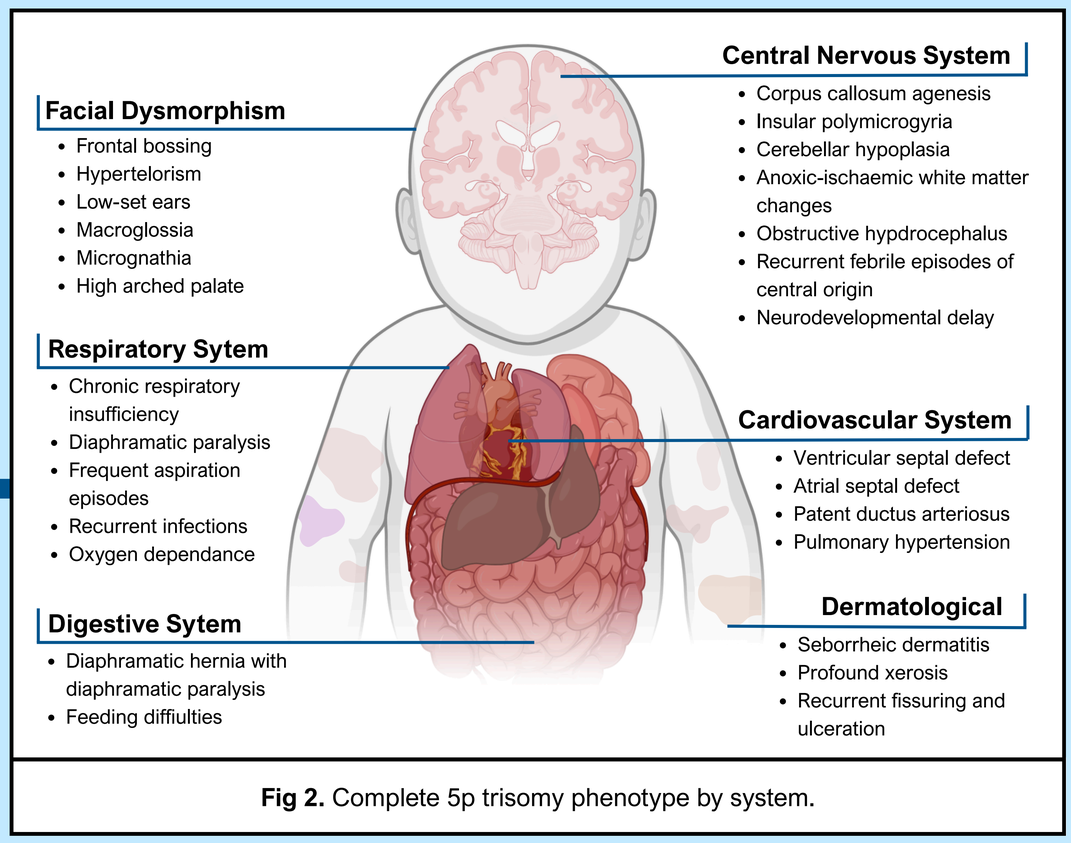


**Fig 2.** Complete 5p trisomy phenotype by system.

## Discussion and Conclusion

- Complete trisomy 5p is considered clinically distinct from partial trisomy 5p
- This report expands the phenotypic spectrum of complete trisomy 5p
- Prolonged survival, beyond one year, has been rarely described
- Illustrates major challenges in:
  - Prognostic counselling
  - Decisions regarding life-sustaining therapies
  - Long-term multidisciplinary care planning

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# From Sedation to Participation: Early Mobilization in the PICU Through a Multidisciplinary Lense

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Kantonsspital Graubünden

## Introduction

Over the past decade, declining mortality in pediatric intensive care units (PICUs) has shifted focus toward preventing PICU-acquired morbidities, including weakness, delirium and agitation. Immobility is a key modifiable risk factor associated with multi-organ dysfunction, delayed recovery, and long-term impairment in quality of life. This poster aims to explore and present the diverse perspectives of PICU care team members regarding early mobilisation.

## Case Report

An 11-year-old girl was admitted to our PICU with severe polytrauma following a ski accident. Injuries included bilateral lung contusions and lacerations, left-sided hemopneumothorax with rib fractures, thoracic spinous process fractures (T2–T6), posterior right hip dislocation, and fractures of the scapula and clavicle. The patient required intubation, chest drainage, vasopressor support, and prolonged mechanical ventilation with two failed extubation attempts. For optimal pain control a thoracic epidural catheter was placed. Despite the severity of her injuries, early mobilization was initiated after 72 hours with bedside activities while the patient was awake and intubated. Mobilization was performed twice daily through close interdisciplinary coordination. Following successful extubation, the patient was mobilized out of bed standing on day 15. Neurologically, she showed no signs of traumatic brain injury and was able to communicate non-verbally while intubated.

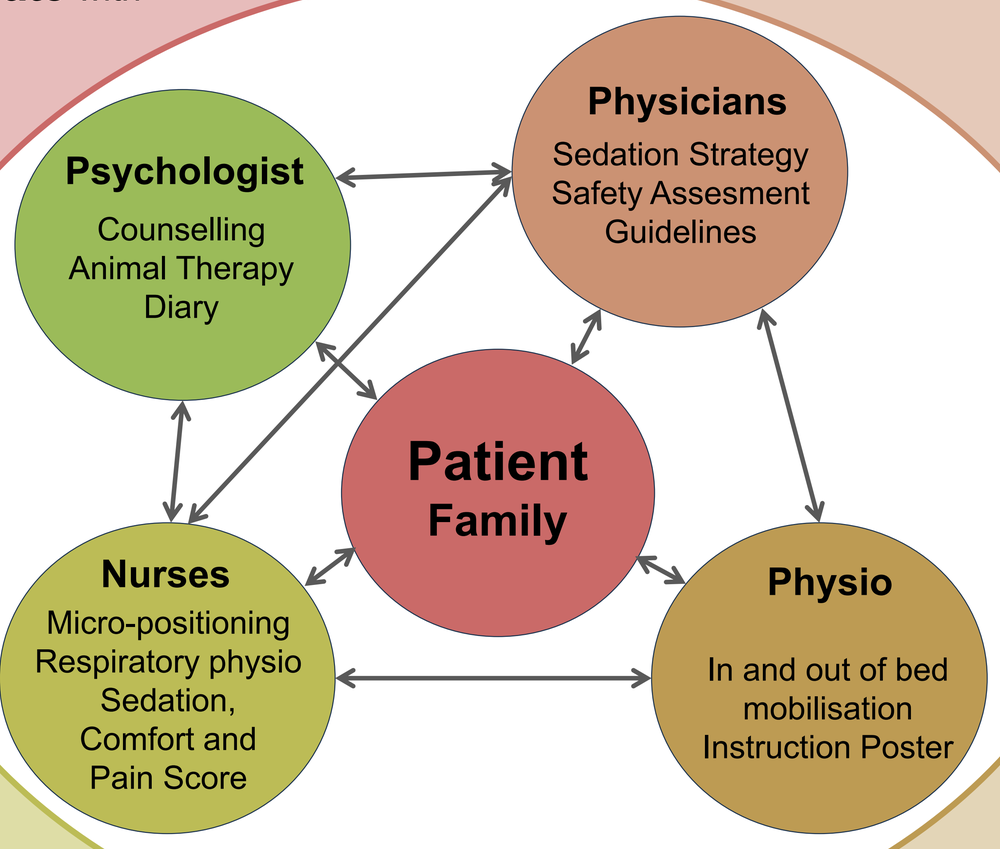
"I **don't remember** the intubation - the first two weeks are gone. Actually, I'm glad."

"I was surprised that C. could **communicate** with us in a **semi-awake state**."

"The nurses' **diary** helped **fill the gap** of what happened while she slept. She cannot remember the moments anymore, but with the help of the pictures she can **understand and process** it."

"**Thoracic epidural analgesia** was particularly helpful for mobilization, as it allowed **reduced sedation** and therefore active participation."

"A key challenge was **balancing** team **confidence** in safe early mobilization while **avoiding excessive demands** on the patient."




