Palynziq (pegvaliase pqpz)

FDA approval: May 24, 2018

Indication: to reduce blood phenylalanine (Phe) concentrations in adult patients with PKU with uncontrolled blood Phe > 600 micromol/L on existing management

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Disclaimer

The views expressed in this presentation are those of the speaker and do not necessarily represent an official FDA position

The speaker has no financial interests to disclose

Overview

- Quantitating the clinical benefit in PKU
- Palynziq efficacy evaluation and remaining questions
- Palynziq safety evaluation and risk mitigation strategies to ensure safe use
- PKU patient perspectives on unmet needs and safety risk tolerance
- Palynziq Benefit-Risk Assessment

Management of PKU in adults

- Blood Phe reduction
  - goal range (<600 µmol/L?, 120-360 µmol/L?)
  - what is more (most) important?
    - mean Phe vs Phe variability vs Phe/Tyr ratio vs life-long Phe control within a certain range
  - how low is good enough
  - what degree of Phe reduction leads to long-term clinical benefit ? what type of benefit? how much benefit?
- Improvement in clinical symptoms
  - Executive dysfunction
  - Inattention
  - Anxiety, depression
- Dietary management
  - Optimal growth
  - Minimize risk of vitamin deficiencies

Quantitation of benefit in Palynziq trials (1)

- Blood Phe reduction
  - Eligibility criterion: blood Phe >600 µmol/L
  - Mean blood Phe in patients enrolled in trial 165-301 (I/T/M) ~1,200 µmol/L
  - Reduction ≥20% from baseline considered a "response"
    - Is ≥20% blood Phe reduction from baseline associated with clinical benefit in PKU?
    - Review team assessed that a reduction to <600 µmol/L may be reasonable threshold as patients were enrolled based on this criterion and this threshold Phe concentration defines a diagnosis of PKU (when untreated)
  - Biochemical response was highly variable among treated patients (immunogenicity) with minority of originally enrolled patients achieving the pre-defined response criterion for inclusion in trial 165-302 (DB,PBO-controlled)
- Remaining questions
  - what is the relationship between Phe concentration and specific clinical outcomes (concentration-response)?
  - what degree of Phe reduction leads to clinical benefit in PKU manifestations?
  - Does the timing of Phe reduction matter? (treatment in infancy vs childhood vs adulthood)
  - Should the goals of treatment (benefit) be different in children vs adults with PKU?

Quantitation of benefit in Palynziq trials (2)

- Neuropsychiatric disease
  - Instruments used in pegvaliase trials not optimized to assess potential clinically meaningful changes within the trial duration
  - Tools that require self-report not appropriate for adults with PKU who may lack self-awareness
  - COA tool study prior to use in phase 3 trials?

- Diet liberalization
  - Most patients in the trials were on unrestricted diet at enrollment
  - Of those who were on restricted diet at trial enrollment, most liberalized diet throughout trial
  - Dietary intake not a trial endpoint but apparent differences in dietary intake throughout the trial

Safety review

- Majority of patients experienced at least 1 TEAE during the clinical program
- High incidence rate of immune-mediated AEs
  - Highest during I/T period, reduced during M period (but remained relatively high)
- Variable duration of exposure in treated patients
- Different dosage regimens used among trials and among trial participants
- Appropriate analytical methods of quantitating AEs to account for the variable time of exposure and different doses
- Recoding of AEs for comprehensive, inclusive account of AEs, especially HAEs
- Adjudicated all anaphylaxis events by using NIAID/FAAAI anaphylaxis criteria (Sampson criteria)
- Embryofetal animal studies
  - maternal toxicity
  - fetal toxicity/malformations

Table 2: Adverse Reactions* Reported in at least 15% of PKU Patients Treated with Palynziq in an Induction/Titration/Maintenance Regimen in Clinical Trials – Incidence and Exposure-Adjusted Rates

