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RARE DISEASE WORKSHOP SERIES
Improving the Clinical Development Process

The development of phenylalanine blood levels as a surrogate endpoint in phenylketonuria

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November 8, 2011



Phenylketonuria: Defect in Phenylalanine (Phe) Metabolism

- Genetic deficiency in phenylalanine hydroxylase
- Key enzyme in Phe metabolism
- High Phe levels
- Severe CNS toxic effects
- Mental retardation, severe (IQ<50) if untreated
- Treatment using dietary restriction of Phe
- New Treatment: tetrahydrobiopterin to activate PAH enzyme activity and reduce Phe

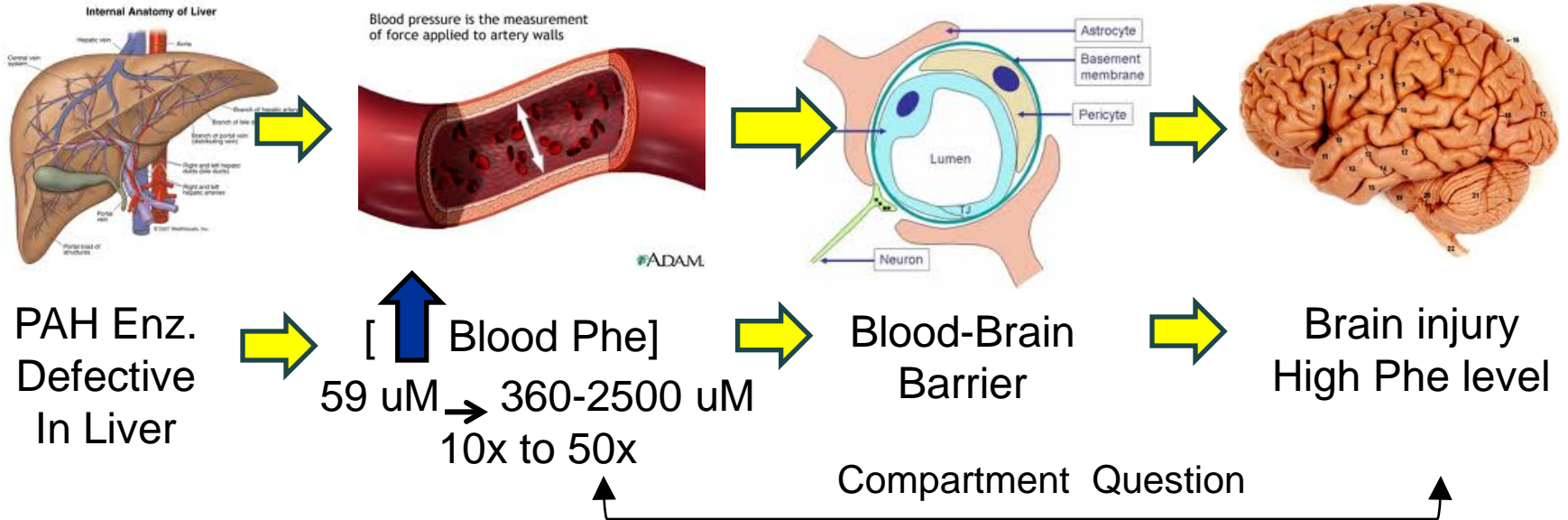


Using Phe level as a Surrogate Endpoint

- Historical use of Phe for clinical management using diet therapy
- Phe is a direct toxin of the brain
- Development using IQ loss is not plausible both in time and ethically
- Sponsor sought to establish data to support use of Phe



Pathophysiologic Map of Phe in PKU



Measure Blood Phe Level → Degree of long-term Brain Injury

BH4 Increases PAH in Liver → [↓ Blood Phe] → BBB → Brain injury reduced due to lower Phe level



Value of Phe as an endpoint

- Precision and accuracy of measurement
- Measures immediate effects of drug
- Accurate assessment of intermediate effects of the drug
- Development or Intellectual Quotient?
 - Long time frame for clinical evolution of change over years
 - Long time delay between injury and outcome on scale of years
 - Measurement less precise and accurate
 - Complex choice of measures: IQ, behavior, adaptation
 - Effects in young patients unethical to study
- How to achieve use of Phe as a primary endpoint in a pivotal clinical program?