"The main challenges were **multiple injuries** and effective **pain management**."

"Mobilisation was **staff-intensive** and depended on **personnel availability**."

"Nonverbal **communication** was challenging."

"Early mobilisation required close **coordination** to create a good daily schedule with appropriate rest periods, **optimal medical dosing** and **clear communication** between shifts."

"**Clear guidelines** on mobilisation limits were essential."

"**Complex injuries** with diverse mobility limitations, **pain**, and **fear** made early mobilisation challenging."

## Discussion

In pediatric patients, early mobilization remains underutilized due to resource and time constraints, safety concerns, restrictive sedation practices, and limited patient ability or motivation to cooperate. These barriers were also encountered in our case. Initial concerns included the risk of hemodynamic instability and accidental dislodgement of tubes or lines during mobilization. Clear medical guidance and defined mobilization limits helped address these safety concerns. Careful adjustment of analgesia and sedation allowed the patient to remain awake while minimizing pain and anxiety. In addition, early mobilization required close interdisciplinary coordination between physicians, nurses, and physiotherapists, as well as sufficient staffing and active family involvement to support the patient throughout the recovery process.

**Image 1-3.** 11-year-old patient depicted at various stages of early mobilisation. Images are illustrated with patient consent.

## Conclusion

Our case demonstrates that concerns among the care team surrounding early mobilization in critically ill pediatric polytrauma patients can be overcome through clear guidelines, coordinated interdisciplinary teamwork, effective communication, and optimized sedation strategies, allowing early mobilization to be safely implemented.

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# Effect of Long-Term Sepiapterin Treatment on Dietary Phenylalanine Tolerance in Participants with Phenylketonuria: Interim Results from the APHENITY Extension Study

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aphenity extension study

## 1. Introduction

- PKU is an inborn error of Phe metabolism caused by pathogenic variants in the *PAH* gene encoding the PAH enzyme[1]
- PAH converts Phe to Tyr; therefore, a deficiency in the enzyme leads to elevated blood Phe levels, which, if left untreated, can cause neurocognitive and psychosocial problems[1,2]
- A lifelong Phe-restricted diet represents the current standard of care for patients with PKU;[2–5] however, this can adversely affect their growth, nutrition and HRQoL.[1,3,6] It is also challenging to adhere to, particularly as children transition to adolescence and adulthood[3]
  - Diet liberalization could therefore be an important treatment goal that may help to improve outcomes for those with PKU[7]
- Synthetic sepiapterin, a novel formulation of endogenous sepiapterin, is an oral therapy approved for use in adult and pediatric patients with PKU in the EU and Australia (all ages) and in the USA (aged ≥ 1 month)[8–11]
  - **Scan the QR code** for a video on the mechanism of action of sepiapterin
- In the Phase 3 APHENITY study (NCT05099640), 6 weeks of treatment with sepiapterin resulted in significant and clinically meaningful reductions in blood Phe levels compared with placebo in a wide range of participants with PKU[8]

## 2. Objectives

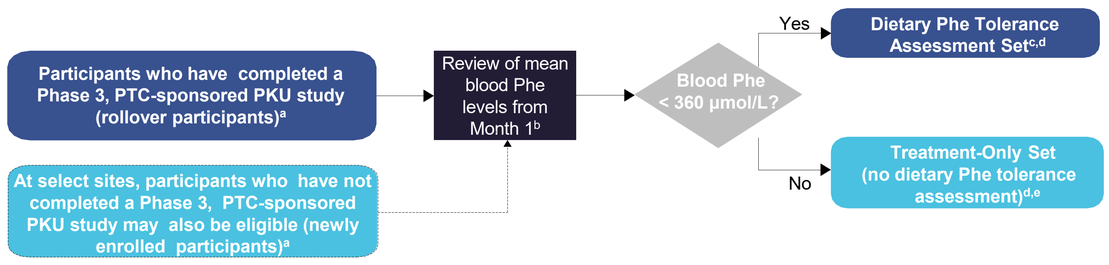
- To evaluate the long-term safety of sepiapterin and its effect on dietary Phe tolerance in children and adults with PKU in the ongoing Phase 3 open-label APHENITY Extension Study (NCT05166161)

## 3. Methods

### The APHENITY Extension Study is a long-term, ongoing, Phase 3, open-label, multicenter study

- The extension study (data cutoff: February 4, 2025) includes participants with PKU who have completed a PTC-sponsored Phase 3 PKU trial (rollover participants) as well as newly enrolled participants (**Figure 1**)

**Figure 1.** APHENITY Extension Study design (NCT05166161)




[a]All participants were to receive oral sepiapterin once daily for ≥ 1 year; as per Part 1 of the APHENITY trial, the dose was based on age and weight (aged 0 to < 6 months: 7.5 mg/kg/day; aged 6 to < 12 months: up to 15 mg/kg/day; aged 1–2 years: up to 30 mg/kg/day; aged ≥ 2 years: up to 60 mg/kg/day). [b]The mean blood Phe value from days 5, 10 and 14 was used to determine whether the participant qualified for enrollment in the 26-week dietary Phe tolerance assessment. [c]Participants underwent a 26-week dietary Phe tolerance assessment with dietary Phe adjustments performed every 2 weeks for 26 weeks, and mean blood Phe and dietary Phe intake values for Week 26 were calculated from the average from Weeks 25 and 26. [d]Details of AEs, concomitant medications and diet records were collected at each study visit. Blood Phe and Tyr tests were performed monthly, and HRQoL was assessed every 6 months. [e]Gradual diet liberalization was optional in these participants if diet was stable with blood Phe levels < 360 µmol/L for 2 consecutive months.

- The expected minimum treatment duration is ≥ 1 year
- At the Month 2, Day 1 visit, mean blood Phe levels from Month 1 were reviewed; participants with levels < 360 µmol/L were eligible to undergo a 26-week concurrent dietary Phe tolerance assessment
  - During the assessment, mean blood Phe and dietary Phe intake (from 3-day diet records) were assessed every 2 weeks, with changes in dietary Phe permitted according to a prespecified algorithm (**Table 1**)

**Table 1.** Guidance algorithm for increasing dietary Phe based on blood Phe levels

| Blood Phe level | Action |
|---|---|
| 0–180 µmol/L | Increase dietary Phe intake by 15 mg/kg/day |
| 181–240 µmol/L | Increase dietary Phe intake by 10 mg/kg/day |
| 241–300 µmol/L | Increase dietary Phe intake by 5 mg/kg/day |
| 301–359 µmol/L | No change |
| ≥ 360 µmol/L | • First instance: no change<br>• Second instance: remove last step of increase in dietary Phe intake<br>• Third consecutive increase: no change to Phe prescription and maintain the reduced Phe prescription set after the second instance<br>• Fourth consecutive increase: remove another step of dietary increase |

- Participants with mean blood Phe levels ≥ 360 µmol/L continued receiving daily treatment but did not participate in the dietary Phe tolerance assessment
- The primary endpoints are the change from baseline to Week 26 in dietary Phe intake during the dietary Phe tolerance assessment and the long-term safety of sepiapterin
  - Dietary Phe intake was evaluated in the Dietary Phe Tolerance Assessment Set, which comprised participants who received ≥ 1 dose of study drug during the 26-week dietary Phe tolerance assessment period
  - Safety was evaluated in the Safety Analysis Set, which consisted of all participants who received ≥ 1 dose of study drug

## 4. Results

### As of February 4, 2025, 223 participants had received sepiapterin and 117 had taken part in the dietary Phe tolerance assessment

- At the data cutoff, 136 participants (61.0%) had completed 6 months of the study and 126 participants (56.5%) had completed 12 months
- The median (min, max) age of all 223 participants was 13.0 (0.2, 55.0) years (see **Table S1** via the QR code)
  - Overall, 70.4% of participants were aged < 18 years and 2.7% were aged < 6 months
- In total, 117 participants (of whom 36 were newly enrolled) had mean blood Phe levels < 360 µmol/L during Month 1 and comprised the Dietary Phe Tolerance Assessment Set
- **Scan the QR code** for details on participant disposition

