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| Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables | | | | |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author:  Burton et al., 2011  Country:  US, Canada, Poland, Germany, UK, Spain, France, Ireland, Italy  Enrollment period: 7/20062  Funding:  BioMarin Pharmaceutical, Inc.  Author industry relationship disclosures: Received grant support, honoraria, consulting fees, former / current employee & shareholders of BioMarin Pharmaceutical  Design: Uncontrolled Open label extension study | **Intervention:**  Multicentre, multinational, Phase 3b, extension trial of BH4 (PKU-008)  **G1:** Sapropterin  Dosage & duration: 5-20 mg/kg BH4 orally once daily for 3 years or until one of the following occurred: subject withdrew consent and discontinued the study; discontinued the study at the discretion of the investigator and in accordance with the investigator's clinical judgment; the drug became available via the appropriate marketing approval; or the study was terminated  All subjects from PKU-004 began PKU-008 at the dose they were taking at the end of PKU-004.  Subjects enrolled from PKU-006 began PKU-008 at 20 mg/kg/day BH4 despite PKU-006 Rx assignment (BH4 or placebo).  Dose levels adjusted in increments of 5 mg/kg/day within a range of 5-20 mg/kg/day in accordance with local clinical site recommendations.  Formulation: BH4 dissolved in 120-240 mL of water / apple juice for at least first 3 months. Modified later to allow intact tablets: taken before morning meal.  **No dietary restriction**  **Assessments:**  Drug safety at 3 month intervals for adverse events (AEs) and serious AEs , Blood Phe measures (2.5-5 hrs after meal), clinical lab | Inclusion criteria:   * BH4 responders who completed either PKU-004 or PKU-006 or subjects in PKU-006 who terminated early due to elevated Phe after increases in Phe intake   Exclusion criteria:   * Screening alanine aminotransferase value > 2× upper limit of normal * Concurrent use of levodopa or folate inhibitors * Pregnant females or subjects of childbearing potential not currently using or unwilling to continue with birth control.   Age, mean/yrs ± SD (range):  G1: 16.4 ± 10.2 (4-50)  **Other characteristics, mean days ± SD (range):**  Overall exposure to drug:  **G1:** 658.7 ± 221.3 (56-953) median = 595  While on dissolved tablet:  **G1:** 472.2 ± 284.2  While on intact tablet: **G1:** 378.0 ± 185  **Mean dose, mg/kg/day:**  Overall:  **G1:** 16.4 ± 4.4  While on dissolved tablet:  **G1:** 16.2 ± 4.6  While on intact tablet: **G1:** 16.8 ± 4.4 | **Cognitive:**  **IQ:**  NR  **Phe level, mean µmol/L ±** **SD (range):**  **G1:** 613.1 ± 328.5 (10-1533)  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **Phe level (µmol/L), n (%):**  Transitory low Phe levels after Rx:  ≤ 26 **G1:** 5 (4.5)  ≤120  **G1:** 27 (24.0)  Overall, BH4 controlled blood Phe levels throughout the study  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms:**  Any adverse event, %:  **G1:** 84  Drug-related AEs 37 (33.3%)  Most common drug-related AEs: viral gastroenteritis, vomiting, and headache (each 4.5)  Adverse events in ≥ 5% of patients:  headache, rhinorrhea, pharyngolaryngeal pain, diarrhea, and vomiting (commonly reported and consistent with PKU-004 & 006)  **Treatment emergent adverse events (TEAEs), n subjects [# events] (%):**  Infection and infestations:  **All1:** 74 [198] (66.7)  d-r\*: 11 [27] (9.9)  URI:  **All1:** 22 [28] (19.8)  d-r: 2 [2] (1.8) |
| Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued) | | | | |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Burton et al., 2011 (continued) | evaluations, physical & vital sign measurements  **Primary endpoint**:  Safety of long term exposure to sapropterin  **Secondary endpoints:** NR  **RX compliance**:  Minor deviations in compliance reported. 94.6% of subjects were at least 80% compliant.  **Length of follow-up:**  End of 3 years  **Groups, n at enrollment:**  **G1:** 111  (71 from PKU-004; 40 from PKU-006)  N at follow-up:  G1: 90 |  |  | Nasopharyngitis:  **All1:** 20 [30] (18.0)  d-r: 3 [6] (2.7)  Influenza:  **All1:** 9 [15] (8.1)  d-r: 1 [2] (0.9)  Viral infection:  **All1:** 8 [12] (7.2)  d-r: 1 [1] (0.9)  Gastroenteritis viral:  **All1:** 8 [9] (7.2)  d-r: 5 [6] (4.5)  Pharyngitis:  **All1:** 7 [13] (6.3)  d-r: 0  Gastroenteritis:  **All1:** 7 [7] (6.3)  d-r: 0  Bronchitis:  **All1:** 6 [7] (5.4)  d-r: 0  Gastrointestinal disorders:  **All1:** 43 [73] (38.7)  d-r: 14 [18] (12.6)  Vomiting:  **All1:** 20 [24] (18.0)  d-r: 5 [6] (4.5)  Diarrhea:  **All1:** 10 [16] (9.0)  d-r: 3 [3] (2.7)  Respiratory, thoracic,and mediastinal disorders:  **All1:** 36 [77] (32.4)  d-r: 4 [9] (3.6)  Cough:  **All1:** 21 [28] (18.9)  d-r: 3 [5] (2.7)  Pharyngolaryngeal pain:  **All1:** 10 [15] (9.0)  d-r: 1 [4] (0.9)  Nasal congestion: **All1:** 9 [13] (8.1)  d-r: 0  Rhinorrhoea:  **All1:** 6 [8] (5.4) |
| Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued) | | | | |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Burton et al., 2011 (continued) |  |  |  | d-r: 0  General disorders and administration site conditions  **All1:** 25 [33] (22.5)  d-r: 4 [5] (3.6)  Pyrexia:  **All1:** 18 [25] (16.2)  d-r: 4 [5] (3.6)  Nervous system disorders:  **All1:** 16 [53] (14.4)  d-r: 6 [25] (5.4)  Headache:  **All1**: 13 [48] (11.7)  d-r: 5 [23] (4.5)  **Total: n = 111**  **AEs by tablet type, n (%):**  Dissolved:  **G1:** 29 (26.4)  Intact:  **G1:**11 (19.6)  [n = 56]  **Withdrawal / discontinued Rx, n (%):**  **G1:** 3 (2.7)  One each of difficulty concentrating, decreased platelet count, and intermittent diarrhea. One patient with possible idiopathic thrombocytopenic purpura had consistently low platelet counts that were considered  possibly related to study drug and resulted in study withdrawal) |
| Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued) | | | | |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Burton et al., 2011 (continued) |  |  |  | **Severe AE, n subjects:**  **G1: 6 (**1 subject had difficulty concentrating and mood swings which resolved with altering timing of BH4 to avoid coinciding with levothyroxin medication)  **Serious AEs, n subjects:**  **G1:** 7  1 hospitalization for gastroesophageal reflux; patient had concomitant use of ibuprofen.  Other serious AEs reported include a testicular mass and subsequent lymphadenectomy, incontinence required surgical correction, tonsillectomy. menorrhagia and dysmenorrheal, neck injury due to a traffic accident, and gastroesophageal reflux.  No deaths or discontinuation due to serious AEs.  No age specific differences in AE reporting.  **Lab values:**  2 patients had clinically significant ALT and AST values, that  decreased after early terminiation  N=3 with Neutrophil counts < 1.0 x 10 9  N=24 < 1.5 x 10 9  All decreased in neutrophil count |
| **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Burton et al., 2011 (continued) |  |  |  | were transitory  N=13 with platelet  counts below lower limit of normal.  N=4 platelet count < 100 x 10 9,  **Modifiers:**  NR |

Comments:

Subjects here are from study # 800 (PKU-003), #771 (PKU-004) OR #1346 (PKU-006)  
1 All = all reported TEAEs; d-r = drug-related TEAEs   
No. (%) subjects who reported the event, No of events  
2 reported as 3-year extension trial that began in July 2006.