Treatment Phase Treatment Duration	**Induction/Titration Phase (N = 285)** 135 person-years Mean: 178 days Median: 116 days Range: 1 to 1607 days		**Maintenance Phase (N = 223)** 444 person-years Mean: 739 days Median: 697 days Range: 5 to 1561 days	
Adverse Reaction	**N (%)†**	**Episodes (Rate)†**	**N (%)†**	**Episodes (Rate)†**
Injection site reactions‡	252 (88%)	2964 (21.9)	161 (72%)	1754 (4)
Arthralgia§	210 (74%)	1035 (7.6)	137 (61%)	661 (1.5)
Hypersensitivity reactions¶	152 (53%)	633 (4.7)	135 (61%)	663 (1.5)
Headache#	100 (35%)	211 (1.6)	111 (50%)	778 (1.8)
Generalized skin reaction lasting at least 14 days‖	61 (21%)	95 (0.7)	82 (37%)	133 (0.3)
Pruritus	58 (20%)	100 (0.7)	53 (24%)	402 (0.9)
Nausea	51 (18%)	66 (0.5)	57 (26%)	106 (0.2)
Dizziness	46 (16%)	64 (0.5)	38 (17%)	72 (0.2)
Abdominal pain**	39 (14%)	53 (0.4)	55 (25%)	128 (0.3)
Oropharyngeal pain	38 (13%)	43 (0.3)	51 (23%)	70 (0.2)
Fatigue	37 (13%)	81 (0.6)	48 (22%)	86 (0.2)
Vomiting	36 (13%)	53 (0.4)	58 (26%)	100 (0.2)
Cough	27 (9%)	33 (0.2)	50 (22%)	65 (0.2)
Diarrhea	25 (9%)	31 (0.2)	50 (22%)	91 (0.2)
Anxiety	14 (5%)	23 (0.2)	41 (18%)	79 (0.2)
Alopecia	13 (5%)	14 (0.1)	39 (17%)	50 (0.1)
Nasal congestion	12 (4%)	15 (0.1)	41 (18%)	50 (0.1)

Palynziq USPI, 2018

Table 3: Laboratory Abnormalities Reported in at least 10% of PKU Patients Treated with Palynziq in an Induction/Titration/Maintenance Regimen in Clinical Trials – Incidence and Exposure-Adjusted Rates

Treatment Phase Treatment Duration	**Induction/Titration Phase (N = 285)** 135 person-years Mean: 178 days Median: 116 days Range: 1 to 1607 days		**Maintenance Phase (N = 223)** 444 person-years Mean: 739 days Median: 697 days Range: 5 to 1561 days	
Laboratory Measurement	**N (%)***	**Episodes (Rate)***	**N (%)***	**Episodes (Rate)***
Complement factor C3 below LLN	195 (68%)	446 (3.3)	188 (84%)	1719 (3.9)
C-reactive protein (CRP) above ULN	182 (64%)	358 (2.6)	151 (68%)	947 (2.1)
Complement factor C4 below LLN	177 (62%)	318 (2.4)	108 (48%)	604 (1.4)
Hypophenylalaninemia† on a single measurement	53 (19%)	204 (1.5)	137 (61 %)	1128 (2.5)
Blood creatine phosphokinase (CPK) above ULN	50 (18%)	87 (0.6)	96 (43%)	277 (0.6)
Hypophenylalaninemia† on 2 or more consecutive measurements	45 (16%)	60 (0.4)	93 (42%)	140 (0.3)
Hs-CRP above 0.287 mg/dL over a 6 month period	34 (12%)	34 (0.4)	23 (10%)	26 (0.06)

* N (%) = Number of patients with at least 1 laboratory abnormality (%); Rate = Exposure-Adjusted Rate of Laboratory Abnormalities (Laboratory Abnormalities/Person-Years)

† Blood phenylalanine concentration below 30 micromol/L

LLN – lower limit of normal

ULN – upper limit of normal

Hs – high sensitivity

Palynziq USPI, 2018

Identified serious risk which requires a REMS for approval

- Anaphylaxis: 9% of patients had at least one episode of anaphylaxis during the trials

- REMS (with ETASU)
  - to ensure that patients and prescribers are educated on the anaphylaxis risk and have appropriate intervention (injectable epinephrine) available at all times to mitigate the risk, if needed

Risk Evaluation and Mitigation Strategy (REMS)

- Medication Guide
- Communication Plan
  - Dear healthcare provider letter
  - Journal articles
- Elements to assure safe use (ETASU)
- Implementation System
  - Generally limited to REMS w/ETASU
- Timetable for Submission of Assessments

Elements to Assure Safe Use (ETASU)

