Appendixes for Comparative Effectiveness Review of Treatment for Phenylketonuria

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APPENDIX A. Search Strategies

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Last updated August 1, 2011

Table A-1: MEDLINE search strategies (pubmed.gov interface)

Search terms		Search results
#1	phenylketonurias[mh] OR phenylketonuria[tiab] OR phenylketonurias[tiab] OR phenylalanine hydroxylase deficiency[tiab] OR phenylalanine hydroxylase/deficiency[mh] OR pku[tiab] OR hyperphenylalaninemia[tiab]	6949
#2	therapy[sh] OR pharmaceutical preparations[mh] OR therapeutics[mh] OR diet therapy[mh] OR "diet therapy"[Subheading] OR diet[tiab] OR dietary[tiab] OR 5,6,7,8-tetrahydrobiopterin[nm] OR sapropterin[tiab] OR tetrahydrobiopterin[tiab] OR bh4[tiab] OR kuvan[tiab] OR amino acids, neutral[mh] OR large neutral amino acid[tiab] OR large neutral amino acids[tiab] OR lnaa[tiab]	6,456,812
#3	#1 AND #2 AND eng[la] AND humans[mh]	2281
#4	#3 AND editorial[pt]	23
#5	#3 AND letter[pt]	89
#6	#3 AND comment[pt]	48
#7	#3 AND case reports[pt]	260
#8	#3 AND review[pt]	315
#9	#3 AND news[pt]	6
#10	#3 AND practice guideline[pt]	6
#11	#3 AND meta-analysis[pt]	5
#12	#3 AND historical article[pt]	18
#13	#3 AND jsubsetk	2
#14	#4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13	699
#15	#3 NOT #14	1582

Key: jsubsetk consumer health subset; [la] language; [mh] medical subject heading; [nm] substance name; [sh] subheading; [tiab] keyword in title or abstract.

Table A-2: CINAHL search strategies (EBSCO Host interface)

Search terms		Search results
#1	(MH "Phenylketonuria+") OR phenylketonuria OR hyperphenylalaninemia OR pku OR phenylalanine hydroxylase deficiency	385
#2	(MH "Therapeutics+") OR therapeutics OR (MH "Drug Therapy+") OR drug therapy OR (MH "Amino Acids+") OR (MH "Nutritional Support+") OR (MH "Natural and Biologically Based Therapies+") OR (MH "Diet+") OR (MH "Diet Therapy+") OR (MH "Dietary Supplements+") OR diet OR diet therapy OR dietary OR sapropterin OR tetrahydrobiopterin OR bh4 OR kuvan OR large neutral amino acids OR lnaa	744,844
#3	#1 AND #2	234
#4	#3 AND limiters: English language; Human	86
#5	#3 AND limiters: English language; Human; Exclude MEDLINE records	9

Table A-3: EMBASE Drugs and Pharmacology search strategies (Ovid interface)

Search terms		Search results
#1	(phenylketonuria or pku or hyperphenylalaninemia).mp or exp phenylketonuria/ or exp hyperphenylalaninemia/	7703
#2	(therapy or therapies or treatment or treatments or management or diet or dietary or medical food or medical foods or nutriceutical or nutraceutical or therapeutic or therapeutics or sapropterin or tetrahydrobiopterin or bh4 or kuvan or large neutral amino acid or large neutral amino acids or lnaa).mp. or exp therapy/ or sapropterin/ or tetrahydrobiopterin/ or kuvan/	7,754,746
#3	1 and 2	3983
#4	limit 3 to human and English language	2527
#5	4 and review.pt	445
#6	4 and conference paper.pt	221
#7	4 and editorial.pt	39
#8	4 and letter.pt	72
#9	4 and note.pt	42
#10	4 and short survey.pt	36
#11	4 and case report/	266
#12	4 and practice guideline/	46
#13	4 and systematic review/	8
#14	4 and meta analysis/	6
#15	5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14	1104
#16	4 not 15	1423

Key: / all fields; exp explode term; .mp map term as keyword; .pt publication type.

Table A-4: AGRICOLA results (National Agricultural Library interface, keyword search)

Search terms		Search results
#1	(phenylketonuria phenylketonurias pku hyperphenylalaninemia) AND (therapy therapies treatment treatments management diet diets dietary medicine medication medications therapeutic therapeutics sapropterin tetrahydrobiopterin bh4 kuvan large neutral amino acid large neutral amino acids lnaa) Note: limited to English language, terms searched as any of these, keywords anywhere	262

Table A-5: PsycINFO results (CSA Illumina interface)

Search terms		Search results
#1	DE=phenylketonuria OR phenylketonuria OR "phenylalanine hydroxylase deficiency" OR pku OR hyperphenylalaninemia	1963
#2	DE="drug therapy" OR DE="medical treatment general" OR "dietary restraint" OR "medical management" OR "diet therapy" OR dietary OR "drug therapy" OR sapropterin OR tetrahydrobiopterin OR bh4 OR kuvan OR "large neutral amino acid" OR "large neutral amino acids" OR lnaa	127,501
#3	#1 and #2	377
#4	limit #3 to human and English language	314
#5	#4 AND (PT=(abstract collection) or PT=(authored book) or PT=(bibliography) or PT=(book) or PT=(chapter) or PT=(classic book) or PT=(column/opinion) or PT=(comment/reply) or PT=(dissertation abstract) or PT=(dissertation) or PT=(edited book) or PT=(editorial) or PT=(electronic collection) or PT=(encyclopedia entry) or PT=(encyclopedia) or PT=(handbook/manual) or PT=(letter) or PT=(obituary) or PT=(publication information) or PT=(reference book) or PT=(reprint) or PT=(review-book) or PT=(review-media) or PT=(review-software) or PT=(textbook/study guide) or PT=(conference proceedings))	113
#6	#4 AND (PT=(journal article) or PT=(journal) or PT=(peer reviewed journal) or PT=(peer-reviewed status-unknown))	207*

Key: DE descriptor; PT publication type
*****articles may be indexed as more than one publication type

APPENDIX B. Data Extraction Forms

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Treatment for Phenylketonuria (PKU)
Abstract Review Form

First Author, Year: _____ Reference #_____ Abstractor Initials: _____

Primary Inclusion/Exclusion Criteria			
1. Original research (exclude editorials, commentaries, letter, reviews, etc.)	Yes	No	Cannot Determine
2. Study includes any of the following: - Infants with PKU <2 years of age: - Children with PKU 2-12 years of age - Adolescents with PKU 13-21 years of age - Adults with PKU 21+ years of age - Pregnant women with PKU	Yes	No	Cannot Determine
3. Eligible study size (N ≥ 10) **N=**_____ (please record even if < 10)	Yes	No	Cannot Determine
4. Assesses effectiveness of the following interventions: __a. Sapropterin Dihydrochloride (Kuvan) __b. Large Neutral Amino Acids (LNAAs) __c. Dietary intervention (medical foods/formulas, nutritional supplements, Phe-restricted diet) AND / OR Addresses one or both of these key questions: __**KQ1a.** What is the evidence that any specific phenylalanine (Phe) levels are optimal for minimizing or avoiding cognitive impairment in individuals with phenylketonuria (PKU)? __**KQ1b.** What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?	Yes	No	Cannot Determine

Retain for: _____BACKGROUND/DISCUSSION _____REVIEW OF REFERENCES _____Other

Reason for Other: _____

COMMENTS:

Treatment for Phenylketonuria (PKU)
Full Text Review Form

First Author, Year: _____ Reference #_____ Abstractor Initials: _____

1. Original research (exclude editorials, commentaries, letter, reviews, etc.)	Yes	No
2. (A) Study includes relevant population: __PKU __Hyperphenylalaninemia __BOTH PKU & Hyperphenylalaninemia	Yes	No
(B) Please check subgroups that apply: __Infants <2 years of age __Children 2-12 years of age __Adolescents 13-21 years of age __Adults 21+ years of age __Pregnant women	--	--
3. Eligible study size (N ≥ 10 individuals with PKU and/or Hyperphe) N =_____ (please record if < 10)	Yes	No
4. Study includes assessment of phenylalanine (Phe) levels AND a measure of cognitive function for: __KQ1a: What is the evidence that any specific Phe levels are optimal for minimizing or avoiding cognitive impairment in individuals with PKU? __KQ1b: What is the evidence that different target Phe levels are appropriate for minimizing or avoiding cognitive impairment for different age groups?	Yes	No
5. Study addresses one or more of the following key questions (check applicable KQ below):	Yes	No
__KQ2: What is the comparative effectiveness of sapropterin dihydrochloride with dietary intervention versus dietary intervention alone for affecting outcomes, including measures of cognition (including executive function), quality of life, and nutritional status, in individuals with PKU? __KQ3: What is the comparative effectiveness of sapropterin dihydrochloride with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects? __KQ4: What is the comparative effectiveness of large neutral amino acids (LNAAs) with dietary intervention versus dietary intervention alone for affecting outcomes, including measures of cognition (including executive function), quality of life, and nutritional status, in individuals with PKU? __KQ5: What is the comparative effectiveness of LNAAs with dietary intervention versus dietary intervention alone in pregnant women with PKU for affecting outcomes in their infants, including prevention of neurological impairment, microcephaly, and cardiac defects? __KQ6: What are the harms, including adverse events, associated with the use of sapropterin dihydrochloride, LNAAs, and/or dietary intervention in individuals with PKU? __KQ7: What is the evidence for the effectiveness of the addition of sapropterin dihydrochloride or LNAAs to dietary intervention for affecting outcomes in subgroups of patients (e.g. demographic, clinical, genotypic, adherence, etc.)?		
6. For comparative effectiveness studies (answered "Yes" to #5), eligible study design __Randomized controlled trial (RCT) __Prospective cohort __Case series __Retrospective cohort __Case control __Non-randomized controlled trial	NA	Yes	No
7. Study published in English		Yes	No

8. Review the reference list (included papers only) and list author name/year for EPC to verify if included in database: _____9. If excluded, retain for ____Background/Discussion ____Other: _____

Comments:

APPENDIX C. Evidence Tables

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Studies Addressing Sapropterin Dihydrochloride

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Study Description	**Intervention**	**Inclusion/ Exclusion Criteria/ Population**	**Baseline Measures**	**Outcomes**
Author: Burton et al., 2011 Country: USA, Canada, Poland, Germany, UK, Spain, France, Ireland, Italy Enrollment period: 7/2006^ 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 trial See also Levy et al., Lee et al.	**Intervention:** Multicentre, multinational, Phase 3b, extension trial of sapropterin (PKU-008) **G1:** Sapropterin Dosage & duration: 5-20 mg/kg sapropterin 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 sapropterin despite PKU-006 Rx assignment (sapropterin 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: Sapropterin 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**	Inclusion criteria: • Sapropterin 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:** Overall exposure to drug, mean days ± SD (range): **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:** **G1:** NR **Phe level, mean µmol/L ± SD (range):** **G1:** 613.1 ± 328.5 (10-1533) **Nutritional:** **G1:** NR **Quality of Life:** **G1:** NR	**Cognitive:** **IQ:** **G1:** NR **Phe level (µmol/L), n (%):** Transitory low Phe levels after Rx: ≤26 G1: 5 (4.5) ≤120 G1: 27 (24.0) Overall , sapropterin controlled blood Phe levels throughout the study **Nutritional:** **G1:** NR **Quality of Life:** **G1:** 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**

Author: Burton 2011 (cont.)	**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 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		**events (TEAEs), n subjects [# events] (%):** Infection and infestations **all*:** 74 [198] (66.7) d-r*: 11 [27] (9.9) URI **all:** 22 [28] (19.8) d-r: 2 [2] (1.8) Nasopharyngitis **all:** 20 [30] (18.0) d-r: 3 [6] (2.7) Influenza **all:** 9 [15] (8.1) d-r: 1 [2] (0.9) Viral infection **all:** 8 [12] (7.2) d-r: 1 [1] (0.9) Gastroenteritis viral **all:** 8 [9] (7.2) d-r: 5 [6] (4.5) Pharyngitis **all:** 7 [13] (6.3) d-r: 0 Gastroenteritis **all:** 7 [7] (6.3) d-r: 0 Bronchitis **all:** 6 [7] (5.4) d-r: 0 Gastrointestinal disorders **all:** 43 [73] (38.7) d-r: 14 [18] (12.6) Vomiting **all:** 20 [24] (18.0) d-r: 5 [6] (4.5) Diarrhea **all:** 10 [16] (9.0) d-r: 3 [3] (2.7) Respiratory, thoracic,and mediastinal disorders **all:** 36 [77] (32.4) d-r: 4 [9] (3.6) Cough **all:** 21 [28] (18.9)

Author: Burton 2011 (cont.)		d-r: 3 [5] (2.7) Pharyngolaryngeal pain **all:** 10 [15] (9.0) d-r: 1 [4] (0.9) Nasal congestion **all:** 9 [13] (8.1) d-r: 0 Rhinorrhoea **all:** 6 [8] (5.4) d-r: 0 General disorders and administration site conditions **all:** 25 [33] (22.5) d-r: 4 [5] (3.6) Pyrexia **all:** 18 [25] (16.2) d-r: 4 [5] (3.6) Nervous system disorders **all:** 16 [53] (14.4) d-r: 6 [25] (5.4) Headache all: 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

Author: Burton 2011 (cont.)		resulted in study withdrawal) **Severe AE, n subjects:** **G1: 6 (**1 subject had difficulty concentrating and mood swings which resolved with altering timing of sapropterin 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 < 1.0×10^{9} N=24 < 1.5×10^{9} All decreased in

Author: Burton 2011 (cont.)	neutrophil count were transitory N=13 with platelet counts below lower limit of normal. N=4 platelet count <100 x 10 [9,] **Modifiers:** NR

Subjects here are from study # 800 (PKU-003), #771 (PKU-004) OR #1346 (PKU-006)

*all = all reported TEAEs; d-r = drug-related TEAEs
No. (%) subjects who reported the event, No of events
^reported as 3-year extension trial that began in July 2006.

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:** **G1:** NR **Phe level:** **G1:** range: µmol/L 433-1215 **Phe tolerance: n (%)** <700mg/day, 11 (91.7) ≥700 mg/day, 1 (8.3) **Nutritional:** **G1:** NR **Quality of Life:** **G1:** NR	**Cognitive:** **IQ:** **G1:** 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:** **G1:** NR **Quality of Life:** **G1:** Report great improvement by patients & their families, no other data reported **Harms:** No side-effects were observed **Modifiers:** NR

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	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:** **G1:** 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)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Lambruschini, 2005 cont.	**Length of follow-up:** after 1 year of Rx **Groups, N at enrollment:** **G1:**14 N at follow-up: **G1:**11 (9 mild PKU, 2 Moderate PKU)			**Plasma selenium (n=11), mean, ± SD:** **G1:** 85 ± 21.4 µg/L (*P* = 0.02) **% 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:** **G1:** NR **Harms:** No adverse effects reported **Modifiers:** NR

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Lee, 2008 Country: UK, Ireland, Canada, USA, France, Germany, Italy, Poland Enrollment period: NR Funding: BioMarin Pharmaceutical Author industry relationship disclosures: PKU advisory board, BioMarin Design: Uncontrolled open label trial See also Levy et al., 2007	**Intervention:** **G1:** Phase III, Multicenter, study of Sapropterin Dihydrochloride **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 <240umol/L at week 6 10 mg/kg/day: >600 umol/L at week 2 and > 240 umol/L at week 6 or > 240umol/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 sapropterin dihydrochloride which contains 77 mg sapropterin 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 wks Safety assessed by	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 study results	**Cognitive:** **IQ:** **G1a, G1b, G1c:** NR **Phe level, mean ± SD:** **G1:** 844 ± 398 µmol/L **Nutritional:** **G1a, G1b, G1c:** NR **Quality of Life:** **G1a G1b, G1c:** NR	**Cognitive:** **IQ:** **G1a, G1b, G1c:** NR **Phe level, mean ± SD (µmol/L):** **G1a** (6wks): 639.9 ± 381.8 **G1b** (10wks): 645.2 ± 393.4 **G1c** (Wk 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 (46%)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Lee, 2008 cont.	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	Age, mean/yrs ± SD: 20.4 ± 9.6, range: 8-49 **Other characteristics:** NR		**Nutritional:** **G1a, G1b, G1c**: NR **Quality of Life:** **G1a, G1b, G1c:** 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 sapropterin include, n: Upper abdominal pain, 1 Nausea, 2 Headache, 1 Dizziness, 1 Increased alanine amino-transferase, 1 Moderate nausea, 1 AEs that were considered to be possibly related to sapropterin and

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Lee, 2008 cont.				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 sapropterin 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. Neither the severe AE nor any of the three serious AEs were considered related to sapropterin **Modifiers:** NR

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Levy, 2007 Country: USA, 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 See also Lee et al., 2008	**Intervention:** Multicentre, Phase III, placebo-controlled trial of tetrahydobiopterin, 6R-BH4 **G1:** Sapropterin **G2:** placebo Dosage: 10mg/kg sapropterin & placebo orally once daily for 6 weeks Formulation: Sapropterin & 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) **Length of follow-up:** end of 6 weeks	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 sapropterin 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: please see inclusion criteria Age, mean/yrs ± SD: **G1:** 21.5 ± 9.5 **G2:** 19.5 ± 9.8 **Other characteristics:** NR	**Cognitive:** **IQ:** **G1:** NR **G2:** 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:** **G1:** NR **G2:** NR **Quality of Life:** **G1:** NR **G2:** NR	**Cognitive:** **IQ:** **G1:** NR **G2:** 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) Efficacy at 6 wks

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Levy, 2007 cont.	**Groups, N at enrollment:** **G1:** 42 **G2:** 47 N at follow-up: **G1:** 41 **G2:** 46			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:** **G1:** NR **G2:** NR **Quality of Life:** **G1: NR** **G2:** NR **Harms:** **Drug related, n (%):** **G1:** 11/47 (23) **G2:** 8/41 (20), *P* = 0.80 Adverse effects, n (%): Any adverse event on or after 1st dose: **G1:** 21 (51)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Levy, 2007 cont.				**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

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Trefz, 2009 Country: USA, 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 Sapropterin dihydrochloride 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: Sapropterin (100mg) tablets were dissolved in 120 to 240 mL of water or apple juice and the solution was administered within 30 minutes. **Groups:** **G1:** Sapropterin **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	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:** **G1:** NR **G2:** 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:** **G1:** NR **G2:** NR **Quality of Life:** **G1:** NR **G2:** NR	**Cognitive:** **IQ:** **G1:** NR **G2:** 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

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Trefz, 2009 cont.	analysis • 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			wk 3 & BL: **G1:** -148.5 ± 134.2, *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:** **G1:** NR **G2:** NR **Quality of Life:** **G1:** NR **G2:** 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 (0) Pyrexia: **G1:** 3 (9)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Trefz, 2009 cont.				**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