| **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | |
| --- | --- | --- | --- | --- |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author: Humphrey, 2011  Country:  Australia  Enrollment period:  10/2002 to 12/2010  Funding:  NR  Author industry relationship disclosures:  NR  Design: Prospective Cohort  Humphrey, 2011 (continued)  Humphrey, 2011 (continued)  Humphrey, 2011 (continued)  Humphrey, 2011 (continued) | **Intervention:** Tetrahydrobiopterin  **Groups:**  **G1:** BH4 responders **G2:** BH4 non-responders  Mean Dosage: NR  Mean duration of Rx: NR  Formulation: NR  **Assessments:**  Blood Phe levels, tyrosine levels, Phe/Tyr ratios along with their variability, at different ranges of Phe levels  **Primary endpoint**: Comparison of BH4 Rx effect on blood Phe/Tyr ratios and Phe variability over time in BH4 responders and BH4 non-responders  **Secondary endpoints:** Comparison of BH4 Rx effect on tyrosine level and variability over time in BH4 responders and BH4 non-responders, and on Phe levels, tyrosine levels, Phe/Tyr ratios and variability at different ranges of Phe concentrations  L**ength of follow-up:**  End of Rx  **Groups, N at enrollment:**  **G1:** 9 (1384 blood samples)  **G2:** 25 (4415 blood samples)  N at follow-up:  **G1:** 9 (1384 blood samples)  **G2:** 25 (4415 blood samples) | Inclusion criteria:  All newborn babies with hyperphenylalaninaemia > 400 µmol/L on initial screening and a BH4 load of 20 mg/kg prior to starting treatment  Blood samples collected over time from both responders & non-responders during treatment with BH4  Exclusion criteria:  See inclusion criteria  Age, mean/yrs ± SD:  NR  **Other characteristics:** On BH4 only:  n=2  Dietary modification: n=32 | **Cognitive:**  **IQ:**  NR  **Phe level, range,**  **µmol/L:**  **G1:** 566-1200 (n=7 subjects)  > 1200 (n=2 subjects)  **G2:** NR  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **Phe level,**  Median (95% CI), Mean (95% CI), N samples, µmol/L:  Phe:  **G1:** 338 (329–346)  358 (350–366), 1384  **G2:** 337 (332–344), 370 (332–344)  4415  t-test *P* = 0.025  Per Table 1 and Results section text the median is 337; per the abstract the median is 338. Per Table 1 the CI for the mean is 332-344; per the abstract the CI for the mean is 364-376.  **Phe level by Phe concentration range**, Median (95% CI), Mean (95% CI), N samples, µmol/L:  Phe:  For Phe range 0-200 µmol/L:  **G1:** 160 (155-166),  153 (148–158),  187  **G2:** 136 (133-138),  130 (127–133),  1183  t-test *P* < 0.000137  For Phe range 201-400 µmol/L:  **G1:** 306 (302-310),  304 (300-308),  745  **G2:** 302 (300-304),  302 (300-304),  2624  t-test *P* = 0.31  For Phe range 401-600 µmol/L:  **G1:** 469 (464-475),  477 (471-482),  349  **G2:** 482 (479-485),  488 (486-491),  1730  t-test *P* = 0.00019  For Phe range 601-800 µmol/L:  **G1:** 659 (648-670),  669 (658-680),  78  **G2:** 678 (673-682),  682 (678-686),  629  t-test *P* = 0.034  For Phe >800 µmol/L:  **G1:** 872 (800-943),  959 (888-1031),  20  **G2:** 898 (876-920),  963 (941-985),  307  t-test Not done  Variation in blood Phe greater in G2  Phe < 400 µmol/L, N samples (%):  **G1:** 934 (66.7)  **G2:** 2409 (62)  Phe > 600 µmol/L, N samples (%):  **G1:** 94 (7.5)  **G2:** 493 (12.7)  **Tyrosine level,** Median (95% CI), Mean (95% CI), N samples, µmol/L:  **Tyrosine:**  **G1:** 59 (58–61),  67 (66–69), 1384  **G2:** 62 (61–63),  70 (69–71), 4415  t-test *P* = 0.0083  **Tyrosine level by Phe concentration range**, Median (95% CI), Mean (95% CI), N samples, µmol/L:  Tyrosine:  For Phe range 0-200 µmol/L:  **G1:** 56 (52-60),  63 (59-67),  187  **G2:** 64 (62-66),  73 (70-75),  1183  t-test *P* < 0.000345  For Phe range 201-400 µmol/L:  **G1:** 57 (55-59),  64 (62-65),  745  **G2:** 59 (58-60),  67 (66-68),  2624  t-test *P* = 0.0031  For Phe range 401-600 µmol/L:  **G1:** 64 (60-67),  72 (68-75),  349  **G2:** 58 (57-59),  65 (64-66),  1730  t-test *P* = 0.0004  For Phe range 601-800 µmol/L:  **G1:** 79 (71-86),  84 (77-92),  78  **G2:** 62 (59-66),  70 (67-74),  629  t-test *P* = 0.0012  For Phe > 800 µmol/L:  **G1:** 85 (72-98),  87 (74-100),  20  **G2:** 64 (58-69),  74 (70-79),  307  t-test Not done  Variation in Tyr levels greater in G2  **Phe/Tyr ratio:**  Median (95% CI), Mean (95% CI), N samples:  Phe/Tyr ratio:  **G1:** 5.4 (5.3–5.6),  6.1 (5.9–6.3), 1384  **G2:** 5.4 (5.2–5.5),  6.4 (6.3–6.6), 4415  t-test *P* = 0.0042  **Phe/Tyr ratio by Phe concentration range**, Median (95% CI), Mean (95% CI), N samples:  Phe/Tyr ratio:  For Phe range 0-200 µmol/L:  **G1:** 2.6 (2.4-2.8),  2.8 (2.6-3.0),  187  **G2:** 1.9 (1.9-2.0),  2.2 (2.1-2.3),  1183  t-test *P* < 0.000173  For Phe range 201-400 µmol/L:  **G1:** 5.1 (5.0-5.3),  5.6 (5.4-5.7),  745  **G2:** 5.0 (4.9-5.1),  5.4 (5.3-6.5),  2624  t-test *P* = 0.047  For Phe range 401-600 µmol/L:  **G1:** 7.4 (7.0-7.7),  7.9 (7.6-8.3),  349  **G2:** 8.4 (8.2-8.6),  9.0 (8.8-9.1),  1730  t-test *P* < 0.000551  For Phe range 601-800 µmol/L:  **G1:** 8.7 (7.8-9.5),  9.2 (8.4-10.1),  78  **G2:** 11.0 (10.6-11.4),  11.7 (11.3-12.1),  629  t-test *P* < 0.000453  For Phe > 800 µmol/L:  **G1:** 12.5 (10.6-14.5),  12.3 (10.4-14.3),  20  **G2:** 14.5 (13.8-15.2),  15.4 (14.7-16.1)  307  t-test *P* = 0.007  Phe/Tyr ratio difference noticeable at blood Phe levels > 400 μmol/L and widened as Phe increased  **Genotype**:  NR  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms:**  **G1& G2:** Mild diarrhea  **Modifiers:**  NR |

| Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued) | | | | |
| --- | --- | --- | --- | --- |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author:  Burton, 2010  Country:  US  Enrollment period:  9/2003 to 9/2009  Funding:  BioMarin  Author industry relationship disclosures: BioMarin  Design: Retrospective case series | **Intervention:**  Sapropterin:  Dosage: 20mg/kg/day, single dose rounded up to the next 100mg increment  Duration: mean=19 months (range: 12-31 months)  **Assessments:** Blood Phe every 2 weeks for those < 12 years of age and once a month for ages over 12 years,  Compliance with dietary therapy by 3 day diet records  Compliance with BH4 , questioned at clinic visits & over the telephone but not by any pill count  Dietary phe intake was increased to the maximum level tolerated while maintaining blood Phe levels less than 360 umol/L  **Length of follow-up:**  End of treatment  **Groups**: **G1:** Sapropterin  **Groups, N at enrollment:**  **G1:** 37  N at follow-up:  **G1:** 37  **Responsiveness:**  A decline in blood phe of ≥ 30% after 2 weeks of treatment for those  subjects with baseline blood phe of at least 3 mg/dl or a decline in blood phe of 25% and improvement in  Symptoms. Those with baseline Phe < 3mg/dl were considered responsive if dietary Phe tolerance was ≥ 200mg/day by 4 wks of treatment | Inclusion criteria:   * Diagnosis of PKU and were receiving care in the PKU Clinic at Children's Memorial Hospital * Those responsive to BH4 during a 2- to 4-week treatment trial * On BH4 therapy for a minimum of 1yr at the time of data collection * To have a minimum of six blood phe levels available before and six after starting BH4 therapy   Exclusion criteria:  See inclusion criteria  Age, mean/yrs :  G1: 12.6 (range: 1.5-32)  Other character- istics, n :  Mild to moderate PKU: 22  Classical PKU: 17 | **Cognitive:**  **IQ:**  NR  **Phe level, mean ± SD:**  **G1:** 6.67 ± 4.2 mg/dl  **Phe Variability:**  **G1:** Within-subject variance: 6.897 (0.43)  **Nutritional:**  NR  **Quality of Life:**  NR | **Post treatment: Cognitive:**  **IQ:**  NR  **Phe level, mean ± SD:**  **G1:** 5.16 ± 3.78  Post Rx/ BL, *P* = 0.0002  **Phe Variability:**  **G1:** Within-subject variance: 4.799 (0.27)  Post RX/BL, significantly different (likelihood ratio test, chi-square=12.7, df = 2, *P* = 0.0017).  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms:**  NR  **Modifiers:** Increasing age associated with increasing phe variability , with older ages associated with higher levels of phe (for each 1 year increase in age, phe increases by  0.24 (0.05), p < .0001 after adjusting for repeated measurements).  A clear increase  in variance in older subjects  Phe variability as a function of age:  Between subjects Age < 3: 1.4708  Between subjects Age 3-10: 6.2798 |
| Burton, 2010 (continued) |  |  |  | Between subjects Age > 10: 7.6354  Within subjects: Age < 3: 3.6962  Within subjects: Age 3–10: 8.7274  Within subjects age ≥ 10: 9.4995 |

| **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | |
| --- | --- | --- | --- | --- |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author:  Trefz, 2010  Country: Germany  Enrollment period:  NR  Funding:  NR1  Author industry relationship disclosures:  NR  Design: Prospective case series | **Intervention:**  **G1:** Tetrahydobiopterin  Mean Dosage: 16mg/kg/ day (range: 5-26 mg/kg)  Mean duration of Rx: 56 months (range: 24-110 months)  Dietary restriction: n=7  Formulation: Tablets dissolved in a glass of water & taken once in the morning  **Assessments:**  Blood Phe measures at weekly intervals during 1st year of life, twice monthly from 2nd year & once / month in adults  **Primary endpoint:**  NR  **Secondary endpoints:** Long-term effects of BH4 treatment (Phe levels & Phe tolerance)  **Poor Dietary compliance:**  N = 2  **Length of follow-up:** End of Rx  **Groups, N at enrollment:**  **G1:** 16  N at follow-up:  **G1:** 16 | Inclusion criteria:   * Patients with Phenylketonuria * All patients must have received treatment for PKU in accordance with treatment guidelines: infants and children with Phe levels > 600μmol/l; adolescents and adults with Blood Phe of > 1200 μmol/L * Required a clear response to BH4 treatment with a > 30% reduction in blood Phe levels evident after either an acute BH4 -overload test (20 mg/kg body weight over 24 h) or long BH4 -overload test (20 mg/kg body weight over 8 days)   Exclusion criteria:  See inclusion criteria  Age:  G1: Range: 2-38.3 years (n=16)  **Other characteristics:**  BH4 therapy over 9 years:  n=1  Diet + BH4 :  n=9/16 | **Cognitive:**  **IQ:**  NR  **Phe level, mean ±** **SD, µmol/L:**  **G1:** range: 828-1454 (n=16)  **Phe intake** (among those with continued dietary restriction):  N = 7  200-300 mg/day  **Nutritional:**  **G1:** Body weight & height: 3rd percentile (n=1)  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  **G1:** Psychomotor development was within normal range in those with ages 5-6 years (HAWIK III)  14/16 achieved long-term Phe control (87.5%)  BH4  Responders: n=14 Non-responders: n=2  **Phe level , mean ±** **SD, µmol/L:**  **G1:** 321 ± 236, n=14  Phe decrease from BL:  **G1:** 54.6% (range: 28.4-85.6 %, n=16)  **Not dietary restriction and stable Phe control**; N=7  **Continued dietary restriction with increased Phe intake** h) to  800-1000 mg/day  (n=6)  Phe tolerance increased  4 times (n=5)  3 times(n=1)  2 times (n=1)  None (n=2)  **Genotype**: PAH genotype: p.R261Q/p.R243L (n=1)  p.R158Q/IVS4+5G>T (n=1) account for high (blood Phe) fluctuation index  **Nutritional:**  **G1:** Body weight & |
