03 May 2019
EMA/227084/2019
Committee for Orphan Medicinal Products

Orphan Maintenance Assessment Report

Palynziq (Pegylated recombinant phenylalanine ammonia lyase)

Treatment of hyperphenylalaninaemia

EU/3/09/708 (EMA/OD/112/09)

Sponsor: BioMarin International Limited

Note

Assessment report as adopted by the COMP with all information of a commercially confidential nature deleted.

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1. Product and administrative information

Product	
Active substance	Pegylated recombinant phenylalanine ammonia lyase
International Non-Proprietary Name	Pegvaliase
Orphan indication	Treatment of hyperphenylalaninaemia
Pharmaceutical form	Solution for injection
Route of administration	Subcutaneous use
Pharmaco-therapeutic group (ATC Code)	A16ABXX
Sponsor's details:	BioMarin International Limited Shanbally Ringaskiddy County Cork Ireland
Orphan medicinal product designation procedural history	
Sponsor/applicant	BioMarin Europe Ltd United Kingdom
COMP opinion date	05 November 2009
EC decision date	28 January 2010
EC registration number	EU/3/09/708
Post-designation procedural history	
Transfer of sponsorship	Transfer from BioMarin Europe Ltd.to BioMarin International Limited – EC decision of 08 August 2016
Marketing authorisation	
Rapporteur / co-Rapporteur	Johann Lodewijk Hillege, Joseph Emmerich
Applicant	BioMarin International Limited
Application submission date	06 March 2018
Procedure start date	29 March 2018
Procedure number	EMA/H/C/004744
Invented name	Pegylated recombinant phenylalanine ammonia lyase
Therapeutic indication	For the treatment of hyperphenylalaninaemia in adults with phenylketonuria Further information on Palynziq can be found in the European public assessment report (EPAR) on the Agency's website https://www.ema.europa.eu/en/search/search?search_api_views_fulltext=EU/3/09/708
CHMP opinion date	28 February 2019
COMP review of orphan medicinal product designation procedural history	
COMP Co-ordinators	E.J. Rook / A. Lorence
Sponsor's report submission date	07 March 2018
COMP discussion and adoption of list of questions	19-21 February 2019
Oral explanation	19 March 2019
COMP opinion date	21 March 2019

2. Grounds for the COMP opinion at the designation stage

The COMP opinion that was the basis for the initial orphan medicinal product designation in 2010 was based on the following grounds:

- hyperphenylalaninaemia (hereinafter referred to as “the condition”) was estimated to be affecting approximately 1.7 in 10,000 persons in the Community, at the time the application was made;
- the condition is chronically debilitating (if untreated) due to mental retardation;
- although satisfactory methods of treatment of the condition have been authorised in the Community, justifications have been provided that pegylated recombinant phenylalanine ammonia lyase may be of significant benefit to those affected by the condition based on potential clinically relevant advantage in particular in patients who do not respond to current treatment. This has been shown in a relevant clinical study.

3. Review of criteria for orphan designation at the time of marketing authorisation

Article 3(1)(a) of Regulation (EC) No 141/2000

Intention to diagnose, prevent or treat a life-threatening or chronically debilitating condition affecting not more than five in 10 thousand people in the Community when the application is made

Condition

Hyperphenylalaninaemia (HPA) is a group of inherited disorders in which plasma phenylalanine (Phe) concentrations are abnormally elevated, giving a clinical presentation involving abnormal development of the central nervous system with cognitive impairment in untreated children.

When performed, genetic testing has shown HPA to be most frequently related to mutations (one or more loss-of-function or reduced function mutations) in the phenylalanine hydroxylase (PAH) gene, which encodes the PAH enzyme. PAH catalyses the conversion of the essential amino acid phenylalanine to tyrosine, and this enzymatic activity is facilitated by tetrahydrobiopterin (BH4). Mutations in the PAH gene account for approximately 98% of HPA cases. The remaining cases arise from mutations in genes encoding enzymes involved in BH4 biosynthesis or regeneration.