Key needs for the surrogate endpoint

- Clinical impact of Phe level takes many years
- Early effects manifest later in life
 - Phe level injury and clinical outcome are disconnected in time
- Proper treatment requires early intervention
 - Well known from diet treatment experience
- Cannot study older patients and determine an effect on IQ
- Common problem in neurologic disorders



Science behind Phe as Endpoint

- Disease Cause/mechanism understood
- Drug Understood, activation of PAH increases normal Phe metabolism
- Phe Marker direct in pathophysiology mechanism not parallel
- Marker The blood compartment does reflect the brain compartment
- Assay Sensitive and specific
- Compartment Blood does reflect brain primarily



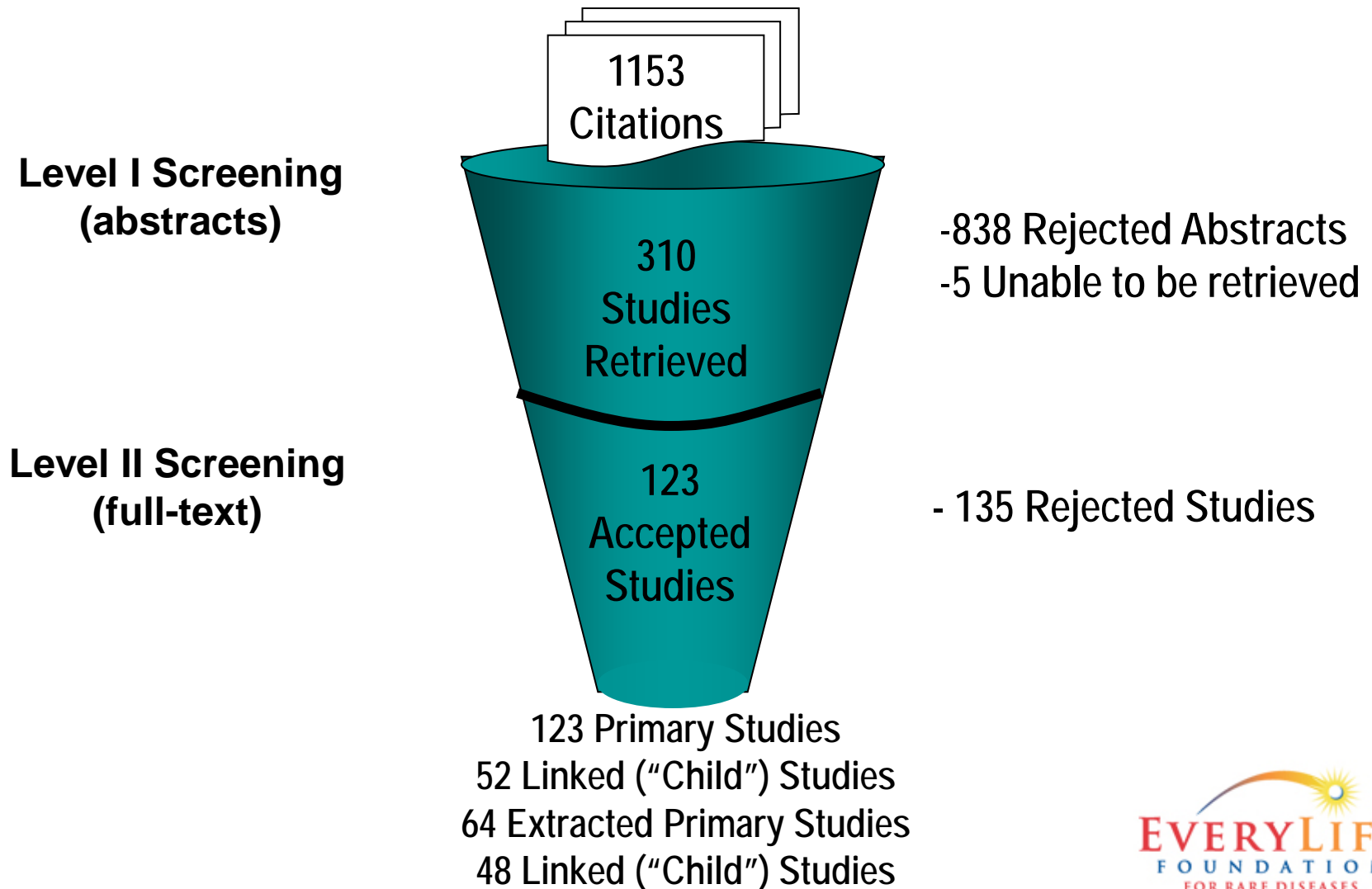
Qualification of Phe as likely predictive