| Trefz, 2010 (continued) |  |  |  | height increased to > 50th percentile after relaxation of diet with a higher content of natural protein (n=1) & increased body weight observed after an increase of BH4 dose to 10mg/kg/day (n=1)  **Quality of Life:**  NR  **Harms:**  No Rx related side effects were observed; BH4 was well tolerated  **Modifiers:**  NR |

Comments:   
1 BH4 provided from Schircks laboratories, Switzerland: For 3 subjects BH4 was provided by BioMarin Pharmaceutical Inc.  
HAWIK III=Hamburg Wechsler Intelligence test fur Kinder

| **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | |
| --- | --- | --- | --- | --- |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author:  Vernon, 2010  Country:  US  Enrollment period: 1/2008 to 9/2009  Funding:  NCRR, NIH  Author industry relationship disclosures:  NR  Design:  Uncontrolled open label trial | **Intervention:**  Started with a 7-day trial of BH4 at 10 mg/kg/day. At day 8, plasma phe measured.  Responders were those with a 30% reduction in plasma Phe or reduction to treatment range of < 360 µmol/L after day 7.  BH4 increased to 20 mg/kg/day for non-responders, and levels rechecked again in 8 days. Patients who were not responders at this time continued BH4 for a total of 30 days and had Phe levels checked.  Responders on a Phe-restricted diet underwent gradual liberalization of their diet to the maximum tolerated natural protein intake while still maintaining plasma levels in the range of 120–360 lmol/L  **Groups:**  **G1:** Completed trial **G1a:** Responders **G1b:** Non-responders  **Dose required for response: G1a:**  7-15mg/kg/day: n=14  15-20mg/kg/day: n=4  Formulation: 100 mg pill dose closest to 10 mg/kg  **Assessments:**  Plasma Phe levels  **Length of follow-up:**  After the end of 30 days Rx  **Groups, N at enrollment:**  36  N at follow-up:  **G1:** 29  **G1a:** 18 **G1b:** 11 | Inclusion criteria:  Patients with Variant (plasma Phe 401-1199 µmol/L) OR Classical PKU (plasma Phe of > 1200 µmol/L)  No limiting dietary / trial baseline plasma Phe criteria  Exclusion criteria:  See inclusion criteris  Age, years:  mean=23.4, median=19, range: 3-58, n=39  **Other characteristics:**  **n (%):**  Disease classification:  Classical PKU: 15 (52) Variant PKU: 14 (48) | **Cognitive:**  **IQ:**  NR  **Phe level, µmol/L:**  Those on restricted diet, n (%): **G1:** 17 (59),  Phe=587.0  Range: 225-1363  Among those not on Phe-restricted diet, n:  **G1:** 12  Phe=1372.6  Range: 444-1847  G1a & Phe-restricted diet , 14:  Phe=484.9  Range: 225-1061  G1a & not on diet, 4: Phe=1049  Range: 444-1461  G1b: Phe=1422.3  Range: 783-1847  G1b & on protein-restricted diet, 3:  Phe=1063.7  Range: 783-1363  G1b & on unrestricted diet, 8:  Phe=1534.4  Range:1363-1847  **Phe tolerance:**  G1a on restricted diet: 21 mg/kg/day  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **G1a, n (%):** 18 (62)  Classical PKU, 4/15 (26.6)  Variant PKU, 14/14 (100)  Not on Phe-restricted diet, 4/12 (33.3)  On Phe-restricted diet, 14/17 (82.3)  **Phe level: Means, µmol/L:**  G1a & on Phe-restricted diet : Phe=226.1  Range: 28-696 (*P* < 0.0001) &  G1a & not on Phe-restricted diet : Phe=553.7  Range: 162-793 (*P* = 0.035, paired T-test)  G1b, n (%): 11 (38)  Phe=1332.6  Range: 731-1798  G1b & on protein-restricted diet, n=3:  Phe=978.7  Range: 731-1304  G1b & on unrestricted diet, n=8:  Phe=1465.4  Range: 1148-1798  **Phe Tolerance**  G1a on restricted diet: 41 mg/kg/day  Able to liberalize to unrestricted diet (n=2)  Positive behavioral improvements in 1 severely affected |
| Vernon, 2010 (continued) |  |  |  | untreated PKU  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms:**  NR  **Modifiers:**  NR |

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| **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | |
| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author:  Burlina, 2009  Country:  Italy  Enrollment period:  NR  Funding:  Centro Regionale Malattie  Metaboliche Ereditarie, Regione Veneto and COMETAASMME, Italy & in part by the Swiss National Science Foundation Grant  Author industry relationship disclosures:  NR  Design: Retrospective case series | **Intervention:**  **G1:** Long-term 6R BH4 treatment given to patients with PKU & Phe levels > 450 µmol/L and positive at BH4 loading  Dosage:10mg/kg, twice a day  Diet was relaxed based on Phe concentration  **Assessments:**  Blood Phe measured by tandem mass spectrometry  Dietary Phe tolerance by repeated 3- day dietary protocols  **Length of follow-up**:  6 months – 7 years  **Groups, N at enrollment:**  **G1:** 12  N at follow-up:  **G1:** 12 | Inclusion criteria:   * Known mutations in the PAH gene * Normal pterin profile and dihydropteridine reductase activity (no BH4 deficiency) * Patient or parental