Phenylketonuria (PKU) is the inherited, autosomal recessive disease characterised by a deficiency in PAH. PAH deficiency results in abnormally elevated concentrations of phenylalanine, which is toxic to the brain.

At the time of designation, the orphan condition was “hyperphenylalaninaemia”. The initial orphan condition remains acceptable for maintenance of this particular orphan designation. Nevertheless, it should be highlighted that at the time of this review and for future designations the COMP generally designates the orphan condition “phenylalanine hydroxylase deficiency”.

The approved therapeutic indication “Palynziq is indicated for the treatment of patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior management with available treatment options” falls within the scope of the designated orphan indication “Treatment of hyperphenylalaninaemia”.

Intention to diagnose, prevent or treat

Based on the CHMP assessment, the intention to treat the condition has been justified.

Chronically debilitating and/or life-threatening nature

At the time of designation and review at initial marketing authorisation, the COMP agreed that the condition was chronically debilitating and life-threatening.

At the time of this review, PKU continues to be described as causing serious health and mental problems, including severe intellectual disability and neurological impairments, as well as behavioural, emotional, and social problems, if not managed from birth and continuously throughout life. Uncontrolled blood Phe in adulthood is associated with significant morbidity, including heterogeneous neurocognitive and psychiatric deficits. Evidence from a systematic literature review and meta-analysis found that executive functioning impairment impacts daily life by interfering with the ability to perform basic cognitive tasks such as focusing, memory, planning, and impulse control. These tasks play a critical role in fulfilling responsibilities of adulthood such as acquiring/maintaining employment, managing money, raising a family, and driving.

The condition is not considered to be life-threatening.

The COMP concluded that the condition remains chronically debilitating due to intellectual impairment, deterioration of cognitive performance and motor skills, and heterogeneous psychiatric deficits that have a significant impact on daily living.

Number of people affected or at risk

At the time of designation the prevalence was agreed to be approximately 1.7 per 10,000. It has been noted there has been considerable evolution in the classification of HPA/PKU since the initial designation. Both the 2017 EU and 2014 US guidelines for the diagnosis and treatment of PKU recognise this evolution, and that there remains a lack of agreement on the blood phenylalanine level defining HPA.

Prevalence has been estimated to be approximately 1 per 10,000 for this review. For the calculation of the prevalence, a systematic literature search has been performed defining HPA/PKU as phenylalanine level >360 umol/L, in accordance with the latest EU treatment guidelines. The identified epidemiological reports seem relatively outdated. There are ongoing infantile screening programs in the EU, but data do not seem to be available in the public domain.

The prevalence was estimated by using the formula P=I*D taking into consideration the identified HPA/PKU incidence and the average life expectancy in the EU for male and females (81 years according to Eurostat 2016). The COMP noted a high heterogeneity across EU member states with reported prevalence figures of up to 2 per 10,000 (table 1 and 2) and concluded on less than 2 per 10,000 in order to cover the heterogeneous epidemiological reporting.

Table 1. Summary of Estimated Prevalence of HPA Patients in the European Community

