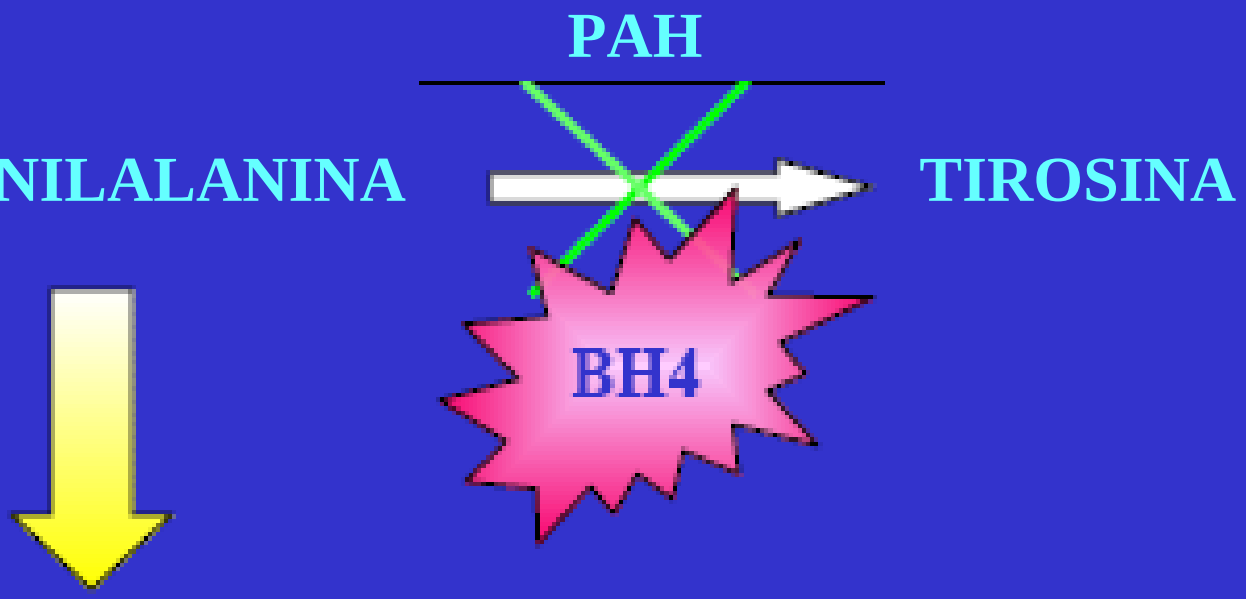
FUNZIONI DELLA TETRAIDROBIOPTERINA (BH4)

•1)COFATTORE DELL'ENZIMA FENILALANINA – IDROSSILASI (PAH)



FUNZIONI DELLA TETRAIDROBIOPTERINA (BH4)

- **2)COFATTORE DELL'ENZIMA TIROSINA-IDROSSILASI E TRIPTOFANO-IDROSSILASI**

NEUROTRASMETTITORI

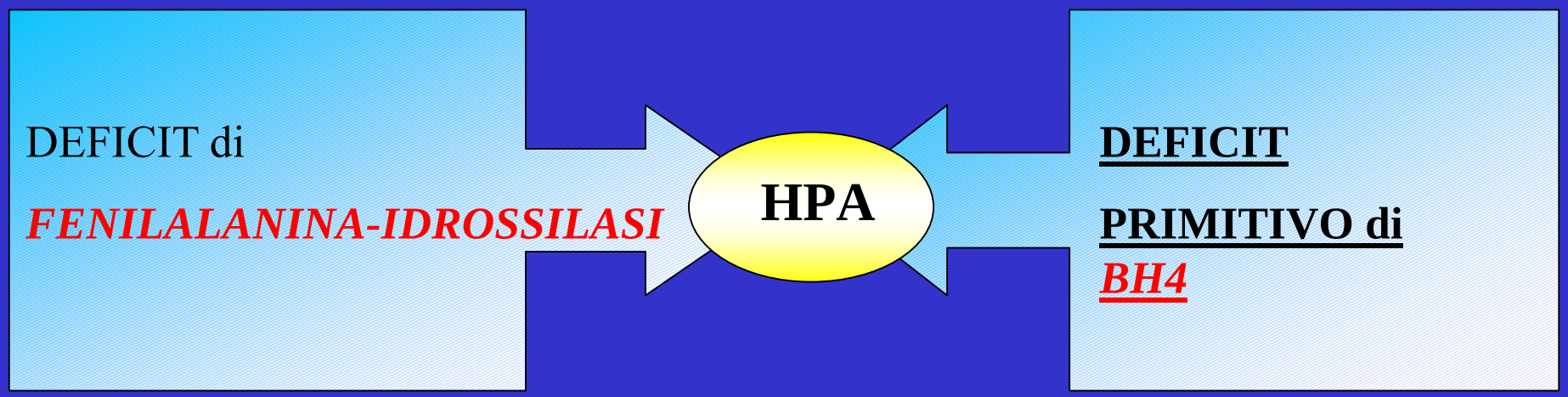
- **3)COFATTORE OSSIDO NITRICO- SINTETASI**