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Vernon, 2010 Country: USA 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 sapropterin 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. Sapropterin 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 sapropterin 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 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:** **G1:** 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:** **G1:** NR **Quality of Life:** **G1:** NR	**Cognitive:** **IQ:** **G1:** 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

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Vernon, 2010 cont.				improvements in 1 severely affected untreated PKU **Nutritional:** **G1:** NR **Quality of Life:** **G1:** NR **Harms:** NR **Modifiers:** NR

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Burton 2010 Country: USA 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 sapropterin during a 2- to 4-week treatment trial • On sapropterin 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 sapropterin therapy Exclusion criteria: see inclusion Age, mean/yrs : **G1:** 12.6 (range: 1.5-32) Other characteristics, n : Mild to moderate PKU: 22 Classical PKU: 17 *	**Cognitive:** **IQ:** **G1:** NR **Phe level, mean ± SD:** **G1:** 6.67 ± 4.2 mg/dl **Phe Variability:** **G1:** Within-subject variance: 6.897 (0.43) **Nutritional:** **G1:** NR **Quality of Life:** **G1:** NR	**Post treatment:** **Cognitive:** **IQ:** **G1:** 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:** **G1:** NR **Quality of Life:** **G1:** 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 Between subjects Age >10: 7.6354 Within subjects: Age <3: 3.6962 Within subjects: Age 3–10: 8.7274

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Burton 2010 (cont.)				Within subjects Age≥10 : 9.4995

Studies Addressing Large Neutral Amino Acids (LNAA)

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Matalon, 2007 Country: Russia, Ukraine, USA, Italy, Brazil, Denmark Enrollment period: NR Funding: Genetics Research Trust, the Mid-Atlantic Connection for PKU and Allied Disorders (MACPAD), the South Texas Association for PKU and Allied Disorders (STAPAD), and PKU and Allied Disorders of Wisconsin (PADOW), PreKUNil and NeoPhe by PreKU lab, Denmark * Author industry relationship disclosures: None Design: RCT	**Intervention:** Double-blind placebo controlled crossover trial of tablets of Large neutral Amino Acid (LNAA-NeoPhe) & placebo, with a random order of placebo & LNAA **Groups:** **G1:** LNAA / placebo **G2:** Placebo /LNAA **Dosage**: **G1:** 0.5 g/kg/day in 3 divided doses to be taken with meals, which is about one tablet/ kg/day. **G2:** same as G1 & contained lactose monohydrate, microcrystalline cellulose and colloidal hydrated silica. 1 week washout period prior to the next week of crossover trial Diet was continued as before the trial **Assessments:** Blood Phe determined at the beginning & then twice wkly **Length of follow-up:** a wk after treatment **Groups, N at enrollment:** **G1/G2:** 20 N at follow-up: **G1/G2:** 20	Inclusion criteria: Should have PKU and old enough to swallow pills Exclusion criteria: see inclusion Age: G1/G2: range (11-32 years) Other characteristics, n: Disease classification: Classical PKU, 19	**Cognitive:** **IQ:** **G1:**NR **G2:**NR **Phe level, mean:** **G1/G2:** 932.9 µmol/L Those adhered to PKU formula (n=7): 531.6 µmol /L **Nutritional:** **G1:** NR **G2:** NR **Quality of Life:** **G1:** NR **G2:** NR	**Cognitive:** **IQ:** **G1:** NR **G2:** NR **Phe level, mean ± SD:** (µmol/L) **G1:** 568.4 (average decline of 364.5 ± 232.),39% reduction (*P* < 0.0001) **G1 and adhered to formula:** 281.5 (average decline of 250.1 ± 173.7), 47% reduction (*P* = 0.009) **G2**: 882.66 (decline of 5.4%) (*P* = 0.07) **Nutritional:** **G1:** NR **G2:** NR **Quality of Life:** **G1:** NR **G2:**NR **Harms:** NR **Modifiers:** NR

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Matalon, 2006 Country: USA, Ukraine, Russia Enrollment period: NR Funding: Genetics Research Trust * Author industry relationship disclosures: None Design: Uncontrolled open label trial	**Intervention:** Open-label study of LNAAs (NeoPhe) **Groups :** **G1:** 0.5g/kg/day of NeoPhe **G2:** 1.0 g/kg/day of NeoPhe Duration: 1 week Formulation: NeoPhe divided into 3 doses and taken before meals Instructed to continue with their diet as before the trial **Assessments:** Blood Phe at baseline, 1 wk and 1 wk after Rx **Length of follow-up:** 1 week after the end of Rx **Groups, N at enrollment:** **G1:** 8 **G2:** 3 N at follow-up: **G1:** 8 **G2:** 3	Inclusion criteria: •Should have PKU •Old enough to swallow pills Exclusion criteria: see inclusion Age, mean/yrs : **G1:** 20.5 **G2:** 16.5 **Other characteristics:** **G1+G2:** all 11 patients were Classical PKU 2 responded to BH4 loading, none were on BH4 during study	**Cognitive:** **IQ:** **G1:** NR **G2:** NR **Phe level, mean µmol/L:** **G1:** 957.4 **G2:** 1230 **Nutritional:** **G1:** NR **G2:** NR **Quality of Life:** **G1:** NR **G2:** NR	**Cognitive:** **IQ:** **G1:** NR **G2:** NR **Phe level, mean µmol/L ± SD:** G1**:** 458.4 G2**:** 549 Drop in Phe, mean ± SD: 601 + 370, n=11, (P = 0.0003) **% decline in Phe:** **G1:** 52, **G2:** 55 (G1/BL, p=.004)) **Nutritional:** **G1:** NR **G2:** NR **Quality of Life:** **G1:** NR **G2:** NR **Harms:** NR **Modifiers:** NR

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Schindeler, 2007 Country: **Australia** Enrollment period: NR Funding: SHS International Author industry relationship disclosures: NR Design: RCT	**Intervention:** Double-blind, randomized crossover study with LNAA Dosage: 250mg/kg/day of LNAA, 3equal daily doses 4 phases of study: G1A:Phase 1: Usual Medical product, usual Phe restricted diet & LNAA tablets G1B:Phase 2: Usual Medical product, usual Phe restricted diet & Placebo tablets G1C:Phase 3: No Medical product, took usual Phe restricted diet & energy intake, LNAA tablets G1D:Phase 4: No Medical product, took usual Phe restricted diet & energy intake, Placebo tablets Duration: Each phase for 14 days with a 4 week washout period between phases **Assessments:** Brain Phe by MRS Plasma Phe at the completion of each phase 3 day food diary to assess intake of dietary protein Intelligence by WASI Components of attention & executive function by CPT-II, CANTAB, D-KEFS Self-report of mood ratings by DASS Length of follow-up: end of each phase All on diet & medical products for PKU At the end of each phase: median (min,max), Phe intake mg/kg/day G1A: 18.6 (5.3, 27.9) G1B: 18.5 (6.4, 43.9) G1C: 17.5 (4.5, 29.7) G1D: 21.8 (6.2, 27.9)	Inclusion criteria: Early treated Classical PKU (plasma Phe at some stage >1000 µmol/L) currently on diet & medical products for PKU Exclusion criteria: see inclusion Age, median/yrs: 24y 9 m, range (11y 8m to 45y 1m) Other characteristics, n (%): Classical PKU subjects=16 (100),	**Cognitive:** **IQ: mean (SD)** 101 (16) **Phe level:** Previous year Median blood Phe levels used as baseline Excellent control (<450 µmol/L), n=0 Good control (450-750 µmol/L), n=9 Marginal control (750-1000 µmol/L), n=6 Poor control (>1000 µmol/L), n=1 **Nutritional:** G1A:NR G1B:NR G1C: NR G1D: NR **Quality of Life:** G1A:NR G1B:NR G1C: NR G1D: NR	**Cognitive:** **IQ:** G1C vs. G1D: Better performance on measures of verbal generativity (*t*=2.657, *P*=0.018) and non verbal cognitive flexibility (*t*=2.66, p=.018) G1C vs. G1A: Better verbal self monitoring (*t*=2.179, *p*=0.046) G1A & G1B vs. G1C & G1D: better performances on attention measures (*F*=23.64, *p*=0.000) **Phe level:** Brain Phe, µmol/L, range: 176-365 (no significant differences between phases) Plasma Phe µmol/L, at the end of each phase, median (min,max): G1A: 639 (149, 1044) G1B: 734 (19, 1231) G1C:958 (553, 1500) G1D: 1180 (641, 1744) Significant differences in plasma Phe

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Schindeler, 2007 cont.	Protein total g/kg/day G1A: 1.62 (0.96, 2.10) G1B: 1.43 (0.88, 1.85) G1C: 0.63 (0.34,0.93) G1D: 0.51 (0.17,0.62) LNAA total g/kg/day G1A: 0.90 (0.53, 1.27) G1B: 0.75 (0.32, 1.05) G1C: 0.35 (0.24,0.46) G1D: 0.15 (0.05,0.21) Compliance on LNAA supplement - good **Groups, N at enrollment:** G1A/G1B/G1C/G1D:16 N at follow-up: G1A/G1B/G1C/G1D:16			between G1C & G1D (p=0.001), between G1A & and G1C (p=0.001), between G1A & G1D (p<0.0005), between G1B and G1D (p=0.001), and between G1B and G1C (p=0.023). There was no significant difference between G1A and G1B (p=0.22), however, plasma Phe was reduced in most subjects (9 of 16) by an average of 24.9% during G1A **Plasma Phe/Tyr ratio:** median (min,max) ; G1A: 10 (1.2, 17.9) G1B:14 (0.2, 27.5) G1C:18 (8.6, 36.6) G1D: 30 (11.9, 52.1) **Plasma Phe/Tyr ratio:** significant differences between G1A and G1B (*p*=0.017), between phase G1C and G1D (*p*=0.001), between G1A and G1C (*p*=0.02), between G1A and G1D (*p*<0.001), and between G1B and G1D (*p*<0.001) No significant diff between G1B & G1C

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Schindeler, 2007 cont.				(p=.23) **Nutritional:** G1A:NR G1B:NR G1C: NR G1D: NR **Quality of Life:** G1A:NR G1B:NR G1C: NR G1D: NR **Harms:** Higher levels of anxiety symptoms while on LNAA (F=5.2, p=.039), G1A & G1C compared to G1B & G1D **Modifiers:** No correlation between Plasma & brain Phe when Plasma Phe <1200 µmol/L G1D: Significant correlation between plasma & brain phe (r=0.90, p=.04, where phe ≥1200 µmol/L n=5) No significant correlations Between plasma Phe or Phe/Tyr ratio with total dietary LNAA intake, or dietary Phe intake G1A: significant negative correlations were obtained between plasma Phe and semantic verbal Fluency (VF-Category; r=- 0.525, p=0.018.

Study Description	Intervention	Inclusion/ Exclusion Criteria/ Population	Baseline Measures	Outcomes
Author: Schindeler, 2007 cont.				G1B: plasma Phe and inattention Negatively correlated (CPT-Errors, r = -0.441, *p*=.044). G1C: a negative correlation between spatial working memory and plasma Phe (SWM, r= - 0.464, *p*=0.035). G1D: no significant correlations **Across phases,** Statistically significant negative correlations between plasma Phe and verbal generativity (VF-Letters; r= - 0.465, (*p*=0.035) and non-verbal self monitoring (DF-reps, r = -0.488, *p*=0.027).

Studies Addressing Phe Levels and IQ

Study (Author / Year)	Type of Phe Measurement	Disease Type	PKU subjects (N)	Age, mean± SD (range)	Diet	Blood Phe, Mean ± SD (range) µmol/L	IQ scale(s) used	IQ Mean ± SD (range)	Correlation (p value)
Azadi 2009	Concurrent	Classic	10	13.28 ± 4.13 (6.58-19.83)	Restricted	1363.80 ± 410.44 (704-2025)	Raven	108.40 ± 12.45 (90-128)	0.21 (0.57)
Anastasoaie 2008	Critical	Classic, moderate, mild, unclassified	46	7.5 ± 3.3 (2.9-15.5)	Restricted	312 ± 132 (125-852)	Wechsler	104±15 (68-143)	-0.17 (0.38)
Wasserstein 2006	Concurrent	Classic	10	28.80 ± 3.82 (23-35)	Restricted	1137.00 ± 327.10 (408-1584)	NR	98.8 ± 18.13 (74-124)	-0.21 (0.56)
	Historical			29.1 ± 3.64 (23-35)		607.6 ± 246.8 (282-1170)		98.5 ± 18.1 (74-124)	-0.28 (0.24)
	Critical			28.80 ± 3.82 (23.00-35.00)		433.2 ± 98.5 (282-576)		98.8 ± 18.1 (74-124)	-0.24 (0.51)
Pfaendner 2005	Historical	NR	31	29 (18-40)	Mixed	399.3 ± 163.3 (208.1-686.1)	Hamburg Wechsler	107.5 ±18.7 (64-148)	-0.46 (<0.01)
	Critical			29 (18-40)		308.6 ± 102.2 (181.5-570.5)		107.5 ±18.7 (64-148)	-0.52 (<0.01)

Study (Author / Year)	Type of Phe Measurement	Disease Type	PKU subjects (N)	Age, mean± SD (range)	Diet	Blood Phe, Mean ± SD (range) µmol/L	IQ scale(s) used	IQ Mean ± SD (range)	Correlation (p value)
Rupp 2001	Concurrent		17	22.24 ± 2.54 (17-27)		1175.88 ± 319.61 (660-1780)		104.06 ± 15.67 (61-129)	-0.60 (0.01)
	Historical	Classic		22.24 ± 2.54 (17-27)	Mixed	654.71 ± 184.73 (420-970)	WAIS-R	104.06 ± 15.67 (61-129)	-0.65 (0.01)
Weglage 2001	Historical,	Classic	15	18.47 ± 3.96 (14-30)	Unrestricted	661.33 ± 267.62 (230-1420)	CFT20	98.4 ± 14.0 (77-132)	-0.36 (0.05)
	Critical			18.47 ± 4.03 (14-30)		519.33 ± 198.58 (230-880)		98.40 ± 14.0 (77-132)	-0.70 (.005)
Griffiths 2000	Critical	Classic	57	8.14 ±0.3	Restricted	466 ±154	Multiple	85.8 ±13.9	-.035 (<0.01)
Weglage 2000	Concurrent	Classic	42	14.7± 2.9 (10-18)	Not Clear	894 ± 360	CFT20	100 ±14 (76-127)	-0.25 (ns)
	Critical					528 ± 96		100 ±14 (76-127)	-0.33 (<.05)
Cerone 1999	Concurrent	Classic	16	11.1 ± 0.72(10-12)	Unrestricted	1826.3 ± 462.9 (1320-3000)	Multiple	104.9 ± 4.7 (98-114)	0.05 (0.84)
Weglage 1995	Historical	NR	20	10y11m ±1.3 (8.9-13.1)	Not Clear	11yrs:474±144 (282-810) 14 yrs:534 ± 174 (276-1014)	CFT20	101.4 ±10.2 (88-121) 107.4±10.2 (88-135)	-0.33 (ns) -0.41 (<.05)

Study (Author / Year)	Type of Phe Measurement	Disease Type	PKU subjects (N)	Age, mean± SD (range)	Diet	Blood Phe, Mean ± SD (range) µmol/L	IQ scale(s) used	IQ Mean ± SD (range)	Correlation (p value)
Leuzzi 1998	Historical	NR	14	12.30 ± 2.50 (9.00-17.60)	Mixed	543.79 ± 148.13 (230-800)	WISC-R WAIS	90.64 ± 13.52 (59-110)	-0.42 (0.13)
Ris 1994	Concurrent	Classic	25	22 (18-26)	Mixed	1323.28 ± 445.29 (254-2252)	WAIS-R	89.80 ± 11.17 (71-119)	-0.35 (0.09)
Jones 1995	Concurrent	Classic	32	17.81 ± 6.31 (7.50-29)	Mixed	1193.28 ± 425.21 (348-2010)	Multiple	91.91 ± 21.79 (44-127)	-0.20 (0.28)
Schmidt 1994	Concurrent	NR	17	20.5 (17-24)	Mixed	1233.18 ± 390.16 (564-1932)	WAIS	110.00 ± 10.96 (89-132)	-0.42 (0.09)
Welsh 1990	Concurrent	NR	11	4.64 ± 0.47 (4.08-5.75)	Restricted	564.55 ± 256.58 (66-1074)	Multiple	104.73 ± 13.94 (82-120)	0.13 (0.70)
	Critical			4.64 ± 0.46 (4.08-5.75)		570.55 ± 195.1 (66-1074)		104.73 ± 13.6 (82-120)	-0.04 (0.86)
				4.64 ± 0.47 (4.08-5.75)					
	Historical					576.55 ± 118.3 (438-840)		104.73 ± 13.94 (82-120)	-0.42 (0.19)

Study (Author / Year)	Type of Phe Measurement	Disease Type	PKU subjects (N)	Age, mean± SD (range)	Diet	Blood Phe, Mean ± SD (range) µmol/L	IQ scale(s) used	IQ Mean ± SD (range)	Correlation (p value)
Seashore 1985*	Historical & Critical	Classic	14	11.33 ± 2.19 (8.17-14.50)	Unrestricted	1613.6 ± 245.2 (1080-2040)*	Multiple	90.0 ± 13.32 (68-112)	-0.56 (0.04)

CFT=Culture Fair Intelligence Test; IQ=intelligence quotient; NR=not reported; Phe=phenylalanine; PKU=phenylketonuria; WAIS=Wechsler Adult Intelligence Scale; WAIS-R=Wechsler Adult Intelligence Scale-Revised; WISC=Wechsler Intelligence Scale for Children; WISC-R=Wechsler Intelligence Scale for Children-Revised

* Imputed Phe values

Mixed diet=some participants adhering to restricted diet and some not adhering to restricted diet

APPENDIX D. Tools Used to Assess the Quality of the Literature

APPENDIX D. Tools Used to Assess the Quality of the Literature

Quality Assessment Form: Studies Addressing IQ and Phe Levels

Question	NA	-	+
1. Was the approach to recruiting participants into the study clearly documented and applied consistently?			
2. Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?			
3. Was there a high rate of attrition?			
4. Were all eligible participants included in the analysis?			
5. Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up?			
6. Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?			
7. Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?			
8. Are confounding variables assessed using valid and reliable measures, implemented consistently across all study participants?			
9. Are the potential outcomes pre-specified by the researchers?			
10. Are all pre-specified outcomes reported?			