Country	HPA Incidence (Birth rate)	Live Births 2017[3] (Predicted HPA births)	Point Prevalence (Patients) P= I x D[3]	2017 Population[3]	Expected HPA Prevalence, 2017	References for the HPA incidence (birth rate)
Austria[1]	1:7,902 (1.27/10,000)	87,633 (11)	891	8,822,300	1.01/10,000	Loeber, 2007
Bulgaria	1:28,370 (0.35/10,000)	63,955 (2)	162	7,050,000	0.23/10,000	Tansek, 2015
Belgium[1]	1:24,244 (0.41/10,000)	119,690 (5)	405	11,413,100	0.35/10,000	Loeber, 2007
Croatia	1:12,000 (0.83/10,000)	36,556 (3)	243	4,105,500	0.59/10,000	Tansek, 2015
Czech Republic	1:13,952 (0.72/10,000)	114,405 (8)	664	10,610,100	0.63/10,000	Loeber, 2007
Denmark	1:13,434 (0.74/10,000)	61,397 (5)	370	5,781,200	0.64/10,000	Loeber, 2007
France[1]	1:17,769 (0.56/10,000)	767,691 (43)	3,483	67,221,900	0.52/10,000	Loeber, 2007
Germany[1]	1:8,553 (1.17/10,000)	785,000 (92)	7,452	82,850,000	0.90/10,000	Loeber, 2007
Greece	2:45,000 (0.44/10,000)	88,523 (4)	324	10,738,900	0.30/10,000	Loukas, 2010
Ireland	1:6,200 (1.61/10,000)	62,084 (10)	811	4,838,300	1.68/10,000	Loeber, 2007
Italy[1]	1:3,654 (2.74/10,000)	458,151 (125)	10,125	60,484,000	1.67/10,000	Loeber, 2007
Netherlands	1:12,985 (0.77/10,000)	169,200 (13)	1,055	17,181,100	0.61/10,000	Loeber, 2007
Poland	1:8,068 (1.24/10,000)	401,982 (50)	4,036	37,976,700	1.06/10,000	Loeber, 2007
Portugal	1:12,163 (0.82/10,000)	86,154 (7)	567	10,291,000	0.55/10,000	Vilarinho, 2010
Norway	1:11,457 (0.87/10,000)	189,474 (19)	400	5,295,600	0.76/10,000	Loeber, 2007
Romania	1:10,000 (1.00/10,000)	189,474 (19)	1,539	19,523,600	0.79/10,000	Tansek, 2015
Slovenia	1:3,042 (3.29/10,000)	20,241 (7)	567	2,066,900	2.74/10,000	Loeber, 2007
Spain	1:6,532 (1.53/10,000)	390,024 (60)	4,836	46,659,300	1.04/10,000	Loeber, 2007
Sweden	1:12,681 (0.79/10,000)	115,416 (9)	737	10,120,200	0.73/10,000	Loeber, 2007
Switzerland	1:7,584 (1.32/10,000)	87,381 (12)	933	8,482,200	1.10/10,000	Loeber, 2007
United Kingdom	1:10,444 (0.96/10,000)	755,043 (72)	5,832	66,238,000	0.88/10,000	Shakespear 2010
EU	Mean expected prevalence = 0.89/10,000 EU Population (2017) = 513,000,000 Total calculated HPA patients in the EU = 45,886 patients					

Table 2. Summary of Estimated Prevalence of PKU Patients in the European Community

Country	PKU Incidence (Birth rate)	Live Births 2017[3] (Predicted PKU births)	Point Prevalence (Patients) P= I x D[3]	2017 Population[3]	Expected PKU Prevalence, 2017	References for the PKU incidence (birth rate)
Estonia	1:6,010 (1.66/10,000)	13,784 (2)	162	1,319,100	1.23/10,000	Ounap, 1998
Finland[1]	<0.1/10,000	50,321 (0.5)	41	5,513,100	0.07/10,000	Guldberg, 1995
France[1]	1:17,124 (0.58/10,000)	767,691 (45)	3,645	67,221,900	0.54/10,000	Abadie, 2001
Germany[2]	1:12,755 (0.78/10,000)	785,000 (62)	5,022	82,850,000	0.61/10,000	Lindner, 2011
Italy[1]	1:11,963 (0.84/10,000)	458,151 (38)	3,078	60,484,000	0.51/10,000	Romeo, 1983
Portugal	1:12,163 (0.82/10,000)	86,154 (7)	567	10,291,000	0.55/10,000	Vilarinho, 2010
Slovenia[2]	1:6,769 (1.48 /10,000)	20,241 (3)	243	2,066,900	1.18/10,000	Smon, 2015
Sweden	1:30,850 (0.32/10,000)	115,416 (4)	324	10,121,200	0.32/10,000	Alm, 1981
EU	Mean expected prevalence = 0.63/10,000 EU Population (2017) = 513,000,000 Total calculated PKU patients in the EU = 32,127					

Article 3(1)(b) of Regulation (EC) No 141/2000

Existence of no satisfactory methods of diagnosis prevention or treatment of the condition in question, or, if such methods exist, the medicinal product will be of significant benefit to those affected by the condition.