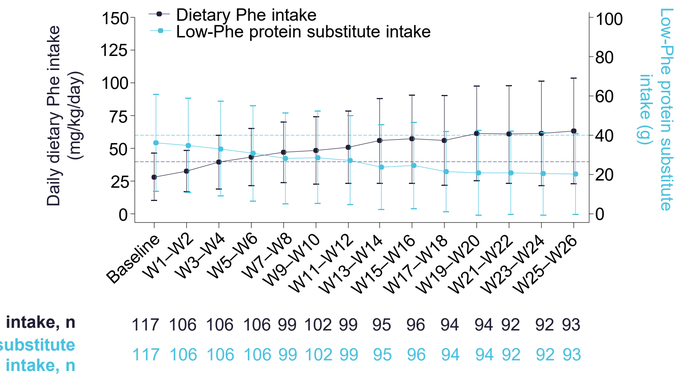
### Sepiapterin allowed for meaningful diet liberalization while maintaining blood Phe levels within the target range

- Dietary Phe intake was assessed in the Dietary Phe Tolerance Assessment Set (n = 117)
- Nearly all participants (94.0%) increased their dietary Phe intake at any time point during the 26-week dietary Phe tolerance assessment period; 68.4% doubled and 32.5% tripled their Phe intake from baseline
  - The mean (SD) dietary Phe intake increased from 28.5 (18.2) mg/kg/day at baseline (n = 117) to 63.5 (40.6) mg/kg/day at Week 26 (n = 93) (**Figure 2**); this represents an LS mean change of 36.8 (95% CI: 31.6, 42.0) mg/kg/day
  - The corresponding LS mean (SE) increase in daily dietary protein intake was 28.2 (2.5) g/day (170.7% increase) (**Figure S1**)
- Overall, 69.1% of participants were able to reach their age-adjusted RDA for protein intake
  - At the same time, the mean (SD) low-Phe protein substitute decreased from 36.2 (24.7) g/day at baseline (n = 117) to 20.3 (20.4) g/day at Week 26 (n = 93) (Figure 2); this represents an LS mean (SE) change of –17.1 (1.4) g/day (46.7% decrease)

## 4. Results (continued)

- Mean (SD) blood Phe levels remained below the recommended target of 360 µmol/L at Week 26 (355.51 [234.8] µmol/L; n = 92)
- The LS mean change in daily dietary Phe intake from baseline to Week 26 by subgroup (age, response to $BH_4$, pharmacological therapy at screening and biochemically diagnosed classic PKU) was consistent with the results of the primary analysis (see **Figure S2** via the QR code)
  - Of the participants receiving $BH_4$ at screening, 42.9% doubled their Phe intake from baseline to Week 26

**Figure 2.** Dietary Phe intake and low-Phe protein substitute intake from baseline to Week 26 in participants in the Dietary Phe Tolerance Assessment Set (n = 117)




Baseline is the mean of the Month 1 values for the daily dietary Phe intake. Dashed lines indicate the RDA for dietary Phe intake (dark blue) and low-Phe protein substitute intake (light blue).

### Sepiapterin was well tolerated for up to 3 years

- Safety was assessed in the Safety Analysis Set (N = 223)
- The median (min, max) exposure to sepiapterin in the Safety Analysis Set was 376 (1, 1087) days
- Overall, 60 participants (26.9%) had treatment-related TEAEs (**Table 2**), the majority of which were mild or moderate in severity
- The most common treatment-related TEAEs reported in ≥ 2% of participants were GI-related symptoms, as well as headache and fatigue (see **Table S2** via the QR code)
- Three participants (1.3%) discontinued sepiapterin owing to treatment-related TEAEs

**Table 2.** Summary of TEAEs reported in Safety Analysis Set

| AE category, n (%), number of events | Total (N = 223) |
|---|---|
| TEAEs[a] | |
| Any | 154 (69.1), 986 |
| Treatment-related[b] | 60 (26.9), 147 |
| Treatment-related TEAEs reported in ≥ 2% of participants | |
| Diarrhea | 16 (7.2), 18 |
| Discolored feces | 16 (7.2), 19 |
| Headache | 15 (6.7), 21 |
| Fatigue | 5 (2.2), 6 |
| Constipation | 5 (2.2), 7 |
| Vomiting | 5 (2.2), 8 |
| TEAEs grade 3 or higher | |
| Any | 9 (4.0), 12 |
| Treatment-related[b] | 1 (0.4), 1 |
| Increased bleeding tendency[c] | 1 (0.4), 1 |
| TEAEs leading to discontinuation | |
| Any | 3 (1.3), 4 |
| Treatment-related[b] | 3 (1.3), 4 |
| Constipation and nausea | 1 (0.4), 2 |
| Increased bleeding tendency[c] | 1 (0.4), 1 |
| Headache[d] | 1 (0.4), 1 |
| Serious TEAEs | |
| Any | 4 (1.8), 7 |
| Treatment-related[b] | 0 |
| TEAEs with an outcome of death | 0 |

[a]TEAEs were defined as AEs that occurred or worsened after the first dose of the study drug. [b]TE AEs assessed by the investigator to be 'probably related' or 'possibly related' to the study drug, or those with a reported relationship of 'missing'. [c]One participant experienced increased bleeding time (hemorrhagic diathesis) without laboratory findings pointing to hematological or immunological reasons; this resolved early after discontinuation of sepiapterin and recurred soon after re-challenge. The participant was on concomitant therapy (long-acting β agonist/inhaled corticosteroid inhaler), which may have resulted in a drug–drug interaction. [d]Headache was ongoing at the last assessment; the other events resolved upon treatment discontinuation.

## 5.CONCLUSIONS

- Interim results from this long-term extension study demonstrate that treatment with sepiapterin allowed a wide range of participants with PKU to meaningfully increase their dietary Phe intake
  - This includes those who were $BH_4$ non-responsive, those who had previously been treated with $BH_4$ and those who had biochemically diagnosed classic PKU
- Sepiapterin was well tolerated in children and adults, with no safety concerns emerging with long-term use
- These data provide further evidence for the clinical benefit of sepiapterin, allowing for diet liberalization in patients with PKU while maintaining blood Phe levels within target guidelines, which is a key goal for the treatment of PKU

**Abbreviations**
AE, adverse event; BH4, tetrahydrobiopterin; CI, confidence interval; GI, gastrointestinal; HRQoL, health-related quality of life; LS, least-squares; max, maximum; min, minimum; n, number of participants, PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; RDA, recommended daily allowance; SD, standard deviation; SE, standard error; TEAE, treatment-emergent adverse event; Tyr, tyrosine; W, week.

**References**
**1.** Elhawary NA et al. Hum Genomics 2022;16:22. **2.** van Wegberg AMJ et al. Orphanet J Rare Dis 2017;12:162. **3.** Anton-Păduraru D-T et al. Children 2025;12:199. **4.** van Wegberg AMJ et al. Mol Genet Metab 2025;109125. **5.** Smith WE et al. Genet Med 2025;27:101289. **6.** Oloffson S et al. Eur J Health Econ 2022;23:993–1005. **7.** Evers RAF et al. Nutrients 2022;14:3874. **8.** Muntau AC et al. Lancet 2024;404:1333–45. **9.** PTC Therapeutics. Summary of product characteristics, Sephience. EMA, 2025. https://www.ema.europa.eu/en/documents/product-information/sephience-epar-product-information_en.pdf (Accessed August 2025). **10.** PTC Therapeutics. Prescribing information, Sephience. FDA, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219666s000lbl.pdf (Accessed August 2025). **11.** PTC Therapeutics. Australian product information, Sephience. TGA, 2025. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2025-PI-01833-1&d=20250804172310101 (Accessed August 2025).