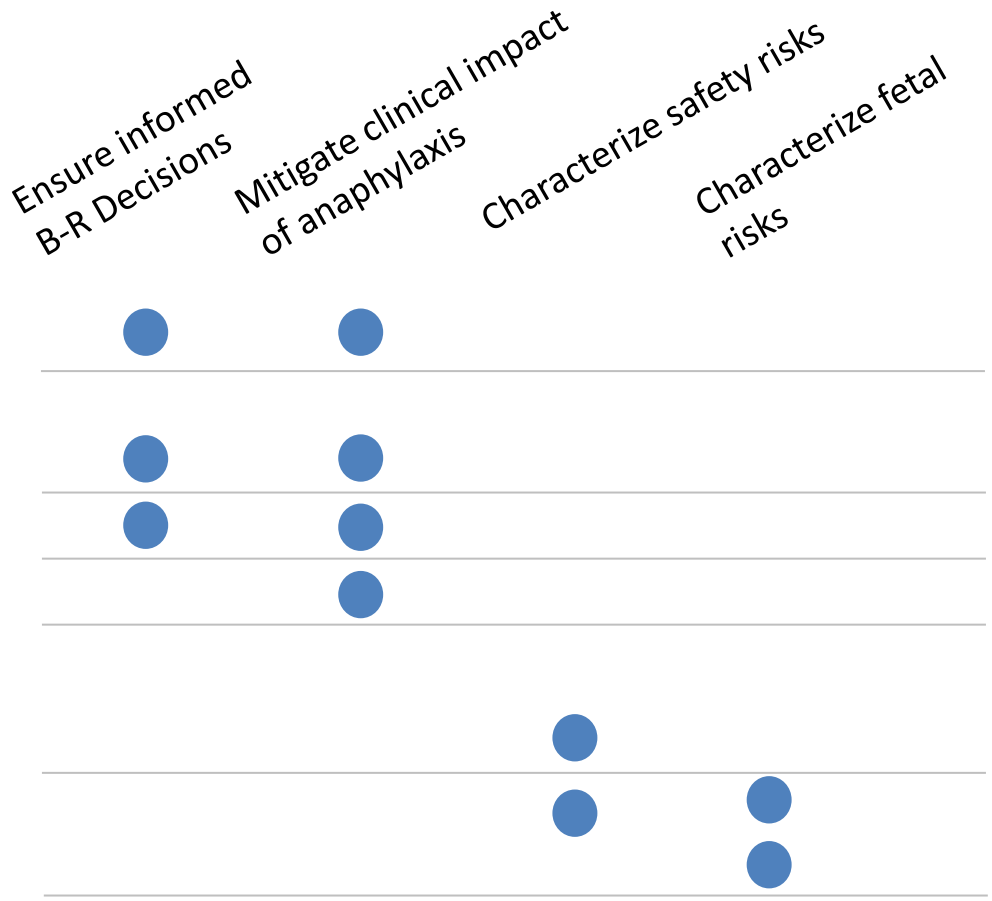
A	Prescribers have specific training/experience or special certifications
B	Pharmacies, practitioners or healthcare settings that dispense the drug are specially certified
C	Drug may only be dispensed in certain healthcare settings (e.g. infusion center, hospital)
D	Drug may only be dispensed with evidence of safe-use conditions (e.g. laboratory test results)
E	Each patient using the drug is subject to monitoring
F	Each patient using the drug is enrolled in a registry

Potential serious risk

- Embryofetal toxicity signal in animals
  - Post-approval animal study to better define/describe this potential safety signal
  - Post-approval pregnancy observational study
  - Description of potential embryofetal risks from Palynziq and from untreated PKU

Safety: Strategies and Goals

- Product labeling
- REMS with ETASU
  - Patient, prescriber education
  - Patient-provider agreement
  - Availability of epinephrine
- Post-approval studies
  - Observational safety study
  - Observational pregnancy study
  - Animal studies



Patient perspectives

- NPKUA meeting with FDA
- Patient meeting with DGIEP review team during BLA review
- Perspectives on both desired benefits and acceptable risks
  - What matters?
  - What is missing?
  - What degree(s) of (safety) risk are they willing to take to achieve what matters?