VASODILATAZIONE

ATTUALE APPLICAZIONE FARMACOLOGICA della BH4

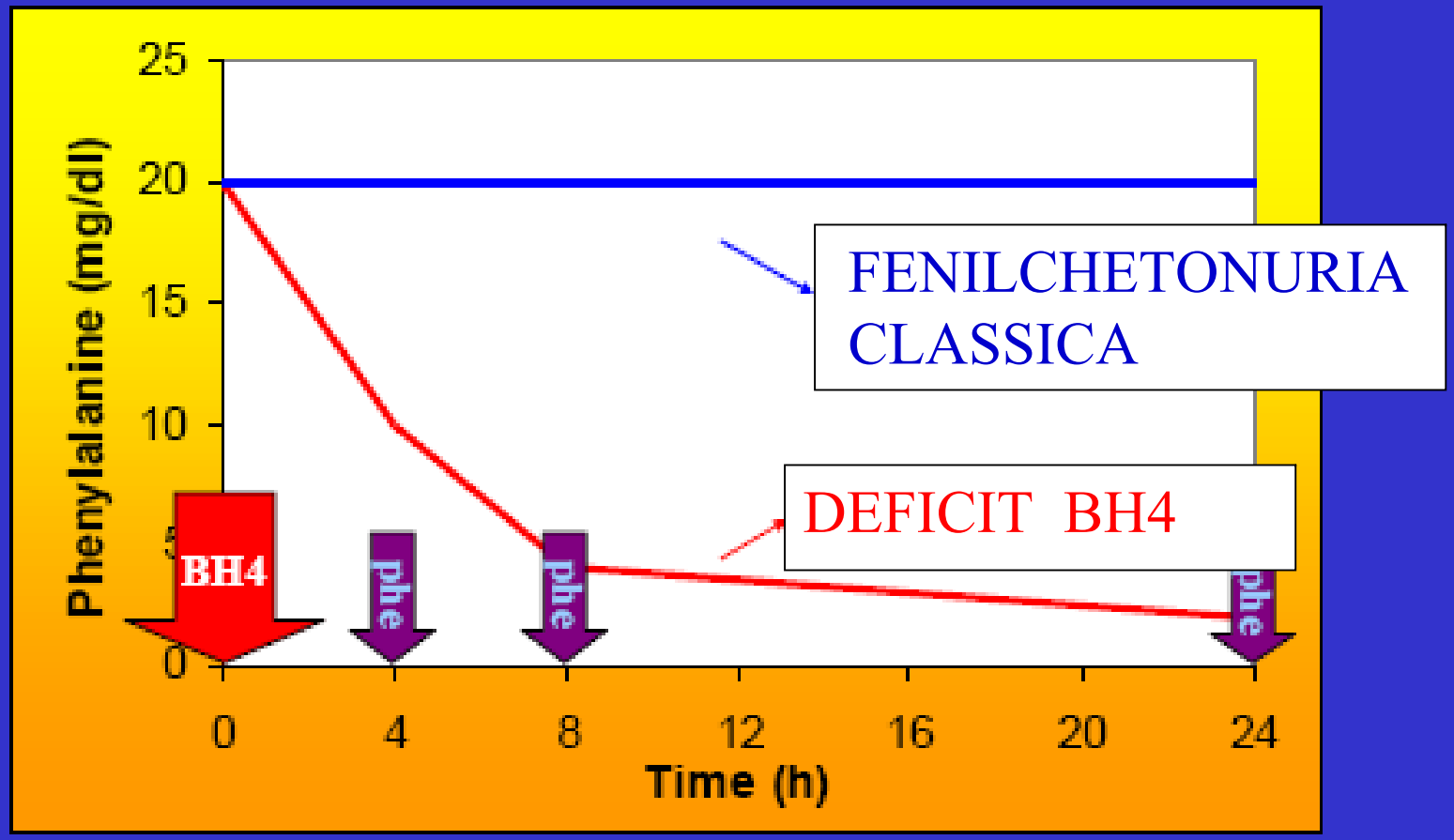
DIAGNOSI DIFFERENZIALE DELLE IPERFENILALANINEMIE

Dopo screening neonatale

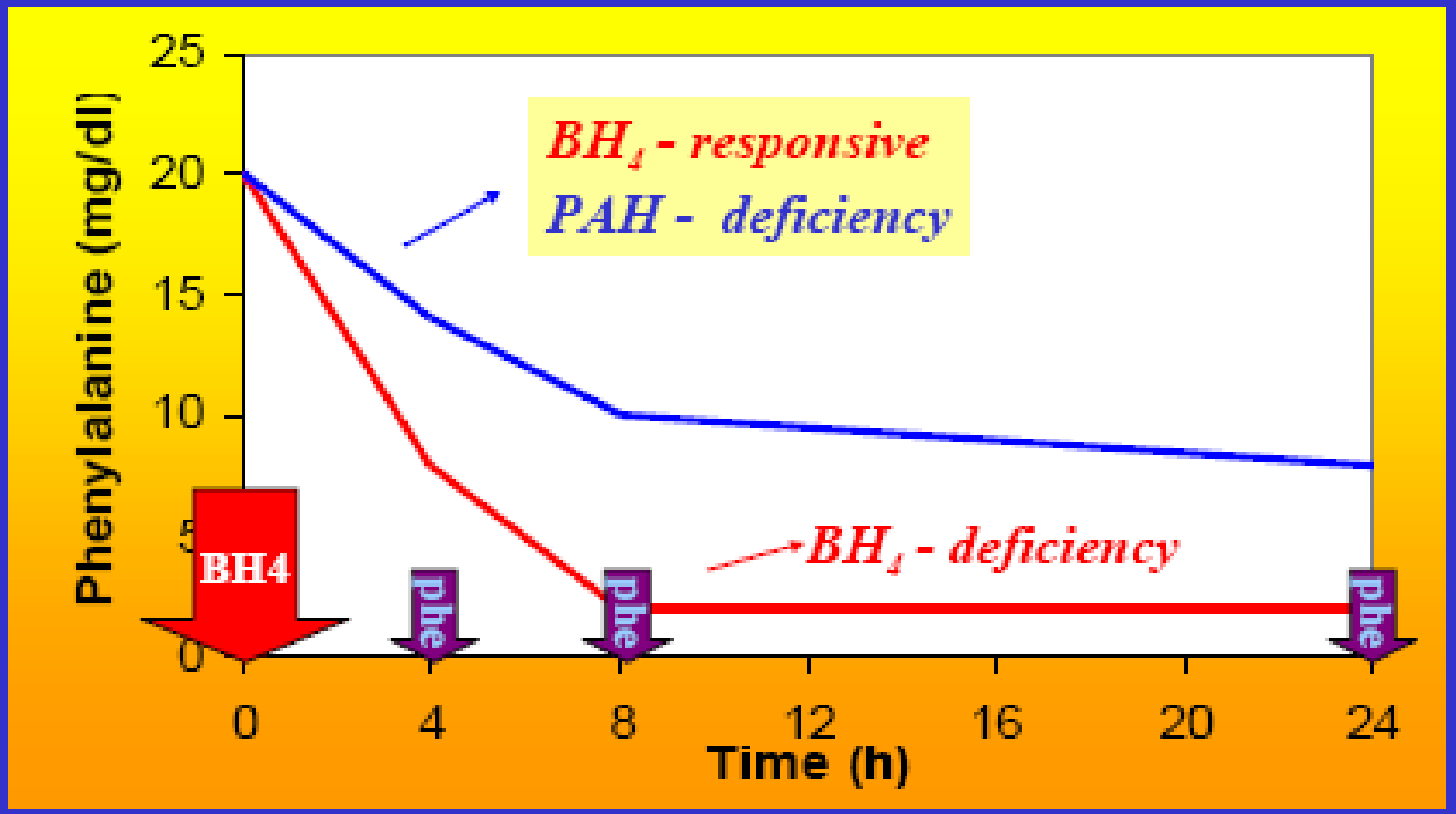


ATTUALE APPLICAZIONE FARMACOLOGICA della BH4

TEST DA CARICO con BH4



TERAPIA FARMACOLOGICA
IN SOGGETTI HPA RESPONSIVI ALLA BH4