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P-39

# Sepiapterin Treatment and PKU-QOL Outcomes in Children, Adolescents and Adults with PKU: Results from the Dietary Phenylalanine Tolerance Subgroup in the APHENITY Long-Term Extension Study

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aphenity extension study

## 1. Introduction

- PKU is a rare autosomal-recessive inborn error of metabolism caused by a deficiency of phenylalanine hydroxylase, an enzyme that converts Phe to Tyr[1–3]
- This enzyme deficiency leads to elevated blood Phe levels, which, if left untreated, can cause severe intellectual disability and a reduced HRQoL[1–3]
- A lifelong Phe-restricted diet remains the mainstay of treatment for PKU; this negatively impacts HRQoL, and adherence to such a diet becomes increasingly challenging as children get older[1,3,4]
- Although avoided in patients whose blood Phe level is well controlled in infancy and childhood, adverse neurocognitive and psychiatric outcomes can develop later in life with the relaxation of Phe control[5]
- Synthetic sepiapterin, a novel formulation of endogenous sepiapterin, is an oral therapy approved for use in adult and pediatric patients with PKU in the EU and Australia (all ages) and in the USA (aged ≥ 1 month)[3,6–8]
  - **Scan the QR code** for a video on the mechanism of action of sepiapterin
- In the Phase 3 APHENITY study (NCT05099640), 6 weeks of treatment with sepiapterin resulted in significant and clinically meaningful reductions in blood Phe levels compared with placebo in participants with PKU[3]

## 2. Objectives

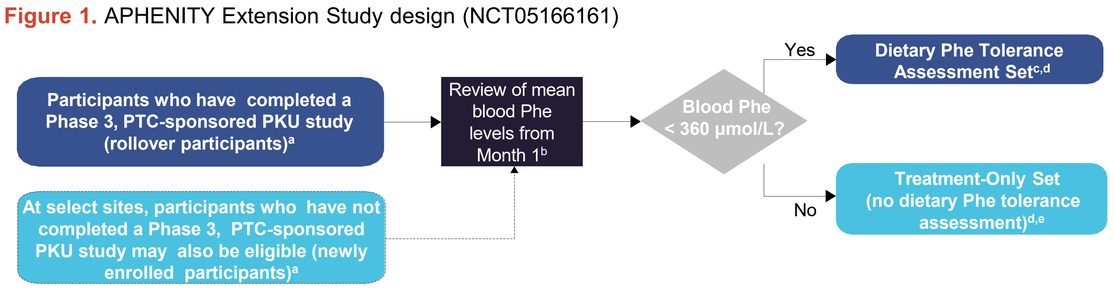
- To assess long-term HRQoL in sepiapterin-treated participants in the APHENITY Extension Study (NCT05166161) undergoing dietary Phe tolerance assessment

## 3. Methods

**The APHENITY Extension Study is a long-term, ongoing, Phase 3, open-label, multicenter study**

- The study comprises participants with PKU who (1) completed a PTC-sponsored Phase 3 PKU trial (rollover participants); and (2) were not previously involved in a PTC-sponsored Phase 3 trial (newly enrolled participants) (**Figure 1**)
- All participants were to receive oral sepiapterin once daily for ≥ 1 year, with dosing based on age and weight
- At the Month 2, Day 1 visit, mean blood Phe levels from Month 1 were reviewed; participants with levels < 360 µmol/L underwent a 26-week concurrent dietary Phe tolerance assessment
- During this assessment, mean blood Phe and dietary Phe intake (from 3-day diet records) were assessed every 2 weeks. Prescribed dietary Phe intake was adjusted using an algorithm designed to increase Phe intake while maintaining blood Phe < 360 µmol/L (**Table S1**)

**Figure 1.** APHENITY Extension Study design (NCT05166161)




[a]All participants were to receive oral sepiapterin once daily for ≥ 1 year; as per Part 1 of the APHENITY trial, the dose was based on age and weight (aged 0 to < 6 months: 7.5 mg/kg/day; aged 6 to < 12 months: up to 15 mg/kg/day; aged 1–2 years: up to 30 mg/kg/day; aged ≥ 2 years: up to 60 mg/kg/day). [b]The mean blood Phe value from Days 5, 10 and 14 was used to determine whether the participant qualified for enrollment in the 26-week dietary Phe tolerance assessment. [c]Participants underwent a 26-week dietary Phe tolerance assessment with dietary Phe adjustments performed every 2 weeks for 26 weeks, and mean blood Phe and dietary Phe intake values for Week 26 were calculated from the average from Weeks 25 and 26. [d]Details of AEs, concomitant medications and diet records were collected at each study visit. Blood Phe and Tyr tests were performed monthly, and HRQoL was assessed every 6 months. [e]Gradual diet liberalization was optional in these participants if diet was stable with blood Phe levels < 360 µmol/L for 2 consecutive months.

**Primary outcomes of the study include long-term safety and dietary Phe tolerance with sepiapterin treatment, and a secondary outcome of HRQoL**

- HRQoL was assessed using the self-administered PKU-QOL questionnaire
  - Use of the PKU-QOL© questionnaires is with permission from the copyright holder – PKU-QOL© BioMarin Pharmaceutical Inc. – 2015 – All Rights Reserved
- This questionnaire comprises four primary modules: PKU symptoms, PKU in general, supplement administration and dietary protein restriction
  - These modules contain various relevant domains, dependent upon the questionnaire version used (parent, child, adolescent or adult)
  - Scores range from 0 to 100, with lower scores associated with a better outcome
- In this analysis, PKU-QOL assessments were conducted at 6-month intervals using age- and language-appropriate questionnaires
- Conducting the PKU-QOL was not required in cases where the questionnaire was not available in the participant's primary language
- Twenty-four domains were evaluated, considering items common across the questionnaires for all participants aged ≥ 9 years who used the child, adolescent or adult questionnaire

## 4. Results

**At data cutoff (September 2, 2024), 169 participants were enrolled, of whom 102 underwent the dietary Phe tolerance assessment**

- Mean (SD) dietary Phe intake increased from 27.6 (18.0) mg/kg/day at baseline to 62.5 (41.5) mg/kg/day at Week 26 in participants who underwent the dietary Phe tolerance assessment (data from the February 4, 2025 cutoff are available in Poster 587)
- Of the 102 participants who underwent the assessment, 72 were aged ≥ 9 years (range: 9–54 years)
- Depending on the PKU-QOL domain, 49–57 participants reported baseline PKU- QOL assessments
- Baseline demographics and characteristics, including baseline PKU-QOL scores, are provided in **Table 1**

**Sepiapterin treatment was associated with improvements from baseline in several PKU-QOL domains**

- Consistent improvements were seen in 21 of the 24 domains across the four modules over 8–14 months of treatment (**Table S2**); no reduction in the symptom of 'Stomach aches' or improvements in 'Taste – supplements' or 'Taste – low- protein food' were observed

## 4. Results (continued)

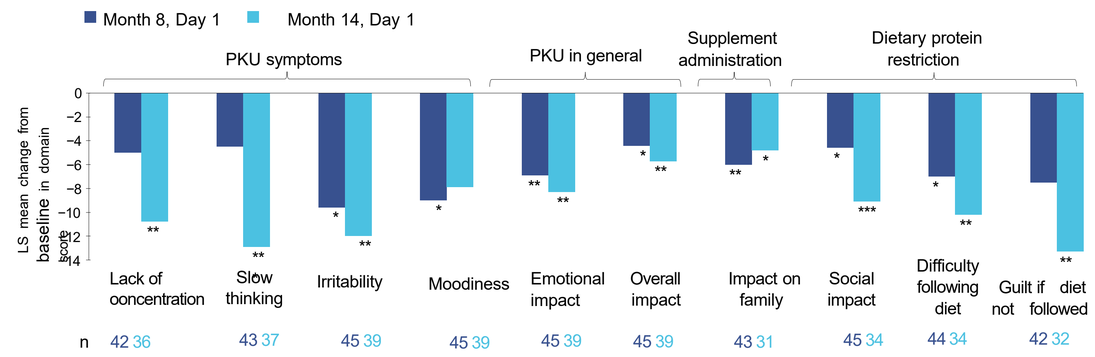
- Improvements from baseline (nominal $p < 0.05$) occurred in 10 domains at Month 8 or 14 (**Figure 2**). Sepiapterin treatment for 8–14 months was associated with various reductions in domain scores (i.e. improvements); LS mean changes from baseline are given in the following list
  - Marked improvements were found in the PKU symptoms module, including for slow thinking (−12.9; $p = 0.0002$) and lack of concentration (−10.8; $p = 0.01$)
  - An improvement was found in the emotional impact of PKU (−8.3; $p = 0.0019$), which represented a key driver towards the improvement in overall impact (−5.7; $p = 0.0079$) for the PKU in general module
  - Improvements in the impact of protein supplements on family (−4.8; $p = 0.0322$) and on the social impact of dietary protein restriction (−9.1; $p < 0.0001$) were found across the supplement administration and dietary protein restriction modules, respectively
- Sepiapterin was well tolerated in children and adults, with no safety concerns emerging with long-term use (see Poster 587 for long-term safety data)