Comments:

Quality Assessment Form: Before-and-After Studies

Reviewer initials:	Date:	Study ID:
1. Were patients enrolled consecutively?		
☐ Yes -"Consecutive enrollment" was explicitly stated; OR - All, or a random sample of, patients treated within a given date range were included	☐ Unclear - No information on the enrollment process was reported	☐ No - Patients were selected by the investigator
Notes:		
2. Were incomplete outcome data adequately addressed?		
☐ Yes - ≤ 10% of enrolled patients withdrew/ dropped out of the study before the last outcome assessment; OR - ≤ 25% of enrolled patients withdrew/ dropped out *and* reasons for withdrawal were described and unrelated to treatment	☐ Unclear - Proportion of patients that withdrew from study was unclear; OR - 10% < x <25% of enrolled patients withdrew, but reasons were not reported	☐ No - 10% < x <25% of enrolled patients withdrew and reasons were related to treatment; OR - >25% of enrolled patients withdrew
Notes:		
3. Was a standardized approach used to assess outcomes?		
☐ Yes - One or more key outcomes were assessed blindly, in duplicate, or by an independent observer	☐ Unclear - Approach to outcome assessment was not reported	☐ No - Outcomes were assessed by the investigator or treatment provider; OR - All outcomes were patient self-reported
Notes:		

Quality Assessment Form: RCTs and Other Intervention Studies

Risk of Bias	Criterion
Selection bias and confounding	Was treatment adequately randomized (e.g., random number table, computer-generated randomization)?
	Was the allocation of treatment adequately concealed (e.g.,. pharmacy- controlled randomization or use of sequentially numbered sealed envelopes)?
	Are baseline characteristics similar between groups?
	Does the analysis control for baseline differences between groups?
	Did the strategy for recruiting participants into the study differ across study groups?
Performance bias	Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?
	Did variation from the study protocol compromise the conclusions of the study?
	Was there a high rate of differential or overall attrition?
	Did attrition result in a difference in group characteristics between baseline (or randomization) and follow-up?
	Is the analysis conducted on an intention-to-treat (ITT) basis?
Detection bias	Were the outcome assessors blinded to the intervention or exposure status of participants?
	Are the inclusion/exclusion criteria measured using valid and reliable measures, implemented consistently across all study participants?
	Are interventions/exposures assessed using valid and reliable measures, implemented consistently across all study participants?
	Are primary outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
Reporting bias	Are the potential outcomes, including harms, pre-specified by the researchers?
	Are all pre-specified outcomes reported?

+, -, NA, Cannot Determine

Quality Assessment Form: Harms Reporting

1. Were the harms PRE-DEFINED using standardized or precise definitions?
2. Were SERIOUS events precisely defined?
3. Were SEVERE events precisely defined?
4. Were the number of DEATHS in each study group specified OR were the reason(s) for not specifying them given?
5. Was the mode of harms collection specified as ACTIVE?
6. Was the mode of harms collection specified as PASSIVE?
7. Did the study specify WHO collected the harms?
8. Did the study specify the TRAINING or BACKGROUND of who ascertained the harms?
9. Did the study specify the TIMING and FREQUENCY of collection of the harms?
10. Did the author(s) use STANDARD scale(s) or checklists(s) for harms collection?
11. Did the authors specify if the harms reported encompass ALL the events collected or a selected SAMPLE?
12. Was the NUMBER of participants that withdrew or were lost to follow-up specified for each study group?
13. Was the TOTAL NUMBER of participants affected by harms specified for each study arm?
14. Did the author(s) specify the NUMBER for each TYPE of harmful event for each study group?
15. Did the author(s) specify the type of analyses undertaken for harms data?

+, -, NA

APPENDIX E. Quality of the Literature

APPENDIX E. Quality of the Literature

Randomized Trials

Domain	Selection bias & confounding					Performance bias	Attrition bias			Detection bias				Reporting bias		Final rating
Author, Year	Random assignment adequate	Allocation adequately concealed	Baseline characteristics similar between groups	Analysis controlled for baseline differences	Recruitment strategy differed across groups	Impact of concurrent interventions ruled out	High rate of attrition	Attrition resulted in group differences	ITT analysis	Outcome assessors blinded to intervention status	Inclusion/exclusion criteria measured with valid & reliable instruments	Interventions assessed with valid & reliable measures	Outcomes assessed with valid & reliable measures	Outcomes and harms pre-specified	Pre-specified outcomes reported	
Sapropterin																
Trefz 2009[1]	+	+	+	+	-	+	-	NA	-	+	+	+	+	-	+	Fair
Levy 2007[2]	+	+	+	NA	-	+	-	NA	+	+	+	+	+	+	+	Good
LNAAs																
Schindeler 2007[3]	+	+	NA	NA	-	+	-	NA	+	+	+	+	+	-	+	Fair
Matalon 2007[4]	-	-	NA	NA	-	+	-	NA	NA	+	+	+	+	-	+	Poor

+=yes/positive, -=no/negative; LNAAs=large neutral amino acids

Uncontrolled Open Label Trials

Author, Year	Consecutive enrollment	Incomplete outcome data adequately addressed	Standard approach for outcome assessment	Final rating
Sapropterin				
Burton 2011[5]	+	+	-	Fair
Vernon 2010[6]	+	+	+	Good
Lee 2008[7]	+	+	+	Good
LNAAs				
Matalon 2006[8]	-	+	-	Poor

+=yes, -=no; LNAAs=large neutral amino acids

Sapropterin Case Series

Domain	Selection bias & confounding	Performance bias	Attrition bias		Detection bias						Reporting bias		Final Rating
Author, Year	Confounding and modifying variables considered	Impact of concurrent interventions ruled out	High rate of attrition	Attrition resulted in group differences	Outcome assessors blinded	Inclusion/exclusion assessed with valid & reliable measures	Interventions measured with valid & reliable measures	Outcomes assessed with valid & reliable measures	Confounders assessed with valid & reliable measures	Accounted for secular trends & regression to mean	Outcomes and harms pre-specified	Pre-specified outcomes reported	
Burton 2010[9]	+	+	-	NA	-	+	-	-	+	NA	-	+	Poor
Burlina 2009[10]	-	+	-	NA	-	+	+	+	+	-	-	+	Poor
Lambruschini 2005[11]	+	+	+	+	-	+	+	+	+	NA	+	+	Poor

+=yes, -=no, NA=not applicable

Harms Reporting in Studies of Sapropterin and LNAAs

Author, Year	Harms predefined using standardized/precise definitions	Serious events precisely defined	Severe events precisely defined	Deaths/group specified	Active harms collection	Passive harms collection	Specified who collected harms	Training/background of individuals(s) collecting harms specified	Timing of harms collection specified	Standard scale for harms collection used	Specified whether reported harms encompass all events collected	Number participants withdrawing/lost to followup reported by group	Total number participants affected by harms specified by group	Number for each type of harm specified by group	Analyses for harms data specified
Sapropterin															
Burton 2011[5]	-	+	+	+	+	+	-	-	+	-	+	+	+	+	+
Burton 2010[9]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
Vernon 2010[6]	-	-	-	-	-	-	-	-	-	-	-	+	-	-	-
Burlina 2009[10]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
Trefz 2009[1]	-	U	-	-	+	+	+	+	+	-	+	+	+	+	+
Lee 2008[7]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	U
Levy 2007[2]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
Lambruschini 2005[11]	-	-	-	-	U	U	+	-	-	-	NA	+	NA	NA	NA
LNAAs															
Schindeler 2007[3]	-	-	-	-	-	+	-	-	-	U	-	NA	-	-	-
Matalon 2007[4]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-
Matalon 2006[8]	-	-	-	-	-	-	-	-	-	-	-	NA	-	-	-

+= yes/positive; -=no/negative; LNAA=large neutral amino acids; NA=not applicable; U=unsure

Studies Addressing Phe Levels and IQ

Author, Year	Recruitment approach clearly documented	Impact of concurrent intervention ruled out	High rate of attrition	All eligible participants included in analysis	Attrition resulted in group differences	Inclusion/exclusion criteria measured with valid &reliable instruments	Outcomes assessed with valid & reliable instruments	Confounders assessed with valid & reliable instruments	Outcomes pre-specified	Pre-specified outcomes reported	Final Rating
Azadi 2009[12]	-	+	-	-	NA	+	+	-	+	+	Poor
Anastasoie 2008[13]	-	-	NA	-	-	+	+	-	+	+	Poor
Wasserstein 2006[14]	-	+	-	-	NA	+	-	-	+	+	Poor
Pfaender 2005[15]	-	+	-	-	NA	+	+	-	+	+	Poor
Rupp 2001[16]	+	+	+	-	NA	+	+	-	+	+	Poor
Weglage 2001[17]	-	+	NA	-	NA	-	+	-	+	+	Poor
Griffiths 2000[18]	-	+	NA	-	NA	+	+	+	+	+	Fair
Weglage 2000[19, 20]	-	+	-	-	NA	+	+	+	+	+	Fair
Cerone 1999 [21]	-	+	NA	-	NA	+	+	-	+	+	Poor
Weglage 1995[22-24]	-	+	-	-	NA	CD	+	-	+	+	Poor
Leuzzi 1998[25]	+	+	-	-	NA	+	+	-	+	+	Fair
Ris 1997[26, 27]	+	+	-	+	NA	+	+	+	+	+	Good
Jones 1995[28]	-	+	-	-	NA	+	+	-	+	+	Poor
Schmidt 1994[29]	-	+	+	-	CD	+	+	-	+	+	Poor
Welsh 1990[30]	-	+	-	-	NA	+	+	-	+	+	Poor
Seashore 1985[31]	+	+	-	-	NA	+	+	-	+	+	Fair

+=yes, -=no, CD=cannot determine, NA=not applicable

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APPENDIX F. Meta Analysis Methods

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The association of blood phenylalanine levels with IQ was meta-analyzed using a hierarchical mixed-effects model, estimated using Markov chain Monte Carlo (MCMC) methods[1]. The advantages of using a Bayesian approach to meta-analysis were recognized over a decade ago[2] and they have been applied extensively ever since[3,4,5,6,7,8,9,10]. It allows for straightforward probabilistic inference across studies, and readily combines both fixed and random effects. In contrast to the more indirect measures of inference afforded by classical methods, all inference from Bayesian models is in the form of probability statements that describe the uncertainty in the unknown quantities of interest , given the information at hand (:

The left side of this equation is the posterior distribution of all unknown parameters in the model, while right side shows that this posterior quantity is the product of a data likelihood and the prior distribution (i.e. before data are observed) of the model. While the use of priors allows for the incorporation of extant information into the analysis, we used uninformative priors on all parameters, allowing the results from the included studies to provide all the evidence.

A powerful aspect of using random effects for meta-analyses is the notion of partial pooling[1]. This permits us to abandon the tenuous assumption that the effects across studies are independent and identically distributed. Rather, we view them as *exchangeable* samples from a "population" of PKU studies. Using a random effect to partially pool across studies expresses our desire to neither combine studies in a single estimate (which assumes they are identical) nor keep them entirely separate (which assumes they are completely different), but rather, some mixture of the two extremes. In contrast, fixed effects models force one of these unlikely extremes. Moreover, the degree to which studies are pooled is dictated by the heterogeneity across studies, rather than via arbitrary weighting factors.

In an effort to partially pool the information from the included set of studies, we specified random effects for the intercept and slope parameters of a linear relationship between blood Phe level and IQ. Importantly, this allowed each study to have its own parameters, each sampled from a notional population of parameters. Those with smaller sample sizes were automatically shrunk towards the population means for each parameter, with larger studies influencing the estimate of the population mean more than being influenced by it. In turn, the magnitude of the effect (*i.e.* slope) was specified partly as a function of a fixed effect for whether measurements of Phe were carried out during the critical period. Hence, the overall model was a hierarchical mixed effects model. Bayesian hierarchical models are very easily estimated using Markov chain Monte Carlo (MCMC) methods[11].

The core of the model is a linear relationship between the expected IQ (μ) and Phe (x):

The subscript *j[i]* denote parameters for study *j* corresponding to observation *i*. Hence, both the intercept and slope are allowed to vary by study. Note that by "observation" we refer here not to individuals, but to groups of individuals within a study that share a characteristic. For example, within the same study, one group of individuals might have been measured for Phe in the critical period, and others not; these groups were considered separate observations in this analysis. One study[12] reported a range of Phe measurements, rather than a single value, so we imputed values by randomly sampling at every iteration from a uniform distribution across the reported range.

Though age was included as an additional linear predictor in early versions of the model, it did not appear to be an important covariate, and models in which it was included did not exhibit good convergence. Hence, age was omitted from the final model. We suspect that the important aspects of age might be adequately characterized by the four combinations of historical or concurrent Phe measurement and measurement in or outside the critical period.

The intercept was modeled as a random effect, where each study is assumed to be an exchangeable sample from a population of PKU studies:

The slope of the relationship included a study-level random effect and fixed effects corresponding to whether the Phe measurement was concurrent with the measurement of IQ (an indicator variable):

Finally, the expected value of IQ was used to model the distribution of observed IQ values y_i, with error described by the inverse variance τ

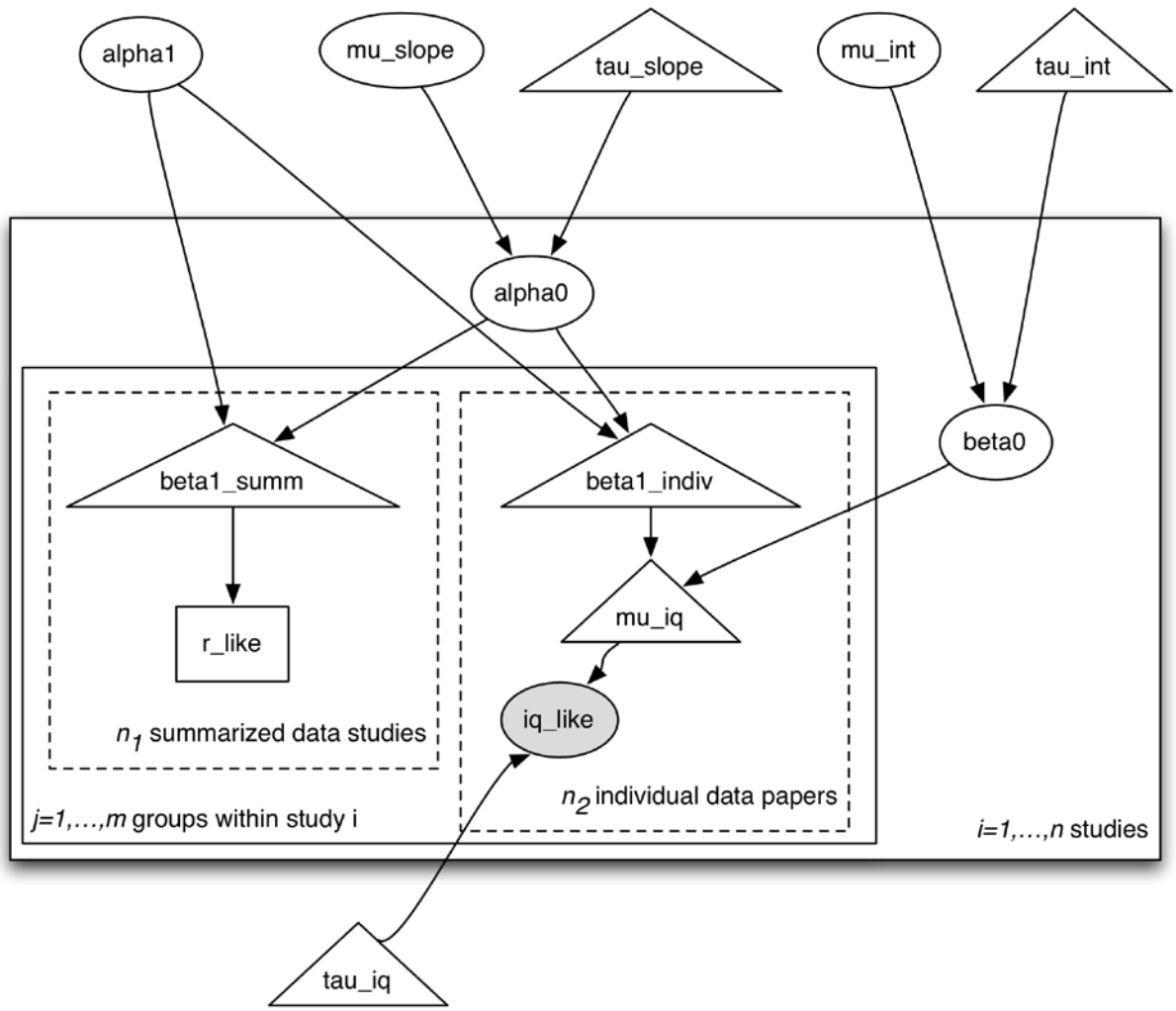
For studies that provided only data summaries of Phe and IQ, we employed reported correlation coefficients to obtain additional inference regarding the relationship of these variables. Inference regarding the correlation coefficient (ρ) can be obtained using the Fisher transformation, which uses the inverse hyperbolic function to transform the correlation to a normally-distributed random variable:

where r_j is the reported Pearson correlation from study *j*, with a standard error that is solely a function of the corresponding sample size (for a Spearman correlation, the standard error is the inverse square root of n-2). The expected correlation (ρ) is obtained in the model by converting the slope of the relationship between Phe and IQ:

where s_{xj} and s_{yj} are the reported standard deviations of the Phe levels and IQs, respectively, for study j.

The full model structure is illustrated in Figure F-1. Note the distinction between the influence of studies with group-summarized data and that of studies with individual-level data.

Figure F-1: Directed acyclic graph (DAG) showing the meta-analysis model structure



Note: Unfilled circles represent stochastic nodes, shaded circles represent data, triangles represent deterministic nodes and squares represent factor potentials (arbitrary log-probability terms).The large enclosing square represents the collection of n unique studies in the meta-analysis; the smaller enclosing box represents the distinct groups (i.e. subsets that had distinct covariates) within each study. Different information was contributed depending on whether the study provided group-summarized data (n_1 studies) or individual-level data (n_2 studies), as indicated by the dashed boxes; group-level data provided inference on the slope parameter only, while individual-level data informed both the slope and intercept.

All stochastic parameters were specified using diffuse prior distributions. For continuous parameters on the real line (e.g. linear model coefficients), a normal distribution with mean zero

and precision (inverse-variance) 0.01 was used. For precision parameters, the standard deviation was modeled uniformly on the interval (0, 1000) and then transformed to inverse variance; this provides a better non-informative prior than modeling the precision directly[13].