BH4

Il test da carico con tetraidrobiopterina (BH4) viene utilizzato per discriminare le forme di iperfenilalaninemia (PKU da deficit di cofattore) e per valutare la responsività dei pazienti alla BH4

La responsività al test dipende dal genotipo, dal dosaggio utilizzato e dalle caratteristiche farmacocinetiche della tetraidrobiopterina

Test da carico con BH4 & responsività alla BH4 nei nuovi nati con HPA

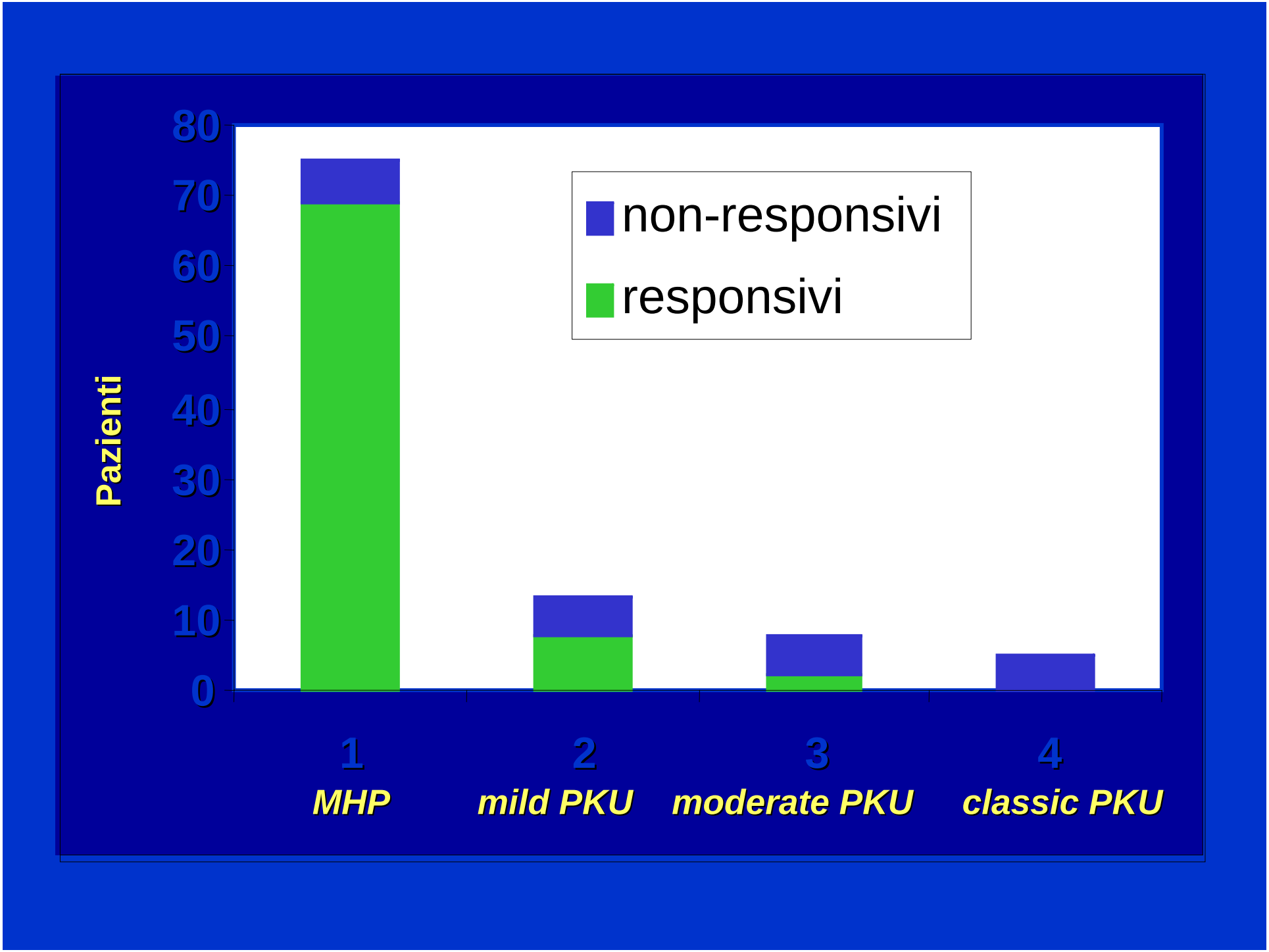
I pazienti nati in Lombardia tra Gennaio 2000 e Novembre 2004 (N = 101) sono stati indagati dal nostro centro per valutare la possibile responsività alla tetraidrobiopterina dopo somministrazione orale di BH4 (99.9% di 6R-BH4- forma attiva)