Meta-analysis of significant Clinical PKU data treated with diet therapy

- Systematic meta-analysis of PKU Literature
- Commissioned study by professional group
- Formal protocol driven analysis
- Develop a relationship between Phe and IQ outcome using controlled studies published looking at dietary control and IQ outcome
- Use data to support predictive value



Analysis Funnel of Literature





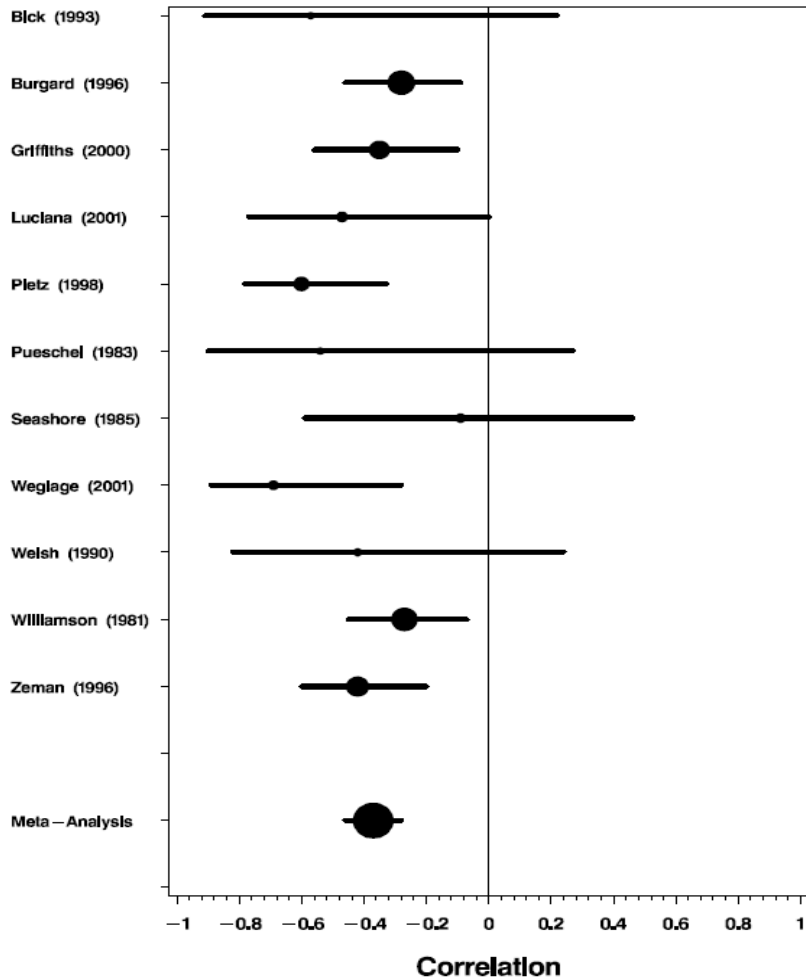
Negative Relationship Between Phe level in 0-6 yr age and IQ outcome