In order to evaluate the effect of particular levels of Phe on the likelihood of cognitive impairment, we chose a threshold value of IQ to bound the definition of impairment. While discretizing a continuous variable into one dichotomous variable is subjective and problematic, we felt that for a standardized measure like IQ, a boundary of one standard deviation below the mean (IQ=85) was a reasonable choice. This threshold value was used to define indicator variables that were set to one if the value of the predicted IQ was below 85 during the current iteration of the MCMC sampler, and zero otherwise. Hence, for each combination of predictors, the total number of ones divided by the number of MCMC iterations represents a posterior probability of observing IQ<85. This corresponds to the integral of the posterior distribution of IQ up to an 85 score. To estimate the sensitivity of this probability to Phe, this probability was calculated for a range of blood Phe levels from 200 to 3000 μmol/L, in increments of 200. This was done for critical period and non-critical period Phe measurement, under both the historical and concurrent measurement models.

This model was coded in PyMC version 2.1[14], which implements several MCMC algorithms for fitting Bayesian hierarchical models. The model was run for 1 million iterations, with the first 900,000 discarded as a burn-in interval. The remaining sample was thinned by a factor of 100 to account for autocorrelation, yielding 1000 samples for inference. Convergence of the chain was checked through visual inspection of the traces of all parameters, and via the Geweke[15] diagnostic. Posterior predictive checks[1] were performed, which compare data simulated from the posterior distribution to the observed data. This exercise showed no substantial lack of fit for any of the studies included in the dataset.

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APPENDIX G. Excluded Studies

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Reasons for exclusion:

X-1=Not original research
X-2=Ineligible population
X-3=Ineligible study size
X-4=Not relevant to key question 1
X-5= Not relevant to key questions 2-7
X-6=Ineligible study design
X-7=Unable to obtain study

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APPENDIX H. Studies Addressing Executive Function

APPENDIX H. Studies Addressing Executive Function

Azadi, 2009[1] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Iran Cross Sectional **G1:** PKU subjects	**G1:** 10/10 Concurrent PKU classification: : NR **G1:** 13.3 ± 4.1 (6.6 – 19.8)	**Concurrent Phe (µmol/l):** Patient 1: 704 Patient 2: 1418 Patient 3: 1402 Patient 4: 1207 Patient 5: 2025 Patient 6: 1600 Patient 7: 704 Patient 8: 1487 Patient 9: 1400 Patient 10: 1691	**Tower of London (TOL) - Average number of moves to complete:** **2-move problems:** **G1:** 2.3 ± 0.51 **3-move problems:** **G1:** 4.12 ± 1.12 **4-move problems:** **G1:** 8.85 ± 3.38 **5-move problems:** **G1:** 10.47 ± 4.24 **TOL - Planning times (s):** **2-move problems:** **G1:** 7.14 ± 3.43 **3-move problems:** **G1:** 10.84 ± 8.19 **4-move problems:** **G1:** 9.45 ± 8.78 **5-move problems:** **G1:** 8.38 ± 4.29 **TOL - Subsequent thinking times (s):** **2-move problems:** **G1:** 17.16 ± 8.03 **3-move problems:** **G1:** 32.11 ± 19.66 **4-move problems:**	**Spearman correlations:** **Concurrent phe and:** **TOL - Average number of moves to complete:** **2-move problems:** **G1:** 0.17 **3-move problems:** **G1:** -0.14 **4-move problems:** **G1:** 0.06 **5-move problems:** **G1:** 0.23 **TOL - Planning times:** **2-move problems:** **G1:** -0.09 **3-move problems:** **G1:** 0.08 **4-move problems:** **G1:** 0.17 **5-move problems:** **G1:** -0.01 **TOL -Subsequent thinking times:** **2-move problems:** **G1:** 0.07

Azadi, 2009[1] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
			G1: 60.69 ± 27.46 **5-move problems:** **G1:** 71.68 ± 31.18 **Continuous Performance Test (CPT):** **Commission errors (number):** **G1:** 5.50 ± 3.59 **Omission errors (number):** **G1:** 4.80 ± 2.97 **Mean reaction time (s):** **G1:** 0.79 ± 0.22 **Successfully recognized matches (number):** **G1:** 67.7 ± 19.90 **Stroop single-task test:** **Time in dots card (s):** **G1:** 19.32 ± 7.79 **Errors in dots card (number):** **G1:** 0.11 ± 0.33 **Time in word card (s):** **G1:** 31.33 ± 18.45 **Errors in word card (number):** **G1:** 0.11 ± 0.33 **Time in color card (s):** **G1:** 41.77 ± 15.73 **Errors in color card (number):** **G1:** 0.33 ± 0.70 **Difference index:** **G1:** 22.78 ± 11.87	**3-move problems:** **G1:** 0.03 **4-move problems:** **G1:** 0.3 **5-move problems:** **G1:** 0.4 **Continuous Performance Test (CPT):** **Commission errors (number):** **G1:** 0.27 **Omission errors (number):** **G1:** 0.15 **Mean reaction time:** **G1:** -0.03 **Successfully recognized matches (number):** **G1:** -0.15 **Stroop single test:** **Time in dots card:** **G1:** 0.02 **Errors in dots card (number):** **G1:** 0.27 **Time in word card:** **G1:** 0.03

Azadi, 2009[1] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				Errors in word card (number): **G1:** -0.27 **Time in color card:** **G1:** 0.2 **Errors in color card (number):** **G1:** 0.43 **Difference index:** **G1:** 0.41

Appendix B. Studies Addressing Executive Function, continued

Sharman, 2009[2] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Australia Prospective Cohort **G1:** PKU subjects	**G1:** 12/10 PKU classification: NR Age (years): Baseline: **G1:** 14.4 ± 2.08 Follow-up: **G1:** 14.4 ± 2.16	**Baseline (Jan. 2006) concurrent phe (µmols):** 601.30 ± 204.95 (270.00-970.00) **Follow-up (Mar. 2006) concurrent phe (µmols):** 478.00 ± 274.26 (210.00-1100.00) **Mean average phe age < 12 years (µmols):** **G1:** 383.00 ± 96.91 (267.00-580.00) **Mean average phe age > 12 years (µmols):** **G1:** 491.75 ± 127.83 (367.00-742.00) **Mean lifetime phe (µmols):** **G1:** 395.80 ± 102.83 (276.00-626.00) **Average phe in 2005:** **G1:** NR	**BRIEF Inhibit Scale T-scores:** **Baseline:** **G1:** 54.30 ± 14.38 **Follow-up:** **G1:** 58.40 ± 17.59	**Phe level in 2005 and BRIEF Inhibit scale:** **Baseline:** **G1:** 0.671, $p < 0.05$ **Follow-up:** **G1:** 0.752, $p < 0.05$ **Lifetime phe and BRIEF Inhibit scale:** **Baseline:** **G1:** 0.737, $p < 0.01$ **Baseline:** **G1:** 0.883, $p < 0.01$

Appendix B. Studies Addressing Executive Function, continued

Moyle, 2007[3] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Australia Cross Sectional **G1:** PKU patients	**G1:** 12/12 PKU classification: NR Lifetime, Recent Age (years) ± SE: **G1:** 28.5 ± 3.3	**Lifetime phe level:** **G1:** NR **Phe level obtained most recently before assessment:** **G1:** NR	**Wechsler Adult Intelligence Scale-III (WAIS-III) mean scores ± SE:** **Working Memory Index (WMI):** **G1:** 103 ± 5.7 **Wechsler Memory Scale Third Edition (WMS-III) mean scores ± SE:** **Working Memory (WM):** **G1:** 104 ± 6.0 **Trail Making Test Part A (TMT-A):** **G1:** 35 ± 4.8 **Trail Making Test Part B (TMT-B):** **G1:** 75 ± 14.9	**Lifetime phe with:** **WAIS-III - Working Memory Index (WMI):** **G1:** -.50 **WMS-III - Working Memory (WM):** **G1:** -.51 **Trail Making Test Part A (TMT-A):** **G1:** .20 **Trail Making Test Part B (TMT-B):** **G1:** .54 **Phe level obtained most recently before assessment with:** **WAIS-III - Working Memory Index (WMI):** **G1:** -.24 **WMS-III - Working Memory (WM):** **G1:** -.35 **Trail Making Test Part A (TMT-A):** **G1:** .38 **Trail Making Test Part B (TMT-B):**

Moyle, 2007[3] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				G1: .68*, $p < .05$ *Text in the Results section states "r(11) = -.68, p=.02."

Appendix B. Studies Addressing Executive Function, continued

Author/Year Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
Christ, 2006[4] USA Prospective Cohort **G1:** PKU subjects	**G1:** 26/26 Concurrent PKU classification: NR **G1:** 11.2 ± 3.1 years (6-18)	**Recent Phe (mg/dL):** **G1:** 7.0 ± 5.6 (0.2-20.2)	**Go/no-go:** **Reaction time (milliseconds):** **Neutral:** **G1:** 335 ± 60 **Inhibitory:** **G1:** 443 ± 67 **Error rate (%):** **Neutral:** **G1:** 2.0 ± 2.0 **Inhibitory :** **G1:** 31.7 ± 17.4 **Antisaccade:** **Reaction time (msec):** **Neutral:** **G1:** 306 ± 61 **Inhibitory :** **G1:** 392 ± 77 **Error rate (%):** **Neutral:** **G1:** 0.3 ± 0.7 **Inhibitory :** **G1:** 12.1 ± 11.5 **Flanker:** **Reaction time (msec):** **Neutral:** **G1:** 766 ± 212 **Inhibitory:**	**Correlation of Phe levels with Go/no-go, antisaccade, Flanker, and Stroop tests:** NR

	G1: 777 ± 219 **Facilitatory:** **G1:** 736 ± 195 **Error rate (%):** **Neutral:** **G1:** 5.8 ± 5.7 **Inhibitory :** **G1:** 7.1 ± 8.9 **Facilitatory:** **G1:** 4.6 ± 6.1 **Stroop:** **Reaction time (msec):** **Neutral:** **G1:** 811 ± 173 **Inhibitory:** **G1:** 875 ± 186 **Facilitatory:** **G1:** 785 ± 164 **Error rate (%):** **Neutral:** **G1:** 1.1 ± 2.0 **Inhibitory:** **G1:** 2.2 ± 3.2 **Facilitatory:** **G1:** 0.6 ± 1.1

Appendix B. Studies Addressing Executive Function, continued

Wasserstein, 2006[5] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
USA Cross Sectional **G1:** PKU patients	**G1:** 10/10 Concurrent, lifetime Classic Age: Mean NR Age at test (years): Patient 1 – 26 Patient 2 – 23 Patient 3 – 27 Patient 4 – 30 Patient 5 – 30 Patient 6 – 29 Patient 7 – 35 Patient 8 – 24 Patient 9 – 33 Patient 10 – 31	**Concurrent Phe (mg/dl):** Patient 1 – 17.1 Patient 2 – 17.6 Patient 3 – 17.5 Patient 4 – 25.8 Patient 5 – 19.2 Patient 6 – 6.8 Patient 7 – 18.1 Patient 8 – 22.0 Patient 9 – 26.4 Patient 10 – 19.0 **Phe level from birth to 12 years (mg/dl):** Patient 1 – 6.2 Patient 2 – 5.6 Patient 3 – 6.3 Patient 4 – 6.5 Patient 5 – 9.6 Patient 6 – 8.5 Patient 7 – 9.5 Patient 8 – 7.7 Patient 9 – 4.7 Patient 10 – 7.6 **Phe level over 12 years (mg/dl):** Patient 1 – 15 Patient 2 – 11.8	**California Verbal Learning Test Words remembered correctly:** **G1:** 11.02, SD-NR **Dependence on semantic clues:** **G1:** 6.11, SD-NR	**Phe levels and CVLT test outcomes:** NR

Wasserstein, 2006[5] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
		Patient 3 – 9.6 Patient 4 – 7.8 Patient 5 – 19.5 Patient 6 – 12.1 Patient 7 – 16.8 Patient 8 – NR Patient 9 – 13.4 Patient 10 – 14.2		

Appendix B. Studies Addressing Executive Function, continued

Gassio, 2005[6] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Spain Cross Sectional **G1:** individuals with PKU **G2:** individuals with hyper-phenyl-alanemia	**G1:** 37/37 **G2:** 35/35 Concurrent, Historical **G1:** PKU classification: NR **G2:**Hyperphenylalanemia **G1:** 9.75 ± 5.25 years (2.7- 19.3) **G2:** 7.8 ± 3.2 years (2.7-17.25)	**Phe from the day of study (µmol/l):** **G1:** 388 ± 205 (123-1013) **G2:** 237 ± 86 (98-413) **Phe at diagnosis (µmol/l):** **G1:** 1504 ± 739 (371-2802) **G2:** 253 ± 106 (112-544) **Index of Dietary Control** (IDC, average of medians of plasma phe obtained every 6 months)**, most recent 6-mo period:** **G1:** 427 ± 191 (116-880) **G2:** 231 ± 76 (106-359) **IDC, first 6 yrs of life:** **G1:** 354 ± 113 (182-656) **G2:** NR **IDC, 7 to 12 yrs of life:** **G1:** 444 ± 145 (250-820) **G2:** NR	**Wisconsin Card Sorting test, preservative errors:** **G1:** 50 ± 11.2 **G2:** 48 ± 10.5 **Trail Making Test:** **Trail A:** **G1:** 43 ± 12.4 **G2:** 48 ± 14.1 **Trail B:** **G1:** 44 ± 12.3 **G2:** 50 ± 10.1 **Conners' Continuous Performance Test (CPT):** **Omissions:** **G1:** 56 ± 11.5 **G2:** 56 ± 9.1 **Commissions:** **G1:** 51 ± 10.3 **G2:** 48 ± 11.7 **Stroop:** **Word reading:** **G1:** 45 ± 8.0 **G2:** 50 ± 8.3 **Color naming:** **G1:** 40 ± 8.9	**Phe day of study with Stroop color:** **G1:** r=-0.457, p=0.019 **Phe day of study with Stroop color word interference:** **G1:** r=-0.462, p=0.018 **IDC first 6 yrs of life with Stroop color-word interference:** **G1:** r=-0.547, p=0.013 **IDC 7-12 yrs of life with Stroop Word reading:** **G1:** r=-0.423, p=0.035 **IDC 7-12 yrs of life with Stroop color-word interference:** **G1:** r=-0.413, p=0.04

Gassio, 2005[6] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
			G2: 48 ± 6.9 **Color word interference:** **G1:** 42 ± 9.8 **G2:** 50 ± 6.6 **Resistance to interference:** **G1:** 49 ± 6.4 **G2:** 51 ± 5.7	

Appendix B. Studies Addressing Executive Function, continued

Anderson, 2004[7, 8] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Australia Cross Sectional **G1:** PKU participants **G1a:** PKU participants with MRI **G1b:** PKU participants with MRI and with no white matter abnormalities **G1c:** PKU participants with MRI and mild white matter abnormalities **G1d:** PKU participants with MRI and moderate white matter abnormalities **G1e:** PKU	**G1:** 33 **G1a:** 32 **G1b:** 6 **G1c:** 12 **G1d:** 14 **G1e:** 5 **G1f:** 9 **G1g:** 5 Historical, Concurrent Classic **G1:** 11.18 ± 3.4 **G1a:** 11.2 ± 3.5 **G1b:** 9.1 ± 2 **G1c:** 9.8 ± 2.1 **G1d:** 13.2 ± 3.9 **G1e:** 8.3 ± 0.7 **G1f:** 8.9 ± 1.5 **G1g:** 9.2 ± 2.6	**Concurrent phe (µmol/l) ± SD:** **G1:** NR **G1a:** NR **G1b:** 400.3 ± 131.5 **G1c:** 435.3 ± 196.4 **G1d:** 786.2 ± 284.4 **Concurrent phe (µmol/l) ± SE:** **G1e:** 362.20 ± 92.3 **G1f:** 372.00 ± 68.8 **G1g:** 665.20 ± 92.3 **Lifetime phe (average of yearly median) (µmol/l) ± SD:** **G1:** NR **G1a:** NR **G1b:** 330.8 ± 42.2 **G1c:** 369.8 ± 46.2 **G1d:** 542.5 ± 132.7 **Lifetime phe (average of yearly median) (µmol/l) ± SE:** **G1e:** 354.05 ± 35.3 **G1f:** 380.03 ± 26.3 **G1g:** 451.23 ± 35.3	**Neuropsychological Measures**:** **TEA-Ch-Sky Search ± SE:** **G1:** 17.6 ± 0.5 **G1a:** NR **G1b:** 17.9 ± 1.1 **G1c:** 18.5 ± 0.8 **G1d:** 16.5 ± 0.8 **TEA-Ch-Code Transmission ± SE:** **G1:** 35.21 ± 0.8 **G1a:** NR **G1b:** 37.7 ± 2 **G1c:** 34.7 ± 1.3 **G1d:** 34.6 ± 1.3 **TEA-Ch-Digital Distraction ± SE:** **G1:** 3.56 ± 0.3 **G1a:** NR **G1b:** 3.7 ± 0.7 **G1c:** 3.7 ± 0.4 **G1d:** 3.4 ± 0.3 **TEA-Ch-Sky Search Dual Task ± SE:** **G1:** 125.12 ± 6.7 **G1a:** NR **G1b:** 118.6 ± 17.2 **G1c:** 116.6 ± 11 **G1d:** 137.7 ± 11.2	**Lifetime Phe with:** **Working memory (Digit span):** **G1a:** R=-0.40, p=0.05 **Mental flexibility (CNT errors and self-corrections):** **G1a:** R=0.55, p=0.005 **Early Phe (first 6 months) with:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:** **G1:** r=-.09 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:** **G1:** r=-.22 **Executive Function:** **G1:** r=-.08 **Recent Phe (previous 12 months) with:**

Anderson, 2004[7, 8] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
participants with MRI and no white matter abnormalities - on strict dietary restrictions **G1f:** PKU participants with MRI and mild white matter abnormalities -on strict dietary restrictions **G1g:** PKU participants with MRI and moderate white matter abnormalities - on strict dietary restrictions		**Early phe (first 6 months) (µmol/l) ± SE:** **G1:** NR **G1a-d:** NR **G1e:** 356.00 ± 51.7 **G1f:** 401.33 ± 38.5 **G1g:** 396.00 ± 51.7 **Recent phe (previous 12 months) (µmol/l ± SE:** **G1:** NR **G1a-d:** NR **G1e:** 383.00 ± 62.0 **G1f:** 352.67 ± 46.2 **G1g:** 592.00 ± 62.0	**WISC III - Digit span – forwards ± SE:** **G1:** 5.32 ± 0.2 **G1a-d:** NR **WISC III - Digit span – backwards ± SE:** **G1:** 3.27 ± 0.2 **G1a-d:** NR **WAIS-III or WISC-III Digit Span ± SE:** **G1:** NR **G1a:** NR **G1b:** 9 ± 1.3 **G1c:** 8.3 ± 0.9 **G1d:** 8.3 ± 0.9 **Tower of London (TOL) extra attempts ± SE:** **G1:** 7.72 ± 0.7 **G1a:** NR **G1b:** 5.8 ± 1.8 **G1c:** 7.9 ± 1.2 **G1d:** 8.5 ± 1.2 **Contingency Naming Test (CNT) - errors and self-corrections ± SE:** **G1:** 23.50 ± 2.8 **G1a:** NR **G1b:** 19.3 ± 7.2 **G1c:** 15.7 ± 4.6	**Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:** **G1:** r=-.20 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:** **G1:** r=-.22 **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:** **G1:** r=-.37 **Concurrent Phe with:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:** **G1:** r=-.19 **Memory/Learning** (Digit span forwards and backwards, RAVLT and