Existing methods

There is one authorised product for the treatment of the orphan condition in the EU. Kuvan (Sapropterin dihydrochloride) is indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with phenylketonuria (PKU) who have been shown to be responsive to such treatment. Kuvan is also indicated for the treatment of hyperphenylalaninaemia (HPA) in adults and paediatric patients of all ages with tetrahydrobiopterin (BH4) deficiency who have been shown to be responsive to such treatment.

There is a European consensus treatment guideline on phenylketonuria (van Wegberg et al. Orphanet J Rare Dis. 2017; 12: 162), which has been developed by the scientific advisory committee of the European Society for Phenylketonuria and Allied Disorders Treated as Phenylketonuria (ESPKU) with support of a group of European PKU experts. Dietary treatment is the basis of PKU management. It consists of 3 parts: natural protein restriction, Phe-free-L-amino acid supplements, and low protein food. The majority of patients fail to achieve adequate low phenylalanine levels based on the diet alone.

Significant benefit

In line with the therapeutic indication, significant benefit needs to be demonstrated for Palynziq in patients with phenylketonuria (PKU) aged 16 years and older who have inadequate blood phenylalanine control (blood phenylalanine levels greater than 600 micromol/l) despite prior

management with available treatment options. Taking into consideration the authorisation status of medicinal products, it was considered that significant benefit needs to be demonstrated over Kuvan.

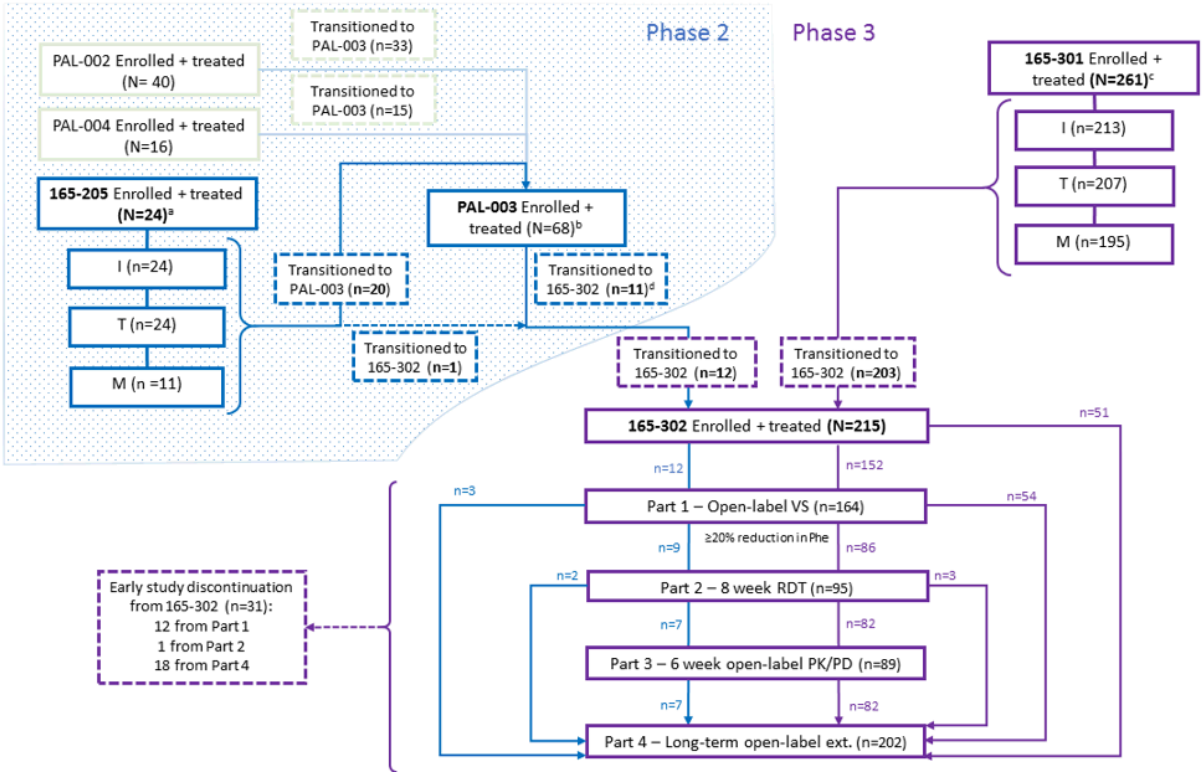
The applicant did not seek EMA protocol assistance on significant benefit issues from the COMP during their development.