Meta-Analyses of Within-Study Correlations: IQ and Critical Blood Phe						
Population	Critical Blood Phe (author defined)*			Critical Blood Phe (0-6 yr)		
	t	N	r [95% CI]**	t	N	r [95% CI]**
Early-treated PKU	12	459	-0.35 [-0.44, -0.27]	8	281	-0.33 [-0.50, -0.13]***
Classic PKU:						
Total	11	382	-0.39 [-0.48, -0.29]	8	303	-0.36 [-0.49, -0.21]
Early-treated	10	338	-0.38 [-0.48, -0.28]	7	260	-0.34 [-0.50, -0.16]
Mixed treatment history	2	50	-0.45 [-0.65, -0.18]	1	43	-0.45 [-0.66, -0.17]
Mixed/unspecified PKU:						
Total	4	156	-0.28 [0.042, -0.12]	2	49	-0.07 [-0.56, 0.45]
Early-treated	3	147	-0.26 [-0.40, -0.09]	2	49	-0.07 [-0.56, 0.45]
Mixed treatment history	1	9	-0.66 [-0.92, 0.01]			none reported

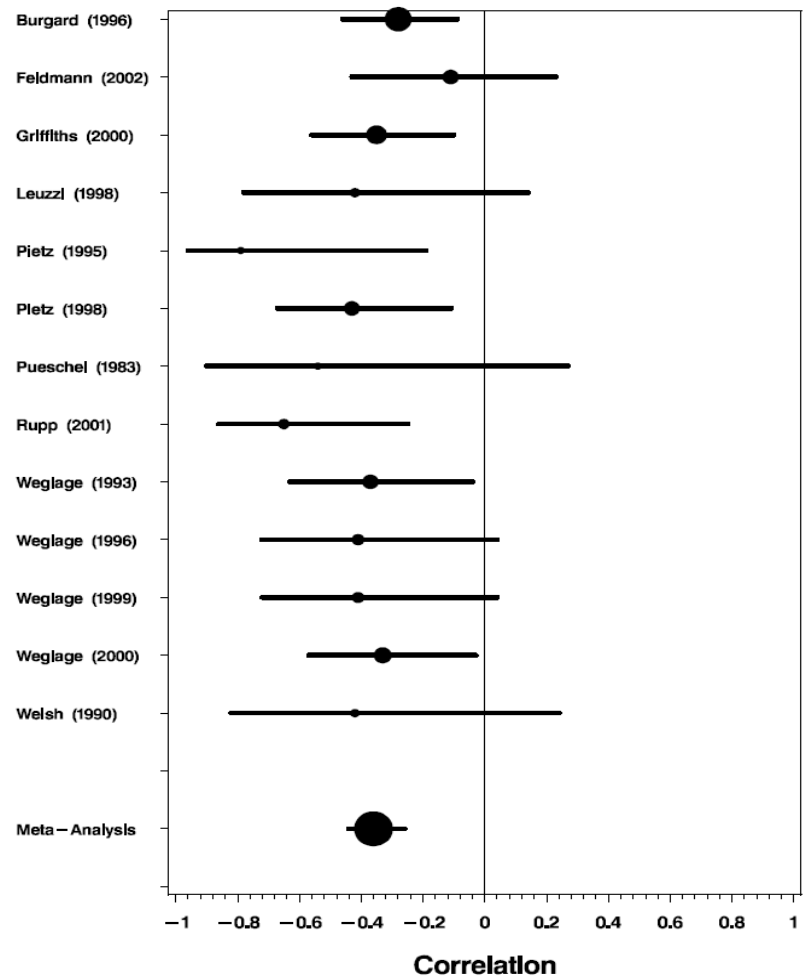


Correlations of Phe Control with Outcome

Critical period (0-6 yr) Phe control



Life long Phe control





MRI White Matter Abnormalities and IQ

Meta-Analyses of Within-Study Correlations: MRI and Concurrent Blood Phe*			
Population	t	N	r [95% CI]**
Early-treated PKU	11	184	0.33 [0.18, 0.46]
Classic PKU:			
Total	11	175	0.34 [0.17, 0.50]
Early-treated	8	139	0.35 [0.18, 0.50]
Mixed treatment history	4	42	0.37 [-0.36, 0.82]***
Mixed/unspecified PKU:			
Total	8	203	0.50 [0.36, 0.62]
Early-treated	3	43	0.21 [-0.16, 0.52]
Mixed treatment history	7	186	0.50 [0.32, 0.64]***