Anderson, 2004[7, 8] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
			G1d: 32.7 ± 4.6 **Means for G1b, G1c, and G1d adjusted for age at testing and socioeconomic status. Means for G1 adjusted for age **Cognitive Domains***:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task) **± SE:** **G1:** NR **G1a:** NR **G1b:** -0.02 ± 0.3 **G1c:** -0.12 ± 0.2 **G1d:** -0.60 ± 0.2 **G1e:** 0.49 ± 0.5 **G1f:** -0.74 ± 0.4 **G1g:** -1.46 ± 0.4 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals) **± SE:** **G1:** NR **G1a:** NR **G1b:** -0.23 ± 0.4 **G1c:** -0.27 ± 0.2 **G1d:** -0.56 ± 0.2 **G1e:** -0.48 ± 0.5 **G1f:** -0.66 ± 0.3	RVDLT trials 1 and totals)**:** **G1:** r=-.29 **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:** **G1:** r=-.19 **Lifetime Phe with:** **Attention** (TEA-Ch Sky Search, Code Transmission, Digital Distraction, and Dual Task)**:** **G1:** r=-.32 **Memory/Learning** (Digit span forwards and backwards, RAVLT and RVDLT trials 1 and totals)**:** **G1:** r=-.49, p<.01 **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words)**:**

Anderson, 2004[7, 8] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
			G1g: -1.12 ± 0.4 **Executive Function** (TOL extra attempts, RCF copy accuracy, CNT errors and self-corrections, and COWAT total words) **± SE:** **G1:** NR **G1a:** NR **G1b:** -0.10 ± 0.4 **G1c:** -0.01 ± 0.2 **G1d:** -0.70 ± 0.2 **G1e:** -0.68 ± 0.3 **G1f:** -0.62 ± 0.2 **G1g:** -1.26 ± 0.3 *** Means adjusted for age, socioeconomic status and gender	**G1:** r=-.40

Appendix B. Studies Addressing Executive Function, continued

Channon, 2004[9-11] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
UK Cross Sectional **G1:** off-diet PKU subjects **G2:** on-diet PKU subjects **G3:** PKU subjects continuously treated	**G1:** 25 **G2:** 25 **G3:** 20 Lifetime, Recent, Concurrent Classic, atypical **G1:** 27.48 ± 4.55 (18-38) **G2:** 26.68 ± 4.92 (18-33) **G3:** 24.60 ± 4.62 (18-33)	**Mean Phe (µmol/l):** **1-4 years of age:** **G1:** 460.59 ± 181.91 (171.75-786.69) **G2:** 450.58 ± 123.97(255.75-727.5) **G3:** 418.13 ± 94.35 (255.75-596.67) **5-8 years of age:** **G1:** 586.5 ± 199.91 (276-986.25) **G2:** 456.85 ± 127.3 (237.13-740) **G3:** 430.64 ± 127.75 (225.00-680.00) **9-12 years of age:** **G1:** 917.69 ± 209.53 (430-1380) **G2:** 697.3 ± 280.65 (175-1275) **G3:** 715.34 ± 280.96 (175.00-1275.00) **13-16 years of age:** **G1:** 1153.24 ± 242.91 (859-1710) **G2:** 775.7 ± 255.9 (422.25-	**N-back percentage accuracy:** **0-back:** **G1:** 97.08 ± 2.46 **G2:** 98.83 ± 1.09 **G3:** NR **1-back:** **G1:** 95.65 ± 3.24 **G2:** 97.78 ± 1.53 **G3:** NR **2-back:** **G1:** 84.55 ± 7.62 **G2:** 88.93 ± 5.69 **G3:** NR **N-back speed per item (s):** **0-back:** **G1:** 0.43 ± 0.05 **G2:** 0.45 ± 0.08 **G3:** NR **1-back:** **G1:** 0.60 ± 0.15 **G2:** 0.55 ± 0.13 **G3:** NR **2-back:** **G1:** 1.54 ± 1.17 **G2:** 1.34 ± 0.67 **G3:** NR **Flanker percentage accuracy:**	**N-back accuracy:** **0-back with:** **mean phe level age 1-4:** **G1:** r=-0.19 **G2:** 0.29 **mean phe level age 5-8:** **G1:** -0.05 **G2:** 0.23 **mean phe level age 9-12:** **G1:** 0.16 **G2:** -0.41 **mean phe level age 13-16:** **G1:** 0.15 **G2:** -0.17 **mean phe level age 17-20:** **G1:** -0.09 **G2:** -0.15 **mean phe level age 21-24:** **G1:** -0.11 **G2:** -0.26 **mean phe level age 25-28:** **G1:** -0.10 **G2:** -0.36

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
		1411.5) **G3:** 790.72 ± 265.98 (453.38-1411.50) **17-20 years of age:** **G1:** 1345.79 ± 282.26 (845-2013) **G2:** 867.73 ± 248.89 (448.00-1443.13) **G3:** 891.88 ± 251.19 (448.00-1443.13) **21-24 years of age:** **G1:** 1362.55 ± 268.87 (850-1774.5) **G2:** 850.74 ± 229.44 (323.75-1216.81) **G3:** 818.46 ± 238.35 (323.75-1216.81) **25-28 years of age:** **G1:** 1408.19 ± 426.96 (989-2815.5) **G2:** 868.63 ± 187.40 (572-1170.79) **G3:** 878.94 ± 194.34 (493.56-1170.09) **29-32 years of age:** **G1:** 1320.46 ± 262.99 (995-1736) **G2:** 795.75 ± 228.62	**Compatible trials:** **G1:** 98 ± 1.57 **G2:** 99.35 ± 1.03 **G3:** NR **Incompatible trials:** **G1:** 97.05 ± 2.28 **G2:** 97.65 ± 3.41 **G3:** NR **Flanker speed per item (s):** **Compatible trials:** **G1:** 0.49 ± 0.07 **G2:** 0.45 ± 0.06 **G3:** NR **Incompatible trials:** **G1:** 0.52 ± 0.08 **G2:** 0.47 ± 0.05 **G3:** NR **Attention:** **Telephone search per minute:** **G1:** NR **G2:** NR **G3:** 19.94 ± 4.82 **Telephone search and counting per minute:** **G1:** NR **G2:** NR **G3:** 18.46 ± 4.88 **Self-ordered pointing:** **6-word trials per minute:**	**mean phe level age 29-32:** **G1:** -0.29 **G2:** -0.56 **Concurrent phe level:** **G1:** -0.07 **G2:** -0.33 **Recent phe level:** **G1:** -0.08 **G2:** -0.38 **1-back with**: **mean phe level age 1-4:** **G1:** -0.12 **G2:** -0.47 **mean phe level age 5-8:** **G1:** 0.04 **G2:** -0.48 **mean phe level age 9-12:** **G1:** 0.44 **G2:** -0.01 **mean phe level age 13-16:** **G1:** 0.21 **G2:** 0.13 **mean phe level age 17-20:** **G1:** -0.15 **G2:** 0.18 **mean phe level age 21-**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
		(470.32-1194.25) **G3:** NR **Concurrent Phe (µmol/l):** **G1:** 1285.68 ± 197.83 (990-1651) **G2:** 758.79 ± 261.27 (221.00-1233.00) **G3:** 858.80 ± 285.28 (333.00-1432.00) **Recent Phe (year preceding test) (µmol/l):** **G1:** 1317.77 ± 221.78 (1013.67-1710) **G2:** 797.62 ± 240.80 (283.40-1153.00) **G3:** 788.90 ± 225.24 (338.09-1208.75)	**G1:** NR **G2:** NR **G3:** 15.45 ± 4.17 **9-word trials per minute:** **G1:** NR **G2:** NR **G3:** 12.90 ± 2.64 **12-word trials per minute:** **G1:** NR **G2:** NR **G3:** 12.25 ± 2.70	**24:** **G1:** -0.54 **G2:** 0.02 **mean phe level age 25-28:** **G1:** -0.12 **G2:** 0.20 **mean phe level age 29-32:** **G1:** -0.25 **G2:** -0.04 **Concurrent phe level:** **G1:** -0.24 **G2:** -0.14 **Recent phe level:** **G1:** -0.19 **G2:** -0.07 **2-back with:** **mean phe level age 1-4:** **G1:** 0.13 **G2:** -0.21 **mean phe level age 5-8:** **G1:** 0.02 **G2:** -0.11 **mean phe level age 9-12:** **G1:** 0.24 **G2:** 0.21 **mean phe level age 13-16:**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				G1: -0.17 **G2:** 0.39 **mean phe level age 17-20:** **G1:** -0.24 **G2:** 0.34 **mean phe level age 21-24:** **G1:** -0.26 **G2:** 0.22 **mean phe level age 25-28:** **G1:** -0.49 **G2:** 0.59 **mean phe level age 29-32:** **G1:** -0.22 **G2:** 0.32 **Concurrent phe level:** **G1:** -0.24 **G2:** -0.07 **Recent phe level:** **G1:** -0.19 **G2:** -0.08 **N-back speed:** **0-back with:** **mean phe level age 1-4**: **G1:** -0.58, p<0.01 **G2:** 0.36

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				mean phe level age 5-8: **G1:** -0.46 **G2:** 0.55, p<0.01 **mean phe level age 9-12:** **G1:** 0.01 **G2:** 0.03 **mean phe level age 13-16:** **G1:** -0.14 **G2:** 0.09 **mean phe level age 17-20:** **G1:** -0.04 **G2:** 0.10 **mean phe level age 21-24:** **G1:** 0.37 **G2:** 0.11 **mean phe level age 25-28:** **G1:** 0.10 **G2:** -0.17 **mean phe level age 29-32:** **G1:** 0.33 **G2:** -0.64 **Concurrent phe level:** **G1:** 0.55, p<0.01 **G2:** 0.22

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				Recent phe level: **G1:** 0.44 **G2:** -0.37 **1-back with:** **mean phe level age 1-4:** **G1:** -0.45 **G2:** -0.03 **mean phe level age 5-8:** **G1:** -0.38 **G2:** 0.19 **mean phe level age 9-12:** **G1:** -0.19 **G2:** 0.02 **mean phe level age 13-16:** **G1:** -0.14 **G2:** 0.13 **mean phe level age 17-20:** **G1:** 0.09 **G2:** 0.13 **mean phe level age 21-24:** **G1:** 0.28 **G2:** 0.05 **mean phe level age 25-28:** **G1:** 0.11 **G2:** -0.24

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				mean phe level age 29-32: **G1:** 0.38 **G2:** -0.38 **Concurrent phe level:** **G1:** 0.38 **G2:** 0.26 **Recent phe level:** **G1:** 0.31 **G2:** 0.06 **2-back with:** **mean phe level age 1-4:** **G1:** -0.14 **G2:** -0.39 **mean phe level age 5-8:** **G1:** -0.30 **G2:** -0.15 **mean phe level age 9-12:** **G1:** 0.01 **G2:** 0.17 **mean phe level age 13-16:** **G1:** -0.54, p<0.01 **G2:** 0.10 **mean phe level age 17-20:** **G1:** -0.53 **G2:** -0.18 **mean phe level age 21-**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				24 **G1:** 0.07 **G2:** -0.30 **mean phe level age 25-28:** **G1:** -0.43 **G2:** -0.01 **mean phe level age 29-32:** **G1:** -0.11 **G2:** -0.29 **Concurrent phe level:** **G1:** -0.06 **G2:** 0.23 **Recent phe level:** **G1:** -0.14 **G2:** 0.08 **Flanker speed:** **Compatible trials with:** **mean phe level age 1-4:** **G1:** -0.36 **G2:** 0.24 **mean phe level age 5-8:** **G1:** -0.40 **G2:** 0.41 **mean phe level age 9-12:** **G1:** -0.32 **G2:** -0.11

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				mean phe level age 13-16: **G1:** -0.10 **G2:** 0.15 **mean phe level age 17-20:** **G1:** -0.08 **G2:** 0.18 **mean phe level age 21-24** **G1:** 0.35 **G2:** 0.22 **mean phe level age 25-28:** **G1:** 0.26 **G2:** 0.17 **mean phe level age 29-32:** **G1:** 0.43 **G2:** -0.59 **Concurrent phe level:** **G1:** 0.44 **G2:** -0.18 **Recent phe level:** **G1:** 0.41 **G2:** -0.20 **Flanker speed: Incompatible trials with:** **mean phe level age 1-4:**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				G1: -0.38 **G2:** 0.27 **mean phe level age 5-8:** **G1:** -0.41 **G2:** 0.33 **mean phe level age 9-12:** **G1:** -0.26 **G2:** -0.13 **mean phe level age 13-16:** **G1:** -0.11 **G2:** 0.08 **mean phe level age 17-20:** **G1:** -0.13 **G2:** 0.08 **mean phe level age 21-24** **G1:** 0.28 **G2:** 0.19 **mean phe level age 25-28:** **G1:** 0.26 **G2:** 0.03 **mean phe level age 29-32**: **G1:** 0.25 **G2:** -0.63 **Concurrent phe level:**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				G1: 0.38 **G2:** -0.24 **Recent phe level:** **G1:** 0.32 **G2:**-0.21 **Correlations between N-back accuracy, N-back speed, and Flanker speed with phe levels for G3:** NR **Attention (combined Telephone search and Telephone search with counting) and:** **mean phe level age 1-4:** **G3:** .19 **mean phe level age 5-8:** **G3:** .18 **mean phe level age 9-12:** **G3:** .21 **mean phe level age 13-16:** **G3:** -.06 **mean phe level age 17-20:** **G3:** -.03 **mean phe level age 21-**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				24: **G3:** -.18 **mean phe level age 25-28:** **G3:** -.59, p<0.05 **Concurrent phe level:** **G3:** -.16 **Recent phe level:** **G3:** -.19 **Self-ordered pointing (combined levels) and mean phe level age 1-4:** **G3:** .03 **mean phe level age 5-8:** **G3:** -.06 **mean phe level age 9-12:** **G3:** -.01 **mean phe level age 13-16:** **G3:** -.13 **mean phe level age 17-20:** **G3:** .44 **mean phe level age 21-24:** **G3:** -.63, p<.05 **mean phe level age 25-28:**

Channon, 2004[9-11] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				G3: -.77, p<.01 **Concurrent phe level:** **G3:** -.49, p<.05 **Recent phe level:** **G3:** -.67, p<.01 **Correlations between attention and self-ordered pointing for G1 and G2:** NR

Appendix B. Studies Addressing Executive Function, continued

Antshel 2003[12, 13] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
United States Cross Sectional **G1:** participants with PKU	**G1:** 46 Current PKU classification: NR **G1:** 10.75 ± 2.1 years (8-14)	**Current Phe (mg/dl)** **G1:** 8.1 ± 6.2 (0.9 – 22.8)	**California Verbal Learning Test – Children's Version (CVLT-C) Semantic Cluster Ratio:** **G1:** 39.9 ± 7.4 **CVLT-C Trial 5 Number Correct:** **G1:** 40.3 ± 9.2 **Stroop Color and Word Test Interference trial:** **G1:** 50.7 ± 8.3 **Stroop Word Reading T score:** **G1:** 44.0 ± 9.9	**Current Phe level with:** **CVLT-C Semantic Cluster Ratio:** **G1:** r = -.543, p<.001 **CVLT-C Trial 5 Number Correct:** **G1:** r = -.291, p<.001 **Stroop Word Reading:** **G1:** r = -.498, p<.001

Appendix B. Studies Addressing Executive Function, continued

Huijbregts 2002[14] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Netherlands Retro-spective case series **G1:** PKU subjects **G1a:** PKU subjects age <11 **G1b:** PKU subjects age ≥11 **G1c:** PKU subjects with concurrent phe≤360 µmol/l **G1d:** PKU subjects with concurrent phe≤360 µmol/l age<11 **G1e:** PKU subjects with concurrent	**G1:** 57 **G1a:** 27 **G1b:** 30 **G1c:** 22 **G1d:** 11 **G1e**:11 **G1f:** 35 **G1g:** 16 **G1h:** 19 Lifetime, Concurrent Classical **G1:** 11.0 ± 2.1 **G1a:** 9.1 ± 1.1 **G1b:** 12.7 ± 1.1 **G1c:** 11.2 ± 2.2 **G1d:** 9.4 ± 1.4 **G1e:** 12.9 ± 1.3 **G1f:** 10.9 ± 2.1 **G1g:** 8.9 ± 0.9 **G1h:** 12.6 ± 1.0	**Concurrent phe (µmol/l):** **G1:** 461 ± 259 **G1a:** 424 ± 218 **G1b:** 494 ± 291 **G1c:** 206 ± 99 **G1d:** 218 ± 77 **G1e:** 194 ± 119 **G1f:** 621 ± 190 **G1g:** 566 ± 161 **G1h:** 668 ± 203 **IDC (mean of all half-year median phe levels) (µmol/l):** **G1:** 344 ± 115 **G1a:** 354 ± 150 **G1b:** 335 ± 75 **G1c:** 295 ± 67 **G1d:** 281 ± 64 **G1e:** 307 ± 70 **G1f:** 372 ± 128 **G1g:** 396 ± 169 **G1h:** 351 ± 75	**ANT Mean RT sustained attention (ms):** **G1d:** 1331, SD-NR **G1e:** 1040, SD-NR **G1g:** 1658, SD-NR **G1h:** 1110, SD-NR **Mean series time (MST); see following set of values for SD:** **G1d:** 15.98 **G1e:** 12.48 **G1g:** 19.90 **G1h:** 13.32 **Standard deviation of Mean series time (a measure for the stability of performance (Fluctuation in Tempo)):** **G1d:** 2.77 **G1e:** 1.98 **G1g:** 3.77 **G1h:** 2.24 **MST Corrected for Accuracy:** **G1d:** 17.04, SD-NR **G1e:** 13.23, SD-NR **G1g:** 21.62, SD-NR **G1h:** 14.15, SD-NR	**Tempo (Mean series time corrected for accuracy) with:** **Phe between ages 5 and 7:** r=0.36, p=0.004 **IDC:** r=0.27, p=0.026 **Phe between ages 2.5 and 4:** r=0.26, p=0.029 **Fluctuation in Tempo with:** **Phe between ages 5 and 7:** r=0.38, p=0.002 **IDC:** r=0.28, p=0.021 **Phe between ages 2.5 and 4:** r=0.24, p=0.045 **Bias with** **Phe between ages 5 and 7:** r=0.29, p=0.019