agreement with the BH4 loading tests * Patients who previously responded positively to the BH4 loading test performed after 6 months of age * Patients who do not fully comply with a Phe restricted diet   Exclusion criteria:  See inclusion criteria  Age, mean/yrs ± SD:  G1: 5.5 ± 4.7, range: 2-16  Other characteristics, n (%):  Normal Psychomotor development: 2 (16.7)  Study group:  Mild-moderate PKU | **Cognitive:**  **IQ:**  NR  **Phe level:**  **G1:** range: µmol/L  433-1215  **Phe tolerance: n (%)** < 700mg/day:  11 (91.7)  ≥ 700 mg/day:  1 (8.3)  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **Phe tolerance** on BH4 (mg/day)  Increased up to 2 to 3 fold from 498 + 49 to 1475 + 155 mg/day Range: 800-2700  A combined diet with Phe intake of 100mg/kg needed to maintain blood levels < 360 µmol/L in 5 patients  50% were BH4 responders with Phe levels of 450-900 µmol/L  **Genotype:** Mutations reported to be BH4 responsive were p.E390G, p.L48S, p.V388M, p.R158Q, p.G48S, IVS10-11g >a and p.I65V  **Nutritional:**  NR  **Quality of Life:**  **G1:** Report great improvement by patients & their families, no other data reported  **Harms:**  No side-effects were observed  **Modifiers:** NR |

| **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | |
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| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author:  Trefz, 2009  Country:  US, Germany, Spain & Poland  Enrollment period:  2/2006-11/2006  Funding:  BioMarin  Author industry relationship disclosures: National PKU advisory Board, Bio-Marin & Merck Serono S.A.-Geneva  Design:  RCT | **Intervention:**  Phase III, double-blind, randomized placebo-controlled trial of BH4  Part 2:After a washout period of ≥ 1 week, responders from Part 1 \* were randomized (3:1) to receive a 10-week course of sapropterin, 20 mg/kg/d, or placebo tablets, once daily.  Subjects with a blood Phe concentration of ≥1200 µmol/L in 2 consecutive weekly recordings were instructed to discontinue study drug treatment and receive dietary counseling. At the week 10 visit, follow-up visit was scheduled for Wk 14.  A stable Phe-restricted diet to be maintained throughout the study  After three weeks a dietary Phe supplement was added or removed every weeks according to Phe level  Formulation:BH4 (100mg) tablets were dissolved in 120 to 240 mL of wateror apple juice and the solution was administered within 30 minutes.  **Groups: G1:** BH4 **G2:** Placebo  **Assessments:**   * Phe levels at wkly intervals from wk 0 to wk 10 * Medical & dietary history * Use of concomitant medications * Blood chemistries * Hematology, urine analysis | Inclusion criteria:   * 4 to 12 years of age, had a diagnosis of PKU with PAH deficiency, an estimated Phe tolerance ≤1000 mg/d, * Under dietary control with a Phe-restricted diet, as evidenced by a mean blood Phe ≤ 480 µmol/L over the 6 months before study enrollment, as well as at screening   Exclusion criteria:   * History of organ transplantation, use of any investigational agent within 30 days before screening, serum alanine aminotransferase levels of > twice the upper limit of normal * Concurrent disease that might interfere with participation (including untreated neuropsychiatric disorders) * A requirement for treatment with any drug that inhibits folate synthesis, * Concurrent use of levodopa, or a diagnosis of primary BH4 deficiency   Age, mean/yrs ± SD:  G1: 7.7 ± 2.8 G2: 7.1 ± 2.0  **Other characteristics:** NR | **Cognitive:**  **IQ:**  NR  **Phe level, µmol/L:**  Over prior 6 months, mean ± SD:  **G1:** 314 ± 107  **G2:** 303 ± 74  Range: **G1:** 112-474 **G2:** 176-447  Mean blood Phe < 300 over prior 6 months, n (%):  **G1:**16 (48) **G2:** 5 (42)  **Part 2:**  Wk 0: Phe, mean ± SD: **G1:** 275.7 ± 135.2 **G2:** NR  **Dietary Phe intake (mg/kg/day), mean ±** **SD:**  **G1:** 16.3 ± 8.4, n=30 **G2:** 16.8 ± 7.6, n=9  **Tolerance, mg/kg/day:**  **G1:** 0  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **Part 2:**  Week 10: Phe supplement tolerated at last visit when blood Phe < 360umol/L, mean ± SD:  **G1:** 20.9 ± 15.4 mg/kg/d (95 % CI: 15.4 to 26.4) (*P* < 0.001 vs. BL)  **G2:** 2.9mg/kg/d  Adjusted Mean ± SE of RX difference in tolerated supplement =17.7 ± 4.5 mg/kg/d, 95%CI: 9-27 (*P* < 0.001)  Tolerance range, n (%)  10mg/kg/d:  **G1:** 12/33 (36)  **G2:** NR  11-30mg/kg/d:  **G1:** 10 (30)  **G2:** 0  31-50mg/kg/d:  **G1:** 11 (33)  **G2:** 0  Could not tolerate any supplement:  **G1:** 5 (15)  **G2:** 7/12 (58)  Total Phe intake at wk 10:  (dietary Phe  intake plus total Phe supplement taken)  **G1:** 43.8 (24.6) mg/kg/d (*P* < 0.0001 vs. BL)  **G2:** 23.5 (12.6)mg/kg/d (*P* = ns)  **Phe level, µmol/L:**  Wk3: Phe level,  mean ± SD:  **G1:** 127.2 ± 89.6  Difference between wk 3 & BL:  **G1:** -148.5 ± 134.2. |