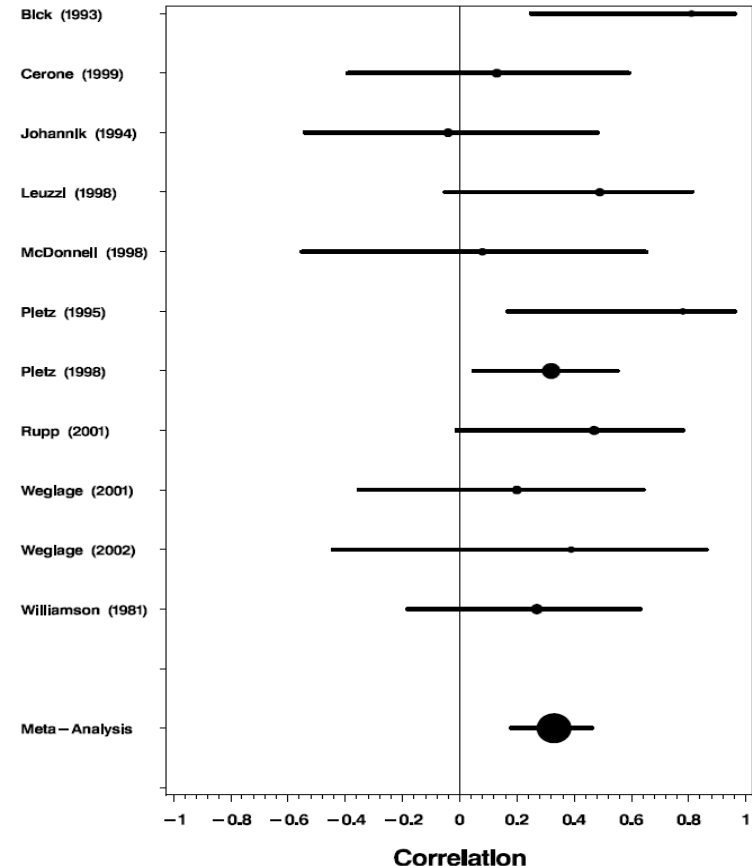
t = number of treatment groups contributing data

N=number of individuals with PKU evaluated

* Blood Phe at time of IQ testing or within prior six months

** A positive correlation coefficient (r) indicates higher MRI abnormalities with higher blood Phe levels

*** Significant between-study heterogeneity (p<0.10)





Meta-analysis showed consistent relationship between early life and life-long Phe levels by diet control and outcomes