**Table 1.** Baseline demographics and characteristics of participants aged ≥ 9 years in the dietary Phe tolerance assessment group

| Demographic/characteristic | Participants (N = 72) |
|---|---|
| Age at study start,[a] years | |
| Mean (SD) | 20.1 (10.1) |
| Sex, n (%) | |
| Male | 36 (50.0) |
| Female | 36 (50.0) |
| Race, n (%) | |
| White | 63 (87.5) |
| Asian | 4 (5.6) |
| American Indian or Alaska Native | 3 (4.2) |
| Other | 2 (2.8) |
| Ethnicity, n (%) | |
| Hispanic or Latino | 17 (23.6) |
| Not Hispanic or Latino | 55 (76.4) |
| BMI,[b] kg/m$^2$ | |
| Mean (SD) | 22.8 (4.9) |
| PKU-QOL module scores,[c] mean (SD) | |
| PKU Symptoms score | 235.1 (179.9) |
| PKU in General score | 106.1 (61.2) |
| Supplement Administration score | 104.5 (74.1) |
| Dietary Protein Restriction score | 159.4 (100.0) |

[a]Age when the participant received the first dose of sepiapterin in the APHENITY Extension Study. [b]BMI available for 70 participants only. [c]Baseline PKU-QOL module scores available for 55–57 participants only.

**Figure 2.** Change from baseline in domain score in the 10 PKU-QOL domains associated with improvements at Month 8 or 14 (nominal $p < 0.05$) in participants aged ≥ 9 years who underwent the dietary Phe tolerance assessment




*$p < 0.05$; **$p \le 0.01$; ***$p < 0.001$ versus baseline.
Lower PKU-QOL scores represent lower severity of PKU symptom, better adherence and lower impact of PKU.

## 5. CONCLUSIONS

- Interim results from the APHENITY Extension Study showed that in a subgroup of participants aged ≥ 9 years who underwent a dietary Phe tolerance assessment, 8–14 months of sepiapterin treatment was associated with improvements in various HRQoL domains
- Clinically meaningful HRQoL improvements from baseline were observed in key relevant domains across all four modules of the PKU-QOL questionnaire, including improvements in patient symptom burden (lack of concentration, slow thinking, irritability and moodiness) and the impact of PKU (including emotional and social)
- These HRQoL data supplement existing evidence regarding the added clinical benefit of sepiapterin for children and adolescents in the APHENITY Extension Study Phe Tolerance Assessment Set

**Abbreviations**
AE, adverse event; BMI, body mass index; HRQoL, health-related quality of life; LS, least-squares; Phe, phenylalanine; PKU, phenylketonuria; PKU-QOL, Phenylketonuria-Quality of Life; SD, standard deviation; Tyr, tyrosine.

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**1.** Blau N *et al. Lancet* 2010;376:1417–27. **2.** van Wegberg AMJ *et al. Orphanet J Rare Dis* 2017;12:162. **3.** Muntau AC *et al. Lancet* 2024;404: 1333–45. **4.** Olofsson S *et al. Eur J Health Econ* 2022;23:993–1005. **5.** Vockley J *et al. Genet Med* 2014;16:188–200. **6.** PTC Therapeutics. Summary of product characteristics, Sephience. EMA, 2025.https://www.ema.europa.eu/en/documents/product-information/sephience-epar-product-information_en.pdf (Accessed August 2025). **7.** PTC Therapeutics. Prescribing information, Sephience. FDA, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/label/2025/219666s000lbl.pdf (Accessed August 2025). **8.** PTC Therapeutics. Australian product information, Sephience. TGA, 2025. https://www.ebs.tga.gov.au/ebs/picmi/picmirepository.nsf/pdf?OpenAgent=&id=CP-2025-PI-01833- 1&d=20250804172310101 (Accessed August 2025).

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P-40

# Sepiapterin Responsiveness Over 14 Days in Children and Adults with Phenylketonuria: Pooled Results from Three Phase 3 Clinical Trials

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aphenity extension study

## 1. Introduction

- PKU is an inborn error of Phe metabolism caused by pathogenic variants in the PAH gene encoding the PAH enzyme[1,2]
- PAH converts Phe to tyrosine; therefore, a deficiency in PAH leads to elevated blood Phe levels that, if left untreated, can lead to neurocognitive impairment and psychosocial disorders[1,2]
- A lifelong Phe-restricted diet represents the current standard of care for patients with PKU;[2–5] however, this is challenging to adhere to and can adversely affect patients' growth, nutrition and health-related quality of life[1,3,6]
- Until recently, only two pharmacological therapies, sapropterin (synthetic $BH_4$) and pegvaliase, were approved for the treatment of PKU. However, these therapies have limitations and are not effective for many patients[1,7]
- Sepiapterin (Sephience) is a novel oral treatment which has a unique dual mechanism of action and is approved for the treatment of children and adults with PKU in several regions, including the USA (aged ≥ 1 month)[8–13]
- The efficacy and safety of oral sepiapterin have been assessed in three international Phase 3 studies: APHENITY (NCT05099640), the APHENITY Extension Study (NCT05166161) and AMPLIPHY (ISRCTN79102999)
  - In the APHENITY and AMPLIPHY studies, treatment with sepiapterin resulted in significant and meaningful reductions in blood Phe levels compared with placebo and sapropterin in a wide range of participants with PKU.[8,14] Furthermore, in the APHENITY Extension Study, sepiapterin treatment allowed participants to liberalize their diet[15]
  - In the APHENITY and AMPLIPHY studies, and in newly enrolled participants in the APHENITY Extension Study, there was an initial, 14-day trial period to assess sepiapterin responsiveness.[8,14,15]
  - Factors such as diet and illness can also influence blood Phe levels and, therefore, assessments of the time to sustained response are needed[16]

## 2. Objectives

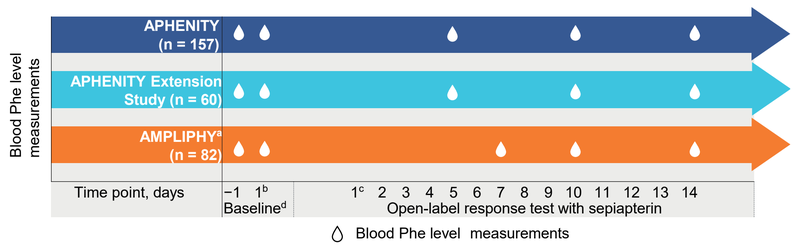
To assess overall response rates to sepiapterin, including time to sustained response during a 14-day period, across APHENITY, the APHENITY Extension Study and AMPLIPHY

## 3. Methods

**Data were pooled from APHENITY, the APHENITY Extension Study and AMPLIPHY 14-day, open-label response tests with sepiapterin**

- In total, 299 children and adults with uncontrolled PKU (blood Phe ≥ 360 µmol/L) in APHENITY (n = 157), the APHENITY Extension Study (n = 60) and AMPLIPHY (n = 82) underwent a 14-day, open-label response test with sepiapterin (≤ 60 mg/kg/day)
- Blood Phe levels were measured at baseline (Days −1 and 1 [pre-dose]) and at three time points during the first 14 days of sepiapterin treatment (APHENITY and the APHENITY Extension Study: Days 5, 10 and 14; AMPLIPHY: Days 7, 10 and 14) (**Figure 1**)
- To assess individual sepiapterin responsiveness, mean blood Phe values from the three time points post treatment initiation were compared with the mean value of the two pre-dose time points
- Participants were considered responsive to sepiapterin treatment if they achieved a mean reduction in blood Phe concentration of ≥ 15% from baseline over the first 14 days of treatment
- The proportion of responsive participants was assessed, and among these, the proportion of participants achieving a reduction of ≥ 30% was also evaluated
- The time to reach a reduction of ≥ 15% and ≥ 30% was estimated using Kaplan–Meier analysis among participants who had a sustained reduction of this magnitude from first occurrence up until Day 14
- TEAEs over the first 14 days of sepiapterin treatment were also assessed