| Trefz, 2009 (continued) | * Adverse events   **Primary endpoints:**  Phe tolerance (Phe tolerance defined as the cumulative increase or decrease in Phe supplement at which blood phe is ≤ 360 µmol/L)  **Secondary endpoints:** Difference in blood Phe in G1 between week 0 (before dosing) and week 3 (before Phe supplementation) and the comparison of G1 & G2 in the amount of Phe supplement tolerated at wk 10  **Length of follow-up: end of treatment 10 wks**  **Groups, N at enrollment:**  Part 2: Total N, 46  **G1:** 34  **G2:** 12  N at follow-up:  Part 2:  **G1:** 33  **G2:** 12 |  |  | *P* < 0.001  **G2:** -96.6 ± 243.6, *P* = 0.20  WK 10: Phe level,  mean ± SD:  **G1:** 340 ± 235  **G2:** 461 ± 235  Mean ± SE difference in Blood Phe between G1& G2 at wk 3:  -135.2 ± 26.9 µmol/L (*P* < 0.001)  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms, n (%):** Highest incidence (> 5% in G1) during part 2 of the study:  Rhinorrhea:  **G1:** 7 (21)  **G2:** 0 (0)  Headache:  **G1:** 7 (21)  **G2:** 1 (8)  Cough:  **G1:** 5 (15)  **G2:** 0 (0)  Pharyngolaryngeal pain:  **G1:** 4 (12)  **G2:** 1 (8)  Diarrhea:  **G1:** 4 (12)  **G2:** 0 (0)  Vomiting:  **G1:** 4 (12)  **G2:** 0 (0)  Abdominal pain  **G1:** 3 (9)  **G2:** 1 (8)  Contusion  **G1:** 3 (9)  **G2:** 1 (8)  Nasal congestion:  **G1:** 3 (9)  **G2:** 0 |
| Trefz, 2009 (continued) |  |  |  | Pyrexia:  **G1:** 3 (9)  **G2:** 2 (17)  Decreased appetite:  **G1:** 2 (6)  **G2:** 0 (0)  Erythema:  **G1:** 2 (6)  **G2:** 0 (0)  Excoriation:  **G1:** 2 (6)  **G2:** 0 (0)  Lymphadenopathy:  **G1:** 2 (6)  **G2:** 0 (0)  Streptococcal infection:  **G1:** 2 (6)  **G2:** 2 (17)  Toothache:  **G1:** 2 (6)  **G2:** 0 (0)  URI:  **G1:** 2(6)  **G2:** 1(8)  AEs considered to be related to study Rx:  **G1:** 27%  **G2:** 25%  Serious AE:  **G1:** 1 streptococcal infection  **G2:** 1 appendicitis (probably not related to study drug)  Severe AE: None  **Modifiers:**  NR |

| | **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | | | --- | --- | --- | --- | --- | | **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** | | | | | |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author:  Lee, 2008  See Levy et al., 2007  Country:  UK, Ireland, Canada, US, France, Germany, Italy, Poland  Enrollment period:  NR  Funding:  BioMarin Pharmaceutical  Author industry relationship disclosures:  PKU advisory board, BioMarin  Design:  Open label extension study | **Intervention:**  **G1:** Phase III, Multicenter, study of BH4  **G1a:** 6-week forced dose-titration phase (5, 20, and 10 mg/kg/day of study drug consecutively for 2 weeks each)  **G1b:** 4-week dose-analysis phase (10 mg/kg/day)  **G1c:** 12-week fixed-dose phase (patients received doses of 5, 10, or 20 mg/kg/day based on their plasma Phe concentrations during the dose titration at weeks 2 & 6)  **Dose during fixed dose period:**  5 mg/kg/day: < 600 umol/L at week 2 and < 240 umol/L at week 6  10 mg/kg/day: > 600 umol/L at week 2 and > 240 umol/L at week 6 or > 240 umol/L and < 600 umol/L at week 6  20 mg/kg/day: > 600 umol/L at week 6  Duration: 22 weeks  Formulation: 100 mg tablet of BH4 which contains 77 mg BH4 base, dissolved in 120–240 ml water, orange juice or apple juice. Doses were calculated by multiplying the patient’s weight in kilograms (at week 0) by the assigned dose (5, 10, or 20 mg/kg/day) and rounding up to the next 100 mg unit dose  **Assessments:**  Blood phe collected at 0, 2, 4, 6,10, 12, 16, 20, 22 weeks | Inclusion criteria:   * ≥ 8 years of age with PKU and hyperphenylalanemia who had been enrolled in the previous 6-wk RCT study where blood Phe level of ≥ 600 or 450 mmol/L after a protocol amendment at screening, after achieving ≥ 30% reduction in plasma Phe concentration during a previous 8-day treatment course with sapropterin * Received at least 80% of the scheduled doses in the previous RCT * Negative urine pregnancy test & using acceptable measures of contraception for Female patients of child-bearing age * Willing to continue with their current diet during study   Exclusion criteria:   * Discontinued the previous study for any reason other than withdrawal because of high plasma Phe concentrations, or if they were expected to require any investigational product or vaccine prior to completion of the study * Pregnancy (or intended pregnancy) or lactation * Concurrent medical conditions or diseases that would interfere with the conduct of the study; the use of dihydrofolate reductase inhibitors, levodopa, * Or other medications that could influence the   Age, mean/yrs ± SD (range):  20.4 ± 9.6 (8-49) | **Cognitive:**  **IQ:**  NR  **Phe level, mean ±** **SD:**  **G1:** 844 ± 398 µmol/L  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **Phe level, mean ±** **SD (µmol/L):**  **G1a** (6 weeks): 639.9 ± 381.8  **G1b** (10weeks): 645.2 ± 393.4  **G1c** (week 22): 652.2 ± 382.5  **Difference in the mean (SE) of the change in Phe from week 0:**  **G1a:**  Receiving 5 & 10 mg/kg/day: 104 ± 22.2 (*P* < 0.0001)  Receiving 5 & 20 mg/kg/day: 163 ± 22.2, (*P* < 0.0001)  Receiving 10 & 20 mg/kg/day: 59 ± 22.2, (*P* = 0.009)  **G1b:**  37 patients (46%) showed a decrease in plasma Phe  of at least 30%, compared with week 0  **G1c:** mean change from week 0:  Overall: -190.5 ± 355.7  **Phe concentration**  Among those on 5mg/kg/day (n=6): 437.8 ± 260.5  10mg/kg/day (n=37): 449.9 ± 193.1  20mg/kg/day (n=37): 895.7 ± 407.2  **Week 22:** Among those on  5mg/10mg/20 mg kg/day, the n (%) with ≥30% Phe reductions were 3(50%), 18(49%), 15 (42%) respectively & overall (G1) 36 |