Huijbregts 2002[14] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
phe≤360 µmol/l age ≥11 **G1f:** PKU subjects concurrent phe>360 µmol/l G1g: PKU subjects concurrent phe>360 µmol/l age<11 G1h: PKU subjects concurrent phe>360 µmol/l age≥11			**Mean number of false alarms 3 dots (FA3):** **G1d:** 7.5, SD-NR **G1e:** 5.6, SD-NR **G1g:** 8.8, SD-NR **G1h:** 4.8, SD-NR **Mean number of Misses 4 dots (MISS):** **G1d:** 20.1, SD-NR **G1e:** 16.7, SD-NR **G1g:** 28.4, SD-NR **G1h:** 22.1, SD-NR **Mean number of false alarms 5 dots (FA5):** **G1d:** 10.7, SD-NR **G1e:** 10.9, SD-NR **G1g:** 13.0, SD-NR **G1h:** 9.8, SD-NR **Number of misses – number of false alarms (BIAS):** **G1d:** 11.0, SD-NR **G1e:** 8.5, SD-NR **G1g:** 16.3, SD-NR **G1h:** 13.2, SD-NR	**IDC:** r=0.29, p=0.018 **Concurrent phe:** r=0.24 p=0.043 **Bias over time with:** **phe level between ages 5 and 7:** r=0.40, p=0.002 **phe level between ages 2.5 and 4:** r=0.28, p=0.023 **IDC:** r=0.35, p=0.007

Appendix B. Studies Addressing Executive Function, continued

Luciana 2001[15] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
United States Cross Sectional **G1:** PKU patients	**G1:** 18 Classic Lifetime, Recent (within 6 months prior to cognitive assessment) 17.88 ± 2.74 years	**Recent phe (mg/dl):** **G1:** 16.3 ± 6.8 (5.3-28.8) **Phe averages for 0-2 years, 3-4 years, 5-8 years, 9-13 years and 14-15 years of life:** **G1:** NR	**Spatial working memory:** **Easy-item errors:** **G1:** .71 ± 1.7 **Hard-item errors:** **G1:** 21.6 ± 16.8 **Strategy score:** **G1:** 32.6 ± 4.6 **Tower of London planning:** **Minimum move solutions:** **G1:** 7.8 ± 1.8 **Average moves to complete 3-move problems:** **G1:** 3.2 ± .4 **Average moves to complete 4-move problems:** **G1:** 5.7 ± 1.2 **Average moves to complete 5-move problems:** **G1:** 7.3 ± 1.9 **Planning Times:** **3- move problems:** **G1:** 5911.9 ± 4383.0 **4-move problems:** **G1:** 9535.7 ± 6772.7 **5-move problems:** **G1:** 8895.0 ± 5755.9	**Spatial Working Memory-Strategy and:** **Phe within past 6 months:** **G1:** .71, p<.01 **Phe 0-2 years:** **G1:** -.11 **Phe 3-4 years:** **G1:** .38, p<.10 **Phe 5-8 years:** **G1:** .23 **Phe 9-13 years:** **G1:** .39, p<.10 **Phe 14-15 years:** **G1:** .65, p<.05 **Spatial Working Memory-Errors and** **Phe within past 6 months:** **G1:** .13 **Phe 0-2 years:** **G1:** -.44, p<.10 **Phe 3-4 years:** **G1:** .26 **Phe 5-8 years:**

Luciana 2001[15] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
			ID/ED set shifting: **Stage reached:** **G1:** 8.1 ± 2.0 **ID errors:** **G1:** 4.4 ± 7.9 **ID trials:** **G1:** 10.5 ± 7.6 **ED errors:** **G1:** 5.5 ± 7.9 **ED trials:** **G1:** 13.3 ± 10.6 **Reversal errors:** **G1:** 5.75 ± 2.8	**G1:** .18 **Phe 9-13 years:** **G1:** .30 **Phe 14-15 years:** **G1:** .15 **Set shifting-Stage and Phe within past 6 months:** **G1:** NR **Phe 0-2 years:** **G1:** .24 **Phe 3-4 years:** **G1:** -.41, p<.10 **Phe 5-8 years:** **G1:** -.49, p<.05 **Phe 9-13 years:** **G1:** -.57, p<.05 **Phe 14-15 years:** **G1:** .03 **Tower of London-Perfect solutions and Phe within past 6 months:** **G1:** -.30 **Phe 0-2 years:** **G1:** .54, p<.05 **Phe 3-4 years:** **G1:** -.05 **Phe 5-8 years:** **G1:** -.09

Luciana 2001[15] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				Phe 9-13 years: **G1:** -.30 **Phe 14-15 years:** **G1:** .04

Appendix B. Studies Addressing Executive Function, continued

Griffiths 1998[16] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
UK Retro-spective case series **G1:** individuals with PKU	**G1:** 11 Concurrent, lifetime Classic Median Age (years): **G1:** 8.83 (5.11-11.92)	**Phe level birth to age 5 years (µmol/l):** **G1:** 342 ± 126 **Lifetime phe (µmol/l):** **G1:** 341 ± 125 (224-600) **Concurrent phe (µmol/l):** **G1:** 388 ± 127 (193-562)	**One-back continuous performance test (CPT):** **Overall mean hit rate out of 80:** **G1:** 72.18 ± 7.17 **Overall mean false alarm frequency:** **G1:** 8.36 ± 7.24 **Overall mean reaction time (milliseconds):** **G1:** 499 ± 81 **Two-back continuous performance test (CPT):** **Overall mean hit rate:** **G1:** 64.55 ± 7.54 **Overall mean false alarm frequency:** **G1:** 9.64 ± 5.89 **Overall mean reaction time (milliseconds):** **G1:** 509 ± 72	**Lifetime phe with any one-back measure or two-back measure:** **G1:** NS **Phe for first 5 years of life with any one-back measure or two-back measure:** **G1:** NS **Concurrent phe with any one-back measure or two-back measure:** **G1:** NS

Appendix B. Studies Addressing Executive Function, continued

Pietz 1998[17] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Germany Cross Sectional **G1:** PKU subjects	**G1:** 57 Classic Lifetime, Concurrent 23.6 ± 3.4 (17-33)	**Phe $_{0\text{-adult}}$ (mean of all half-year medians) (µmol/l):** **G1:** 676 ± 157 (388-994) **Phe $_{0\text{-}12}$ (mean of all half-year medians for first 12 years) (µmol/l):** **G1:** 424 ± 158 (206-806) **Phe $_{12\text{-adult}}$ (mean of all half-year medians from 12 years of age up to adulthood) (µmol/l):** **G1:** 964 ± 194 (642-1424) **Concurrent phe (µmol/l):** **G1:** 1085 ± 303 (362-1733)	**Slow videotracking level (distance):** **G1:** 17.2 ± 6.7 **Slow videotracking stability (distance):** **G1:** 6.5 ± 3.0 **Fast videotracking level (distance):** **G1:** 37.9 ± 15.2 **Fast videotracking stability (distance):** **G1:** 16.6 ± 11.8	**Phe after 12 years of age with videotracking performance:** **G1:** r=-0.34, p<.05 **Concurrent phe with videotracking performance:** **G1:** r=-0.37, p<.01

Appendix B. Studies Addressing Executive Function, continued

Stemerdink 1995[18] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Netherlands Prospective Cohort **G1:** PKU patients	**G1:** 33 Classical Lifetime 11.8 ± 2.9 years (7.3-16.8)	**Phe levels first 4 years (µmol/l):** **G1:** 408, SD-NR (222-650) **Phe levels 2 years preceding testing (µmol/l):** **G1:** 374, SD-NR (125-701)	**Eriksen and Schultz task performance:** **Response times:** **G1:** NR **Error percentages:** **G1:** NR **Memory Search Task:** **Response times:** **G1:** NR **Error percentages:** **G1:** NR	**Mean Phe for first 4 years and:** **Eriksen and Schultz task performance:** **Response times:** **G1:** 0.33, p<0.05 **Error percentage:** **G1:** -0.004 **Memory Search Task:** **Response times:** **G1:** 0.03 **Error percentage:** **G1:** 0.12 **Mean Phe 2 years before testing and:** **Eriksen and Schultz task performance:** **Response times:** **G1:** 0.33, p<0.05 **Error percentages:** **G1:** -0.08 **Memory Search Task:** **Response times:** **G1:** 0.03 **Error percentage:** **G1:** -0.07

Appendix B. Studies Addressing Executive Function, continued

Weglage 1995[19-21] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Germany Prospective Cohort **G1:** PKU patients	**G1:** 20/20 Concurrent, lifetime Classic Age: **G1:** **Test time 1:** 10 years, 11 mos ± 1.3 years (8.9-13.1) (reported as median and mean of 10 years, 11 mos ± 1.3 years in Weglage 1996 and mean of 10.11 ± 1.3 years in Weglage 1995) **Test time 2:** 14 yrs, SD-NR	**Concurrent phe (µmol/l):** **G1:** **Test time 1:** 582 ± 372 (84-1710) (583 ± 377 (85-1709) in Weglage 1995 and 1996) **Test time 2:** 744 ± 456 (66-1944) **Lifetime phe (mean of yearly medians) (µmol/l):** **G1:** **Test time 1:** 474 ± 144 (282-810) (476 ± 144 (279-818) in Weglage 1995 and 1996) **Test time 2:** 534 ± 174 (276-1014) **Phe 6 months prior to test (mean of monthly medians) (µmol/l):** **G1:** **Test time 1:** 624 ± 328 (80-1563) **Test time 2:** NR **Mean of yearly medians**	**Test-d-2 (percentile scores):** **G1:** **Number of items completed:** **Test time 1:** 37.2 ± 26.2 (8.1-90.3) **Test time 2:** 60.0 ± 25.8 **Errors:** **Test time 1:** 57.0 ± 27.6 (15.9-93.3) **Test time 2:** 81.2 ± 26.8 **Number of items completed - errors:** **Test time 1:** 35.5 ± 26.6 (3.0-76.0) **Test time 2:** 65.8 ± 34.9 **CWIT-Stroop tasks:** **G1:** **Reading of color words (sec):** **Test time 1:** 48.2 ± 11.1 (SD=10.6 with a range of (31-81) in Weglage 1996; NR in Weglage 1995) **Test time 2:** 41.1 ± 10.3 **Color naming (sec):** **Test time 1:** 83.5 ± 16.7 (57-121) **Test time 2:** 67.4 ± 11.2 **Interference task time (sec):** **Test time 1:** 153.7 ± 45.9 (105-300) **Test time 2:** 110.6 ± 24.2 **Interference task mistakes**	**Concurrent phe with Number of items completed:** **Test time 1:** r=0.41, p<0.05 (r=-0.41, p<0.05 in Weglage 1996) **Test time 2:** r=-2.42, p<0.05 **Errors:** **Test time 1:** r=-0.38, p<0.05 **Test time 2:** r=-2.39, p<0.05 **Number of items completed - errors:** **Test time 1:** r=-0.39, p<0.05 (reported as r=0.38, p<0.05 in Weglage 1995) **Test time 2:** r=-2.40, p<0.05 **Lifetime phe with Number of items completed:** **Test time 1:** NS **Test time 2:** NS

Weglage 1995[19-21] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
		between test times 1 and 2 (µmol/l): **G1:** 576 ± 174 (276-1014)	**(number):** **Test time 1:** 15.4 ± 14.2 (0-45) **Test time 2:** 11.6 ± 11.7 **WISC-R (short term memory):** **Test time 1:** 10.2 ± 2.2 (6-14) **Test time 2:** NR	**Errors:** **Test time 1:** NS **Test time 2:** NS **Number of items completed - errors:** **Test time 1:** NS **Test time 2:** NS **Phe 6 months prior to test with** **Number of items completed:** **Test time 1:** NR **Test time 2:** NR **Errors:** **Test time 1:** NR **Test time 2:** NR **Number of items completed - errors:** **Test time 1:** r=-0.39, p<0.05 **Test time 2:** NR **Concurrent phe and:** **reading of color words:** **Test time 1:** NS **Test time 2:** NS **Color naming:** **Test time 1:** NS **Test time 2:** NS

Weglage 1995[19-21] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				Interference task time: **Test time 1:** r=0.39, p<0.05 **Test time 2:** NS **Mistakes (number):** **Test time 1:** r=0.38, p<0.05 **Test time 2:** NS **Lifetime phe and:** **reading of color words:** **Test time 1:** NS **Test time 2:** NS **Color naming:** **Test time 1:** NS **Test time 2:** NS **Interference task time:** **Test time 1:** NS **Test time 2:** NS **Mistakes (number):** **Test time 1:** NS **Test time 2:** NS **Correlation of differences in CWIT performances between test times 1 and 2 and mean phe during the 3-year interval:** NS

Weglage 1995[19-21] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
				Concurrent phe with WISC-R (short term memory): **Test time 1:** NS **Test time 2:** NR **Lifetime phe with WISC-R (short term memory):** **Test time 1:** NS **Test time 2:** NR

Appendix B. Studies Addressing Executive Function, continued

Ris 1994[22, 23] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
USA Prospective cohort **G1:** PKU subjects **G1a:** PKU subjects with unaffected siblings	**G1:** 25 **G1a:**10 Concurrent Classic **G1:** 22 years, SD-NR **G1a:** NR	**Concurrent phe (mg/dl):** **G1:** 22, SD-NR **Individual Concurrent Phe (µmol/l):** Subject 1: 993 Subject 2: 1102 Subject 3: 1665 Subject 4: 1968 Subject 5: 1380 Subject 6: 1538 Subject 7: 920 Subject 8: 1162 Subject 9: 1120 Subject 10: 1483 Subject 11: 1084 Subject 12: 1635 Subject 13: 1659 Subject 14: 1804 Subject 15: 503 Subject 16: 1399 Subject 17: 254 Subject 18: 1586 Subject 19: 2252 Subject 20: 1164 Subject 21: 1284 Subject 22: 1810 Subject 23: 1011	**WCST-Perseverative Responses (raw scores):** **G1:** 21 ± 32 **G1a:** 22 ± 39 **Attention Diagnostic Method (seconds):** **G1:** 461 ± 132 **G1a:** 439 ± 125 **Individual WCST-Perseverative Responses:** Subject 1: NR Subject 2: 5 Subject 3: 7 Subject 4: 123 Subject 5: 11 Subject 6: 28 Subject 7: 8 Subject 8: 13 Subject 9: 39 Subject 10: 5 Subject 11: 17 Subject 12: 14 Subject 13: 9 Subject 14: 22 Subject 15: 6	**Concurrent phe with WCST-Perseverative Responses:** **G1:** 0.59, $p<0.01$ **Concurrent phe with Attention Diagnostic Method:** **G1:** 0.34, $p<0.10$

Ris 1994[22, 23] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
		Subject 24: 1368 Subject 25: 938	Subject 16: 12 Subject 17: 6 Subject 18: 4 Subject 19: 115 Subject 20: 4 Subject 21: 16 Subject 22: NR Subject 23: 7 Subject 24: 18 Subject 25: 3	

Appendix B. Studies Addressing Executive Function, continued

Schmidt 1994[24] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
Germany Prospective Cohort **G1:** PKU subjects **G1a:** PKU subjects who completed tests and were able to keep their Phe-levels according to high-low-high study design	**G1:** 19/14 **G1a:**14/14 Concurrent PKU classification: NR Age: **G1:** 20.5 years SD-NR (17-24) **G1a:** NR	**Mean Phe level (mg/dl):** Test time 1: **G1:** 23.4, SD-NR (12-30) **G1a:** 22.0 ± 5.7 Test time 2: **G1:** NR **G1a:** 10.5 ± 3.7 Test time 3: **G1:** NR **G1a:** 23.5 ± 6.1 **Individual phe at Test Time 1 (mg/dl):** Patient 1: 19.1 Patient 2: 19.0* Patient 3: 25.4 Patient 4: 23.1* Patient 5: 15.0 Patient 6: 21.0 Patient 7: 26.7 Patient 8: 24.7 Patient 9: 25.4 Patient 10: 16.8 Patient 11: 16.3* Patient 12: 12.4* Patient 13: 18.7 Patient 14: 29.7 Patient 15: 25.3	**Dot Pattern Exercise (DPE):** **Mean RT of 50 series (level of performance) (s):** **Test time 1:** **G1a:** 10.1 **Test time 2:** **G1a:** 8.09 **Test time 3:** **G1a:** 9.32 **SD of 50 series times (ms) (stability of performance):** **Test time 1:** **G1a:** 1381 **Test time 2:** **G1a:** 777 **Test time 3:** **G1a:** 1356 **Number of Errors (sum of misses, false alarms 3 and false alarms 5 dots):** **Test time 1:** **G1a:** 51.9 **Test time 2:** **G1a:** 36.8 **Test time 3:**	**Phe levels with DPE test outcomes:** NR

Schmidt 1994[24] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
		Patient 16: 16.6 Patient 17: 12.0 Patient 18: 9.4* Patient 19: 32.2 **Individual phe at Test Time 2 (mg/dl):** Patient 1: 11.0 Patient 2: 16.8* Patient 3: 16.1 Patient 4: 8.5* Patient 5: 7.4 Patient 6: 6.1 Patient 7: 16.8 Patient 8: 11.6 Patient 9: 10.9 Patient 10: 7.5 Patient 11: 13.7* Patient 12: 2.0* Patient 13: 4.6 Patient 14: 16.3 Patient 15: 10.4 Patient 16: 8.5 Patient 17: 7.0 Patient 18: 12.4* Patient 19: 12.0 **Individual phe at Test Time 3 (mg/dl):** Patient 1: 16.1	**G1a:** 43.0 **Percentage of Errors:** **Test time 1:** **G1a:** 8.7 **Test time 2:** **G1a:** 6.1 **Test time 3:** **G1a:** 7.2 DPE test outcomes for **G1:** NR	

Schmidt 1994[24] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
		Patient 2: NR* Patient 3: 23.0 Patient 4:18.7* Patient 5: 35.2 Patient 6: 25.2 Patient 7: 25.9 Patient 8: 17.4 Patient 9: 18.4 Patient 10: 20.0 Patient 11: 14.8* Patient 12: 6.5* Patient 13: 20.9 Patient 14: 20.0 Patient 15: 36.6 Patient 16: 18.9 Patient 17: 25.4 Patient 18: 14.3* Patient 19: 25.3 *Data from patients 2, 4, 11, 12 and 18 not included in data analysis.		