**Figure 1.** Blood Phe level measurements during 14 days of sepiapterin treatment in APHENITY, the APHENITY Extension Study and AMPLIPHY




a Prespecified criterion for responsiveness in the AMPLIPHY study was a reduction from baseline of ≥ 20% in blood Phe levels15
b Day 1 pre-dose
c Day 1 post-dose
d Baseline blood Phe levels were measured on Days −1 and 1 pre-dose

## 4. Results

**Blood Phe levels at screening were elevated across all three studies**

- Participant demographics and characteristics at screening are shown in Table 1

**Table 1.** Participant demographics and characteristics at screening

| | APHENITY (n = 157) | APHENITY Extension Study (n = 60) | AMPLIPHY (n = 82) | Overall (N = 299) |
|---|---|---|---|---|
| **Age at screening, years** | | | | |
| Mean (SD) | 17.7 (12.2) | 17.3 (15.3) | 15.3 (10.6) | 17.0 (12.5) |
| Median (min, max) | 14.0 (1.4, 61.0) | 15.0 (0.2, 55.0) | 14.0 (2.0, 66.0) | 14.0 (0.2, 66.0) |
| **Sex, n (%)** | | | | |
| Male | 85 (54.1) | 25 (41.7) | 39 (47.6) | 149 (49.8) |
| Female | 72 (45.9) | 35 (58.3) | 43 (52.4) | 150 (50.2) |
| **Blood Phe level at screening, µmol/L** | | | | |
| Mean (SD) | 713.9 (317.8)[a] | 746.1 (345.6) | 578.6 (172.6) | 683.2 (298.1)[b] |
| Median (min, max) | 649.0 (81.9, 1990.0) | 679.5 (363.0, 2130.0) | 557.3 (348.3, 1332.09) | 613.7 (81.9, 2130.0)[b] |
| **Classic PKU, n (%)** | | | | |
| Yes | 36 (22.9) | 3 (5.0) | 15 (18.3) | 54 (18.1) |
| No | 121 (77.1) | 57 (95.0) | 67 (81.7) | 245 (81.9) |
| **Received pegvaliase or $BH_4$ before screening, n (%)** | | | | |
| Pegvaliase | 1 (0.6) | 3 (5.0) | 0 | 4 (1.3) |
| $BH_4$ | 80 (51.0) | 36 (60.0) | 71 (86.6) | 187 (62.5) |
| Both | 0 | 2 (3.3) | 0 | 2 (0.7) |
| **Receiving pegvaliase or $BH_4$ during screening, n (%)** | | | | |
| Pegvaliase | 1 (0.6) | 0 | 0 | 1 (0.3) |
| $BH_4$ | 27 (17.2) | 23 (38.3) | 38 (46.3) | 88 (29.4) |
| Both | 0 | 0 | 0 | 0 |
| **Responsive to $BH_4$,[c] n (%)** | | | | |
| Yes | 38 (24.2) | 19 (31.7) | 52 (63.4) | 109 (36.5) |
| ≥ 30% blood Phe reduction from baseline[d] | 32 (84.2) | 19 (100) | 47 (90.4) | 98 (89.9) |

[a]Based on 156 participants [b]Based on 298 participants [c]Based on medical history
[d]Percentage of participants calculated based on the number of participants who were BH responsive

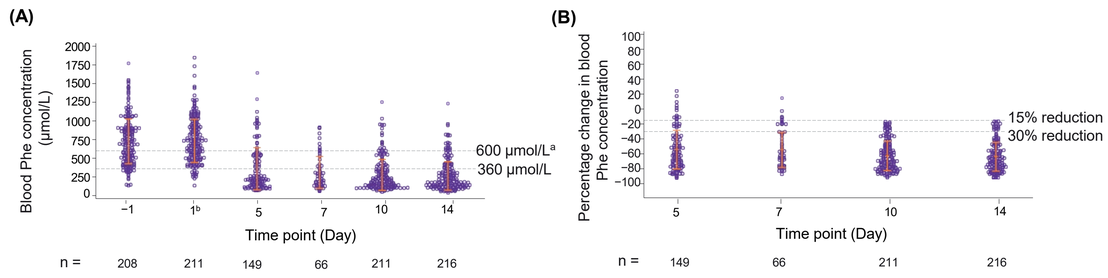
- Across all three studies, the overall mean (SD) blood Phe level at screening was 683.2 (298.1) µmol/L and 18.1% of participants (54/299) had biochemically defined classic PKU
- Before screening, 64.5% of participants (193/299) had received treatment with pegvaliase and/or sapropterin
- There were 81 participants who were not responsive to $BH_4$

## 4. Results (continued)

**Most participants were classified as responsive to sepiapterin within the first 14 days of treatment**

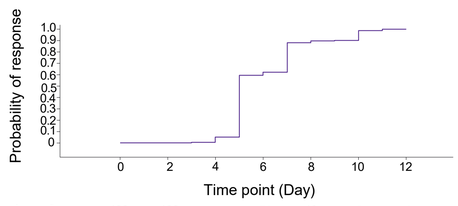
- Overall, 77.2% of participants for whom responsiveness data were available (230/298) were classified as responsive to sepiapterin treatment, with a reduction from baseline in blood Phe of ≥ 15% in the first 14 days of treatment in APHENITY (n = 114), the APHENITY Extension Study (n = 47) and AMPLIPHY (n = 69)
  - Of these participants, 87.8% (202/230) achieved a reduction from baseline in blood Phe levels of ≥ 30% in the first 14 days of treatment
- Among those classified as responsive (n = 230), mean (SD) blood Phe levels decreased from 728.6 (292.8) µmol/L at baseline to 304.2 (226.7) µmol/L over the first 14 days of treatment, representing a mean (SD) absolute reduction of 424.4 (221.0) µmol/L and a mean (SD) percentage reduction of 58.7% (20.3%)
- Most of the participants who achieved a sustained response had a ≥ 15% reduction in blood Phe from baseline by Day 5, although some responded by Days 10–14 (**Figure 2**)
- Among participants who achieved a sustained reduction in blood Phe levels from baseline of ≥ 15% (n = 217) by Day 14, the median time to response was 5 days, with a 90th percentile time of 8 days
- Among participants who achieved a sustained reduction in blood Phe levels from baseline of ≥ 30% (n = 186) by Day 14, the median time to response was 5 days, with a 90th percentile time of 9 days (**Figure 3**)

**Figure 2.** Blood Phe concentrations over time from Day –1 to Day 14 (A) and percentage change from baseline in blood Phe concentrations at each time point (B) in participants who achieved a sustained response




The orange bars represent the mean and SD ranges
[a]European guidelines recommend Phe levels < 600 µmol/L in patients aged ≥ 12 years[4] [b]Day 1 pre-dose

**Figure 3.** Kaplan–Meier curve for the time to ≥ 30% reduction in blood Phe from baseline in the first 14 days of sepiapterin treatment in participants who achieved a sustained response




| ≥ 30% reduction in blood Phe from baseline | Overall |
|---|---|
| **Number of participants, n** | 186 |
| **Time to sustained response, days** | |
| Median (min, max) | 5 (3, 11) |
| 90th percentile (95% CI) | 9 (7–10) |

| Number of participants at risk | 186 | 186 | 176 | 70 | 19 | 2 | 0 |
|---|---|---|---|---|---|---|---|