To substantiate significant benefit over Kuvan, clinical data from the phase II and phase III trials have been submitted (overview in figure 1). Two phase III studies (study 165-301 and 165-302) and three phase II studies (PAL-002, PAL-004 and 165-205) were submitted. Studies PAL-002, PAL-004, 165-205 and also 165-301 are considered dose finding studies.

The same set of data was assessed by the CHMP for the establishment of benefit-risk (please be referred to the see EPAR of Palynziq); study 165-302 was considered by the CHMP as the main study, consisting of four parts. Study 165-302 is a four-part, phase III, randomised, double-blind, placebo-controlled, four-arm, discontinuation study to evaluate the efficacy and safety of subcutaneous injections of pegvaliase self-administered by adults with PKU. All patients who participated in study 165-301 or preceding phase II studies could be subsequently enrolled in study 165-302. The objectives of Part 1 were to screen patients for eligibility (≥20% reduction in blood phenylalanine from baseline treatment-naïve values, thus change from baseline study 165-301) for entry into Part 2 of the study and to characterise the safety of pegvaliase (20 or 40 mg/day) in patients previously exposed to pegvaliase. Safety evaluation was the primary endpoint. In part 2 of the study (randomised double-blind placebo-controlled withdrawal phase) 86 eligible patients were randomised to either continue on their randomised pegvaliase dose (20 or 40 mg/day) or receive a placebo treatment (withdrawal from pegvaliase). The primary efficacy objective of Part 2 was to evaluate the effect on blood phenylalanine in patients previously exposed to pegvaliase in part 1 compared with those who were administered a matching placebo. The Part 2 entry criterion of ≥20% blood phenylalanine reduction was applied. Enrichment criteria with the minimum blood phenylalanine efficacy of 20% reduction from naïve baseline (e.g. baseline study 165-301 or the Phase II study in which they initiated pegvaliase were considered the first signal of pharmacological efficacy from pegvaliase. Part 4 of the study is an open-label long term follow-up that included patients who finalised part 1 to part 3 of the study and patients who were transitioned from study 165-301 however who were not eligible for inclusion in part 1 of study 165-302. In part 4 of the study patients could be treated with pegvaliase doses 5, 10, 20, 40, and 60 mg/day in case the randomised dose of 20 or 40 mg/day did not lead to a reduction of phenylalanine levels ≥20%. During study 165-302 several neurocognitive and neuropsychiatric measures were performed, including the ADHD-RS hyperactivity subscore and ADHD-RS Inattention subscore. Throughout study 165-302 dietary intake was collected by means of a diary, 3 days prior to baseline and at every study visit. The patients were requested to maintain the dietary intake stable during the studies.

The “Induction, Titration, Maintenance Population” (I/T/M population, n=285) was defined to allow for pooled analyses of clinical data across the development program. I/T/M included subjects whose overall pegvaliase treatment followed an induction, titration, and maintenance treatment regimen, similar to the proposed treatment regimen. This population includes data from subjects originally enrolled in parent studies 165-205 and 165-301 and data from the extension studies to which they transferred (PAL-003 and 165-302). For the subjects in the I/T/M Population who reached and completed 12 months of treatment (184/285), blood phenylalanine concentrations were reduced by a mean (SD) of 674.9 µmol/L (579.6; n = 184) to a mean (SD) blood phenylalanine level of 546.6 (520.8) µmol/L at 12 months). Reductions to≤600 μmol/L (controlled phenylalanine) were achieved by 56.0% (n = 103) and reductions to ≤ 120 μmol/L (normalized phenylalanine) were achieved by 37.0% (n = 68). For the subjects in the I/T/M Population who reached and completed 24 months of treatment (67/285), blood phenylalanine concentrations were reduced by a mean (SD) of 913.6 µmol/L (528.3; n = 67) to a mean (SD) blood phenylalanine level of 294.3 (398.0) µmol/L.