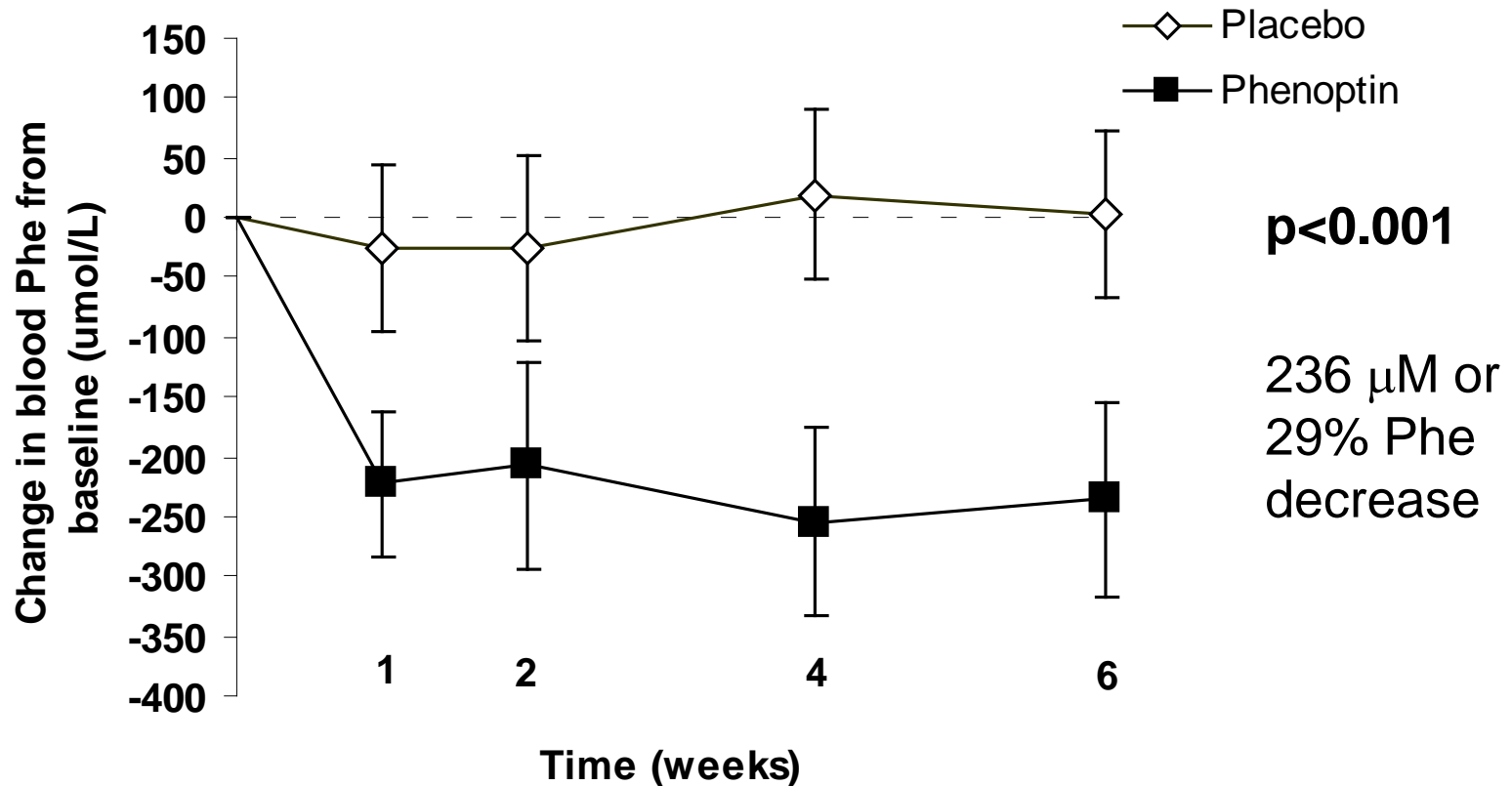
Results:

- **Each 100 $\mu\text{mol/L}$ increase in blood Phe level predicts a 1.4 to 3.9 point decrease in IQ during “critical” early childhood years or “lifetime”**
 - Early-treated individuals with both classic and mild PKU, over a range of blood Phe from 394 to 750 $\mu\text{mol/L}$ (moderate levels)
- A large number of studies, with no single dominant study
- “Critical” Phe meta-analysis included 11 studies (421 subjects)
- “Lifetime” Phe meta-analysis included 13 studies (398 subjects), the largest of which contributed 25% of subjects.
- Results of the meta-analysis were consistent with findings from multiple regression models with IQ-SDS



Tetrahydrobiopterin for PKU Phase 3

Mean Change in Weekly Blood Phe Levels By Treatment Arm



BH4 caused a consistent drop in blood Phe levels in treated versus placebo



Blood Phe has strong science behind its use, but the benefit of extensive clinical data

- Disease cause and mechanism clear
- Drug mechanism clear and direct on surrogate
- Assay precise and accurate with good dynamic range
- Compartment of blood sampling reflective of CNS
- ***Extensive history of human clinical studies with diet control verify relationship between early Phe levels 0-6 years old and IQ late in life***

Very few diseases have the luxury of clinical data like PKU