**Observed TEAEs were consistent with the known safety profile of sepiapterin[9–12]**

- Overall, 41.1% of participants (123/299) experienced at least one TEAE and 21.7% (65/299) experienced at least one treatment-related TEAE during the first 14 days of treatment with sepiapterin
- None of the TEAEs were serious or led to death, and there was only one occurrence of sepiapterin withdrawal, which was due to a TEAE of vomiting
- The most common treatment-related TEAEs were diarrhea (5.4%), discolored feces (4.3%) and headache (2.7%) (**Table 2**)

| TEAE category | Number of participants, n (%) (N = 299) |
|---|---|
| **Any treatment-related TEAEs[a]** | **65 (21.7)** |
| Diarrhea | 16 (5.4) |
| Discolored feces | 13 (4.3) |
| Headache | 8 (2.7) |

[a]TEAEs were assessed as 'possibly' or 'probably' treatment-related by the investigator

## 5.CONCLUSIONS

- Most participants enrolled in the Phase 3 APHENITY and AMPLIPHY studies and the APHENITY Extension Study achieved a sustained response to sepiapterin within 14 consecutive days of treatment, with a large proportion responding within 5 days
- Sepiapterin was well tolerated in the first 14 days of treatment in the pooled population of children and adults with PKU; TEAEs were in line with the known safety profile of sepiapterin and no serious TEAEs or deaths were reported
- These data are limited to the 14-day responsiveness assessment period; a response-testing period of ≥ 4 weeks should be used in clinical practice to account for factors that influence blood Phe levels, such as diet and illness
  - Studies to further evaluate time to response in real-world settings are needed
- These data support the use of a response test conducted over at least 14 consecutive days to effectively identify patients who will benefit from sepiapterin treatment

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**ABBREVIATIONS:** $BH_4$, tetrahydrobiopterin; CI, confidence interval; PAH, phenylalanine hydroxylase; Phe, phenylalanine; PKU, phenylketonuria; SD, standard deviation; TEAE, treatment-emergent adverse event

**DISCLOSURES: ML** has been an advisory board member for Applied Therapeutics, BioMarin Pharmaceutical, Maze Therapeutics and PTC Therapeutics; and has received clinical trial support from BioMarin Pharmaceutical and PTC Therapeutics. **NL** has received research and travel support from PTC Therapeutics; and has been a principal investigator for sponsored clinical trials with Amicus, BioMarin Pharmaceutical, Jnana Therapeutics, PTC Therapeutics and Ultragenyx. **MG** has been an advisory board member for PTC Therapeutics; has participated as a principal investigator for sponsored clinical trials for PTC Therapeutics; and has received speaker fees from Applied Pharma Research, BioMarin Pharmaceutical, Nestlé Polska, Nutricia, PTC Therapeutics, PTC Therapeutics Poland and Vitaflo. **JAT** has been an advisory board member for BioMarin Pharmaceutical; has been a consultant for BioMarin Pharmaceutical and PTC Therapeutics; has been a member of a Data Safety Monitoring Board for Otsuka Pharmaceutical; and has received clinical trial support from BioMarin Pharmaceutical, Homology Medicine, PTC Therapeutics, Sanofi and Synlogic Therapeutics. **AB-Q** has received advisory board fees, speaker fees and travel funding from PTC Therapeutics; and has received fees or funding from BioMarin Pharmaceutical, Danone, Grand Fontaine, Nutricia, Recordati Rare Diseases, Sanofi and Takeda. **IVDS** has received consultancy and symposia fees from PTC Therapeutics. **HP** has been an investigator in clinical trials sponsored by PTC Therapeutics; has received travel support and consultancy fees from PTC Therapeutics; and has participated in advisory boards and presentations from PTC Therapeutics. **KI**, **CH**, **ZZ** and **NS** are employees of PTC Therapeutics, Inc. **ACM** has received research funding and fees from BioMarin Pharmaceutical, Jnana Therapeutics, Otsuka Pharmaceutical, Maze Therapeutics, Pluvia Biotech and PTC Therapeutics.

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# The Swiss Red Blood Cell Disease Registry (RBCR) – an Introduction

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## Introduction

Hereditary red blood cell diseases (RBCD) such as sickle cell disease (SCD), thalassemia (alpha-THAL, beta-THAL), Diamond–Blackfan anemia and other rare anemia disorders (RAD) manifest in childhood and cause lifelong morbidity. Prevalence and disease diversity in Switzerland are increasing due to migration and improved survival. However, **national epidemiological data and harmonized long-term care structures are lacking.**

## Registry Objectives

The RBCR aims to:
1. Document the epidemiology of pediatric and adult RBCD in Switzerland
2. Longitudinally capture clinical course, complications, and treatment outcomes
3. Generate real-world evidence to support:
   - standardized care
   - structured transition from childhood to adult care
   - future interventional studies
   - future research projects linking RBCR data with biobank material

## Methods

**Design:**
Nationwide, prospective, non-interventional multicenter patient registry.

**Data collection**
Data collected centrally via REDCap® as part of routine care. Variables include:
- Demographics,
- Disease characteristics (diagnosis, genetics, laboratory findings, imaging results)
- Treatments (transfusion requirements, pharmacological therapies, curative approaches (HSCT, gene therapy))
- Disease-related complications
- Outcomes (survival, cause of death)

**Founding clinics (N=2):**
*Adult hematology:* University Hospital Zurich
*Pediatric hematology:* University Children's Hospital Zurich

**Amending clinics as of 04/2026 (N=13):**
*Adult hematology:* Centre hospitalier universitaire vaudois, Ente Ospedalierto Cantonal – Instituto Oncologico della Svizzera Italiana, Inselspital Bern, Kantonsspital Baselland, Kantonsspital Fribourg, Kantonsspital Aarau, Universitätsspital Basel
*Pediatric hematology:* Ente Ospedalierto Cantonal, Hôpitaux universitaires de Genève, Inselspital Bern, Kantonsspital Graubünden, Ostschweizer Kinderspital, Universitäts Kinderspital beider Basel

**Ethics & analysis**
Ethics approval will be reached by a two step process. First and currently, ethics application is submitted by the founding clinics to the Ethics committee of the canton of Zurich. Second, amending clinics will be submitting to the ethics committees of the respective cantons by the end of 2026.
Analyses will be primarily descriptive, with exploratory correlations to identify disease modifiers and outcome determinants. Integration with an established biobank is planned for the future.

**Support**
The RBCR is endorsed by the red cell expert group of the Swiss Society of Hematology (SSH) and the Pediatric Hematology Working Group of the Swiss Society of Pediatric Hematology and Oncology (PHWG SSPHO) and funded via competitive and non-competitive industry grants.

## Results

Estimated patient volume was assessed through an email survey conducted in April 2026 among 15 interested Swiss hematology clinics. Clinics reported the number of patients with SCD, alpha-thalassemia, beta-thalassemia, or other rare anemia disorders (RAD) treated in inpatient or outpatient settings.

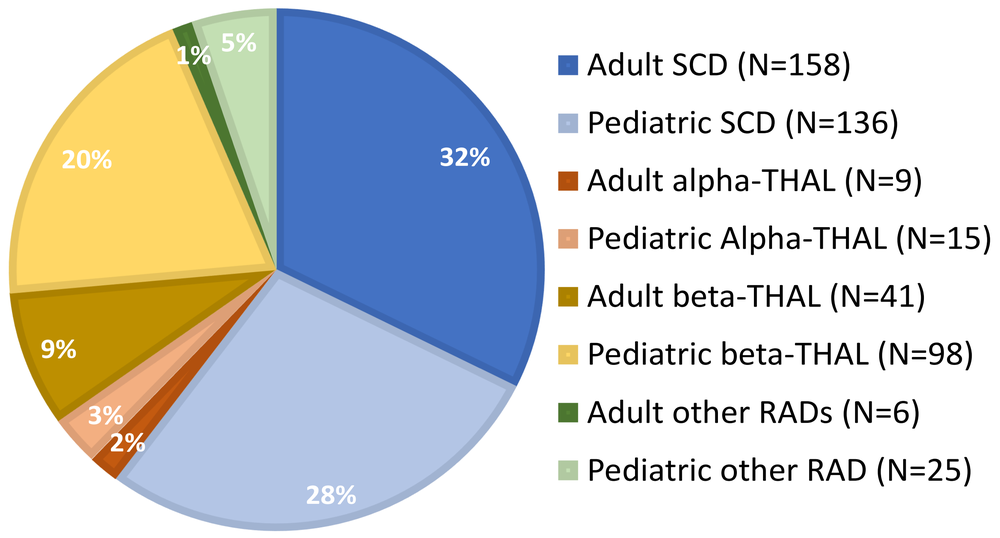


**Figure 1.** Estimated number of patients with rare red blood cell disorders (RAD) in Switzerland across 15 participating clinics (total N=488).