Figure 1. Patient Disposition across the Phase II/Phase III, Multiple Dose Studies



Of main interest for the establishment of significant benefit over Kuvan is a post-hoc subgroup analysis of the I/T/M population, which was performed in order to understand the efficacy of Palynziq in patients that do not respond to Kuvan. It should be noted that the reported studies were not designed to show efficacy and safety of pegvaliase in Kuvan responders and Kuvan non-responders. The post-hoc sub-group analysis was based on an assessment of the investigator within 6 months of the screening visit. For this analysis, 'Kuvan non-responder' was defined as a patient for whom blood phenylalanine did not decrease ≥30 percent from baseline after 1 month of treatment with 20 mg/kg per day Kuvan.

Of all 224 subjects in this post-hoc sub-group analysis, 196 (87.5%) had previously been treated with Kuvan within 6 months of the screening visit (37 subjects were not included because the assessment was not added to the protocol until Amendment 1).

Of the 196 subjects previously treated with Kuvan, 144 (73.5%) were determined by the investigator as Kuvan non-responders (with lack of response defined as no clinically significant decrease in blood phenylalanine level per investigator determination). At baseline, the mean (SD) blood phenylalanine observed in the Kuvan non-responder subgroup was 1278.1 (377.20). Following 12 months of pegvaliase treatment 62.4% of the Kuvan non responder subgroup achieved blood phenylalanine control (< 600 µmol/L). Following 24 months of pegvaliase treatment 79.3% of the Kuvan non-responder subgroup achieved blood phenylalanine control (< 600 µmol/L) demonstrating a reduction in blood phenylalanine over time (table 3). This effect was also observed in Kuvan responders, as presented in table 4.

Table 3. Sapropterin Non-responders Mean (SD) Blood phenylalanine Concentration (µmol/L), Change From Baseline, Percent Change From Baseline Over Time

Demographic or Baseline Characteristic	Sapropterin Non-responders (N = 144)		
Observed blood Phe (µmol/L)	**Baseline**	**Following 12 months of pegvaliase treatment**	**Following 24 months of pegvaliase treatment**
n	144	93	29
Mean (SD)	1278.1 (377.20)	502.5 (530.7)	324.0 (493.0)
Median	1281.5	338.0	46.0
Min, Max	483.0, 2330.0	0, 2001	0, 1640
Blood Phe reduction to ≤ 600 µmol/L, n (%)	NA	58 (62.4%)	23 (79.3%)
Blood Phe reduction to ≤ 360 µmol/L, n (%)	NA	48 (51.6%)	21 (72.4%)
Blood Phe reduction to ≤ 120 µmol/L, n (%)	NA	37 (39.8%)	16 (55.2%)
Change in blood Phe level (µmol/L)[a]			
Mean (SD)	NA	-773.4 (581.2)	-905.8 (513.6)
Median	NA	-775.0	-1002.0
Min, Max	NA	-1898, 596	-1717, 282
Percent change from baseline[a]			
Mean (SD)	NA	-58.8 (42.8)	-74.5 (37.4)
Median	NA	-73.5	-96.2
Min, Max	NA	-100, 62	-100, 31

Max, maximum; Min, minimum; MNT, medical nutritional therapy; SD, standard deviation.
Data collected for Phe in study 302 part 2 RDT phase were excluded for subjects whose treatment was placebo.
Post-baseline values were mapped to the closest monthly visit.
[a] Change and percent change from baseline was based on subjects with available measurements at both time points.