I pazienti nati prima di Gennaio 2000 erano stati trattati con una formulazione di farmaco diversa (33% della forma attiva) e quindi esclusi dallo studio

I pazienti sono stati suddivisi in quattro gruppi in base ai valori di fenilalanina riscontrati alla prima aminoacidemia prima dell'eventuale trattamento dietoterapico:

120-360 mcM/L	MHP	N = 75
360-600 mcM/L	mild PKU	N = 13
600-1200 mcM/L	moderate PKU	N = 8
> 1200 mcM/L	classic PKU	N = 5

N = 101


Pazienti
80
70
60
50
40
30
20
10
0
non-responsivi
responsivi
1
MHP
2
mild PKU
3
moderate PKU
4
classic PKU

Nuovi pazienti HPA N = 101
(2000-2004)

Considerando solo i pazienti in dietoterapia : 26/101

➡ 10/26 (38%) responsività alla BH4
(riduzione ≥ 50%)

➡ 15/26 (57%) responsività alla BH4
(riduzione ≥ 30%)

L Fiori, B Fiege, E Riva, M Giovannini. Mol Gen Met 86 (2005) S67-S74

"Analysis of BH4 loading tests in 209 patients with the standard BH4 loading test protocol confirms only minor importance of the 24 h response: the rate of responsiveness to BH4 after 24 h was shown to be equal to or even lower than after 8 h among most phenotypes. However, extension of the BH4 loading test to 48 h and repeated BH4 administration seems to be useful to detect BH4-responsiveness in more severe phenotypes and allows detecting "slow responders" who may benefit from BH4 therapy".

Fiege B, Giovannini M, Blau N, et al,
Mol Genet Metab. 2005 Dec; 86 Suppl 1:S91-5. Epub 2005 Nov 11

"A 24-h protocol with 20 mg/Kg BH4 is the commonly used method, and multiple administrations of BH4 and extension of the test to up to 1 week may detect additional "slow-responders".

Depending on the severity of hyperphenylalaninemia, selection criteria for the potential treatment with BH4 may range from 20% to 40% blood phenylalanine reduction after 24 hours.

Some authors use a 20% cut off, some a 30% cut off, and some a 50% cut off at 8, 15 or 24 h after a single administration of BH4".

Fiege B, Blau N, J Pediatr. 2007 Jun;150(6):627-30.

RESPONSIVITA' ALLA BH4

?

…attualmente si ritiene significativa una riduzione del 30% della fenilalanina al test da carico con BH4 nelle 24 ore successive alla somministrazione del farmaco…

"…We suggest modifyng the BH4-loading test to include a second administration of 10 to 20 mg/Kg BH4 at 12 h, with assessment of plasma phenylalanine levels at 0, 8, 12 and 24 hours after BH4 administration".

Fiege B, Blau N, J Pediatr. 2007 Jun; 150(6):627-30.

Burton BK et al, J Inherit Metab Dis. 2007 Sep 12; [Epub ahead of print]

The response of patients with phenylketonuria and elevated serum phenylalanine to treatment with oral sapropterin dihydrochloride (6R-tetrahydrobiopterin): a phase II, multicentre, open-label, screening study.