Summary of Benefit-Risk Assessment
Palynziq (pegvaliase-pqpz)

Dimension	Conclusions and Reasons
Analysis of Condition	PKU is a serious disease that can lead to significant functional impact (cognitive, executive function, psychiatric disease), particularly for patients with severe, classical PKU (>70% or patients). Clinical outcomes and symptom severity in PKU depend on long-term Phe control. It is unclear what degree of Phe reduction from baseline reflects a specific clinical benefit. However, the overall goal of clinical management centers around Phe reduction, which is the fundamental pathophysiologic disturbance associated with PKU.
Current Treatment Options	PKU diet is highly-restrictive, difficult to adhere to, has limited clinical benefit in adults (due to lack of adherence), and can produce adverse long-term health effects (nutritional deficiencies, growth problems, social isolation). Kuvan (sapropterin) is FDA-approved for PKU patients who are “responsive” (~30% of all PKU patients).
Benefit	The observed reductions in blood Phe concentration in Trial 165-301 in the adults with PKU who started on and maintained a largely unrestricted dietary protein intake are clinically significant given that the therapeutic goal in PKU management is blood Phe reduction and this is not achieved if dietary protein intake is not restricted.
Risk and Risk Management	*Next slide*

Summary of Benefit-Risk Assessment
Palynziq (pegvaliase-pqpz)

Dimension	Conclusions and Reasons
Analysis of Condition	*Previous slide*
Current Tx Options	
Benefit	
Risk and Risk Management	The safety risks identified in the trials are largely linked to immunogenicity to the product, which is a foreign protein. Serious outcomes from anaphylaxis will be mitigated by: 1) boxed warning and warnings and precautions in PI; 2) REMS with ETASU to ensure patient and prescriber education as well as availability and immediate use of auto-injectable epinephrine in the event of anaphylaxis. Most hypersensitivity events (other than anaphylaxis) were mild to moderate and did not lead to serious or life-threatening outcomes. No end-organ safety signals were detected during the trials to suggest immune-mediated major organ toxicity but PMRs will assess long-term safety and immunogenicity effects. Additional post-approval studies will assess long-term safety during pregnancy and lactation and further define the potential safety risks related to embryofetal toxicity.

Conclusions

- Quantitation of clinical benefit in PKU tightly linked to blood Phe concentration
- Remaining questions regarding degree of Phe reduction that leads to clinical benefit
- Important safety risks of Palynziq related to highly immunogenic foreign protein
- Patient input during drug development and regulatory review provided important insights to the review team
- Approval based on favorable benefit-risk assessment including assurance of safe use for the serious risk of anaphylaxis (REMS w ETASU), product labeling, and post-marketing required studies

Thank you!

Questions/Comments:
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ADMINISTRATION

Back up slides

Phenylketonuria (PKU

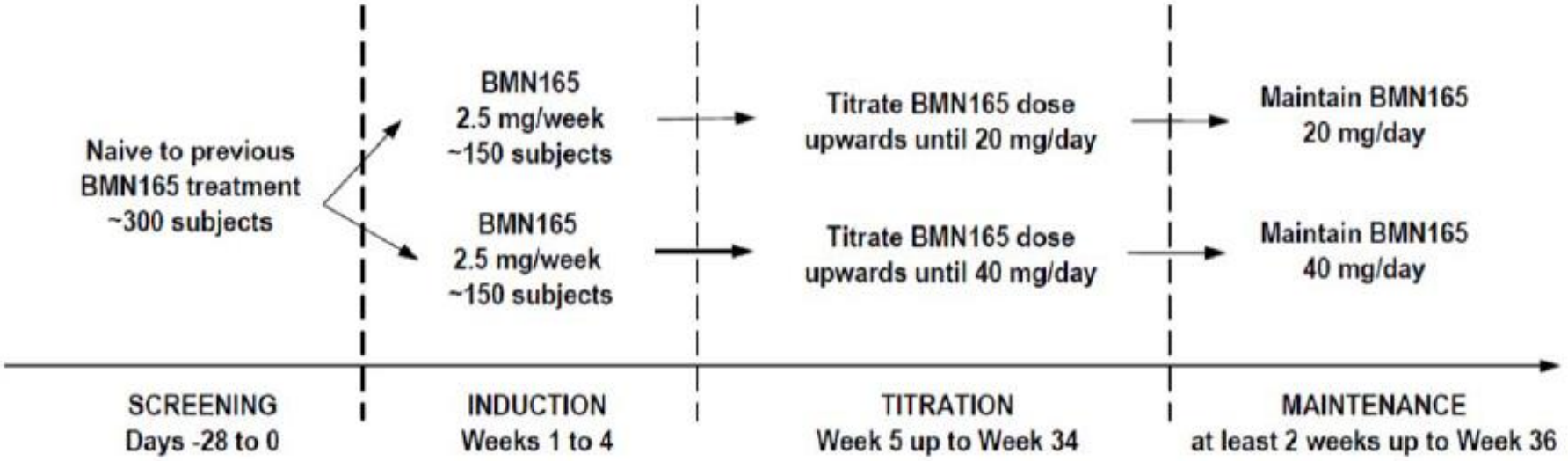
- Phenylalanine hydroxylase (PAH) deficiency
  - Inefficient/absent conversion of Phe to Tyr
  - Accumulation of Phe and related metabolites (neurotoxic)
- Serious, rare, inherited disease which manifests with chronic hyperphenylalaninemia leading to chronic neurologic and psychiatric disease when untreated or undertreated
- Metabolic control through reduction in blood Phe concentrations throughout the patient's lifetime is the overall therapeutic goal in PKU management
- Available therapeutic options include:
  - 1) the PKU diet, which consists of lifetime strict restriction of dietary protein and Phe intake, and
  - 2) Kuvan (sapropterin dihydrochloride), the PAH enzyme cofactor, which is indicated only for those patients with PKU who are "Kuvan responsive" (approximately 30% of all PKU patients).