## International Collaboration

The RBCR will be set up in close collaboration with RADeep (Rare Anaemia Disorders European Epidemiological Platform). RADeep is an initiative of the ERN-EuroBloodNet as an umbrella for both new and already existing European patients' registries of RAD. As RAD are rare diseases the pooling of data in an international context is important to better understand diseases heterogeneity, increase statistical power, enable surveillance and international collaboration. The REDCap® platform for the RBCR will be set up as a mirror platform of RADeep to facilitate easy batch-transfer of collected and anonymized patient to RADeep.




**Figure 2.** RADeep epidemiological data replicated from www.radeepnetwork.eu

# Syncope during sports in an adolescent as the first presentation of a Wolff Parkinson White syndrome

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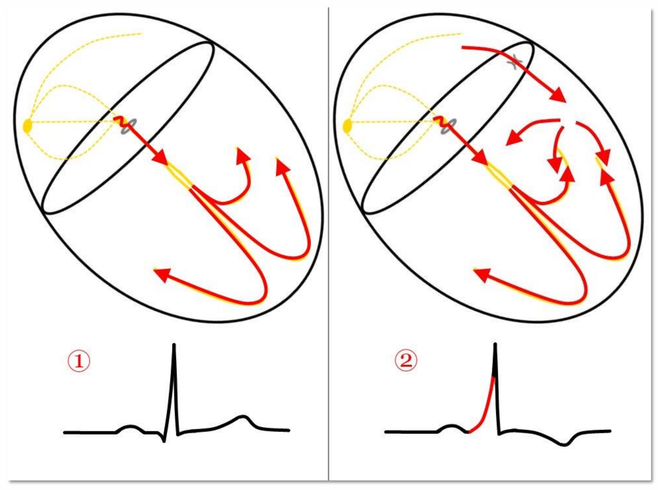
## Background:

Syncope in pediatrics is usually benign, but its occurrence during exercise may indicate a cardiac disorder with increased risk of sudden cardiac death (SCD).

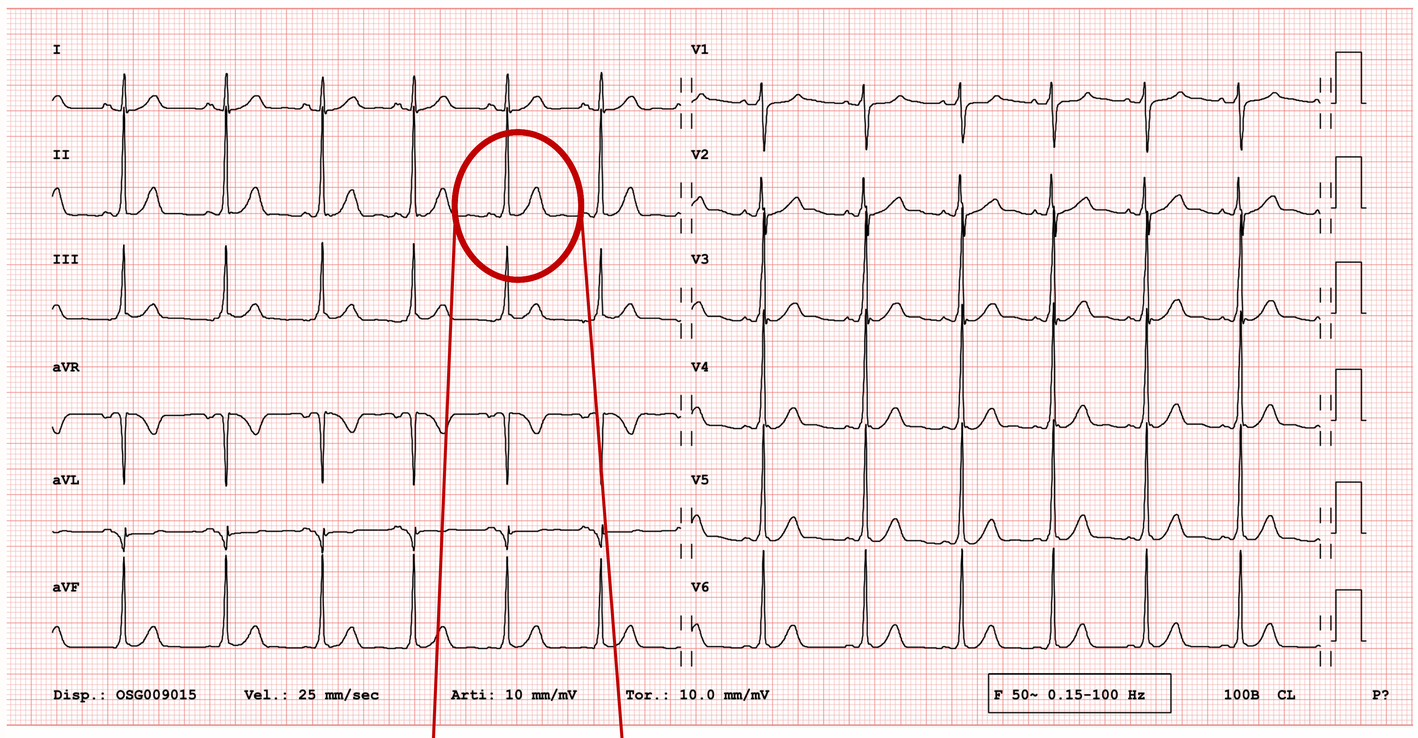
Wolff–Parkinson–White syndrome (WPW-S) is a rare cause of cardiogenic syncope: Prevalence=1:1,000, estimated risk of SCD=1:1,000 WPW patients-years.

SCD in general population due to WPW-S = 1:1,000,000




## Case:

- Patient: 15-year-old **healthy female**
- Presentation: First-ever episode of **palpitations followed by syncope during exercise**
- Characteristics suggesting cardiogenic origin:
  - **Sudden forward fall with facial trauma**
  - **No prodrome**
  - **Duration: approx. 10 seconds**
  - **Post-event confusion**



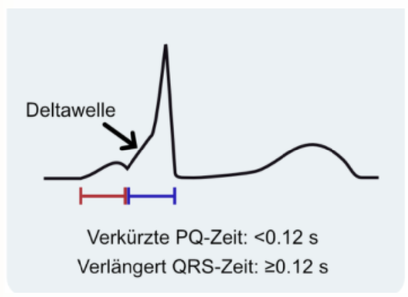




**Figure 1**: Resting ECG in the emergecy room. Ventricular pre-excitation, characterized by the presence of delta waves in all leads (red circle).

## On admission:

- Resting ECG: **ventricular pre-excitation** with delta wave indicating a left anterolateral accessory pathway (Fig.1)
- Diagnosis:
  1. Suspected cardiac syncope
  2. WPW-S
- No arrythmias during monitoring in hospital
- Initiation of **beta - blocker therapy**

## Outpatient Follow up:

- Asymptomatic
- Good tolerance of beta blockers
- Holter: **permanent WPW**

## Due to high–risk presentation:

- Electrophysiological study and Radiofrequency ablation were programmed

## Discussion:

- **Syncope during physical exertion should always raise suspicion and requires careful assessment to exclude a cardiac etiology with potential severe consequences**
- **WPW-S is a rare but significant cause of cardiogenic syncope, and the patient may remain asymptomatic until a first life-threatening event. Ventricular pre-excitation on the ECG is a key diagnostic finding.**
- **Early recognition of WPW-S allows timely risk stratification and appropriate management, including pharmacological treatment, eventual physical restriction and potential healing through radiofrequency ablation**