**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, USCompleted 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 screeningClinical 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 explainedNegative 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 studyWilling and able to comply with study proceduresWilling to continue current diet unchanged while participating in the studyExclusion 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 unavailableUse 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 assessmentsPregnant or breastfeeding, or considering pregnancyALT > 5 times the upper limit of normal (i.e., Grade 3 or higher based on World Health Organization Toxicity Criteria) at screeningConcurrent 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 controlRequirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate) Concurrent use of levodopaClinical diagnosis of primary BH4 deficiency | Trial ID: NCT00104260; EudraCT # 2004-002071-16Study design: non-randomized open label safety/efficacy studyTime frame: NREnrollment: 489Sponsor: BioMarin Pharmaceutical |
| 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, USCompletedSapropterin**Note:** Phenoptin is sapropterin. "Subjects who complete protocol PKU-003 will have the opportunity to be enrolled in an open-label extension study of Phenoptin." | 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 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.
 | Inclusion Criteria:8 years of age and olderReceived at least 7 out of 8 scheduled doses in Study PKU 001Responsive to Phenoptin in Study PKU-001, defined as a reduction in blood Phenylalanine level of ≥30% compared with baselineBlood Phenylalanine level ≥450 μmol/L at screeningWilling 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 explainedNegative 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 studyWilling and able to comply with study proceduresWilling to continue current diet unchanged while participating in the studyExclusion 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 unavailableUse 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 assessmentsPregnant or breastfeeding, or considering pregnancyALT >5 times the upper limit of normal (i.e., Grade 3 or higher based on World Health Organization Toxicity Criteria) at screeningConcurrent 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 recipient)Serious neuropsychiatric illness (e.g., major depression) not currently under medical managementRequirement for concomitant treatment with any drug known to inhibit folate synthesis (e.g., methotrexate)Concurrent use of levodopaClinical diagnosis of primary BH4 deficiency | Trial ID: NCT00104247; EudraCT # 2004-004512-23Study design: RCTTime frame: NREnrollment: 88 Sponsor: BioMarin Pharmaceutical |
| A Phase 3, Multicenter, Open-Label Extension Study of Phenoptin in Subjects With PKU Who Have Elevated Phenylalanine Levels (PKU-004)Ireland, Italy, USCompletedSapropterin**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 olderPrior successful participation in Study PKU-003Willing and able to provide written informed consent or assent and written informed consent (if required) by a parent or legal guardianFor 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 studyWilling and able to comply with study proceduresWilling to continue current diet unchanged while participating in the studyExclusion 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 unavailableWithdrew from, or otherwise did not successfully complete, study PKU-003, except for subjects who were removed from the study because their blood Phe exceeded the alert levelExpected to require any investigational agent or vaccine prior to completion of all scheduled study assessmentsPregnant or breastfeeding, or planning pregnancyConcurrent 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 | Trial ID: NCT00225615; EudraCT # 2004-004513-41Study design: non-randomized safety/efficacy studyTime frame: NREnrollment: 80Sponsor: BioMarin Pharmaceutical |
| 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, USCompleted 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 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
 | 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/dayAt least 6 months of blood Phe control (mean level of ≤480 μmol/L) prior to enrolling in the studyAged 4 to 12 years inclusive at screeningA blood Phe level ≤ 480 μmol/L at screeningFemale subjects of childbearing potential (as determined by the principal investigator) must have a negative blood or urine pregnancy test at entry (prior to the 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 studyWilling 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 proceduresExclusion Criteria:Any condition that, in the view of the PI, renders the subject at high risk from treatment compliance and/or completing the studyPrior history of organ transplantationPerceived 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 assessmentsALT > 2 times the upper limit of normal (i.e., Grade 1 or higher based on World Health Organization Toxicity Criteria) at screeningConcurrent 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) | Trial ID: NCT00272792; EudraCT # 2005-003777-24Study design: RCTTime frame: NREnrollment: 45 Sponsor: BioMarin Pharmaceutical |
| Sapropterin Expanded Access ProgramUS Unknown; status lasted updated April 11, 2008Sapropterin | 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 diseasePatient is not participating in a sapropterin dihydrochloride clinical study Patient is older than 8 years of agePatient 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 guardianIf 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 programPatient is willing and able to comply with program proceduresPatient lives in the United StatesExclusion 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 participationPatient has a concurrent disease or condition that would interfere with program participation or safetyPatient is 8 years old or youngerPatients is eligible for enrolling in PKU-010Patient is participating in an ongoing study with sapropterin dihydrochloridePatient is pregnant, breast feeding or considering pregnancyPatient is taking levodopa | Trial ID: NCT00484991Study design: expanded access programTime frame: NREstimated Enrollment: NRStart date: NREstimated completion date: NRSponsor: BioMarin Pharmaceutical |

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