Palynziq (pegvaliase-pqpz)

- Foreign protein produced through the PEGylation of recombinant phenylalanine ammonia lyase (rAvPAL), derived from the cyanobacterium *Anabaena variabilis.*
- Provides alternate pathway for Phe breakdown via its enzymatic conversion to trans-cinnamic acid (t-CA) and ammonia, both excreted in the urine
- SC injection (PFS)
- Approved dosing regimen[1]:
  - induction, titration, maintenance (I/T/M) with starting dose 2.5 mg once weekly slowly titrated over at least 9 weeks up to target maintenance dose 20 mg once daily.
  - if an adequate therapeutic response (≥20% reduction in blood Phe concentration from baseline or blood Phe ≤ 600 micromole/L) is not reached after at least 24 weeks on 20 mg daily, dose may be increased to 40 mg once daily.
  - If an adequate therapeutic response is not achieved after an additional 16 weeks of 40 mg once daily, then treatment should be discontinued.
  - Dose titration/escalation directed by blood Phe concentration and tolerability.

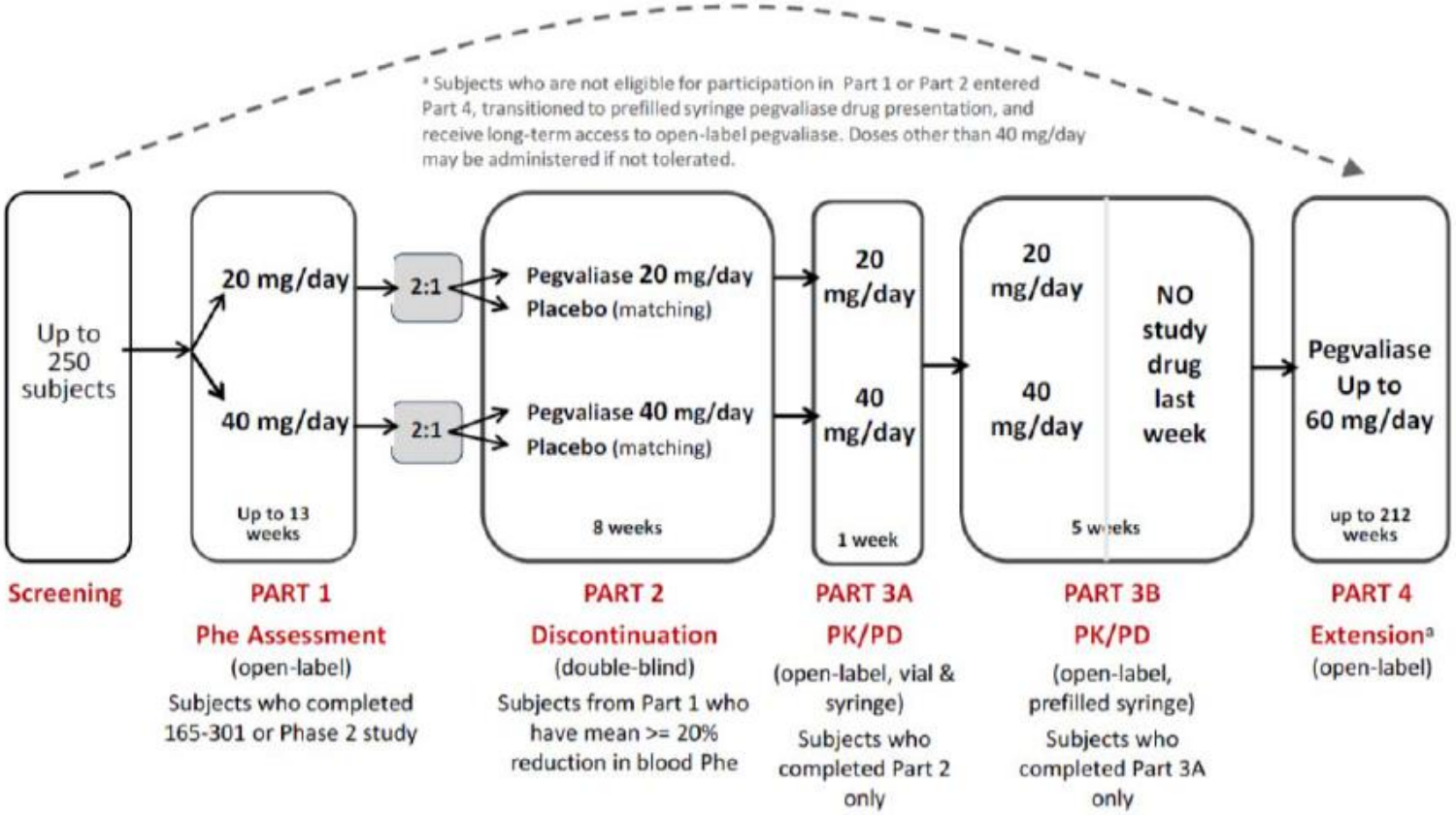
1: Palynziq USPI, 2018

Trial 165-301



Pegvaliase Dosing (Induction, Titration, and Maintenance), Prefilled Syringe						
Study Period	Duration	Total Weekly Fixed Dose (mg)	Total Weekly Volume (mL) [a]	Mg per Dose	Volume (mL) per Dose [a]	Frequency of Administration per Week
Induction	4 weeks	2.5 [b]	0.5	2.5	0.5	1
		2.5 [b]	0.5	2.5	0.5	1
		2.5	0.5	2.5	0.5	1
		2.5	0.5	2.5	0.5	1
Titration	Up to 30 weeks	5	1.0	2.5	0.5	2 [c]
		10	0.5	10	0.5	1
		20	1.0	10	0.5	2 [c]
		40	2.0	10	0.5	4
		70	3.5	10	0.5	7
		140 [d] (20 mg/day)	7.0	20	1.0	7
		280 [d] (40 mg/day)	14.0	40	2.0	7
Maintenance	At least 2 weeks	20 mg/day or 40 mg/day				

Trial 165-302



165-302 part 2
Randomized withdrawal period

Table 26: Trial 165-302: Mixed-Model Repeated Measures of Change in Blood Phe Concentration (micromol/L) from Part 2 Baseline to Part 2 Week 8 (mITT Population)