Appendix B. Studies Addressing Executive Function, continued

de Sonneville 1990[25] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
Germany Prospective Cohort **G1:** PKU patients **G1a:** PKU patients with median concurrent Phe >9.5 mg/dl **G1b:** PKU patients with median concurrent Phe <9.5 mg/dl	**G1:** 32 **G1a:** NR **G1b:** NR PKU classification: NR Lifetime, concurrent **G1:** 8.7 years SD-NR **G1a:** NR **G1b:** NR	**Concurrent phe:** **G1:** NR **G1a:** NR **G1b:** NR **Lifetime phe:** **G1:** NR **G1a:** NR **G1b:** NR	**Dot Pattern Exercise:** **Mean times per series:** **G1:** 19.8 ± 3.7 **G1a:** 22.5 ± 5.3 **G1b:** 17.0 ± 2.5 **Accuracy (%) for false alarms to 3-dot patterns:** **G1:** 4.0, SD-NR **G1a:** NR **G1b:** NR **Accuracy (%) for Miss:** **G1:** 4.0, SD-NR **G1a:** NR **G1b:** NR **Accuracy (%) for false alarms to 5-dot patterns:** **G1:** 4.5, SD-NR **G1a:** NR **G1b:** NR **Calculation exercise (CAE) performance:** **Number of errors-simple additions:** **G1:** 0.9, SD-NR **Number of errors-complex**	**Eight median phe levels (measured at 6-month intervals since birth) with highest correlations with:** **DPE SD series:** Median 18: r=.75, p=.01 Median 14: r=.65, p=.01 Median 17: r=.64, p=.01 Median 04: r=.55, p=.01 Median 15: r=.51, p=.02 Median 12: r=.48, p=.02 Concurrent: r=.47, p=.01 Median 16: r=.47, p=.02 **DPE mean time over series:** Median 18: r=.58, p=.04 Median 14: r=.51, p=.02 Median 17: r=.48, p=.05 Median 16: r=.46, p=.03 Median 01: r=.46, p=.02 Median 04: r=.45, p=.02 Median 15: r=.45, p=.04 Concurrent: r=.37, p=.05 **Calculation exercises**

de Sonneville 1990[25] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
			additions: **G1**: 2.5, SD-NR	**simple additions:** Median 16: r=.46, p=.02 Median 18: r=.42, p=.12 Concurrent: r=.42, p=.02 Median 02: r=.34, p=.05 Median 01: r=.32, p=.07 Median 10: r=.31, p=.09 Median 05: r=.31, p=.09 Median 12: r=.27, p=.16 **Calculation Exercises complex additions:** Concurrent: r=.45, p=.01 Median 15: r=.29, p=.15 Median 01: r=.27, p=.15 Median 18: r=.24, p=.40 Median 13: r=.24, p=.24 Median 02: r=.20, p=.27 Median 12: r=.16, p=.40 Median 06: r=.16, p=.38

Appendix B. Studies Addressing Executive Function, continued

Welsh 1990[26] **Country** **Study Design** **Groups**	**N Enrollment/ Follow-up** **Type of Phe Measure** **Disease Type** **Age**	**Phe level**	**Key Outcomes***	**Correlation**
USA Prospective cohort **G1:** PKU subjects	**G1:** 11/11 Lifetime, Concurrent PKU classification: NR Mean age (years): 4.64, SD-NR (4.08-5.75) Individual Age (years): Subject 1: 4.25 Subject 2: 5.75 Subject 3: 4.08 Subject 4: 5.17 Subject 5: 4.50 Subject 6: 4.83 Subject 7: 4.50 Subject 8: 4.67 Subject 9: 4.42 Subject 10: 4.33 Subject 11: 4.50	**Concurrent phe:** **G1:**NR Subject 1: 13.0 Subject 2: 8.4 Subject 3: 10.6 Subject 4: 9.9 Subject 5: 9.9 Subject 6: 4.9 Subject 7: 17.9 Subject 8: 9.5 Subject 9: 7.5 Subject 10: 10.9 Subject 11: 1.1 **Mean lifetime phe:** **G1:** NR Subject 1: 9.2 Subject 2: 9.9 Subject 3: 7.9 Subject 4: 10.5 Subject 5: 11.4 Subject 6: 10.3 Subject 7: 14.0 Subject 8: 7.3 Subject 9: 8.3 Subject 10: 7.4 Subject 11: 9.5	**Tower of Hanoi:** **G1:** 7.46 ± 7.74	**Tower of Hanoi with:** **Concurrent phe:** **G1:** r=-.46, **Mean phe:** **G1:** r=-.06 **Infant phe:** **G1:** r=-.46

Welsh 1990[26] Country Study Design Groups	N Enrollment/ Follow-up Type of Phe Measure Disease Type Age	Phe level	Key Outcomes*	Correlation
		Highest phe level during infancy, before diet initiation: **G1:** NR Subject 1: 44.5 Subject 2: 45.3 Subject 3: 36.1 Subject 4: 31.9 Subject 5: 51.1 Subject 6: 31.9 Subject 7: 50.1 Subject 8: 20.0 Subject 9: NR Subject 10: 19.1 Subject 11: 43.0		

* All quantities expressed as **mean ± 1 SD (range)** unless otherwise noted.

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APPENDIX I. Studies Addressing Maternal PKU

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Table I-1. Overview of Maternal PKU Collaborative Study (MPKUCS) papers

Author, Year	Title	Study Date	Countries	# of Women	# of Pregnancies	Cognitive Outcomes Reported
			Studies Reporting Cognitive Outcomes			
Rouse et al., 2004[1]	Effect of High Maternal Blood Phenylalanine on Offspring Congenital Anomalies and Developmental Outcome at Ages 4 and 6 Years: The Importance of Strict Dietary Control Preconception and Throughout Pregnancy	NR	US Canada	526 100 matched controls	576 413 live births	• McCarthy at 4 yrs • WISC-R at 6 yrs
Guttler et al., 2003[2]	Impact of the Phenylalanine Hydroxylase Gene on Maternal Phenylketonuria Outcome	NR	US Canada Germany	196 fully evaluated; 236 genotyped	308 pregnancies; 253 live births; 196 offspring fully evaluated	• WISC-R at 6-7 yrs or later
Levy et al., 2003[3]	Pregnancy Experiences in the Woman With Mild Hyperphenylalaninemia	NR	US Canada Germany	48	58	• WISC-R at 2 years • McCarthy Scales of Children's Abilities • Bayley Scales of Infant Development
Waisbren et al., 2003[4]	Cognitive and Behavioral Development in Maternal Phenylketonuria Offspring	NR	US Canada Germany	NR	NR; 228 offspring; 70 controls	• WISC-R at 7 years • Test of Language Development, 2nd edition • Peabody Individual Achievement Test-Revised • Stroop Interference • Visual Motor Integration • Child Behavior

Author, Year	Title	Study Date	Countries	# of Women	# of Pregnancies	Cognitive Outcomes Reported
						Checklist
Koch et al., 2003[5]	The Maternal Phenylketonuria International Study: 1984-2002	1984-2002	US Canada Germany	382	572	• McCarthy at 4yrs • WISC-R at 7 yrs • WISC-R at 10 yrs
Widaman et al., 2003[6]	Relation of Prenatal Phenylalanine Exposure to Infant and Childhood Cognitive Outcomes: Results From the International Maternal PKU Collaborative Study	NR	US Canada Germany	NR	572 pregnancies; 413 offspring evaluated	• Bayley at 1 year • McCarthy at 4 years • TOLD CSLQ at 4 years • WISC-R at 7 years
Antshel et al., 2003[7, 8]	Developmental Timing of Exposure to Elevated Levels of Phenylalanine is Associated with ADHD Symptom Expression	NR	US	NR	15 MPKU offspring; 46 PKU patients; 18 controls	• ADHD symptoms • FSIQ
Platt et al., 2000[9]	The International Study of Pregnancy Outcome in Women with Maternal Phenylketonuria: Report of a 12-year study	1984-1999	US Canada Germany	PKU NR; 101 controls	576 pregnancies; 414 live births	• Bayley at 2 yrs • McCarthy at 4-5 yrs • WISC-R data presented on children who had reached age 7
Koch et al., 2000[10]	The international collaborative study of maternal phenylketonuria: status report 1998	1984-1998	US Canada	NR	572 HPA 99 control	• Congenital anomalies • McCarthy at 4 years
Waisbren et al., 2000[11]	Outcome at Age 4 Years in Offspring of Women With Maternal Phenylketonuria: The Maternal PKU Collaborative Study	1984-2000	US Canada	205 253 offspring received preschool evaluation	572 pregnancies; 412 offspring	• McCarthy at 3-5 years • Test of language development at 4 years • Achenbach at 4 years • Vineland at 4 years • Bayley at 2 yrs

Author, Year	Title	Study Date	Countries	# of Women	# of Pregnancies	Cognitive Outcomes Reported
Waisbren, et al., 1998[12]	Neonatal neurological assessment of offspring in maternal phenylketonuria	NR	US	NR	56 PKU offspring; 45 control offspring	• Dubowitz Neurological Assessment of the Preterm and Full-Term Newborn Infant • Bayley Mental and Motor Scales at 1 year • Receptive-Expressive Emergent Language Scales at 1 year
Hanley et al., 1996[13]	The North American Maternal Phenylketonuria Collaborative Study, developmental assessment of the offspring: preliminary report	1984-1994	US Canada	NR	134 HPA offspring; 58 control offspring	• Bayley at 2 yrs • McCarthy at 4 yrs
Cipcic-Schmidt et al., 1996[14]	German Maternal Phenylketonuria Study	1989-1994, worked with North American study since 1992	Germany Austria	275	43 pregnancies; 34 live births	• Bayley tests at 2 yrs
Koch et al., 1994[15]	The international collaborative study of maternal phenylketonuria: status report 1994	1984-1994 (US) 1986-1994 (Canada) 1993-1994 (Germany)	US Canada Germany	NR	402 pregnancies; 99 control	• Bayley Scales and McCarthy at 3.5 to 4.5 yrs
Koch et al., 1993[16]	The North American Collaborative Study of Maternal Phenylketonuria: Status Report 1993	1984-1992	US Canada	379 HPA	318 HPA; 59 control	• Bayley scale at 12-24 mos • McCarthy Scale between 3.5-5yrs

ADHD=attention deficit hyperactivity disorder; FSIQ=full scale intelligence quotient; MPKU=maternal phenylketonuria; NR=not reported; PKU=phenylketonuria; TOLD CSLQ=Test of Language Development Spoken Language Component; WISC-R=Wechsler Intelligence Scale for Children-Revised

Table I-2. Overview of Additional Maternal PKU Studies

Author, Year	Title	Study Date	Country	# of Women	# of Pregnancies	Cognitive Outcomes Reported
Studies Reporting Cognitive Outcomes						
Maillot et al., 2008[17, 18]	Factors influencing outcomes in the offspring of mothers with phenylketonuria during pregnancy: the importance of variation in maternal blood phenylalanine & Maternal Phenylketonuria: Experiences From the United Kingdom	1977-2005	UK	67	105 offspring	• Griffiths Developmental Quotient at 1 year • McCarthy at 4 years • WISC-III at 8 and 14 years
Levy et al.,1983[19]	Effects of Untreated Maternal Phenylketonuria and Hyperphenylalaninemia on the Fetus	1971-1981	US	22	59 pregnancies 53 offspring	• IQ for children ≥3yrs • DQ for children<3yrs (Bayley, McCarthy, Wechsler, and Stanford-Binet) • Visual-motor coordination (Beery or Bender) • Congenital anomalies

DQ=developmental quotient; IQ=intelligence quotient; WISC-III-=Wechsler Intelligence Scale for Children, Third edition

Table I-3. Summary of maternal PKU studies reporting cognitive outcomes

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
			Maternal PKU Collaborative Study Papers		
Koch et al., 2003[5]	NR/572/414	Pre-pregnancy treatment: 148 (25.9%) Treated in 1st trimester: 263 (46%) Treated in the 2nd trimester: 52 (9.1%) Treated in 3rd trimester: 4 (0.7%) Mild HPA, no treatment offered: 57	NR	NR	**Mental retardation among MPKUCS per maternal off-diet Phe (µmol/L), % affected** ≥1200: 28 901-1199: 8 601-900: 15 180-600: 2 Non-PKU=4.3
Levy et al., 2003[20]	48/58/NR	APL is assigned blood Phe selected as the highest of 2 or 3 plasma Phe on an unrestricted diet measured by amino acid analyzer or fluorometrically when the subject was not pregnant, µmol/L	APL=408±114 Maternal Phe: Average Phe exposure: untreated=270±84 (n=50); treated=269 ± 136 (n=8)	WISC-R, mean±SD (range)	Maternal MHP (n=40): 102±15 (65-125) Controls (n=64): 109±21 (35-147) P=0.07
Antshel et al., 2003[7, 8]	NR/NR/15	Maternal metabolic control defined by number of weeks gestation that elapsed until all subsequent blood phe was <10 mg/dL.	Mean=10.4 wks±4.9wks	Inattentive symptoms: number total of nine on ADHD Rating Scale-IV Hyperactive/Impulsive symptoms=number total of nine on ADHD Rating Scale-IV	**Mean (SD) Inattentive:** 5.9 (1.5**)** **Mean (SD) Hyperactive/Impulsive:** 6.3 (1.4) **Spearman rank coefficients for MPKU offspring ADHD Rating Scale-IV symptoms:** **Age**: -0.37, p<0.001 **Socioeconomic status**: -0.11 **FSIQ estimate**: -0.28, p<0.01 **Weeks to maternal metabolic control**: 0.63, p<0.001 **Maternal IQ**: -0.48, p<0.001

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
Waisbren et al., 1998[12]	NR/NR/56 with PKU, 45 controls	Mild HPA,no dietary intervention: 13% Metabolic control pre-pregnancy: 20% First trimester: 22% 2nd or 3rd trimester: 45%	NR	Dubowitz Neurological Assessment (relationship with other variables determined using Kruskal-Wallace chi-square test); Bayley Scales of Infant Development; Receptive-Expressive Emergent Language Scale; Home Observation for Measurement of the Environment	**Maternal Phe and Dubowitz**: r=4.4, p=0.11 **Maternal Phe and HOME Scale**: r=-.26, p=0.10 **Maternal Phe and DQ**: r=-.24, p=0.09 **Maternal Phe and language score**: r=-.23, p=0.12 **Weeks gestation diet started and Dubowitz rating**: r=2.1, p=0.35 **Weeks gestation diet started and HOME Scale**: r=-.19, p=0.30 **Weeks gestation diet started and DQ**: r=-.35, p=0.02 **Weeks gestation diet started and language score**: r=-.43, p=0.006 **Weeks gestation Phe <600 µmol/L and Dubowitz rating**: r=8.9, p=0.01 **Weeks gestation Phe <600 µmol/L and HOME Scale**: r=-.52, p=0.0008 **Weeks gestation Phe <600 µmol/L and DQ**: r=-.46, p=0.001 **Weeks gestation Phe <600 µmol/L and language score**: r=-.27, p=0.07 **Logistic regression analysis risk for having DQ <85 if metabolic control attained after pregnancy began**: OR=1.06, CI: 0.97-1.16, p=0.2
Hanley et al., 1996[4, 11, 13, 21]	NR/576/414	Maternal metabolic control=plasma Phe <10mg/dL (605 µmol/L) **G1:** Untreated mild HPA on a normal diet, treatment not recommended **G2:** Prior to pregnancy **G3:** 0-10 wks pregnancy **G4:** 10-20 wks pregnancy **G5:** >20 wks pregnancy	Phe (mg/dL) (n=253)	Peabody Individual Achievement Test Developmental Test of Visual Motor Integration Test of Language Development Child Behavior Checklist McCarthy General Cognitive Index WISC-R Bayley	**Waisbren 2000** **McCarthy Scales of Children's Abilities: n, GCI score** **G1:** n=33, 99 (14) **G2:** n=17, 99 (13) **G3:** n=26, 89 (17) **G4:** n=47, 84 (18) **G5:** n=59, 71 (19) **G6:** n=71, 107 (20) **Bayley Scales, Mean±SD:** **Mental Index:** **G1-G5** (n=134): 96±23 **G6** (n=53): 114±18 **Motor index:** **G1-G5** (n=134): 98±19 **G6** (n=53):110±16 **McCarthy Scales, Mean±SD**

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
		G6: Non-HPA control			**General Cognitive Index:** **G1-G5 (**n=134): 85±21 **G6** (n=53**):** 110±20 **Motor scale:** **G1-G5** (n=134): 91 ±17 **G6 (**n=53): 106±15 **Logistic regressions for risk of low GCI (≤86) in treated maternal PKU pregnancies (n=132): OR (95%CI), p** Low maternal IQ (≤85 vs. >85): 2.9(1.3-6.8), p=0.01 Maternal plasma Phe on normal diet (>20 vs ≤20 mg/dL [>1210 vs ≤1210 µmol/L]) [assigned Phe]: 2.5 (1.0-6.2), p=.04 Low HOME (Home Observation for Measurement of the Environment) Score (≤85 vs >85%): 2.0 (0.8-4.6) p=.13 Weeks to metabolic control (vs. metabolic control prior to pregnancy) 0-10 weeks: 2.6 (0.6-11.3) p=.20 10-20 wks: 3.2 (1.0-10.4) p=.06 >20 or never in control: 7.4 (2.3-24.4) p=.001 **Waisbren 2003** **Cognitive:** **FSIQ (on WISC-R), Mean±SD: n applicable to all WISC-R scores** **G1 (n=36):** 106±65–125 **G2** (n=39): 105±73–126 **G3** (n=46): 100±74–139 **G4** (n=44): 93±35–123 **G5** (n=70): 72±35–133 **G6** (n=63): 109±39–147 **Verbal score on WISC-R, Mean±SD:** **G1:** 105±67–125 **G2**: 103±75–129 **G3**: 98±65–142 **G4**: 93±40–122 **G5**: 77±40–127 **G6**: 108±46–154

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
					Performance score on WISC-R, Mean±SD: **G1:** 104±71–129 **G2**: 102±72–129 **G3**: 95±69–128 **G4**: 96±40–129 **G5**: 72±40–131 **G6**: 111±44–142 **TOLD-2 Total Language, Median scores (ranges):** **G1 (n=29):** 96 (70–123) **G2** (n=23): 94 (74–119) **G3** (n=32): 92 (71–121) **G4** (n=41): 85 (64–117) **G5** (n=60): 74 (34–112) **G6** (n=59): 103 (44–136) **Stroop Interference, Median scores (ranges):** **G1** (n=13): 51 (22–64) **G2** (n=9): 51 (47–54) **G3** (n=10): 51 (37–62) **G4** (n=9): 56 (45–65) **G5** (n=7): 55 (47–70) **G6** (n=20): 50 (43–57) **PIAT-R Total Achievement, Median Scores (ranges):** **G1** (n=22): 94 (75–114) **G2** (n=21): 91 (80–132) **G3** (n=31): 92 (72–143) **G4** (n=32): 82 (65–103) **G5** (n=44): 73 (55–104) **G6** (n=43): 100 (56–145) **VMI, median scores (ranges):** **G1** (n=28): 97 (75–114) **G2** (n=36): 99(80–132) **G3** (n=41): 99(72–143) **G4** (n=35): 92 (73–118) **G5** (n=56): 77 (54–114) **G6** (n=44): 103 (55–134) **CBCL, median scores (ranges): n applicable for**