This study aimed to evaluate the response to and safety of an 8-day course of sapropterin dihydrochloride (6R-tetrahydrobiopterin or 6R-BH(4)) 10 mg/kg per day in patients with phenylketonuria (PKU), who have elevated blood phenylalanine (Phe) levels, and to identify a suitable cohort of patients who would respond to sapropterin dihydrochloride treatment with a reduction in blood Phe level. Eligible patients were aged >/=8 years, had blood Phe levels >/=450 mumol/L and were not adhering to a Phe-restricted diet. **Suitable patients were identified by a >/=30% reduction in blood Phe level from baseline to day 8 following sapropterin dihydrochloride treatment.** The proportion of patients who met these criteria was calculated for the overall population and by baseline Phe level (<600, 600 to <900, 900 to <1200 and >/=1200 mumol/L). In total, 485/490 patients completed the study and 20% (96/485) were identified as patients who would respond to sapropterin dihydrochloride. A reduction in Phe level was observed in all subgroups, although response was greater in patients with lower baseline Phe levels. Wide variability in response was seen across all baseline Phe subgroups. The majority of adverse events were mild and all resolved without complications. Sapropterin dihydrochloride was well tolerated and reduced blood Phe levels across all PKU phenotypes tested. Variability in reduction of Phe indicates that **the response to sapropterin dihydrochloride cannot be predicted by baseline Phe level.**

Levy HL et al, Lancet. 2007 Aug 11;370(9586):504-10

Efficacy of sapropterin dihydrochloride (tetrahydrobiopterin, 6R-BH4) for reduction of phenylalanine concentration in patients with phenylketonuria: a phase III randomised placebo-controlled study.

AIM OF THE STUDY: to test the efficacy of sapropterin, a synthetic form of tetrahydrobiopterin (BH4), for reduction of blood phenylalanine concentration. METHODS: We enrolled 89 patients with phenylketonuria in a Phase III, multicentre, randomised, double-blind, placebo-controlled trial. We randomly assigned 42 patients to receive oral doses of sapropterin (10 mg/kg) and 47 patients to receive placebo, once daily for 6 weeks. **The primary endpoint was mean change from baseline in concentration of phenylalanine in blood after 6 weeks.** FINDINGS: …88 of 89 enrolled patients received at least one dose of study drug, and 87 attended the week 6 visit. …After 6 weeks of treatment, patients given sapropterin had a decrease in mean blood phenylalanine of 236 (257) micromol/L, compared with a 3 (240) micromol/L increase in the placebo group ($p<0.0001$). After 6 weeks, 18/41 (44%) patients (95% CI 28-60) in the sapropterin group and 4/47 (9%) controls (95% CI 2-20) had a reduction in blood phenylalanine concentration of 30% or greater from baseline. Blood phenylalanine concentrations fell by about 200 micromol/L after 1 week in the sapropterin group and **this reduction persisted for the remaining 5 weeks of the study** ($p<0.0001$)… INTERPRETATION: **In some patients with phenylketonuria who are responsive to BH4, sapropterin treatment to reduce blood phenylalanine could be used as an adjunct to a restrictive low-phenylalanine diet, and might even replace the diet in some instances.**

RESPONSIVITA' ALLA BH4 TRA I PAZIENTI HPA

LA RESPONSIVITA' ALLA BH4 E' STATA DEFINITA COME

RIDUZIONE > DEL 30%

DEI LIVELLI DI FENILALANINA PLASMATICA

8 ORE DOPO LA SOMMINISTRAZIONE DELLA BH4

FORME DI IPERFENILALANINEMIA RISULTATE MAGGIORMENTE RESPOSIVE ALLA TERAPIA con BH4

- **MHP (phe = 2 - 6 mg/dl)**
- **PKU LIEVE (phe 6 - 10 mg/dl)**
- **PKU MODERATA (phe 10 - 20 mg/dl)**
- **PKU CLASSICA(phe = > 20 mg/dl)**

LA RESPONSIVITA' ALLA BH4 PUO DIPENDERE DA:

- **GENOTIPO**
- **DOSAGGIO**
- **SOMMINISTRAZIONE DOSE SINGOLA O MULTIPLA**
- **INTAKE DIETETICO DI PHE** durante il test DA CARICO
- **ASPETTI FARMACOCINETICI ….**

STUDI SUCCESSIVI RIGUARDO LA TERAPIA CON BH4 SONO NECESSARI PER POTER DEFINIRE:

SICUREZZA FARMACOLOGICA

EFFICACIA TERAPEUTICA

OUTCOME A LUNGO TERMINE