| Lee, 2008 (continued) | Safety assessed by medical hx, monitoring of adverse events by MedDRA & severity of AEs  **RX compliance** **(self report), n (%):**  Took all doses correctly: 48 (60)  Missed at least one does and took no incorrect doses: 14 (18)  Took at least one does incorrectly and did not miss a dose: 7 (9)  Took at least one dose incorrectly and missed at least one dose: 11 (14)  No patient took any dose higher than that prescribed.  **Dietary compliance**:  (19 reported changes in their diet)  During the study, 4 patients reported a decrease in  Phe intake for a period of > 3 days, and  12 patients reported a total of 15 incidences of  increased in Phe intake lasting > 3 days**.**  **Length of follow-up:**  22 weeks  **Groups, N at enrollment:**  **G1:** 80  N at follow-up:  **G1:** 79 | Other characteristics: NR |  | (46%)  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms:**  **G1:** A total 260 AEs were reported by 68 (85%) of patients  All AE were mild or moderate except 1  Severe event, n: Tooth abscess: 1  82 (32%) AEs in 31 (39%) were possibly or probably related to sapropterin  No patient withdrew from the study because of AEs  **Most commonly reported AEs, n (%):**  Headache: 16 (20)  Pharyngo-laryngeal pain: 12 (15)  Nasopharyngitis: 11 (14)  Vomiting: 10 (13)  Diarrhea: 8 (10)  Upper respiratory tract infection: 8 (10)  Cough: 7 (9)  Dysmenorrheaa: 3 (9)  Migraine: 6 (8)  Back pain: 4 (5)  Gastroenteritis: 4 (5)  Influenza: 4 (5)  **AEs considered probably related to BH4 include, n:**  Upper abdominal pain: 1 |
| Lee, 2008 (continued) |  |  |  | Nausea: 2  Headache: 1  Dizziness: 1  Increased alanine amino-transferase: 1  Moderate nausea: 1  **AEs that were considered to be possibly related to BH4 and were reported by more than one patient included, n:**  Urinary tract: 2  Streptococcal infections: 2  Vomiting: 4  Diarrhea: 2  Abdominal pain: 2  Headache: 8  Migraine: 4  Pharyngolaryngeal pain: 3  Cough: 2  Decreased neutrophil counts: 2  Rash: 2  31 AEs possibly related to BH4 were reported by 1 patient each.  One serious AE during the study (n=3). Two of these events, urinary tract infection & spinal cord injury, occurred during G1c & the third event, tibia fracture, occurred after the week-22 visit.  **Modifiers:**  NR |

| **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | |
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| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author:  Levy, 2007  See Lee et al., 2008  Country:  US, Canada, Poland, Germany, France , UK  Enrollment period:  3/2005-2/2006  Funding:  BioMarin pharmaceutical , Merck Serono, The Children’s Hospital Boston General Clinical Research Centre, the University of Mineesota GCRC, NIH  Author industry relationship disclosures: PKU advisory board  BioMarin pharmaceutical  Design:  RCT, double-blind | **Intervention:**  Multicentre, Phase III, placebo-controlled trial of tetrahydobiopterin, 6R-BH4  **G1:** BH4  **G2:** Placebo  Dosage: 10mg/kg BH4 & placebo orally once daily for 6 weeks  Formulation: BH4 & placebo dissolved in 120-240 mL of water, apple juice or orange juice.  Diet to be continued without any modification  **Assessments:**  Blood Phe measures at screening, at 2 baseline assessments (1&2 wks before randomization), & at Rx weeks 0, 1, 2, 4 & 6  **Primary endpoint**: Change in Phe concentration from baseline to week 6.  **Secondary endpoints:** Changes in Phe concentrations in blood at each of the 6 wks of Rx, and the proportion of patients who had blood Phe < 600 μmol/L at wk 6.  Compare adverse events and serious adverse events (classified as per MDRA) between G1 & G2  PAH genotype at screening  **RX compliance**:  82% (72/88) took all doses of the study drug  **Dietary compliance**: Deviations, n (%):  **G1:** 7/14 (17)  **G2:** 12/47 (26) | Inclusion criteria:   * Patients with Phenylketonuria * Responsiveness in PKU-001 (previous phase-1 screening study) defined as a reduction of ≥ 30% in blood Phe after 8 days of treatment with BH4 at a dose of 10mg/kg/day * Blood Phe of ≥ 600 μmol/L or ≥450 μmol/L after a protocol amendment at screening * Age of ≥ 8 years * Willingness and ability to comply with study procedures and to adhere to their current diet. * Negative urine pregnancy test * Sexually active men and women had to adopt acceptable birth control measures to prevent pregnancy   Exclusion criteria:  See inclusion criteria  Age, mean/yrs ± SD:  G1: 21.5 ± 9.5 G2: 19.5 ± 9.8  **Other characteristics:**  NR | **Cognitive:**  **IQ:**  NR  **Phe level, mean ±** **SD,**  **µmol/L:**  **G1:** 842.7 ± 299.6  **G2:** 888.3 ± 323.1  **Phe <600 µmol/L at screening, n (%): G1:** 7 (17)  **G2:** 9 (19)  **Phe ≥600 µmol/L, n (%):**  **G1:** 34 (83)  **G2:** 38 (81)  **Nutritional:**  NR  **Quality of Life:**  NR | **Cognitive:**  **IQ:**  NR  **Phe level (6 weeks), mean ±** **SD, µmol/L:**  **G1:** 606.9 ± 377  Mean change from BL ± SD, µmol/L at 6 weeks:  **G1:** -235.9 ± 257  **G2:** 2.9 ± 239.5, *P* < 0.0001  **G1 vs. G2:** Mean diff between groups ± SD at wk 6: -245 ± 52.5, 95% CI: -350 to -141  Secondary endpoint (weekly Phe levels) mean difference: -230, 95% CI: -317 to -144  6wks: 11-29% reduction in blood Phe, n:  **G1:** 12  **G2:** 10  ≥ 30% reduction of blood phe, n (5%):  **G1:** 18/41 (44), 95% CI: 28-60 **G2:** 4/47 (9), 95%CI: 2-20,  ≥ 50% reduction in phe, n (%):  **G1:** 13/41 (32)  95% CI: 18–48 **G2:** 1/47 (2) 95% CI: 0–11  63% reduction in phe, n:  **G1:** 1  Increased Blood phe, n (5):  **G1:** 7 (17)  **G2:** 21 (45) |