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
					all CBCL scores Internalizing: **G1** (n=35): 49 (33–72) **G2** (n=39): 51 (33–67) **G3** (n=42): 50 (33–80) **G4** (n=43): 48 (33–69) **G5** (n=67): 55 (33–76) **G6** (n=61): 49 (33–76) Externalizing: **G1**: 49 (30–68) **G2**: 51 (30–70) **G3**: 53 (37–71) **G4**: 55 (30–73) **G5**: 56 (43–57) **G6**: 47 (30–77) Total Behavior: **G1**: 49 (30–73) **G2**: 51 (24–65) **G3**: 52 (24–74) **G4**: 54 (24–74) **G5**: 61 (32–81) **G6**: 48 (29–76)
Cipcic-Schmidt et al., 1996[14]	NR/43/34	Time at which Phe was <360 µmol/L	PKU: Pre-pregnancy: 11 (46%) 1-10 wks: 8 (33%) 11-20 wks: 2 (8%) >21 wks: 3 (13%) HPA: No diet: 2 (20%) Pre-pregnancy: 4 (40%) 1-10 wks: 1 (10%) 11-20 wks: 0 >21 wks: 3 (30%)	Bayley Scales of Infant Development	**Mean MDI**: 96.4 (60-140) **Mean PDI**: 90.2 (49-128) **Start of dietary control and developmental quotients**: rMDI=-.43 rPDI=-.60
Additional Maternal PKU Studies					
Lee et al., 2003[17, 18]	67/107/109	Phe during pregnancy, mean ± SD, µmol/L: **G1**: diet begun	**G1:** 203.5 ± 58 **G2:** 269 ± 115 P=0.0003	Griffiths DQ at 1 yr McCarthy GCI at 4 yrs WISC-III IQ at 8 yrs	**DQ:** **G1 (n=73):** 107± 13.8 **G2 (n=27):** 99.3 ± 13.3 P=0.014 **GCI**:

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
		preconception **G2**: diet begun postconception			**G1 (n=54):** 95.2 ± 16.6 **G2 (n=14):** 85.9 ± 28.9 P=NS **IQ**: **G1 (n=30):** 110.6 ± 14.8 **G2 (n=9):** 91.2 ± 23.9 P=0.005 **Pregnancies with mean blood Phe in the target range for the entire pregnancy, SDs for Phe and:** **4 yr GCI**: r=0.362 (n=53); P=0.008 **8 yr IQ**: r=0.446 (n=30); P=0.014 **14 yr IQ**: r=0.761 (n=7); P=0.047 **1 yr DQ**: r=0.057 (n=73); P=NS **SDs for Phe during pregnancy, and:** **4 yr GCI**: r=-0.385 (n=65); p=0.002 **8 year IQ**: r=-0.433 (n=36); p=0.008 **14 year IQ**: r=-0.712 (n=9); p=0.031 **Proportion of time with Phe in target range and:** **4 yr GCI**: r=0.269 (n=77); p=0.041 **8 year IQ**: r=0.437 (n=58); p=0.012 **Time during pregnancy when mean Phe > 300:** **Griffiths DQ**: r=0.036, p=NS **McCarthy GCI**: r=-0.219, p=NS **WISC-III IQ at 8 yrs**: r=-0.564, p=0.001 **WISC-III IQ at 14 yrs**: r=-0.75, p=0.032 **Time during pregnancy when mean Phe > 400 and:** **Griffiths DQ**: r=0, p=NS **McCarthy GCI**: r=-0.334, p=0.01 **WISC-III IQ at 8 yrs**: r=-0.566, p=0.001 **WISC-III IQ at 14 yrs**: r=-0.687, p=0.06 **Mean maternal Phe and developmental outcome** **Trimester 1:** **1 yr Griffiths DQ**: r=-0.019 (n= 90); p=NS **4 yrs McCarthy GCI**: r=-0.365 (n=65); p=0.003 **8 yr WISC-III IQ:** r=-0.593 (n=36); p<0.0005 **14 y WISC-III IQ**: r=-0.73 (n=9); p=0.026 **Trimester 2**: **1 yr Griffiths DQ**: r=-0.134 (n=91); p=NS

Study	#Mothers/ #Pregnancies/ #Children	Maternal Phe, evaluation	Maternal Phe, #	Outcome, Test	Outcome, #
					4 yrs McCarthy GCI: r=-0.106 (n=65); P=NS **8 yr WISC-III IQ:** r=-0.274 (n=36); p=NS **14 y WISC-III IQ**: r=0.249 (n=9); P=NS **Trimester 3**: **1 yr Griffiths DQ**: r=0.069 (n=90); p=NS **4 yrs McCarthy GCI:** r=-0.037 (n=63); p=NS **8 yr WISC-III IQ**: r=-0.46 (n=35); p=0.005 **14 y WISC-III IQ**: r=-0.709 (n=8); p=0.049
Levy et al., 1983[19]	22/59/53	Mean of two maternal Phe levels drawn at times of child evaluation	Range: 165-1370 µmol/L; mean: 697.3 µmol/L	Bayley Scales of Infant Development, McCarthy Scales of Children's Abilities, Wechsler Intelligence Scale for Children-Revised; Standford-Binet Intelligence Test; Visual Motor Coordination by Beery Visual Motor Integration Test or Bender Gestalt Test	**Maternal blood Phe and IQ:** r=-0.82, p<0.001 (n=28)

ADHD=attention deficit hyperactivity disorder; APL=assigned blood phenylalanine level ; CBCL=Child Behavior Checklist ; cm=centimeter; DQ= developmental quotient ; FSIQ=full scale intelligence quotient ; G=group; GCI=McCarthy Global Cognitive Index; HC=head circumference; HOME= Home Observation for Measurement of the Environment; HPA=hyper phenylalaninemia;; IQ=intelligence quotient; MDI= Bayley Mental Development Index; MHP=maternal hyperphenylalaninemia; MPKU=maternal phenylketonuria; MPKUCS= Maternal PKU Collaborative Study; MR=mental retardation; n=number; PDI=Bayley Psychological Development Index ; Phe=phenylalanine; PIAT= Peabody Individual Achievement Test; PKU=phenylketonuria; TOLD=Test of Language Development; VMI=visual motor integration; WISC=Weschler Intelligence Scale for Children

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APPENDIX J. Summary of New Drug Application Studies of Sapropterin

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Table J-1. Summary of New Drug Application studies

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
• A Phase 2, Multicenter, Open-Label Study to Evaluate the Response to and Safety of an 8-Day Course of Phenoptin Treatment in Subjects With Phenylketonuria Who Have Elevated Phenylalanine Levels (PKU-001) • Germany, Italy, US • Completed • Sapropterin **Note:** Phenoptin is sapropterin	Primary Outcomes: • Evaluate the degree and frequency of response to Phenoptin, as demonstrated by a reduction in blood Phe level among subjects with PKU who have elevated Phe levels Secondary Outcomes: • Evaluate the safety of Phenoptin treatment in this subject population, and identify individuals in this subject population who respond to Phenoptin treatment with a reduction in blood Phe level	Inclusion Criteria: • Age ≥ 8 years • Blood Phe level ≥ 450 umol/L at screening • Clinical diagnosis of PKU with hyperphenylalaninemia documented by past medical history of at least one blood Phe measurement ≥ 360 umol/L (6 mg/dL) • Willing and able to provide written informed consent or, in the case of subjects under the age of 18, provide written assent (if required) and written informed consent by a parent or legal guardian, after the nature of the study has been explained • Negative urine pregnancy test at screening (non-sterile females of child-bearing potential only) • Male and Female subjects of childbearing potential (if sexually active and non-sterile) must be using acceptable birth control measures, as determined by the investigator, and willing to continue to use acceptable birth control measures while participating in the study • Willing and able to comply with study procedures • Willing to continue current diet unchanged while participating in the study Exclusion Criteria: • Perceived to be unreliable or unavailable for study participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unavailable • Use of any investigational agent within 30 days prior	Trial ID: NCT00104260; EudraCT # 2004-002071-16 Study design: non-randomized open label safety/efficacy study Time frame: NR Enrollment: 489 Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		to screening, or requirement for any investigational agent or vaccine prior to completion of all scheduled study assessments • Pregnant or breastfeeding, or considering pregnancy • ALT > 5 times the upper limit of normal (i.e., Grade 3 or higher based on World Health Organization Toxicity Criteria) at screening • Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid–dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes, or organ transplantation) • Serious neuropsychiatric illness (e.g., major depression) not currently under medical control • Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) • Concurrent use of levodopa • Clinical diagnosis of primary BH4 deficiency	
• A Phase 3, Randomized, Double-Blind, Placebo-Controlled Study to Evaluate the Safety and Efficacy of Phenoptin in Subjects With Phenylketonuria Who Have Elevated Phenylalanine Levels (PKU-003) • Ireland, Italy, United Kingdom, US • Completed • Sapropterin **Note:** Phenoptin is sapropterin.	Primary Outcomes: • Change in blood Phe levels from baseline to week 6 [US-based sites] • To evaluate the efficacy of Phenoptin in reducing blood Phe levels in subjects with phenylketonuria. The primary efficacy endpoint is the Phe level at Week 6, which will be compared by testing the difference in mean blood Phe levels in the placebo and Phenoptin treatment groups at Week 6. The Week 6	Inclusion Criteria: • 8 years of age and older • Received at least 7 out of 8 scheduled doses in Study PKU 001 • Responsive to Phenoptin in Study PKU-001, defined as a reduction in blood Phenylalanine level of ≥30% compared with baseline • Blood Phenylalanine level ≥450 µmol/L at screening • Willing and able to provide written informed consent or, in the case of subjects under the age of 18, provide written assent	Trial ID: NCT00104247; EudraCT # 2004-004512-23 Study design: RCT Time frame: NR Enrollment: 88 Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
"Subjects who complete protocol PKU-003 will have the opportunity to be enrolled in an open-label extension study of Phenoptin."	mean blood Phe levels in each group will be compared using an analysis of covariance model with baseline Phe level and treatment as the only covariates. The model will utilize a last observation carried forward (LOCF) imputation approach to deal with missing data. Secondary Outcomes: • NR [US-based sites] • To evaluate the safety of Phenoptin versus placebo in this subject population. • To evaluate the efficacy of Phenoptin versus placebo in this subject population with respect to: the mean change in weekly blood Phe levels during the 6 weeks of treatment; the proportion of subjects who have blood Phe levels ≤600 µmol/L at Week 6.	(if required) and written informed consent by a parent or legal guardian, after the nature of the study has been explained • Negative urine pregnancy test at screening (females of child-bearing potential) • Male and Female subjects of childbearing potential (if sexually active) must be using acceptable birth control measures, as determined by the investigator, and willing to continue to use acceptable birth control measures while participating in the study • Willing and able to comply with study procedures • Willing to continue current diet unchanged while participating in the study Exclusion Criteria: • Perceived to be unreliable or unavailable for study participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unavailable • Use of any investigational agent other than Phenoptin within 30 days prior to screening, or requirement for any investigational agent or investigational vaccine prior to completion of all scheduled study assessments • Pregnant or breastfeeding, or considering pregnancy • ALT >5 times the upper limit of normal (i.e., Grade 3 or higher based on World Health Organization Toxicity Criteria) at screening • Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid-dependent asthma or other condition	

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes, or organ transplantation recipient) • Serious neuropsychiatric illness (e.g., major depression) not currently under medical management • Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) • Concurrent use of levodopa • Clinical diagnosis of primary BH4 deficiency	
• A Phase 3, Multicenter, Open-Label Extension Study of Phenoptin in Subjects With PKU Who Have Elevated Phenylalanine Levels (PKU-004) • Ireland, Italy, US • Completed • Sapropterin **Note:** Phenoptin is sapropterin	Primary Outcomes: • To evaluate the safety and tolerability of long-term Phenoptin treatment in subjects with PKU Secondary Outcomes: • To compare the safety and tolerability of three different doses of Phenoptin treatment in subjects with PKU • To determine the effect of various doses of Phenoptin on blood phenylalanine (Phe) levels • To evaluate the population pharmacokinetics of Phenoptin • To evaluate the ability of Phenoptin to reduce phenylalanine (Phe) levels over a 24-hour period • To evaluate the persistence of benefit of Phenoptin treatment in the subject population as evidenced by long-term control of blood Phe levels	Inclusion Criteria: • 8 years of age and older • Prior successful participation in Study PKU-003 • Willing and able to provide written informed consent or assent and written informed consent (if required) by a parent or legal guardian • For females of child-bearing potential only: Negative urine pregnancy test within 24 hours prior to enrollment. Women using acceptable birth control measures must agree to continue to use those measures while participating in the study • Willing and able to comply with study procedures • Willing to continue current diet unchanged while participating in the study Exclusion Criteria: • Perceived to be unreliable or unavailable for study participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unavailable • Withdrew from, or otherwise did not successfully complete, study PKU-003, except for	Trial ID: NCT00225615; EudraCT # 2004-004513-41 Study design: non-randomized safety/efficacy study Time frame: NR Enrollment: 80 Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		subjects who were removed from the study because their blood Phe exceeded the alert level • Expected to require any investigational agent or vaccine prior to completion of all scheduled study assessments • Pregnant or breastfeeding, or planning pregnancy • Concurrent disease or condition that would interfere with study participation or safety (e.g., seizure disorder, oral steroid-dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes) • Requirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) • Concurrent use of levodopa	
• A Phase 3, Double-blind, Placebo-controlled Study to Evaluate the Safety and Efficacy of Phenoptin to Increase Phenylalanine Tolerance in Phenylketonuric Children on a Phenylalanine-restricted Diet (PKU-006) • Germany, Spain, US • Completed • Sapropterin in 100 mg tablets equivalent to 20 mg/mg per day or placebo **Note:** Phenoptin is sapropterin.	Primary Outcomes: • Amount of dietary supplemented phenylalanine (Phe) tolerated in children with PKU [US-based sites] • To evaluate the ability of Phenoptin to increase phenylalanine (Phe) tolerance in children with phenylketonuria who are following a Phe-restricted diet Secondary Outcomes: • Change in Phe levels from baseline to week 3 [US-based sites] • To evaluate the ability of Phenoptin to reduce blood Phe levels in children with phenylketonuria who are following a Phe-restricted diet • To compare the ability of Phenoptin versus	Inclusion Criteria: • Clinical diagnosis of PKU with hyperphenylalaninemia (HPA) documented by at least one blood Phe measurement ≥360 umol/L (6 mg/dL) • Under dietary control with a Phe-restricted diet as evidenced by:· Estimated daily Phe tolerance ≤1000 mg/day • At least 6 months of blood Phe control (mean level of ≤480 µmol/L) prior to enrolling in the study • Aged 4 to 12 years inclusive at screening • A blood Phe level ≤ 480 µmol/L at screening • Female subjects of childbearing potential (as determined by the principal investigator) must have a negative blood or urine pregnancy test at entry (prior to the	Trial ID: NCT00272792; EudraCT # 2005-003777-24 Study design: RCT Time frame: NR Enrollment: 45 Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
	placebo to increase Phe tolerance in children with phenylketonuria who are following a Phe-restricted diet • To evaluate the safety of Phenoptin as compared with placebo in this subject population • To explore the potential reduction in the cost of medical foods and Phe-free formulas	first dose). Note: All female subjects of childbearing potential and sexually mature male subjects must be advised to use a medically accepted method of contraception throughout the study. Female subjects of childbearing potential must be willing to undergo periodic pregnancy tests during the course of the study • Willing and able to comply with all study procedures • Willing to provide written assent (if applicable) and written informed consent by a parent or legal guardian after the nature of the study has been explained and prior to any research-related procedures Exclusion Criteria: • Any condition that, in the view of the PI, renders the subject at high risk from treatment compliance and/or completing the study • Prior history of organ transplantation • Perceived to be unreliable or unavailable for study participation or have parents or legal guardians who are perceived to be unreliable or unavailable • Use of any investigational agent within 30 days prior to screening, or requirement for any investigational agent or vaccine prior to completion of all scheduled study assessments • ALT > 2 times the upper limit of normal (i.e., Grade 1 or higher based on World Health Organization Toxicity Criteria) at screening • Concurrent disease or condition that would interfere with study participation or safety	

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		(e.g., seizure disorder, oral steroid-dependent asthma or other condition requiring oral or parenteral corticosteroid administration, or insulin-dependent diabetes)	
• Sapropterin Expanded Access Program • US • Unknown; status lasted updated April 11, 2008 • Sapropterin	Primary Outcomes: • NR Secondary Outcomes: • NR "The Purpose of this study is to provide patients with hyperphenylalaninemia (HPA) due to Phenylketonuria (PKU) access to sapropterin dihydrochloride and to collect more information about the safety of the drug in an expanded access program (EAP) until commercial product is available."	Inclusion Criteria: • Patient has hyperphenylalaninemia due to PKU, a rare and serious disease • Patient is not participating in a sapropterin dihydrochloride clinical study • Patient is older than 8 years of age • Patient is willing and able to provide written informed consent or, in the case of under the age of 18, provide written assent (if required) and written informed consent by a parent or legal guardian • If female and of child bearing potential, the patient has a negative urine pregnancy test within 24 hours prior to enrollment (females of child-bearing potential only) and will be using adequate contraceptive methods to avoid pregnancy while participating in the program • Patient is willing and able to comply with program procedures • Patient lives in the United States Exclusion Criteria: • Patient is perceived to be unreliable or unwilling to comply with program participation or, if under the age of 18, have parents or legal guardians who are perceived to be unreliable or unwilling to comply with program participation • Patient has a concurrent disease or condition that	Trial ID: NCT00484991 Study design: expanded access program Time frame: NR Estimated Enrollment: NR Start date: NR Estimated completion date: NR Sponsor: BioMarin Pharmaceutical

Study Name, Country, Status, Intervention	Outcomes	Criteria	Study Details
		would interfere with program participation or safety • Patient is 8 years old or younger • Patients is eligible for enrolling in PKU-010 • Patient is participating in an ongoing study with sapropterin dihydrochloride • Patient is pregnant, breast feeding or considering pregnancy • Patient is taking levodopa	

ALT=alanine aminotransferase; EAP=expanded access program; HPA=hyperphenylalaninemia; NR=not reported; Phe=phenylalanine; PI=principal investigator; PKU=phenylketonuria