Table 4. Sapropterin Reponder Subgroup Mean (SD) Blood phenylalanine Concentration (µmol/L), Change From Baseline, Percent Change From Baseline Over Time

Demographic or Baseline Characteristic	**Sapropterin Responders (N = 52)**		
Observed blood Phe (µmol/L)	**Baseline**	**Following 12 months of pegvaliase treatment**	**Following 24 months of pegvaliase treatment**
n	52	34	7
Mean (SD)	1131.8 (363.67)	692.3 (519.2)	166.9 (261.9)
Median	1045.0	687.5	90.0
Min, Max	568.0, 1889.0	0, 1816	0, 735
Blood Phe reduction to ≤ 600 µmol/L, n (%)	NA	14 (41.2%)	6 (85.7%)
Blood Phe reduction to ≤ 360 µmol/L, n (%)	NA	11 (32.4%)	6 (85.7%)
Blood Phe reduction to ≤ 120 µmol/L, n (%)	NA	9 (26.5%)	4 (57.1%)
Change in blood Phe level (µmol/L)a			
Mean (SD)	NA	-380.4 (530.1)	-917.4 (496.5)
Median	NA	-130.0	-817.0
Min, Max	NA	-1727, 251	-1483, -304
Percent change from baselinea			
Mean (SD)	NA	-33.3 (46.1)	-81.8 (26.1)
Median	NA	-14.9	-94.3
Min, Max	NA	-100, 38	-100, -29

Max, maximum; Min, minimum; MNT, medical nutritional therapy; SD, standard deviation.
Data collected for Phe in study 302 part 2 RDT phase were excluded for subjects whose treatment was placebo.
Post-baseline values were mapped to the closest monthly visit.
[a] Change and percent change from baseline was based on subjects with available measurements at both time points.

In conclusion, the sponsor has submitted a dedicated post-hoc subgroup analysis from its clinical development to support significant benefit over Kuvan. The post-hoc subgroup analysis investigated the efficacy of Palynziq on lowering blood phenylalanine levels in patients, who did not respond to Kuvan therapy as determined at the time of screening for the clinical program. The post-hoc analysis demonstrated that patients, who were not adequately responding to Kuvan, achieved a response to Palynziq in terms of reduction of blood phenylalanine levels. This was associated with clinically meaningful improvement in inattention and mood outcomes as well as in the normalisation of diet. The COMP considered that there is sufficient evidence to confirm that Palynziq has significant benefit over Kuvan on the grounds of a clinically relevant advantage in those patients with inadequate control of blood phenylalanine despite Kuvan treatment.

4. COMP position adopted on 21 March 2019

The COMP concluded that:

- the proposed therapeutic indication falls entirely within the scope of the orphan indication of the designated Orphan Medicinal Product;
- the prevalence of hyperphenylalaninaemia (hereinafter referred to as “the condition”) was estimated to remain below 5 in 10,000 and was concluded in to be less than 2 in 10,000 persons in the European Union, at the time of the review of the designation criteria;
- the condition is chronically debilitating due to intellectual impairment, deterioration of cognitive performance and motor skills, and heterogeneous psychiatric deficits that have a significant impact on daily living;
- although satisfactory methods of treatment of the condition have been authorised in the European Union, Palynziq is of significant benefit to those affected by the orphan condition. A post-hoc subgroup analysis of the clinical data demonstrated that patients, who were not adequately responding to the currently authorised product Kuvan (sapropterin dihydrochloride), achieved a response to Palynziq in terms of reduction of blood phenylalanine levels. The reduction in phenylalanine was associated with additional clinically meaningful improvement in inattention, mood outcomes as well as in the normalisation of diet. The COMP considered that significant benefit has been demonstrated on the grounds of an improved clinical efficacy.

The COMP, having considered the information submitted by the sponsor and on the basis of Article 5(12)(b) of Regulation (EC) No 141/2000, is of the opinion that:

- the criteria for designation as set out in the first paragraph of Article 3(1)(a) are satisfied;
- the criteria for designation as set out in Article 3(1)(b) are satisfied.

The Committee for Orphan Medicinal Products has recommended that Palynziq, pegylated recombinant phenylalanine ammonia lyase, pegvaliase, EU/3/09/708 for treatment of hyperphenylalaninaemia is not removed from the Community Register of Orphan Medicinal Products.