| Levy, 2007 (continued) | **Length of follow-up:**  End of 6 weeks  **Groups, N at enrollment:**  **G1:** 42  **G2:** 47  N at follow-up:  **G1:** 41  **G2:** 46 |  |  | Efficacy at 6 wks from screening:  Phe < 600 µmol/L, n (%):  **G1:** 22/41 (54), 95%CI: 38-69 (*P* = 0.004)  **G2:** 11/47 (23), 95%CI: 11-36  Phe < 600 at wk 6 & ≥ 600 µmol/L at screening, n (%):  **G1:** 15/34 (44)  **G2:** 4/38 (11)  *P* = 0.003  Phe <360 µmol/L at wk 6, n (%):  **G1:** 13/41 (32)  **G2:**1/47 (2), *P* < 0.001  **Genotype:** 16/17 fully genotyped had at least 1 non-null mutation. 6 mutations were associated with both responsiveness & non-reponsiveness  1 had two PAH mutations (IVS10-3C->T and G272X), (presumably null) , & had 63% reduction in Phe after 6 weeks of treatment with sapropterin  **Nutritional:**  NR  **Quality of Life:**  NR  **Harms:**  Drug related, n (%):  **G1:** 11/47 (23) **G2:** 8/41 (20), *P* = 0.80  Adverse effects, n (%): |
| Levy, 2007 (continued) |  |  |  | Any adverse event on or after 1st dose: **G1:** 21 (51) **G2:** 34 (72)  Adverse events in ≥ 5% of patients:  URI:  **G1:** 7 (17)  **G2:** 13 (28)  Headache: **G1:** 4(10) **G2:** 7 (15)  Vomiting: **G1:** 2 (5) **G2:** 4 (9)  Abdominal pain: **G1:** 1(2)  **G2:** 4 (9)  Diarrhea:  **G1:** 2 (5)  **G2:** 3(6)  Pyrexia:  **G1:** 2 (5)  **G2:** 2(4)  Back pain:  **G1:** 1(2)  **G2:** 3 (6)  Significant changes in liver enzymes, n:  **G1:** 0  **G2:** 2  Low T4 at wk 0 & 6, n:  **G1:** 1  High TSH at 6 wks, n:  **G1:** 1  No serious event  No deaths  **Modifiers:**  NR |

| **Table C-1. Adjuvant treatment for phenylketonuria (PKU) – BH4 evidence tables (continued)** | | | | |
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| **Study Description** | **Intervention** | **Inclusion/ Exclusion Criteria/ Population** | **Baseline Measures** | **Outcomes** |
| Author: Lambruschini, 2005  Country: Spain  Enrollment period:  NR  **Funding:** REDEMETH, INERGEN (C03/05), and FIS-021450  Author industry relationship disclosures:  NR  Design: Prospective case series | **Intervention:**  BH4 50mg tablet  Start dose of 5 mg/kg/day, given in 3 daily doses. Phe- restricted diet progressively liberalized by adding 200mg Phe/day for 2 months, while gradually reducing the formula (from a mean ±SD of 51 ± 40 g/day) until complete removal was achieved. BH4 therapy discontinued when tolerance could not be increased > 400mg Phe/day and formula could not be completely removed  **Assessments:** Anthropometric (ht and wt), nutritional status (brachial fat and muscle, nutrient intake micronutrient levels, genetic & neuropsychological evaluation  Intelligence by K-ABC WISC-R, Brunet-Lezine  Plasma Phe & tyrosine by chromatography  Phe intake by 3 day QNR  Phe tolerance before the start of BH4 therapy & whenever an increase in daily Phe intake  Phe tolerance defined as the highest phe intake tolerated while keeping blood phe within 120-360 µmol/L  Index of dietary control calculated as the mean of the Median of all Phe values for 1 year  **Length of follow-up:**  After 1 year of Rx  **Groups, N at enrollment:**  **G1:**14 | Disease classification: Mild PKU (tolerance: 400–600mg Phe/day, n=9)  Moderate PKU (tolerance: 350–400mg Phe/day, n=4)  Classic PKU (tolerance: < 350mg Phe/day, n=1)  Inclusion criteria:  Mild/ moderate PKU patients with good response(45-94% decrease in plasma Phe) to the BH4 loading test  Exclusion criteria: Defect in BH4 synthesis or recycling  Age, range in years:  G1: 0.2-12.2  **Other characteristics:**  Anthropometric measurements were within age- and sex-specific percentiles for a healthy population | **Cognitive:**  **IQ, mean ± SD:**  **G1:** 102 ± 9, range: 91-112 (older patients)  **Developmental quotient:**  NR  **Phe level:**  **G1:** 382 ± 229 µmol/L  **Phe tolerance (n=11) mean ± SD (range): G1:** 356 ± 172 mg/day  (201–600)  **Nutritional:**  **G1:** Selenium intake, mean=47.1 µg/day  **Plasma selenium:**  **G1:** 61.6 ± 21.1 µg/L  **% of Urine Biopterin: G1:** 39.4 ± 12.3  **Quality of Life:**  NR | **Cognitive:**  **IQ, mean ± SD:**  **G1:** 108 ± 9; range: 96-118 (*P* = NS) (older patients)  No alterations in attention, executive function tests  **Developmental quotient (ages < 3 yrs), mean ± SD (range):**  **G1:** 104 ± 3 (100-106)  **After 1 yr Rx:**  Phe level:  **G1:** 442 ± 141 (*P* = NS)  IDC (n=10) within the safe range with BH4 therapy at 5mg/kg/day  **Phe tolerance: mean ± SD (range): G1:** 1546 ± 192 mg/day (1240–1801) (*P* =0.004). PKU formula could be removed (n=11)  **Genotype**:  P275S mutation (n=1) associated with long-term BH4 responsiveness (no other data reported)  **Nutritional:** Selenium intake (n=11), mean:  **G1:** 56.2 µg/day (*P* = NS)  **Plasma selenium (n=11), mean, ± SD:**  **G1:** 85 ± 21.4 µg/L (*P* = 0.02) |
| Lambruschini, 2005 (continued) | N at follow-up:  **G1:**11 (9 mild PKU, 2 Moderate PKU) |  |  | **% of Urine Biopterin, mean ± SD:**  **G1:** 69.6 ± 17.7 (*P* = 0.028)  No difference observed in vitamin, oligo-element daily intake  **Quality of Life:**  NR  **Harms:**  No adverse effects reported  **Modifiers:**  NR |

Comments:   
K-ABC=Kaufman Assessment Battery, WISC-R=Wechsler Intelligence Scale for Children-Revised, QNR=questionnaire, IDC=Index of dietary control