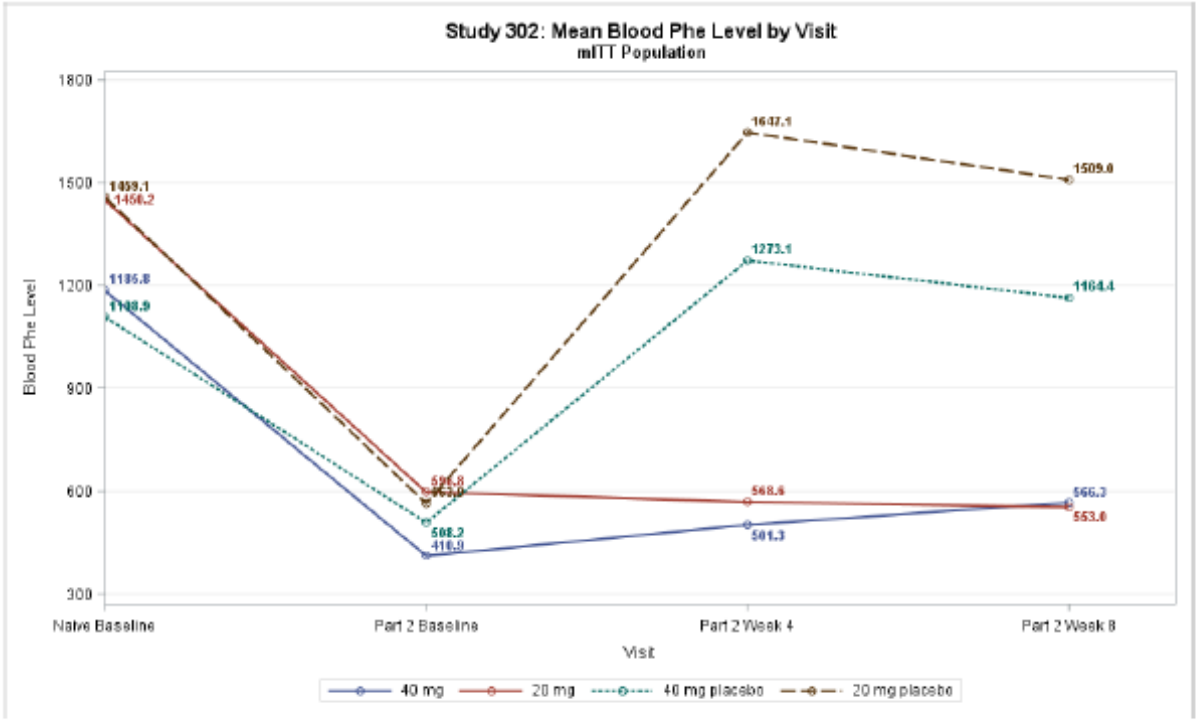
	20 mg/day	20 mg/day Placebo	40 mg/day	40 mg/day Placebo
N	29	14	29	14
Part 2 Baseline Mean (SD)	596.8 (582.7)	563.9 (504.6)	410.9 (439.9)	508.2 (363.7)
Part 2 Week 8 Mean (SD)	553.0 (582.4)	1509.0 (372.6)	566.3 (567.5)	1164.4 (343.3)
Mean (SD) Change from Part 2 Baseline	-65.9 (192.0)	996.4 (555.0)	114.1 (332.4)	599.0 (507.4)
LS Mean Change from Part 2 Baseline (95% CI)	-23.3 (-156.2, 109.7)	949.8 (760.4, 1139.1)	76.3 (-60.2, 212.8)	664.8 (465.5, 864.1)
Difference in LS Means (95% CI)	-973.0 (-1204.2, -741.9)		-588.5 (-830.1, -346.9)	
p-value*	<0.0001		<0.0001	

Source: adapted from Table 14.2.2.1.2 in 165-302 CSR.

* P-value was compared between the active dose group and the according placebo group respectively.

165-301, 165-302

Figure 6: Trial 165-301 and 165-302: Blood Phe Concentration (micromol/L) changes from pre-treatment baseline (165-301) to Part 2 week 8 (165-302)- mITT Population



Source: adapted from Table 9.4.1.3.1 in 165-302 CSR.

Risk Management Goals

- Product is available to patients for whom benefit outweighs the risk(s)
- Patients and providers make informed B-R decisions about:
  - immunogenicity-related risks
  - anaphylaxis risk
  - use during pregnancy and lactation
- Minimize/mitigate impact (sequelae) of anaphylaxis and prevent serious outcomes
  - REMS with ETASU
- Better characterize long-term safety/immunogenicity risks
  - Post-approval required safety studies
- Better characterize risks to fetus or nursing infant
  - Post-approval required safety studies

Risk Management Strategies

- Product labeling
  - Boxed warning
  - Warnings and precautions
- REMS with ETASU
  - Patient, prescriber education
  - Patient-provider agreement
  - Prophylactic prescription/availability of injectable epinephrine (prescriber, pharmacist certification)
- Post-marketing required studies
  - Observational studies to assess and characterize long-term safety and immunogenicity
  - Observational study to assess pregnancy outcomes, fetal risks
  - Animal study to better characterize embryofetal risks